CHEMICAL REVIEWS

REVIEW

pubs.acs.org/CR

Natural Taxanes: Developments Since 1828

Yu-Fang Wang,[†] Qing-Wen Shi,[*,†] Mei Dong,[‡] Hiromasa Kiyota,[*,§] Yu-Cheng Gu,[∥,†] and Bin Cong[*,‡]

[†]School of Pharmaceutical Sciences, Hebei Medical University, Shijiazhuang, Hebei Province, 050017, China

[‡]Department of Forensic Medicine, Hebei Medical University, Hebei Key Laboratory of Forensic Medicine, Shijiazhuang, Hebei Province, 050017, China

[§]Department of Bioscience and Biotechnology for Future Bioindustry, Graduate School of Agricultural Science, Tohoku University, 1-1 Tsutsumidori-Amamiya, Aoba-ku, Sendai 981-8555, Japan

[∥]Syngenta Jealott's Hill International Research Centre, Berkshire, RG42 6EY, U.K.

CONTENTS

1. Introduction 7653
2. Early Investigations 7655
3. Taxonomy and Distribution of Yew 7659
4. Taxanes Isolated from Yew Trees 7661
   - 4.1. 6/8/6-Taxanes 1: Neutral Taxa-4(20),11-dienes (Taxinine A Type, Table 2 and Figure 8) 7661
   - 4.2. 6/8/6-Taxanes 2: Neutral Taxa-4(20),11-dienes with a C-5-Cinnamoyloxy Group (Taxinine Type, Table 3 and Figure 9) 7662
   - 4.3. 6/8/6-Taxanes 3: Basic Taxa-4(20),11-dienes (Table 4 and Figure 10) 7662
   - 4.4. 6/8/6-Taxanes 4: Taxanes with a C-14-Oxygen Functional Group (Taiwanxan Type, Table 5 and Figure 11) 7662
   - 4.5. 6/8/6-Taxanes 5: Taxanes with a C-12, 17-Ether Ring (Taxagifine Type, Table 6 and Figure 12) 7663
   - 4.6. 6/8/6-Taxanes 6: Taxanes with a C-13,17-Ether Ring (Table 7 and Figure 13) 7664
   - 4.7. 6/8/6-Taxanes 7: Taxa-4(20),12-dienes (Table 8 and Figure 15) 7665
   - 4.8. 6/8/6-Taxanes 8: Taxanes with a C-11,12-Epoxy Ring (Table 9 and Figure 17) 7665
   - 4.9. 6/8/6-Taxanes 9: Taxa-4,11-dienes, and 6/8/6-Taxanes 10: 11,12-Epoxytax-4-enes (Tables 10, 11 and Figure 18) 7665
   - 4.10. 6/8/6-Taxanes 11: Tax-11-enes with an Opened Oxetane Ring (Table 12 and Figure 19) 7665
   - 4.11. 6/8/6-Taxanes 12: Taxanes with a C-4,20-Epoxy Ring (Table 13 and Figure 20) 7666
   - 4.12. 6/8/6-Taxanes 13: Taxanes with an Oxetane Ring (Table 14 and Figure 22) 7667
   - 4.13. 6/8/6-Taxanes 14: Taxanes with an Oxetane Ring and a Phenylisoserine Side Chain (Table 15 and Figure 23) 7667
   - 4.14. 6/8/6-Taxanes 15: Others (Table 16 and Figure 24) 7672
   - 4.15. 11(15→1)*Abeo*taxanes 1: Taxanes with 4(20),11-Double Bonds (Table 17 and Figure 25) 7675
   - 4.16. 11(15→1)*Abeo*taxanes 2: Taxanes with an Oxetane Ring (Table 18 and Figure 27) 7675
   - 4.17. 11(15→1)*Abeo*taxanes 3: Taxanes with an Opened Oxetane Ring (Table 19 and Figure 28) 7676
   - 4.18. 11(15→1)*Abeo*taxanes 4: Taxanes with a C-4,20-Epoxy Ring (Table 20 and Figure 29) 7676
   - 4.19. 11(15→1)*Abeo*taxanes 5: Taxanes with a C-2,20-Ether Ring (Table 21 and Figure 30) 7676
   - 4.20. 11(15→1)*Abeo*taxanes 6: Others (Table 22 and Figure 31) 7677
   - 4.21. 11(15→1),11(10→9)Di*abeo*taxanes (Wallifoliol Type, Table 23 and Figure 32) 7677
   - 4.22. 2(3→20)*Abeo*taxanes (Table 24 and Figure 33) 7678
   - 4.23. 3,11-Cyclotaxanes (Table 25 and Figure 35) 7679
   - 4.24. Other Cyclotaxanes (Table 26 and Figure 36) 7679
   - 4.25. Bicyclic Taxanes 1: 3,8-Secotaxa-3,8,11-trienes (Table 27 and Figure 37) 7680
   - 4.26. Bicyclic Taxanes 2: 3,8-Secotaxa-3,7, 11-trien-9-ones (Table 28 and Figure 40) 7683
   - 4.27. Bicyclic Taxanes 3: 3,8-Secotaxatriene-2,6, 9-triol (Table 29 and Figure 41) 7684
   - 4.28. Bicyclic Taxanes 4: 11,12-Secotaxane (Table 30 and Figure 42) 7685
5. Taxane Analogs (Verticillenes) from Other Sources (Figure 43) 7686
6. Isolation and Purification 7687
   - 6.1. Isolation and Purification 7687
   - 6.2. Dereplication of Taxanes 7690
7. NMR Features of Taxanes 7690
   - 7.1. ^{1}H NMR Features of Taxanes 7690

Received: May 16, 2010
Published: October 04, 2011

7.1.1. 6/8/6-Taxanes 7691
7.1.2. 11(15→1)*Abeo*taxanes 7696
7.1.3. 2(3→20)*Abeo*taxanes 7696
7.1.4. 3,11-Cyclotaxanes 7696
7.1.5. Multicyclotaxanes 7697
7.1.6. Bicyclic Taxanes 7697
7.2. ^{13}C NMR Features of Taxanes 7697
8. MS Features of Taxanes 7697
9. Chemical Studies of Paclitaxel Derivatives 7697
10. Mechanism of Action of Paclitaxel 7698
11. Structure−Activity Relationships of Paclitaxel Derivatives 7698
12. Clinical Use, Side Effects, and Development 7699
13. Conclusion 7699
Author Information 7700
Biographies 7700
Acknowledgment 7701
References 7701

1. INTRODUCTION

Yews (*Taxus* spp., Taxaceae) are slow-growing evergreen, nonresinous gymnospermous shrubs commonly used for ornamental landscaping or as construction material to build arbors (Figures 1−3). Their seeds are surrounded by a unique red fleshy cuplike aril when mature, which plays a key role in attracting birds and mammals that disperse the seeds. The most common horticultural varieties are English yew (*T. baccata*), Pacific or Western yew (*T. brevifolia*), American yew (*T. canadensis*), and Japanese yew (*T. cuspidata*). Species in the genus of *Taxus* contain an impressive array of taxanes, a group of diterpenoids with a taxane skeleton as their characteristic constituents. By far, no plant has been reported to contain taxane except these in *Taxus* and *Austrotaxus* of Taxaceae, while *Austrotaxus* was represented by only one species, *Austrotaxus spicata*, distributed in New Caledonia, Oceania, with limited chemical investigations.[1,2] Chemical studies of the yew trees were initiated because of yew poisoning. In ancient times, there were fetal cases that yew extracts were used for various reasons especially for submit to or surrendered by enemies. Long time ago, Native Americans used the bark of *T. brevifolia* as a disinfectant, an abortifacient, and a medicine for healing skin cancer. In various regions of the Himalayas, the Himalayan yew, distributed widely across Southeast and Central Asia and China have been using for headaches, calming nerves, and snakebites by local residents.

In 1856, a white alkaloidal noncrystalline powder, named taxine, was isolated in a yield of 1% from needles of *T. baccata* L. by Lucas.[3] This ill-defined constituent was thought to account for the toxicity of the plant.[4,5] For availability of technology at that time and instability of the compounds, there was no further purification or structure elucidation about that toxic component.[6] Until 1960s, there was not much progress on the chemical studies on yew trees, which was summarized in the cited literature.[7,8]

A turning point came with the supporting of a program in the United States in the early 1950s, when the National Cancer Institute (NCI) started a screening program of plant extracts using tumor system models in vivo and tumor cell lines in vitro. In 1964, the activity of an extract from the bark of *T. brevifolia* Nutt. was confirmed by the KB cytotoxicity assay. Chemical

Figure 1. (a) Japanese yew, *T. cuspidata* and (b) the Pacific yew, *T. brevifolia* (taken by H. Kiyota).

invstigation resulted in a highly active agent, isolated by Wall and Wani in a yield of 0.014% using bioassay-guided scheme, and named it as Taxol (paclitaxel) in 1966 (Figure 4). Its structure was elucidated by NMR techniques as a complex diterpenoid with an unusual oxetane ring and a β-phenylisoserine side chain esterifying at the C-13 position in 1971.[9] Methanolysis of paclitaxel led to the formation of 10-deacetylbaccatin III and methyl ester of (2*R*,3*S*)-*N*-benzoyl-3-phenylisoserine. Wall assumed that no rearrangement had occurred during this reaction and confirmed the structure including the stereochemistry of paclitaxel by the X-ray analysis of both derivatives of 10-deacetylbaccatin III and *N*-benzoyl-3-phenylisoserine methyl ester.[9] However, the antitumor activity of paclitaxel was not remarkable in comparison to vinblastin, colchicine and vincristine.[10] In addition, because of its poor solubility, ambiguous mechanism, modest yield, and purification difficulty, study on paclitaxel was not pursued further. Full clinical potential of paclitaxel was recognized when the antitumor models changed to B16 melanoma against rapidly growing tumors and L1210 leukemia against solid tumors in 1974.[10]

Figure 2. Fruits of (a) *T. baccata* and (b) *T. cuspidata*. Photograph by Q. W. Shi

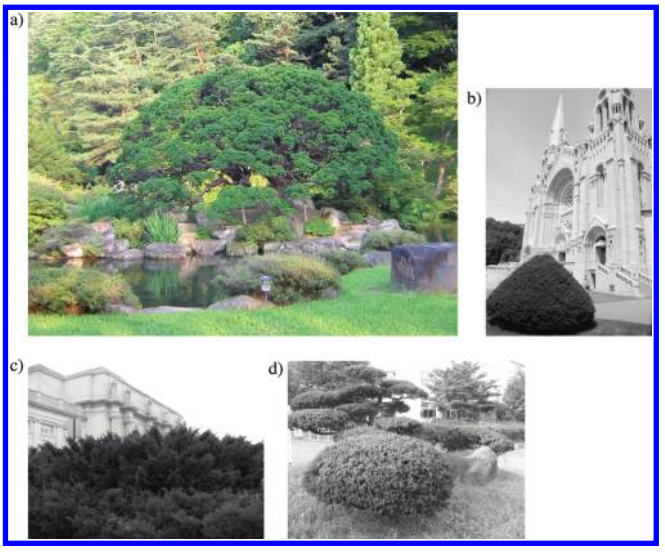


Figure 3. Yews were ornamental trees taken from (a) a Japanese garden, (b) a Quebec Church, (c) Washington Railway Station, and (d) Tohoku University of Japan. (a) Photgraph by H. Kiyota. (b−d) Photograph by Q. W. Shi.

Studies on paclitaxel received particular renewed interest right after the discovery of its mechanism of action, a historic step in the development of paclitaxel. In 1978, Fuchs and Johnson reported that paclitaxel acted as an antimitotic agent.[11] Horwitz at the Albert Einstein College of Medicine in New York under requirement of National Cancer Institute studied the mechanism

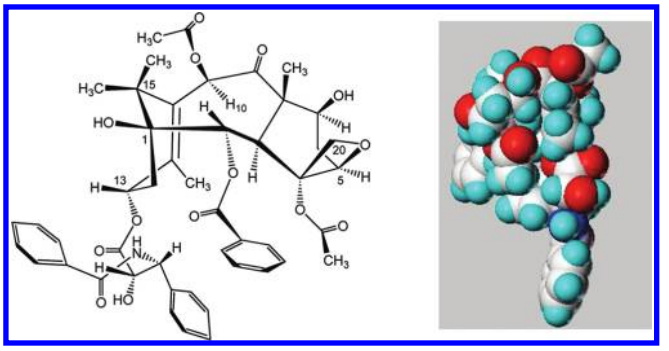


Figure 4. Stereoview of paclitaxel.

Table 1. Distribution of the Different *Taxus* Species

Taxus species	trivial name	distribution
T. baccata L.	European or English yew	Europe and Asia
T. brevifolia Nutt.	Pacific or Western yew	Northwest Pacific
T. canadensis Marsh.	Canadian yew	Canada
T. celebica (Warburg) Li	Chinese yew	China
T. cuspidata Sieb. et Zucc.	Japanese yew	Japan
T. foridana Nutt.	Florida yew	Northwest Florida
T. globosa Schlechtd.	Mexican yew	Mexico/El Salvador
T. wallichiana Zucc.	Himalayan yew	Himalayas
T. fuana Nan Li and R.R. Mill	West Himalayan yew	Western Himalayas

of action of paclitaxel in the spring of 1977.[12] In 1979, Horwitz and Schiff[13] reported that paclitaxel could promote the irreversible assembly of tubulin into microtubules and thus disrupted mitosis,[14] while all natural substances in that period such as vinblastine, colchicine, and maytansine, were known to interact with tubulin by preventing the assembly of tubulin into microtubules. The effect of paclitaxel on microtubules in vitro was well-known,[15] and it was the first compound known to act as a promoter of microtubule assembly. This new mode of action led to the selection of paclitaxel as a new lead structure for further pharmacological exploration and in 80s of the last century paclitaxel was promoted to clinical study. Since then, huge amount of efforts and resources have been put in an extensively investigation on the potency of paclitaxel and its derivatives. Between the 1960s and 1970s, Japanese and American chemists isolated more than 20 taxanes from Japanese and European yews and most of them are derivatives of taxinine and baccatin.[16,17] The taxane-type structures of taxanes were established in 1963 with taxinine as the first example of this special group of natural products.[18,19] In 1980, Miller classified the 30 taxanes isolated before 1975 and discussed the naming system.[20] Ten years later, in 1990, the number of compounds was almost doubled with 55 in three structural types.[21] In 1993, Kingston added another 46 new taxanes to the list, and the structure classes remained unchanged. Of the 101 compounds identified, 96 have a 6/8/6 membered ring system.[22] In Appendino's review covered from March of 1992 to September of 1994, 122 compounds were reported and the structure categories claimed to 5.[23] In 1995, Zhang clamied that 170 compounds were available until 1994,[24] while Parmar and Kingston's review included 270 compounds of 6 types in 1999.[25,26] An updated review by Shi et al. reported 215 new compounds isolated between 1999 and 2005 with skeletons

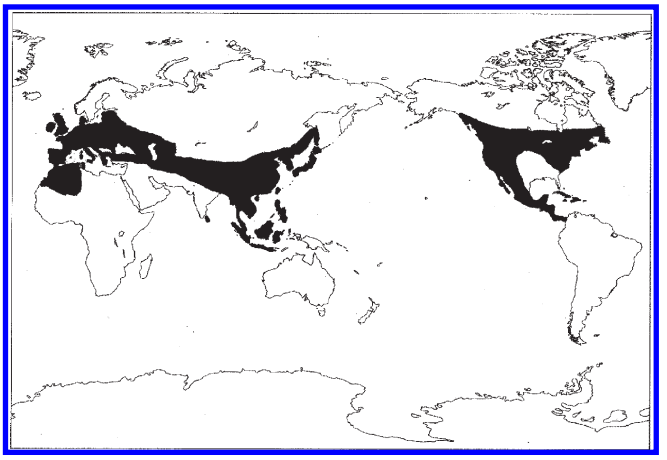


Figure 5. Distribution of *Taxus* species in the world shown in black.

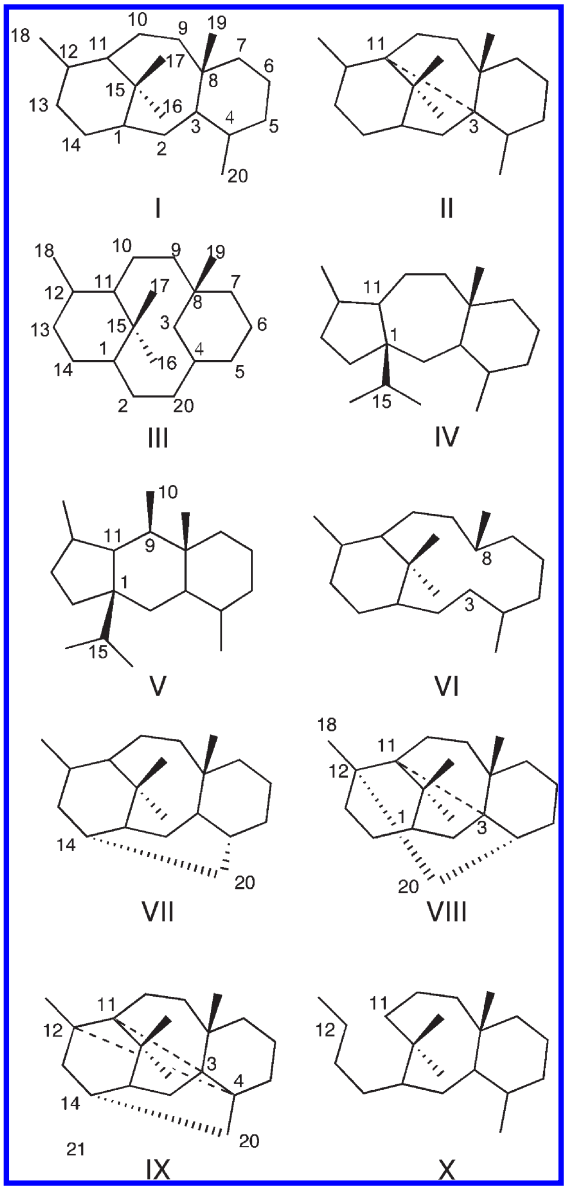


Figure 6. Taxane skeletons.

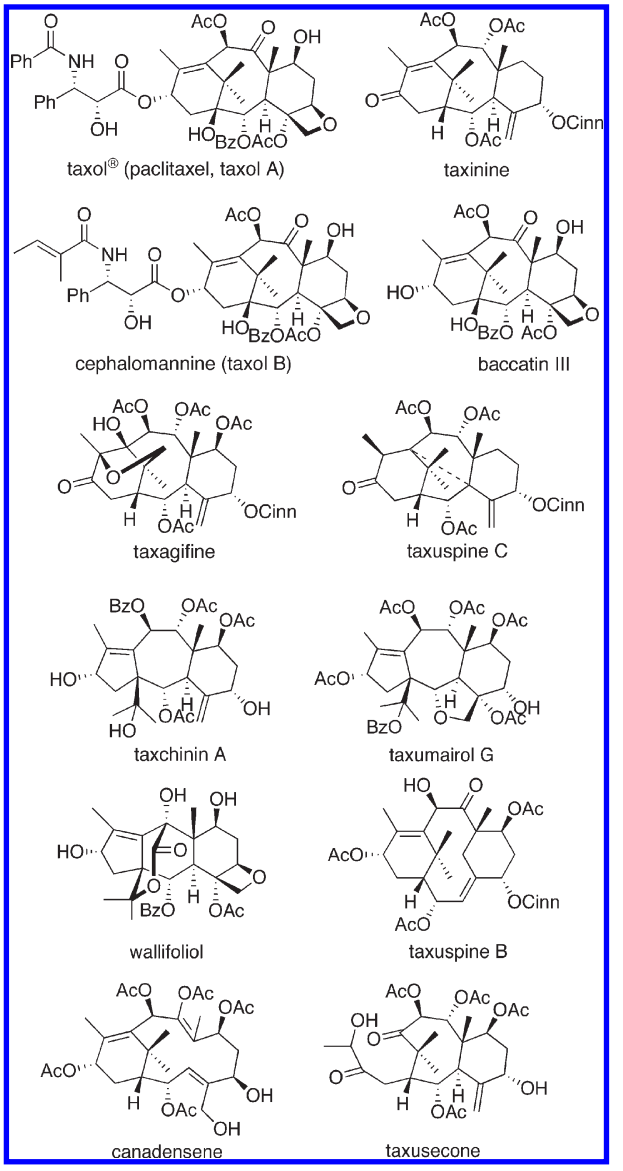


Figure 7. Structures of representative taxanes (Cinn = cinnamoyl = 3-phenylprop-2-enoyl).

increased to 9.[27] This review aim to systematically outline the secondary metabolites (taxane diterpenoids) from *Taxus* spp. up to the end of 2009, covering the recent progress on their phytochemistry, NMR and MS features, mode of action, and structure−activity relationships.

2. EARLY INVESTIGATIONS

The early phytochemical studies of taxanes dated back to 1828 when Peretti reported that the leaves of English yew (*T. baccata* L.) contained "bitter" volatile oil, oxalic acid lime, chlorophyll, and resin, while his methodology was not cited. Lucas[3] analyzed its alkaloid content in yew foliage (*T. baccata* L.). Twenty years later, Marme obtained crystalline taxine for the first time using an extraction method similar to Lucas' method.[28] Hilger and Brande gave the molecular formula for taxine, $C_{37}H_{52}NO_{10}$, based on elemental combustion analysis. In 1921, Winterstein and colleagues made some constructive investigation using acid hydrolysis to study the degradation products of amorphous taxine[29] and recovered a

dx.doi.org/10.1021/cr100147u |*Chem. Rev.* 2011, 111, 7652–7709

Table 2. 6/8/6-Taxanes 1: Neutral Taxa-4(20),11-dienes

compound	no.	source	part	ref.
5α,13α-diacetoxytaxa-4(20),11-diene-9α,10β-diol	**1**	*T. cuspidata*	lv	323
2α,10β,13α-triacetoxytaxa-4(20),11-diene-5α,7β,9α-triol	**2**	*T. cuspidata*	lv	323
		T. canadensis		324
2α,9α,10β,13α-tetraacetoxytaxa-4(20),11-dien-5α-ol (decinnamoyltaxinine E)	**3**	*T. cuspidata*	lv	325
		T. chinensis	sd	184
2α,10β,13α-triacetoxytaxa-4(20),11-diene-5α,9α-diol	**4**	*T. canadensis*	lv	326
2α,9α,13α-triacetoxytaxa-4(20),11-diene-5α,10β-diol	**5**	*T. canadensis*	lv	326
5α,9α,10β,13α-tetraacetoxytaxa-4(20),11-diene (taxusin)	**6**	*T. baccata*	hw	204, 327
		T. mairei	hw	328, 329
		T. cuspidata	hw	330
2α,5α,7β,9α,10β,13α-hexaacetoxytaxa-4(20),11-diene	**7**	*T. chinensis*	lv, st	14
taxuyunnanine D	**8**	*T. yunnanensis*	rt	330
10β,13α-diacetoxytaxa-4(20),11-diene-2α,5α,9α-triol	**9**	*T. chinensis*	lv	332
9α,10β,13α-triacetoxytaxa-4(20),11-dien-5α-ol	**10**	*T. mairei*	tw	333
2-deacetyldecinnamoyltaxinine E	**11**	*T. baccata*	lv	334
5α,10β,13α-triacetoxytaxa-4(20),11-diene-1β,7β,9α-triol (taxawallin G)	**12**	*T. wallichiana*	lv	335
2-deacetoxy-5-decinnamoyltaxinine J	**13**	*T. yunnanensis*	bk	197
		T. wallichiana	bk	336
		T. baccata	lv	334
2α,5α,9α,10β,13α-pentaacetoxytaxa-4(20),11-diene	**14**	*T. baccata*	hw	204
5α,7β,9α,10β,13α-pentaacetoxytaxa-4(20),11-diene	**15**	*T. baccata*	hw	204
		T. mairei	hw	337
2α,7β,9α,10β,13α-tetraacetoxytaxa-4(20),11-dien-5α-ol	**16**	*T. brevifolia*	bk	338
decinnamoyl-1-hydroxytaxinine J	**17**	*T. baccata*	lv	334
13-acetylbrevifoliol	**18**	*T. wallichiana*	lv	201
2α-benzoyloxy-9α,10β,13α-triacetoxytaxa-4(20),11-diene-1β,5α-diol	**19**	*T. chinensis*	st, lv	339
1-hydroxy-2-deacetoxy-5-decinnamoyltaxinine j	**20**	*T. wallichiana*	lv	340
2α,9α-diacetoxy-5α,10β-dihydroxytaxa-4(20),11-dien-13-one	**21**	*T. canadensis*	lv	326
2α,10β-diacetoxy-5α,9α-dihydroxytaxa-4(20),11-dien-13-one	**22**	*T. canadensis*	lv	326
10β-acetoxy-2α,5α,7β,9α-tetrahydroxytaxa-4(20),11-dien-13-one	**23**	*T. yunnanensis*	bk	341
2α,9α,10β-triacetoxy-5α-(β-D-glucopyranosyloxy)taxa-4(20),11-dien-13-one	**24**	*T. cuspidata*	lv	342
taxezopidine C	**25**	*T. cuspidata*	st, sd	343
taxezopidine D	**26**	*T. cuspidata*	st, sd	343
taxuspine G (2-deacetyltaxinine A)	**27**	*T. cuspidate*	st, lv	344
		T. cuspidata	lv, st	345
2,10-di-*O*-acetyl-5-decinnamoyltaxicin I	**28**	*T. baccata*	lv	334
13-dehydro-5,13-deacetyl-2-deacetoxy-decinnamoyltaxinine (taxuspinanane K)	**29**	*T. cuspidata*	st	57
taxinine A	**30**	*T. cuspidata*	lv	16
		T. mairei	sd	346
		T. mairei	bk	347
		T. chinensis	lv	348
triacetyl-5-decinnamoyltaxicin I (1-hydroxytaxinine A)	**31**	*T. baccata*	lv	334
				349
taxinine H	**32**	*T. cuspidata*	lv	16
taxuspine F	**33**	*T. cuspidata*	st, lv	344
9α,10β-diacetoxy-5α-(β-D-glucopyranosyloxy)taxa-4(20),11-dien-13α-ol	**34**	*T. canadensis*	lv	53
2α,9α,10β-triacetoxytaxa-4(20),11-diene-5α,13α-diol	**35**	*T. mairei*	sd	350
9α,10β-diacetoxytaxa-4(20),11-diene-5α,13α-diol	**36**	*T. baccata*	hw	204
		T. mairei	hw	328
taxa-4(20),11-diene-5α,9α,10β,13α-tetraol	**37**	*T. baccata*	hw	351
taxa-4(20),11-diene-1β,2α,5α,9α,10β,13α-hexaol	**38**	*T. chinensis*	st, lv	339
7-debenzoyloxy-10-deacetylbrevifoliol	**39**	*T. wallichiana*	lv	201
2α,9α-diacetoxytaxa-4(20),11-diene-1β,5α,10β,13α-tetraol	**40**	*T. baccata*	lv	114
taxezopidine F	**41**	*T. cuspidata*	sd, st	343

dx.doi.org/10.1021/cr100147u |*Chem. Rev.* 2011, 111, 7652–7709

Table 2. Continued

compound	no.	source	part	ref.
2α-benzoyloxy-9α,10β-diacetoxytaxa-4(20),11-diene-1β,5α,13α-triol	**42**	*T. chinensis*	st, lv	339
brevifoliol	**43**	*T. brevifolia*	lv	98
2α-acetoxybrevifoliol	**44**	*T. baccata*	sd	64
10β-acetoxytaxa-4(20),11-diene-2α,5α,7β,9α,13α-pentaol	**45**	*T. cuspidata*	lv	113
5α,7β,10β-triacetoxy-2α-(α-methylbutyryloxy)taxa-4(20),11-diene	**46**	*T. baccata*	hw	204
		T. mairei	hw	337
2α-(α-methylbutyryloxy)-7β,9α,10β-triacetoxytaxa-4(20),11-dien-5α-ol	**47**	*T. baccata*	hw	204
2α-(α-methylbutyryloxy)-5α,7β,9α,10β-tetraacetoxytaxa-4(20),11-diene	**48**	*T. baccata*	hw	204
2α,5α,9α,10β-tetraacetoxy-13α-(*Z*)-cinnamoyloxytaxa-4(20),11-diene	**49**	*T. cuspidata*	rt	182
5α,9α,10β-triacetoxy-13α-(*Z*)-cinnamoyloxytaxa-4(20),11-diene	**50**	*T. cuspidata*	lv	182
1β,7β,9α,10β-tetraacetoxytaxa-4(20)-dien-5α-ol	**51**	*T. baccata*	rt	189

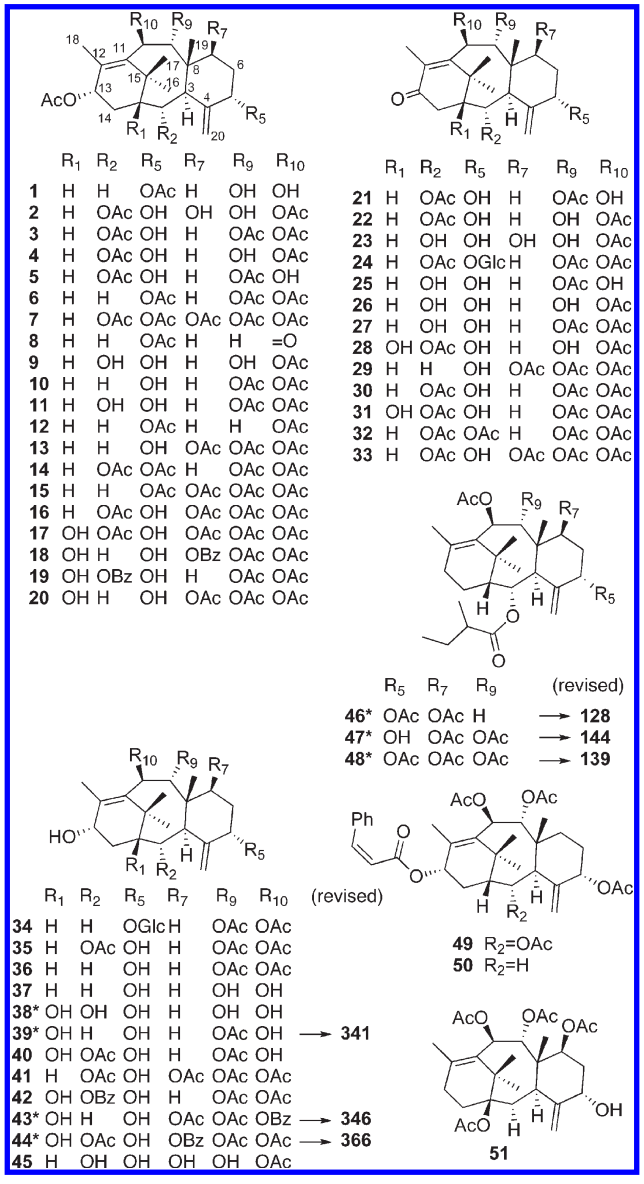


Figure 8. Neutral taxa-4(20),11-dienes. Asterisk (*) indicates structures that were revised later.

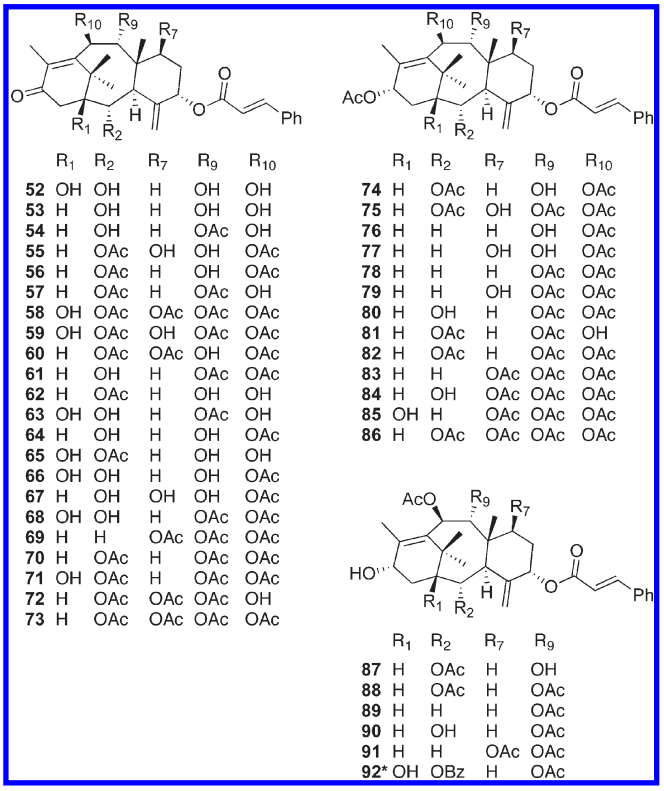


Figure 9. Neutral Taxa-4(20),11-dienes with a C-5-cinnamoyloxy group.

crystalline degradation product identified as β-dimethylamino-β-phenylpropionic acid (Winterstein's acid). Several decades later, Graf and Boeddeker claimed that taxine was a mixture of heterogeneous compounds.[30] Cleavage of the compound resulted in hydrocinnamic acid (determined spectrophotometrically) and dimethylamine (determined by alkaline hydrolysis). On the basis of this result, Graf demonstrated that taxine is a mixture of unstable alkaloids. Spectrophotometry, chromatography, and infrared (IR) analysis in further investigation made it possible to recognize two major types of taxine alkaloids: taxine A and taxine B. In fact, taxine contained several alkaloidal compounds and was easy to get with acid. In 1960s, great progress has been made with the development of NMR and MS techniques. Yet, as evidenced by the references cited in the following sections, detailed structural analysis of the compounds isolated from *Taxus* species only became achievable in recent several decades, probably because of recent advances in modern spectroscopic and spectrometric techniques.

Table 3. 6/8/6-Taxanes 2: Neutral Taxa-4(20),11-dienes with a C-5-Cinnamoyloxy Group

compound	no.	source	part	ref
5α-cinnamoyloxy-1β,2α,9α,10β-tetrahydroxytaxa-4(20),11-dien-13-one	**52**	*T. baccata*	lv	352
5α-cinnamoyloxy-2α,9α,10β-trihydroxytaxa-4(20),11-dien-13-one	**53**	*T. baccata*	lv	352
9α-acetoxy-5α-cinnamoyloxytaxa-2α,10β-dihydroxy-4(20),11-dien-13-one	**54**	*T. baccata*	lv	352
7,9-dideacetyltaxinine B	**55**	*T. canadensis*	lv	353
9-deacetyltaxinine	**56**	*T. cuspidata*	lv, st	354
		T. mairei	sd	346
10-deacetyltaxinine	**57**	*T. cuspidata*	lv	325
		T. mairei	sd	187
1β-hydroxy-7β-acetoxytaxinine	**58**	*T. cuspidata*	lv	355
1β,7β-dihydroxytaxinine	**59**	*T. cuspidata*	lv	355
9-deacetyltaxinine B	**60**	*T. mairei*	sd	350
2-deacetyltaxinine	**61**	*T. mairei*	sd	196, 346
9,10-deacetyltaxinine	**62**	*T. yunnanensis*	sd	356
O-cinnamoyltaxicin I	**63**	*T. baccata*	lv	183
5-cinnamoyl-10-acetyltaxicin II	**64**	*T. baccata*	lv	36
2-*O*-acetyl-5-*O*-cinnamoyltaxicin I	**65**	*T. baccata*	lv	114
5-cinnamoyl-10-acetyltaxicin I	**66**	*T. baccata*	lv	36
taxezopidine E	**67**	*T. cuspidata*	sd, st	343
5-cinnamoyl-9,10-diacetyltaxicin I	**68**	*T. baccata*	lv	112
2-deacetoxytaxinine B	**69**	*T. wallichiana*	lv, tw	357
taxinine (*O*-cinnamoyltaxicin II triacetate)	**70**	*T. baccata*	lv	12, 183, 358
		T. chinensis	lv	348
		T. cuspidata	lv	10, 16
		T. mairei	hw	328
O-cinnamoyltaxicin I triacetate	**71**	*T. baccata*	lv	183
		T. cuspidata	lv	16
10-deacetyltaxinine B	**72**	*T. cuspidata*	lv, tw	37, 359
taxinine B (7β-acetate-*O*-taxinine A)	**73**	*T. cuspidata*	lv	10
		T. mairei	hw	337
9-deacetyltaxinine E	**74**	*T. canadensis*	lv	105
		T. mairei	sd	346
dantaxusin D	**75**	*T. yunnanensis*	lv, st	205
dantaxusin B	**76**	*T. yunnanensis*	bk, lv, tw	360
2-deacetoxy-7,9-dideacetyltaxinine J	**77**	*T. chinensis*	bk	361
5α-cinnamoyloxy-9α,10β,13α-triacetoxytaxa-4(20),11-diene	**78**	*T. mairei*	hw	362
		T. chinensis	lv, st	363
9α,10β,13α-triacetoxy-5α-cinnamoyloxytaxa-4(20),11-dien-7β-ol	**79**	*T. mairei*	tw	333
taxezopidine G	**80**	*T. cuspidata*	sd, st	296
		T. mairei	sd	346
		T. mairei	bk	347
2α,9α,13α-triacetoxy-5α-cinnamoyloxytaxa-4(20),11-dien-10β-ol	**81**	*T. chinensis*	lv, st	363
2α,9α,10β,13α-tetraacetoxy-5α-cinnamoyloxytaxa-4(20),11-diene (taxinine E)	**82**	*T. mairei*	hw	337
		T. cuspidata	lv	10
2-deacetoxytaxinine J	**83**	*T. mairei*	bk	364
		T. mairei	sd	346
		T. cuspidata	st, bk	365
2 α-deacetyltaxinine J (taxuspinanane G)	**84**	*T. cuspidata*	st	366
1-hydroxy-2-deacetoxytaxinine J (taxawallin A)	**85**	*T. wallichiana*	bk	367
		T. wallichiana	lv	335
taxinine J	**86**	*T. mairei*	hw	368
		T. cuspidata	lv	364
		T. mairei	bk	364
		T. chinensis	bk	369

Table 3. Continued

compound	no.	source	part	ref
2α,10β-diacetoxy-5α-cinnamoyloxytaxa-4(20),11-diene-9α,13α-diol	**87**	*T. canadensis*	lv	370
13-deacetyltaxinine E	**88**	*T. cuspidata*	sd	181
9α,10β-diacetoxy-5α-cinnamoyloxytaxa-4(20),11-dien-13α-ol	**89**	*T. yunnanensis*	sd	214
9α,10β-diacetoxy-5α-cinnamoyloxytaxa-4(20),11-diene-2α,13α-diol	**90**	*T. chinensis*	lv, st	363
taxezopidine H	**91**	*T. cuspidata*	sd, st	343
9α,10β-diacetoxy-2α-benzoyloxy-5α-cinnamoyloxytaxa-4(20),11-diene-1β,13α-diol	**92**	*T. chinensis*	st, lv	339, 371, 372

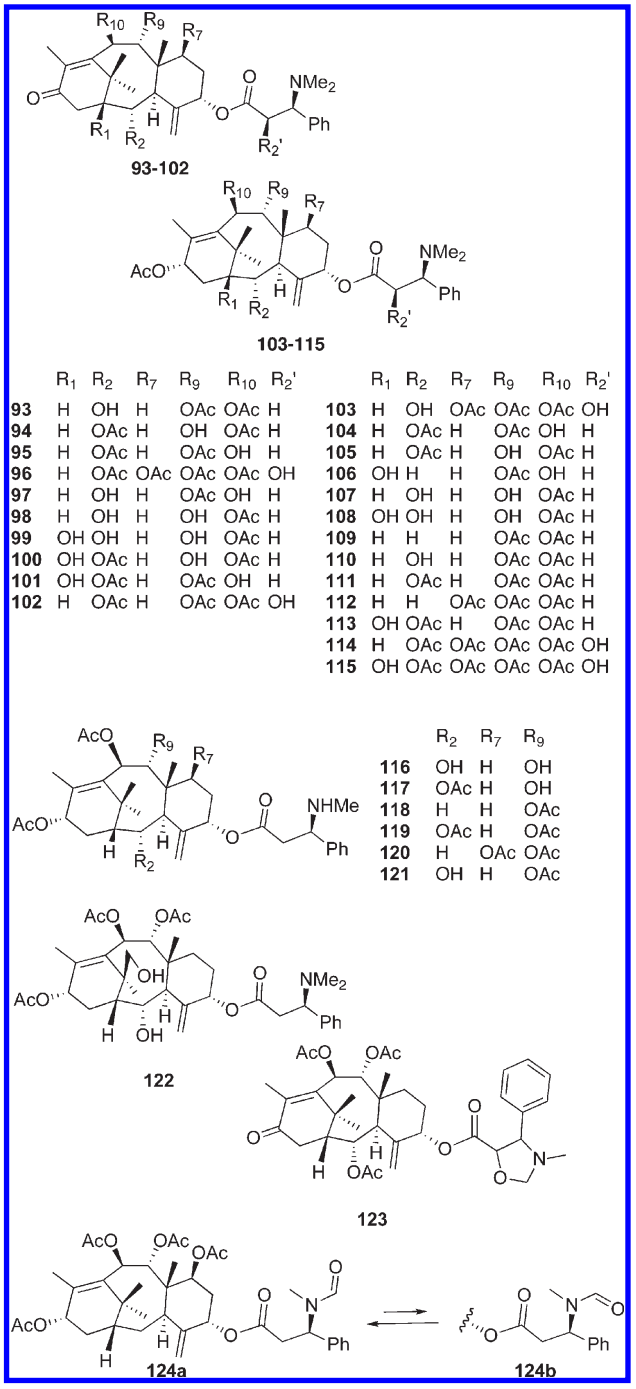
Table 4. 6/8/6-Taxanes 3: Basic Taxa-4(20),11-dienes

compound	no.	source	part	ref
2-deacetyltaxine II	**93**	*T. cuspidata*	sd	373
1-deoxy-2α-acetoxytaxine B	**94**	*T. cuspidata*	sd	373
1-deoxy-2α,9α-diacetoxy-10-deacetyltaxine B	**95**	*T. cuspidata*	sd	373
2α,7β,9α,10β-tetraacetoxy-5α-[(2′*R*,3′*S*)-*N*,*N*-dimethyl-3′- phenylisoseryloxy]taxa-4(20),11-dien-13-one	**96**	*T. cuspidata*	sd	181
2-deacetoxy-9-acetoxytaxine B	**97**	*T. baccata*	lv	6
2-deacetoxy-10-acetyltaxine B	**98**	*T. baccata*	lv	6
taxine B	**99**	*T. baccata*	lv	374−376
		T. chinensis	sd	184
10-acetoxytaxine B	**100**	*T. baccata*	lv	6
9-acetoxytaxine B	**101**	*T. baccata*	lv	6
2′-hydroxytaxine II	**102**	*T. cuspidate*	lv	377
7β,9α10β,13α-tetraacetoxy-5α-[(2′*R*,3′*S*)-*N*,*N*-dimethyl-3′-phenylisoseryloxy]taxa-4(20),11-dien-2α-ol	**103**	*T. canadensis*	lv	234
2α,9α,13α-triacetoxy-5α[-(*R*)-3′-dimethylamino-3′-phenylpropanoyloxy]taxa-4(20),11-dien-10β-ol	**104**	*T. canadensis*	lv	53
2α,10β,13α-triacetoxy-5α-[(*R*)-3′-dimethylamino-3′-phenylpropanoyloxy]taxa-4(20),11-dien-9α-ol	**105**	*T. canadensis*	lv	53
9α,13α-diacetoxy-5α-[(*R*)-3′-dimethylamino-3′-phenylpropanoyloxy]taxa-4(20),11-diene-1β,10β-diol	**106**	*T. mairei*	sd	378
13-deoxo-13α-acetyloxy-1-deoxytaxine B	**107**	*T. baccata*	lv	186
13-deoxo-13α-acetyloxytaxine B	**108**	*T. baccata*	lv	186
7,2′-didesacetoxyaustrospicatine	**109**	*T. wallichiana*	bk	367, 379
		T. mairei	bk	347
taxuspine Z	**110**	*T. cuspidata*	st	380
		T. chinensis	sd	184
2α-acetoxy-2′,7-dideacetoxyaustrospicatine	**111**	*T. chinensis*	sd	184
2′β-deacetoxyaustrospicatine	**112**	*T. wallichiana*	bk, lv	381
		T. baccata	bk	382
(+)-2α-acetoxy-2′,7-dideacetoxy-1-hydroxyaustrospicatine	**113**	*T. baccata*	lv	383
2α-acetoxy-2′β-deacetyl-austrospicatine	**114**	*T. wallichiana*	lv	384
2α-acetoxy-2′-deacetyl-1-hydroxyaustrospicatine	**115**	*T. baccata*		334
10β,13α-diacetoxy-5α-[(*R*)-3′-methylamino-3′-phenylpropanoyloxy]taxa-4(20),11-diene-2α,9α-diol (13-deoxo-13α-acetyloxy-1-deoxynortaxine B)	**116**	*T. canadensis*	lv	234
		T. baccata	lv	186
2α,10β,13α-triacetoxy-5α-[(*R*)-3′-methylamino-3′-phenylpropanoyloxy]taxa-4(20),11-dien-9α-ol	**117**	*T. canadensis*	lv	326
9α,10β,13α-triacetoxy-5α-[(*R*)-3′-methylamino-3′-phenylpropanoyloxy]taxa-4(20),11-diene	**118**	*T. mairei*	sd	385
2α,9α,10β,13α-tetraacetoxy-5α-[(R)-3′-methylamino-3′-phenylpropanoyloxy]taxa-4(20),11-diene	**119**	*T. mairei*	sd	185
7β,9α,10β,13α-tetraacetoxy-5α-[(*R*)-3′-methylamino-3′-phenylpropanoyloxy]taxa-4(20),11-diene	**120**	*T. mairei*	sd	185
taxezopidine O	**121**	*T. cuspidata*	sd	386
9α10β,13α-triacetoxy-5α-[(*R*)-3′-dimethylamino-3′-phenypropanoyloxy]taxa-4(20),11-diene-2α,17-diol	**122**	*T. canadensis*	lv	234
taxine NA-13	**123**	*T. cuspidata*	st	387
7β,9α,10β,13α-tetraacetoxy-5α-[3′-(*N*-formyl-*N*-methylamino)-3′-phenylpropanoyloxy]taxa-4(20),12-diene	**124**	*T. canadensis*	rt	186

3. TAXONOMY AND DISTRIBUTION OF YEW

Taxonomy of *Taxus* is always a point of discussion for the distinction between the species is difficult even the circumscription of the family is doubtful. Most authors placed Taxaceae in a separate family but sometimes fused with Podocarpaceae and Cephalotaxaceae, while in most cases, Cephalotaxaceae was placed separate despite the close relationships between the three members. However, position of *Taxus* within the Taxaceae is not

dx.doi.org/10.1021/cr100147u |*Chem. Rev.* 2011, 111, 7652–7709



	R_1	R_2	R_7	R_9	R_{10}	R_2'
93	H	OH	H	OAc	OAc	H
94	H	OAc	H	OH	OAc	H
95	H	OAc	H	OAc	OH	H
96	H	OAc	OAc	OAc	OAc	OH
97	H	OH	H	OAc	OH	H
98	H	OH	H	OH	OAc	H
99	OH	OH	H	OH	OAc	H
100	OH	OAc	H	OH	OAc	H
101	OH	OAc	H	OAc	OH	H
102	H	OAc	H	OAc	OAc	OH

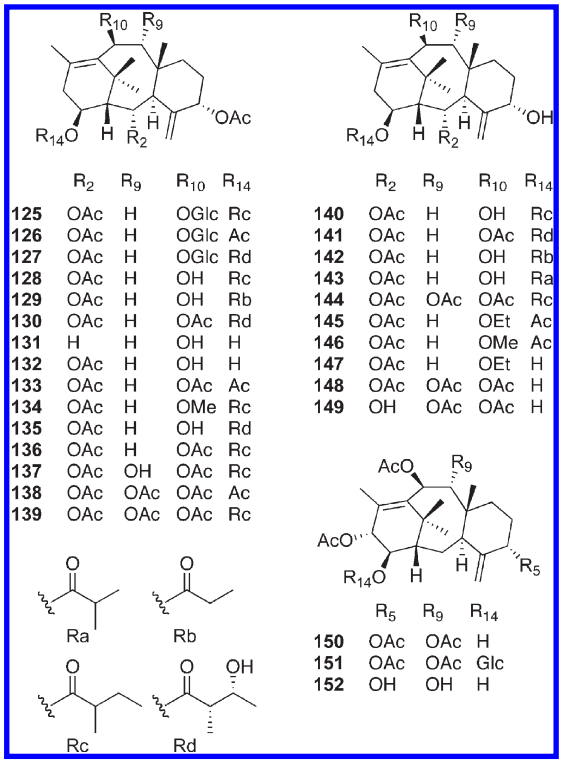
	R_1	R_2	R_7	R_9	R_{10}	R_2'
103	H	OH	OAc	OAc	OAc	OH
104	H	OAc	H	OAc	OH	H
105	H	OAc	H	OH	OAc	H
106	OH	H	H	OAc	OH	H
107	H	OH	H	OH	OAc	H
108	OH	OH	H	OH	OAc	H
109	H	H	H	OAc	OAc	H
110	H	OH	H	OAc	OAc	H
111	H	OAc	H	OAc	OAc	H
112	H	H	OAc	OAc	OAc	H
113	OH	OAc	H	OAc	OAc	H
114	H	OAc	OAc	OAc	OAc	OH
115	OH	OAc	OAc	OAc	OAc	OH

	R_2	R_7	R_9
116	OH	H	OH
117	OAc	H	OH
118	H	H	OAc
119	OAc	H	OAc
120	H	OAc	OAc
121	OH	H	OAc

Figure 10. Basic taxa-4(20),11-dienes.

problematic. Most authors consider *Taxus* to contain nine species: *T. baccata* L., *T. cuspidata* Sieb. and Zucc., *T. canadensis* Marshall, *T. brevifolia* Nutt., *T. floridana* Chapm., *T. globosa* Schltdl., *T. wallichiana* Zucc., *T. fuana* Nan Li and R.R. Mill, and *T. chinensis* (Pilger) Rehder. Furthermore, two hybrids species exist: *T. media* Rehder is a cross between *T. baccata* and *T. cuspidata* and *T. hunnewelliana* Rehder is a cross between *T. cuspidata* and *T. canadensis*.

As pointed out by Appendino,[23] the taxonomy of the genus *Taxus* is difficult because yews are morphologically variable and similar phenotype exists in different species. Krussmann tried to give essential distinguished characteristics, but all are debatable



	R_2	R_9	R_{10}	R_{14}
125	OAc	H	OGlc	Rc
126	OAc	H	OGlc	Ac
127	OAc	H	OGlc	Rd
128	OAc	H	OH	Rc
129	OAc	H	OH	Rb
130	OAc	H	OAc	Rd
131	H	H	OH	H
132	OAc	H	OH	H
133	OAc	H	OAc	Ac
134	OAc	H	OMe	Rc
135	OAc	H	OH	Rd
136	OAc	H	OAc	Rc
137	OAc	OH	OAc	Rc
138	OAc	OAc	OAc	Ac
139	OAc	OAc	OAc	Rc

	R_2	R_9	R_{10}	R_{14}
140	OAc	H	OH	Rc
141	OAc	H	OAc	Rd
142	OAc	H	OH	Rb
143	OAc	H	OH	Ra
144	OAc	OAc	OAc	Rc
145	OAc	H	OEt	Ac
146	OAc	H	OMe	Ac
147	OAc	H	OEt	H
148	OAc	OAc	OAc	H
149	OH	OAc	OAc	H

	R_5	R_9	R_{14}
150	OAc	OAc	H
151	OAc	OAc	Glc
152	OH	OH	H

Figure 11. Taxanes with a C-14 oxygen functional group.

and depend on the development stage of the plant.[31] Rozendaal et al. gave a detail description of the yews based on the taxanes isolated from them.[32] For the taxonomic ambiguity there is some confusion in the literature over the names of certain yews. In particular the Himalayan yew, *T. wallichiana* Zucc., was sometimes referred to as *T. baccata* L., while the Chinese yew, *T. celebica* (Warburg) Li is often considered as *T. chinensis* Rehd., *T. yunnanensis* Cheng et L. K. Fu, or *T. mairei* (Lemee and Lev.) Hu ex Liu. The taxonomic independency of *T. fuana*, *T. wallichiana*, and *T. brevifolia* were clarified by principal component analysis on morphological data and by molecular sequence data.[33] *T. mairei* was considered as a variety species of *T. chinensis* in most Chinese taxonomic books except in Taiwan. Japanese yew, *T. cuspidata* Sieb. et Zucc., also has a variety species *T. cuspidata* Sieb. et Zucc. var. nann Rehder., which often used as a garden tree in Japan. Both of them were called Japanese yew in literature. The botanical summary provided by Appendino[23] was shown in Table 1.

Most *Taxus* species are distributed in the Northern hemisphere (Figure 5). European yew, *T. baccata*, is available in Europe and north region of Middle East. Pacific yew, *T. brevifolia*, as a tall arbor mainly distribute in the northwest coat region of America. Canadian yew, *T. canadensis*, endemic to Canada, is a low trailing shrub ubiquitous to the Quebec region, and its chemical composition has been shown to be very different from other species. Japanese yew, *T. cuspidata*, is distributed in the Japanese islands, North Korea, Northeast region of China, and far east region of Russia and also used as a ornamental tree in Washington Railway Station, U.S.A., the Quebec parliaments, and many churches and yards in North America. The Himalaya yew, *T. wallichiana*, is mainly distributed over multiple regions in Himalaya Mountains including China, India, Pakistan, and Nepal. *T. yunnanensis* is endemic

Table 5. 6/8/6-Taxanes 4: Taxanes with a C-14-Oxygen Functional Group

compound	no.	source	part	ref
2α,5α-diacetoxy-10β-(β-D-glucopyranosyloxy)-14β-[(*S*)-2′-methylbutanoyloxy]taxa-4(20),11-diene	**125**	*T. canadensis*	lv	53
2α,5α,14β-triacetoxy-10β-(β-D-glucopyranosyloxy)taxa-4(20),11-diene	**126**	*T. canadensis*	lv	53
10-deacetyl-10β-(β-D-glucopyranosyloxy)yunnanxane	**127**	*T. yunnanensis*	bk	106
		T. cuspidata	rt	187
		T. canadensis	lv	53
hongdoushan A	**128**	*T. mairei*	st, tw	55
hongdoushan B	**129**	*T. mairei*	st, tw	55
yunnanxane	**130**	*T. yunnanensis*	bk	106
taxuyunnanine J	**131**	*T. yunnanensis*	rt	388
taxuyunnanine G	**132**	*T. yunnanensis*	rt	388
taxuyunnanine C	**133**	*T. yunnanensis*	rt	331
2α,5α-diacetoxy-10β-methoxy-14β-(2-methylbutanoyloxy)taxa-4(20),11-diene	**134**	*T. baccata*	rt	189
10-deacetylyunnanaxane	**135**	*T. media*	rt	35
2α,5α,10β-triacetoxy-14β-(2-methylbutanoyloxy)taxa-4(20),11-diene	**136**	*T. yunnanensis*	st, tw	55
		T. baccata	hw	389
		T. baccata	rt	189
		T. cuspidata	hw	188
		T. wallichiana	hw	390
2α,5α,10β-triacetoxy-14β-(2-methylbutanoyloxy)taxa-4(20),11-dien-9α-ol	**137**	*T. mairei*	tw	333
2α,5α,9α,10β,14β-pentaacetoxytaxa-4(20),11-diene	**138**	*T. mairei*	tw	333
taxuyunnanine B	**139**	*T. yunnanensis*	rt	331
hongdoushan C	**140**	*T. mairei*	st, tw	55
tasumatrol K	**141**	*T. sumatrata*	lv, tw	54
taxuyunnanine H	**142**	*T. yunnanensis*	rt	388
taxuyunnanine I	**143**	*T. yunnanensis*	rt	388
taiwanxan	**144**	*T. mairei*	hw	391, 392
2α,14β-diacetoxy-10β-ethoxytaxa-11,4(20)-dien-5α-ol	**145**	*T. cuspidata*	hw	56
2α,14β-diacetoxy-10β-methoxytaxa-11,4(20)-dien-5α-ol	**146**	*T. cuspidata*	hw	56
2α-acetoxy-10β-ethoxytaxa-11,4(20)-dien-5α,14β-diol	**147**	*T. cuspidata*	hw	56
2α,9α,10β-triacetoxytaxa-4(20),11-diene-5α,14β-diol	**148**	*T. mairei*	rt	393
9α,10β-diacetoxytaxa-4(20),11-diene-2α,5α,14β-triol	**149**	*T. mairei*	rt	393
14β-hydroxytaxusin (5α,9α,10β,13α-tetraacetoxytaxa-4(20),11-dien-14β-ol)	**150**	*T. mairei*	bk	190
5α,9α,10β,13α-tetraacetoxy-14β-(β-D-glucopyranosyloxy)taxa-4(20),11-diene	**151**	*T. baccata*	lv	352
10β,13α-diacetoxytaxa-4(20),11-diene-5α,9α,14β-triol	**152**	*T. canadensis*	lv	191

to China and is mainly distribute in the Yunnan Province of China. Another two species endemic to China are *T. chinensis* and *T. mairei*, which are distributed in middle region of China and South East region of China, respectively. All of these yew trees contain taxane diterpenoids, but they showed some differences in chemical profiles.

4. TAXANES ISOLATED FROM YEW TREES

Structures of taxane diterpenoids isolated and identified could be classified into 11 types based on their carbon ring systems: 6/8/6, 6/5/5/6, 6/10/6, 5/7/6, 5/6/6, 6/12, 6/8/6/6, 6/5/5/5/6, 5/5/4/6/6/6, and 8/6. According to the order that discovered, 10 representative structures were given below (Figure 6): normal 6/8/6-ring taxanes **I**; 3,11-cyclotaxanes **II**; 2(3→20)*abeo*taxanes **III**; 11(15→1)*abeo*taxanes **IV**; 11(15→1),11(10→9)di*abeo*taxanes **V**; 3,8-secotaxanes (bicyclic taxanes) **VI**; 14,20-cyclotaxane **VII**; 3,11:12,20-dicyclotaxane **VIII**; 3,11:4,12,14:20-tricyclotaxane **IX**; and 11,12-secotaxane **X**. Among them, only one compound was found in each of the **VII**, **IX**, and **X** groups.

By the end of 2009, more than 550 taxanes have been isolated from leaves (lv), stems (st), roots (tr), barks (bk), seeds (sd), twigs (tw), and branches (br) of various yews. These diterpenoids were sorted in to the following subgroups based on their skeleton/substitution patterns. Representative taxanes are shown in Figure 7.

4.1. 6/8/6-Taxanes 1: Neutral Taxa-4(20),11-dienes (Taxinine A Type, Table 2 and Figure 8)

A number of the most common taxanes, taxa-4(20),11-dienes, 6/8/6-(membered)taxanes, are assorted by C-5-substituents including hydroxy, acetoxy, and glucosyloxy groups.

The C-1 in compounds of this group normally present with H or OH group except 1,7,9,10-tetraacetoxytaxa-4(20),11-dien-5-ol (**51**), the only compound that has a 1-OAc group. Compounds **49** and **50** are exceptional with a rare *cis*-cinnamoyloxy group at C-13. Compound **34** is the first example of a taxane glycoside with a glucose unit at C-5. Taxanes **51**, **46**, **47**, and **48** were characterized by the absence of moiety at both C-13 and C-14. Structures of **46**, **47**, and **48** were revised to the corresponding

dx.doi.org/10.1021/cr100147u |*Chem. Rev.* 2011, 111, 7652–7709

Table 6. 6/8/6-Taxanes 5: Taxoids with a C-12,17-Ether Ring

compound	no.	source	part	ref
taxumairol R (5-*O*-acetyltaxinine M)	**153**	*T. mairei*	rt, bk	394
		T. yunnanensis	sd	195
5α-[(*R*)-3′-dimethylamino-3′-phenylpropanoyloxy]taxinine M	**154**	*T. wallichiana*	lv	384
taxezopidine N	**155**	*T. cuspidata*	sd	59
2α-deacetyl-5α-decinnamoyltaxagifine	**156**	*T. chinensis*	lv, st	363, 395
5α-decinnamoyltaxagifine	**157**	*T. chinensis*	lv, st	192
5α-acetyl-5α-decinnamoyltaxagifine	**158**	*T. chinensis*	lv, st	192
5-decinnamoyl-11-acetyl-19-hydroxyltaxagifine	**159**	*T. yunnanensis*	bk	197
19-debenzoyl-19-acetyltaxinine M	**160**	*T. wallichiana*	lv	396
taxinine M	**161**	*T. brevifolia*	bk	397
		T. mairei	bk	347
		T. wallichiana	lv	384
tasumatrol L	**162**	*T. sumatrata*	lv, tw	54
taxagifine	**163**	*T. cuspidata*	sd	193
		T. chinensis	Iv, st	192
		T. baccata	lv	81, 398
taxuspine S	**164**	*T. cuspidata*	st	399
taxuspine T	**165**	*T. cuspidata*	st	399
19-acetoxytaxagifine (taxezopidine L)	**166**	*T. chinensis*	bk, tw, lv	400
		T. cuspidata	sd	401
taxacin	**167**	*T. cuspidata*	sd	193
taxagifine III	**168**	*T. chinensis*	lv, st	363, 395
4-deacetyltaxagifine III	**169**	*T. chinensis*	lv, st	363

2α-acetoxy-7β-deacetoxy-14β-(2-methylbutanoyl)oxy-taxane (**128**, **144**, and **139**, respectively) in which ^{13}C NMR resonance of C-1 (δ 60 ppm) provided remarkable clues.[34,35]

4.2. 6/8/6-Taxanes 2: Neutral Taxa-4(20),11-dienes with a C-5-Cinnamoyloxy Group (Taxinine Type, Table 3 and Figure 9)

The cinnamoyloxy group is one of the common substituents on taxanes especially at C-5-position. Taxinine (**70**), the most abundant component (*ca.* 0.1%) in needles,[36,37] fruits,[38] seeds[39] in various *Taxus* species, was isolated initially from the needles of the Japanese yew in 1925.[40] It was the first natural taxane obtained in a pure state, and its structure was elucidated in the 1960s.[41,42] Taxinine could be obtained by thermal elimination of the dimethylamine from C-5 ester moiety of a taxane alkaloid (taxine II), and can be used as a starting material to prepare paclitaxel.[43] 2-Deacetoxytaxinine J (**83**), a nonalkaloidal taxane diterpene, showed significant cytotoxicity on most cell lines and equipotent effective against both parental and β-tubulin mutant tumor cell lines.[44] Taxinine NN-7 (**61**) exhibited moderate activity as a modulator for multidrug-resistant tumor cells.[45] Recently, it was reported that taxinine together with another six tricyclic diterpenoids suppress superoxide generation mainly via suppressing tyrosine or serine/threonine phosphorylation, and the translocation of cytosolic compounds to the cell membrane in human neutrophils. In addition, when concentration reached to the dosage suppressing superoxide generation needed, these compounds showed no effect of hemolysis.[46]

4.3. 6/8/6-Taxanes 3: Basic Taxa-4(20),11-dienes (Table 4 and Figure 10)

Compounds in this group were characterized by the presence of a C-4(20)-double bond and esterification at C-5 with β-aminophenylpropanoic acids (β-dimethylaminophenylpropanoic acid = Winterstein's acid).[47] **122** is a rare example of taxane with a C-17-hydroxy group. No benzoyl group has been found so far in taxine B (**99**) and taxicin-type derivatives. Taxine, a powerful heart poison as described before, was isolated in 1856.[3] Actually it was a mixture of diterpene alkaloids but did not arouse enough attention at that time. With the advances of chromatographic techniques, at least eleven compounds established their presence. Taxines A (**489**), B (**99**), and C (**487**) were obtained as pure compounds in 1956.[29] However, structural elucidation of the major component (taxine B) was not achieved until 1991.[48] Taxine B could also be used as a precursor for the synthesis of paclitaxel and its analogs.[49,50] It was reported that taxine B reduced cardiac contractility and the maximum rate of depolarization of the action potential in the isolated papillary muscle, acting as a class I antiarrhythmic drug.[51] Eliminating dimethylamine of taxine B type taxanes could lead to taxinine type taxanes[36] and they generally coexist in nature. But it is still not clear whether the relationships between these two types of compounds is enzymatic, degradative or both. The presence of an ester of nor-Winterstein acid is interesting, since taxanes of this type might be the intermediates in the biosynthesis of phenylisoserinic side-chain of paclitaxel.[1] Taxane **124** is an exception with an *N*-formyl group composed of cis- and trans-rotamers for these basic taxanes. It showed moderate growth inhibitory activity against HMV-1, KT, T-98 and MM1-CB while inactive against HeLa, HEC-1, SHIN3, HOC-21 and HAC-2, U251-SP cell.[52] **123** is another rare basic taxane reported recently bearing a heterocycle at C-5 side chain.

4.4. 6/8/6-Taxanes 4: Taxanes with a C-14-Oxygen Functional Group (Taiwanxan Type, Table 5 and Figure 11)

Taxanes with a C-4(20)-double bond and an oxygen function group at C-14 were only discovered recently, and most of

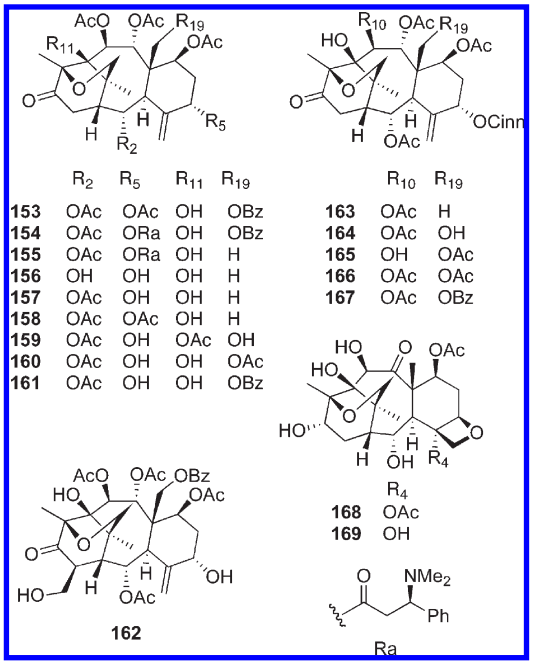


Figure 12. Taxanes with a C-12,17-ether ring.

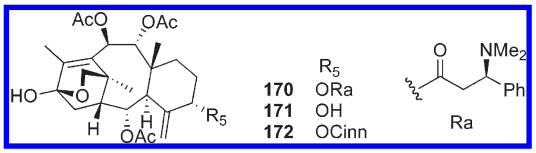


Figure 13. Taxanes with a C-13,17-ether ring.

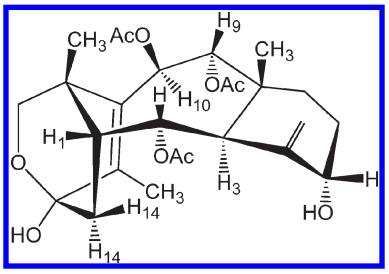


Figure 14. Stereostructure of taxezopidine A (**171**).

them have been found in the heartwood of the Chinese yew, *T. yunnanensis* or *T. chinensis* var. *mairei*, and the Japanese yew, *T. cuspidata*. Taiwanxan (**144**) was the first example of this type taxanes, whose structure was confirmed by X-ray crystallographic analysis. All the groups at C-14 were in β-orientation. Compounds **125**−**127** isolated from *T. canadensis* were the first reported examples of taxanes with a glucose unit on the ring B. Their NMR features will be discussed in the following section.[53] **141** showed strong activity against human liver carcinoma (Hepa 59T/VGH), human large cell carcinoma of the lung, human cervical epitheloid carcinoma (HeLa), human colon adenocarcinoma (DLD-1) and human medulloblstoma (Med) cell lines.[54] Hongdoushans A (**128**) and C (**140**) exhibited weak antiproliferative activity toward murine colon 26-L5 carcinoma and human HT-1080 fibrosarcoma cell lines, while hongdoushans B (**129**) demonstrated moderate activity toward the colon 26-L5

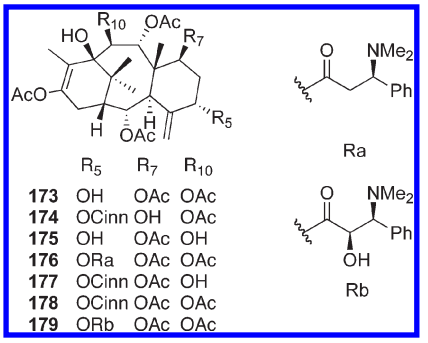


Figure 15. Taxa-4(20),12-dienes.

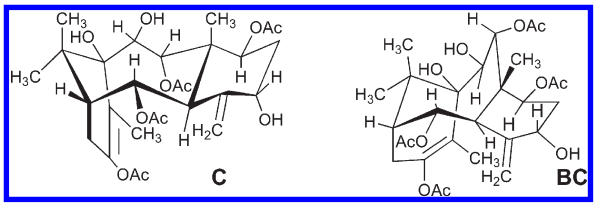


Figure 16. Crown (C) and boat−chair (BC) conformations of **175**.

Table 7. 6/8/6-Taxanes 6: Taxanes with a C-13,17-Ether Ring

compound	no.	source	part	ref
taxezopidine M	**170**	*T. cuspidata*	sd	59
taxezopidine A	**171**	*T. cuspidata*	sd	194
taxezopidine J	**172**	*T. cuspidata*	sd	181, 401

carcinoma cell line with an EC_{50} value of 3.8 μg/mL.[55] **134** and **145**−**147** are very rare group of taxanes with an alkoxy moiety on the skeleton.[56,57]

These taxanes mentioned above contain fused three-ring system A/B/C with transfused B/C junction because of the trans-axial dispositions of C-19 at C-8 and H-3 at C-3, the ring A being in a syn conformation with respect to ring C. The molecule as a whole adopts folded cage-type conformation. The eight-membered B ring is puckered to form sofa like conformation while the six-membered ring A is in a twist conformation.

4.5. 6/8/6-Taxanes 5: Taxanes with a C-12,17-Ether Ring (Taxagifine Type, Table 6 and Figure 12)

Taxanes of this group were oxygenated at C-17, with the oxygen presenting as an oxygen bridge with C-12 and a hydroxy group at C-11. Taxanes **154** and **155** were the only two examples with an alkaloidal side chain (Winsterstein's acid) at C-5 while tasmatrol L (**162**) was the taxane with a C-21-homotaxane cage conformation isolated from any natural source and the most highly oxygenated taxinine M analog with twelve carbons oxidized. Taxagifine (**163**) was the first member of this group, isolated from *T. baccata* in 1982 and its structure was established by single X-ray diffraction analysis. Compound **166** showed weak cytotoxicity against most cell lines such as human KB, A-549 lung carcinoma, HCT-8 colon tumor, CAKI-1 renal, 1A9 ovarian, and 1A9PTX10 β-tubulin mutant cell lines. It indicated that the presence of ether linkage (C-12,17), C-19-acetoxy group, and C-13-carbonyl group reduced cytotoxicity of **166**.[44] However

dx.doi.org/10.1021/cr100147u |*Chem. Rev.* 2011, 111, 7652–7709

Table 8. 6/8/6-Taxanes 7: Taxa-4(20),12-dienes

compound	no.	source	part	ref
5-decinnamoyltaxuspine D	**173**	*T. canadensis*	lv	324
7-deacetoxytaxuspine D	**174**	*T. canadensis*	lv	326
2α,9α,7β,13-tetraacetoxytaxa-4(20),12-diene-5α,10β,11β-triol	**175**	*T. canadensis*	lv	63
taxuspine P	**176**	*T. cuspidata*	st	229
taxezopidine K	**177**	*T. cuspidata*	sd	401
taxuspine D	**178**	*T. cuspidata*	st	60
			sd	181
2α,7β,9α,10β,13-pentaacetoxy-5α-(2′-hydroxy-3′-*N*,*N*-dimethylamino-3′-phenylpropanoyloxy)taxa-4(20),12-dien-11β-ol	**179**	*T. canadensis*	lv	66

Table 9. 6/8/6-Taxanes 8: Taxanes with a C-11,12-Epoxy Ring

compound	no.	source	part	ref
10-deacetyldantaxusin C	**180**	*T. canadensis*	lv	370
taxinine A 11,12-epoxide	**181**	*T. cuspidata*	lv	402
dantaxusin C	**182**	*T. yunnanensis*	lv, st	205
2α,9α,10β-triacetoxy-11,12-epoxy-5α-(β-D-glucopyranosyloxy)tax-4(20)-en-13-one	**183**	*T. cuspidata*	lv	403
2α,9α-diacetoxy-5α-cinnamoyloxy-11,12-epoxy-10β-hydroxytax-4(20)-en-13-one	**184**	*T. cuspidata*	lv	404
2α,10β-diacetoxy-5α-cinnamoyloxy-11,12-epoxy-9α-hydroxytax-4(20)-en-13-one	**185**	*T. cuspidata*	lv	404
decinnamoyltaxinine B 11,12-oxide	**186**	*T. yunnanensis*	lv, st	405

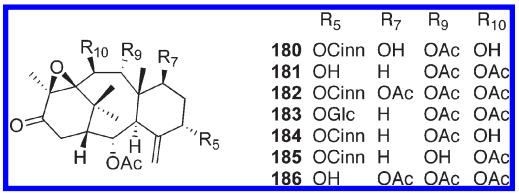


Figure 17. Taxanes with a C-11,12-epoxy ring.

both taxezopidine L (**166**) and taxagifine (**163**) reduced the $CaCl_2$-induced depolymerization of microtubules remarkably in a manner similar to that of paclitaxel.[58] **168** and **169** are taxanes with C-5,20-oxetane and C-12,17-ether bridges, also belonging to section 4.12.

4.6. 6/8/6-Taxanes 6: Taxanes with a C-13,17-Ether Ring (Table 7 and Figure 13)

Taxezopidines M (**170**), A (**171**), and J (**172**) were three taxanes isolated from the Japanese yew with a hemiacetal ring involving C-11-C-12-C-13-C-15-C-17. Though containing an oxabicyclo[2.2.2]octane moiety, they still have a cage-like backbone conformation similar to the taxanes consisting 6/8/6-membered ring system. The eight-membered ring (C-1-C-3, C-8-C-11, and C-15) adopts a boat-chair conformation (Figure 14). Taxezopidine M (**170**) slowed down the process of tubulin depolymerization at higher concentration (50 μM), but did not show cytotoxicity against murine lymphoma L1210 and human epidermoid carcinoma KB cells at 10 μg/mL.[59]

4.7. 6/8/6-Taxanes 7: Taxa-4(20),12-dienes (Table 8 and Figure 15)

Taxanes of this class were characterized by the C-11-hydroxy group and C-12,13-enol acetate moiety as represented by taxuspine D (**178**),[60,61] which was the first taxane reported containing an enol acetate moiety in ring A.[62] An example of conformational exchange (Figure 16) in a natural 6/8/6-membered taxane enolate (**175**) was found.[63] The structures of two stable conformers were established using a combination of 1D and 2D NMR techniques including gs-HMQC, gs-HMBC, NOESY, and T-ROESY. However, little attention was paid to the conformation flexibility of the highly folded taxane skeleton although this phenomenon has been detected in the normal 6/8/6-membered taxane.[64]

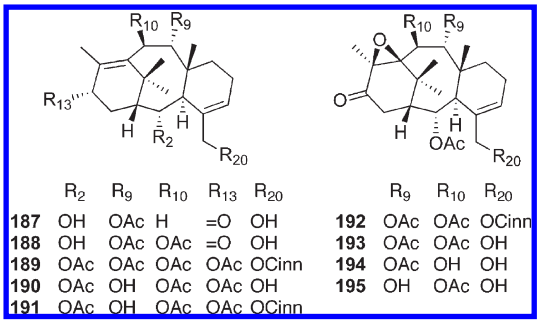


Figure 18. Tax-4-enes.

Taxuspine D (**178**) and taxezopidine K (**177**) reduced $CaCl_2$-induced depolymerization of microtubules significantly with a potency corresponding to half of the activity of paclitaxel. This result was surprising since taxuspine D (**178**) lacks all the key features essential for the bioactivity. Molecular modeling studies indicated that the C-12(13)-double bond caused a substantial change in the conformation of the core skeleton, and the C-5-cinnamoyloxy group in taxuspine D was found to be a mimic part of the C-13 side chain of paclitaxel.[65] Compound **179** is the first example of an alkenyl acetate taxane with a β-*N*,*N*-dimethylamino-β-phenylisoseryloxy substituent at C-5.[66] More interestingly, all the seven taxanes of this group were isolated from Japanese yew and Canadian yew, and both yew trees grow in the cold regions of the northern hemisphere.[66]

dx.doi.org/10.1021/cr100147u |*Chem. Rev.* 2011, 111, 7652–7709

Table 10. 6/8/6-Taxanes 9: Taxa-4,11-dienes

compound	no.	source	part	ref
9α-acetoxy-2α,20-dihydroxytaxa-4,11-dien-13-one	**187**	*T. mairei*	sd	195
9α,10β-diacetoxy-2α,20-dihydroxytaxa-4,11-dien-13-one	**188**	*T. mairei*	sd	196
2α,9α,10β,13α-tetraacetoxy-20-cinnamoyloxytaxa-4,11-diene	**189**	*T. canadensis*	lv	105
		T. mairei	sd	406
2α,9α,13α-triacetoxytaxa-4,11-diene-9α,20-diol	**190**	*T. canadensis*	lv	326
2α,10β,13α-triacetoxy-20-cinnamoyloxytaxa-4,11-dien-9α-ol	**191**	*T. canadensis*	lv	370

Table 11. 6/8/6-Taxanes 10: 11,12-Epoxytax-4-enes

compound	no.	source	part	ref
2α,9α,10β-triacetoxy-20-cinnamoyloxy-11β,12β-epoxytaxa-4,11-dien-13-one	**192**	*T. canadensis*	lv	326
2α,9α,10β-triacetoxy-11β,12β-epoxy-20-hydroxytaxa-4,11-dien-13-one	**193**	*T. canadensis*	rt	103
2α,9α-diacetoxy-11β,12β-epoxy-10β,20-dihydroxytaxa-4,11-dien-13-one	**194**	*T. cuspidata*	lv	404
2α,10β-diacetoxy-11β,12β-epoxy-9α,20-dihydroxytaxa-4,11-dien-13-one	**195**	*T. cuspidata*	lv	404

Table 12. 6/8/6-Taxanes 11: Tax-11-enes with an Opened Oxetane Ring

compound	no.	source	part	ref
7-deacetyltaxuspine L	**196**	*T. canadensis*	lv	407
7,9-deacetyltaxuspine L	**197**	*T. canadensis*	lv	324
taxumairol N	**198**	*T. mairei*	rt	408
taxumairol O	**199**	*T. mairei*	rt	408
taxumairol L	**200**	*T. mairei*	rt	409
		T.yunnanensis	bk	410
taxumairol E	**201**	*T. mairei*	rt	411
taxuspine L	**202**	*T. cuspidata*	st	412
taxchin A	**203**	*T. chinensis*		207
2,20-*O*-diacetyltaxumairol N	**204**	*T. chinensis*	st, lv	47
taxuspine R	**205**	*T. cuspidata*	st	398
5α,7β,9α,10β,13α-pentaacetoxy-2α-benzoyloxytax-11-ene-4α,20-diol	**206**	*T. mairei*	hw	413
(2α,5α,7β,9α,10β,13α)-5,10,13,20-tetraacetoxytax-11-ene-2,7,9-triol	**207**	*T. cuspidata*	lv, tw	414
7β,9α,10β,13α,20-pentaacetoxy-2α-benzoyloxytax-11-ene-4α,5α-diol	**208**	*T. mairei*	hw	413
taxumairol A	**209**	*T. mairei*	rt	415
taxchin B	**210**	*T. chinensis*	st, lv	416

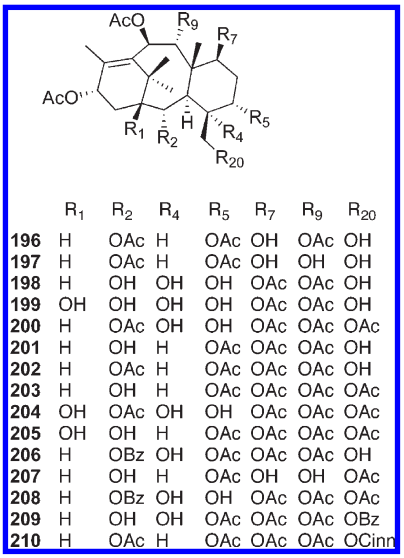


Figure 19. Tax-11-enes with an opened oxetane ring.

4.8. 6/8/6-Taxanes 8: Taxanes with a C-11,12-Epoxy Ring (Table 9 and Figure 17)

The presence of a C-13-oxo group, an epoxy ring at C-11,12, and oxygenated substitutions at C-2, C-5, C-9, and C-10 were the key features of these taxanes. The first one of this group was **186** reported from *T. yunnanensis* in 1996, followed by **181** obtained from Japanese yew in 1999.

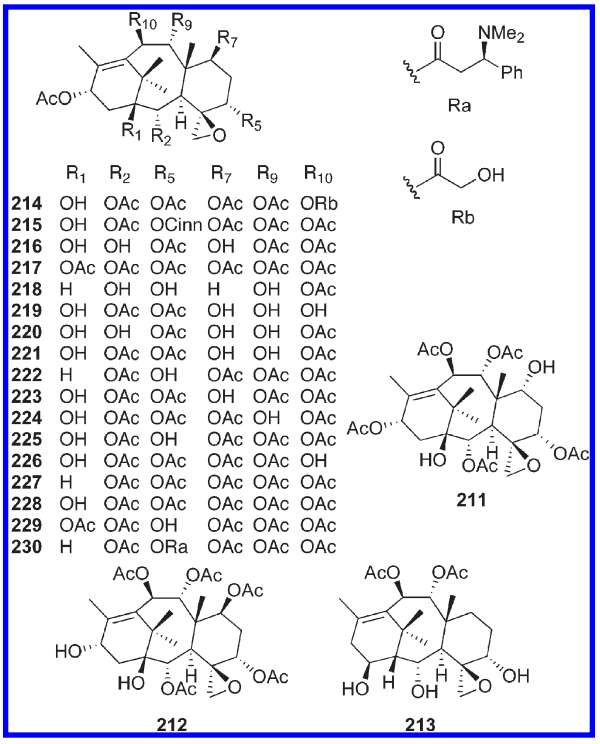
4.9. 6/8/6-Taxanes 9: Taxa-4,11-dienes, and 6/8/6-Taxanes 10: 11,12-Epoxytax-4-enes (Tables 10, 11 and Figure 18)

Taxanes **187**−**191** are characterized by the migration of C-4(20)-double bond to C-4(5). **192**−**195** are a smaller group of taxanes with C-11,12-epoxy bridge, C-4(5)-double bond, and **192** bears a rare cinnamoyl moiety at C-20. Metabolites of this group were mainly obtained from *T. canadensis* and *T. cuspidata*. However, rare information has been reported on their activity or biosynthesis.

4.10. 6/8/6-Taxanes 11: Tax-11-enes with an Opened Oxetane Ring (Table 12 and Figure 19)

A number of taxanes have been isolated in recent years which could be derived by opening the oxetane ring of taxanes related to

dx.doi.org/10.1021/cr100147u |*Chem. Rev.* 2011, 111, 7652–7709



	R1	R2	R5	R7	R9	R10
214	OH	OAc	OAc	OAc	OAc	ORb
215	OH	OAc	OCinn	OAc	OAc	OAc
216	OH	OH	OAc	OH	OAc	OAc
217	OAc	OAc	OAc	OAc	OAc	OAc
218	H	OH	OH	H	OH	OAc
219	OH	OAc	OAc	OH	OH	OH
220	OH	OH	OAc	OH	OH	OAc
221	OH	OAc	OAc	OH	OH	OAc
222	H	OAc	OH	OAc	OAc	OAc
223	OH	OAc	OAc	OH	OAc	OAc
224	OH	OAc	OAc	OAc	OH	OAc
225	OH	OAc	OH	OAc	OAc	OAc
226	OH	OAc	OAc	OAc	OAc	OH
227	H	OAc	OAc	OAc	OAc	OAc
228	OH	OAc	OAc	OAc	OAc	OAc
229	OAc	OAc	OH	OAc	OAc	OAc
230	H	OAc	ORa	OAc	OAc	OAc

Figure 20. Taxanes with a C-4,20-epoxy ring.

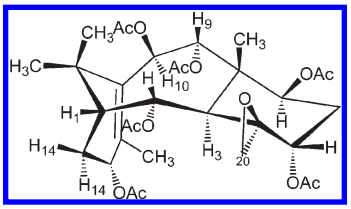
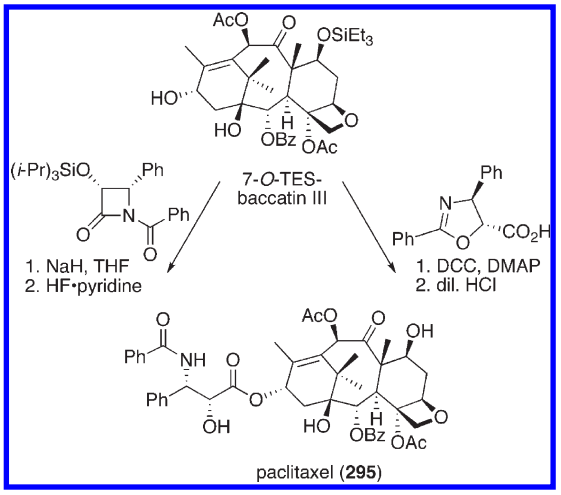
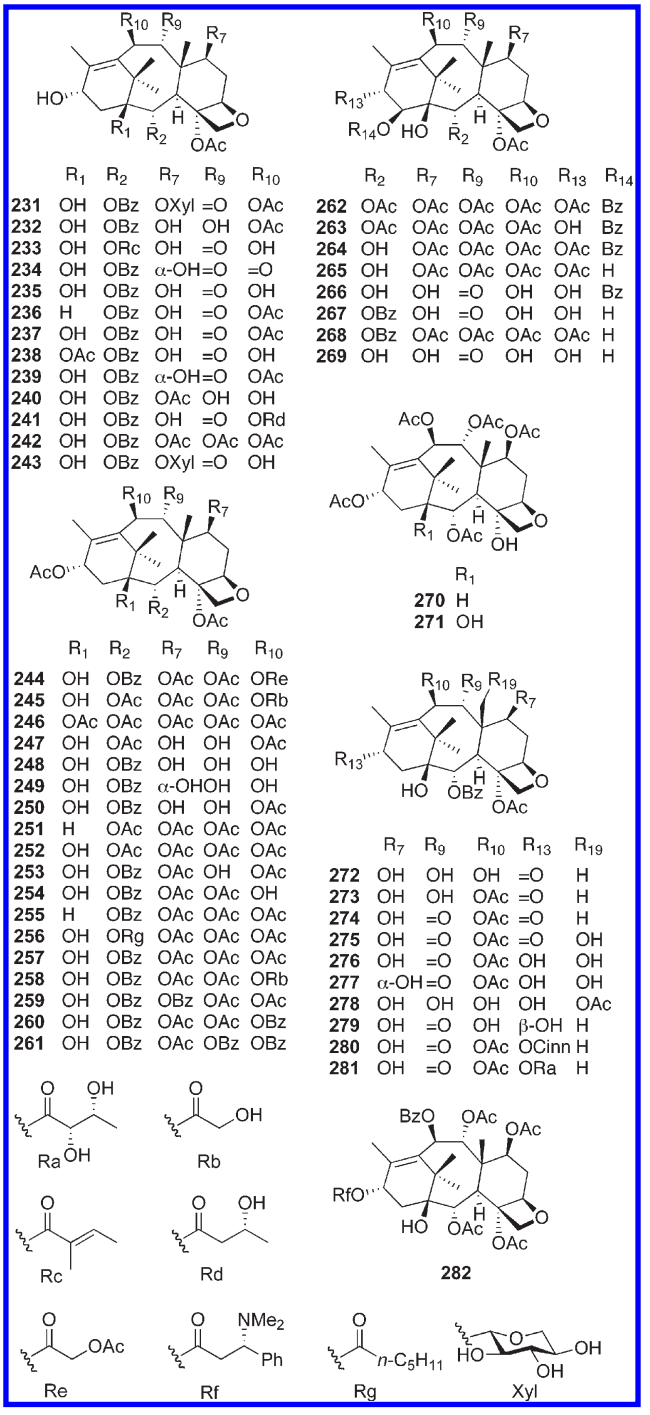


Figure 21. Stereostructure of baccatin I (**227**).

Scheme 1. Alternative Method of Semisynthesis of Paclitaxel from 7-*O*-TES-baccatin III



baccatin III (**237**) or the oxirane ring of taxanes related to baccatin I (**227**). Since oxirane rings can be opened easily under basic conditions, and the oxetane ring of baccatin III can be opened under a variety of conditions.[67] It is conceivable that some members of this class were artifacts of an isolation process. It is also arguable that they might be genuine natural products and acted as the intermediates in the taxane biosynthesis in the plants.



	R1	R2	R7	R9	R10
231	OH	OBz	OXyl	=O	OAc
232	OH	OBz	OH	OH	OAc
233	OH	ORc	OH	=O	OH
234	OH	OBz	α-OH	=O	=O
235	OH	OBz	OH	=O	OH
236	H	OBz	OH	=O	OAc
237	OH	OBz	OH	=O	OAc
238	OAc	OBz	OH	=O	OH
239	OH	OBz	α-OH	=O	OAc
240	OH	OBz	OAc	OH	OH
241	OH	OBz	OH	=O	ORd
242	OH	OBz	OAc	OAc	OAc
243	OH	OBz	OXyl	=O	OH

	R1	R2	R7	R9	R10
244	OH	OBz	OAc	OAc	ORe
245	OH	OAc	OAc	OAc	ORb
246	OAc	OAc	OAc	OAc	OAc
247	OH	OAc	OH	OH	OAc
248	OH	OBz	OH	OH	OH
249	OH	OBz	α-OH	OH	OH
250	OH	OBz	OH	OH	OAc
251	H	OAc	OAc	OAc	OAc
252	OH	OAc	OAc	OAc	OAc
253	OH	OBz	OAc	OH	OAc
254	OH	OBz	OAc	OAc	OH
255	H	OBz	OAc	OAc	OAc
256	OH	ORg	OAc	OAc	OAc
257	OH	OBz	OAc	OAc	OAc
258	OH	OBz	OAc	OAc	ORb
259	OH	OBz	OBz	OAc	OAc
260	OH	OBz	OAc	OAc	OBz
261	OH	OBz	OAc	OBz	OBz

	R2	R7	R9	R10	R13	R14
262	OAc	OAc	OAc	OAc	OAc	Bz
263	OAc	OAc	OAc	OAc	OH	Bz
264	OH	OAc	OAc	OAc	OAc	Bz
265	OH	OAc	OAc	OAc	OAc	H
266	OH	OH	=O	OH	OH	Bz
267	OBz	OH	=O	OH	OH	H
268	OBz	OAc	OAc	OAc	OAc	H
269	OH	OH	=O	OH	OH	H

	R1
270	H
271	OH

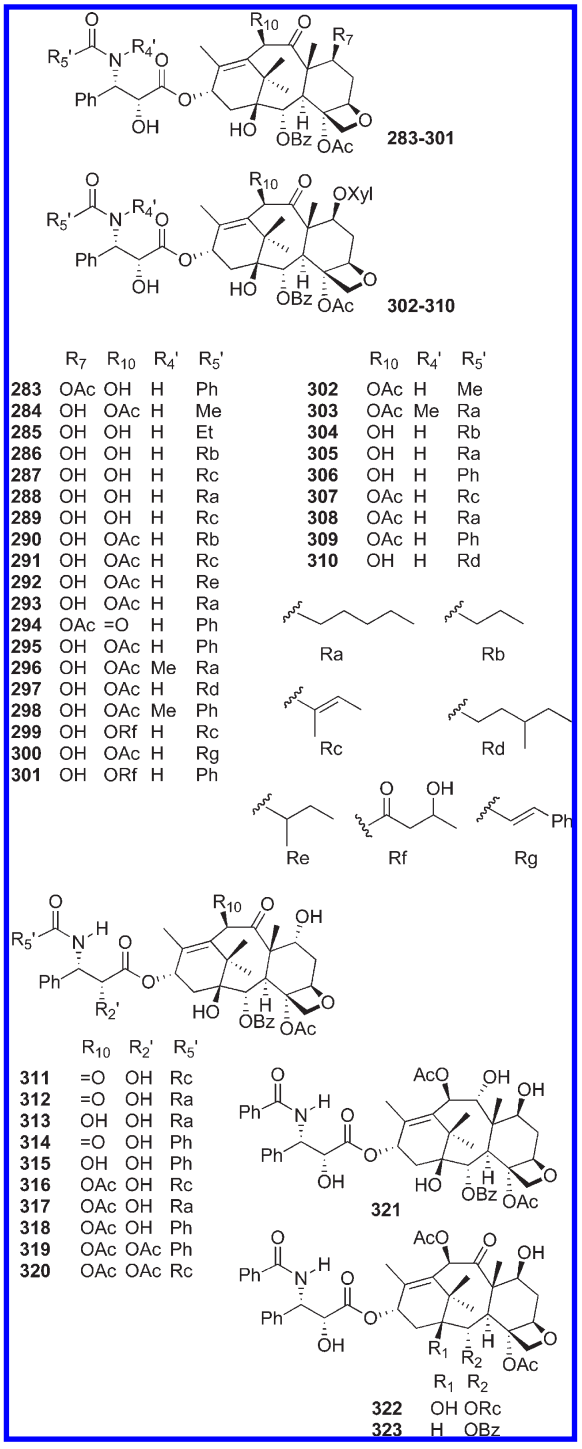
	R7	R9	R10	R13	R19
272	OH	OH	OH	=O	H
273	OH	OH	OAc	=O	H
274	OH	=O	OAc	=O	H
275	OH	=O	OAc	=O	OH
276	OH	=O	OAc	OH	OH
277	α-OH	=O	OAc	OH	OH
278	OH	OH	OH	OH	OAc
279	OH	=O	OH	β-OH	H
280	OH	=O	OAc	OCinn	H
281	OH	=O	OAc	ORa	H

Figure 22. Taxanes with an oxetane ring.

4.11. 6/8/6-Taxanes 12: Taxanes with a C-4,20-Epoxy Ring (Table 13 and Figure 20)

Baccatin I (**227**, Figure 21) is the first taxane structure elucidated with a C-4,20-epoxy group. Members of this group differ primarily in the number and position of acetyl groups and hydroxy groups around the periphery of their ring system. Yet, a

dx.doi.org/10.1021/cr100147u |*Chem. Rev.* 2011, 111, 7652–7709



	R_7	R_{10}	R_4'	R_5'
283	OAc	OH	H	Ph
284	OH	OAc	H	Me
285	OH	OH	H	Et
286	OH	OH	H	Rb
287	OH	OH	H	Rc
288	OH	OH	H	Ra
289	OH	OH	H	Rc
290	OH	OAc	H	Rb
291	OH	OAc	H	Rc
292	OH	OAc	H	Re
293	OH	OAc	H	Ra
294	OAc	=O	H	Ph
295	OH	OAc	H	Ph
296	OH	OAc	Me	Ra
297	OH	OAc	H	Rd
298	OH	OAc	Me	Ph
299	OH	ORf	H	Rc
300	OH	OAc	H	Rg
301	OH	ORf	H	Ph

	R_{10}	R_4'	R_5'
302	OAc	H	Me
303	OAc	Me	Ra
304	OH	H	Rb
305	OH	H	Ra
306	OH	H	Ph
307	OAc	H	Rc
308	OAc	H	Ra
309	OAc	H	Ph
310	OH	H	Rd

	R_{10}	R_2'	R_5'
311	=O	OH	Rc
312	=O	OH	Ra
313	OH	OH	Ra
314	=O	OH	Ph
315	OH	OH	Ph
316	OAc	OH	Rc
317	OAc	OH	Ra
318	OAc	OH	Ph
319	OAc	OAc	Ph
320	OAc	OAc	Rc

Figure 23. Taxanes with an oxetane ring and a phenylisoserine side chain.

few exceptions do exist: **218**, **222**, **227**, and **230** have no substitution at C-1 and **215** bears a cinnamoyl group at C-5. These findings suggested that the esterification pattern might have great relevance in the biosynthesis of taxanes. One attractive possibility is that acetylation and benzoylation play a role in the trafficking of intermediates between cytosolic and membranous sites of biosynthesis. Taxane **214** is a taxane with a rare hydroxy acetate at C-10. Compounds **223** and **224** provide the first examples of intramolecular transesterification in this family of taxane metabolites, and were found to isomerize readily via acyl migration between C-7 and C-9 under mild acid catalyzed conditions, even when standing in $CDCl_3$.[68] Such migration was also observed in the components isolated from *T. yunnanensis*.[69] Taxanes with a C-4,20-epoxy ring, a suspected biosynthetic precursors of those with an oxetane ring, have received less attention comparing to other taxane types.

4.12. 6/8/6-Taxanes 13: Taxanes with an Oxetane Ring (Table 14 and Figure 22)

Taxanes in this group are structurally related to baccatin III (**237**), IV (**252**), V (**239**), VI (**257**), and VII (**256**), characterized by the presence of an oxetane bridge between C-5 and C-20, an oxo or hydroxy group at C-9, and hydroxy groups at C-1, C-2, C-4, C-7, C-10, and C-13. Some of them have more interesting esterification patterns, for example, a 2,3-dihydroxy-3-phenylpropanoyl group at the C-13 position of baccatin III and a tiglyl substituent at C-2 in place of the more normal benzoyl group. What's more, there are rare taxanes with both C-13 and C-14 oxygenated like **262**−**269**. With the core skeleton of paclitaxel, some compounds of this group can be used as the starting material of semisynthesis. For instance, paclitaxel and docetaxel could be achieved by connecting an appropriate side chain to the C-13-hydroxy group of baccatin III and 10-deacetylbaccatin III (**235**, Scheme 1). Compound 9-dihydro-13-acetylbaccatin III (**250**)[70−72] also provided a new template for the preparation of paclitaxel analogs. The overall required transformations were the removal of the C-10 and C-13 acetates and selective acylation of the C-13 hydroxy with the desired side chain.[73−76] In addition to the roles mentioned above, baccatin III,[77−79] 10-deacetylbaccatin III[79] and 14β-hydroxy-10-desacetylbaccatin III (**267**)[80] were extensively studied to synthesis series of analogs for structure−activity relationship (SAR) studies.

The content of **235** in the needles of European yew is higher (1 g/kg fresh leaves[81]) than that in the bark of Pacific yew. 5-Decinnamoyltaxagifine (**157**) is the most abundant metabolite in rooted cuttings of the Canadian yew followed by 10-deacetylbaccatin III and paclitaxel (**295**), while the three major metabolites in the needles of the mature Canadian yew are 9-dihydro-13-acetylbaccatin III (9-DHAB-III, **250**), taxinine (**70**), and taxinine E (**82**). The role of these secondary metabolites in the plant or in the rooted cuttings is presently unknown, but the difference between the metabolites of these various sources is intrigued. Due to the possibility of C-2-Ac → C-14 migration, which could take place under relatively mild condition, some compounds may be isolated as artifacts.[82]

4.13. 6/8/6-Taxanes 14: Taxanes with an Oxetane Ring and a Phenylisoserine Side Chain (Table 15 and Figure 23)

Taxanes of this class include paclitaxel (**295**) and a number of related compounds such as taxol B (**291**), taxol C (**293**), and taxol D (**290**) as well as cephalomannine (**291**) (which in spite of its name was isolated from *T. wallichiana*, previously thought to be from *Cephalotaxus munnii*).[83] The differences among them are *N*-acyl groups of the side chain. Several C-7-xylosyl paclitaxels and 7-*epi*-isomers of paclitaxel derivatives (**311**-**320**) were isolated from different yew trees. With regards to baccatin III derivatives, epimerization of the hydroxy group at C-7 can be prepared by base-induced isomerization of the corresponding natural taxanes.[84] *N*-Methyltaxol C (**296**) and taxcultine (**290**) showed activity close to that of paclitaxel in a tubulin assembly assay.[85] The IC_{50} values of 7-*epi*-cephalomannine (**316**) and 10-deacetyl-10-oxo-7-*epi*-taxol (**314**) were 80 and 64 nM, respectively,

Table 13. 6/8/6-Taxanes 12: Taxanes with a C-4,20-Epoxy Ring

compound	no.	source	part	ref
7β-deacetoxy-1β,7α-dihydroxybaccatin I	**211**	*T. baccata*	bk	417
taxumairol F	**212**	*T. mairei*	rt	398
9α,10β-diacetoxy-4,20-epoxytax-11-ene-2α,5α,14β-triol	**213**	*T. mairei*	rt	393
10-deacetyl-10-glycolyl-1β-hydroxybaccatin I	**214**	*T. canadensis*	lv	407
2α,7β,9α,10β,13α-pentaacetoxy-5α-cinnamoyloxy-4β,20-epoxy-tax-11-en-1β-ol	**215**	*T. cuspidata*	lv	325
2α,7β-deacetyl-1β-hydroxybaccatin I	**216**	*T. chinensis*	lv, st	419
1-acetoxybaccatin I	**217**	*T.yunnanensis*	lv, tw	420
10β,13α-diacetoxy-4β,20-epoxytax-11-ene-2α,5α,9α-triol	**218**	*T. chinensis*	lv	332, 421
7β,9α,10β-trideacetyl-1β-hydroxybaccatin I (taxumairol C)	**219**	*T. mairei*	rt	411
2,7,9-trideacetyl-1-hydroxybaccatin I	**220**	*T. yunnanensis*	bk	197
7,9-deacetyl-1β-hydroxybaccatin I (taxumairol B)	**221**	*T. canadensis*		202
		T. mairei	rt	411, 415
5α-deacetylbaccatin I	**222**	*T. baccata*		422
2α,5α,9α,10β,13α-pentaacetoxy-4β,20-epoxytax-11-ene-1β,7β-diol	**223**	*T. brevifolia*	bk	68
2α,5α,7β,10β,13α-pentaacetoxy-4β,20-epoxytax-11-ene-1β,9α-diol	**224**	*T. brevifolia*	bk	68
1β-hydroxy-5α-deacetylbaccatin I (taxuspine V)	**225**	*T.yunnanensis*	lv, st	200
		T. cuspidata	st	423
1β-hydroxy-10-deacetylbaccatin I (taxumairol D)	**226**	*T. yunnanensis*	rt	69
		T. mairei	rt	411
baccatin I	**227**	*T. baccata*		422
1β-hydroxybaccatin I	**228**	*T. baccata*		422
		T.wallichiana	lv, st, rt	82
		T. baccata	hw	424
		T. mairei	hw	337
		T. chinensis	lv, st	419
		T. cuspidata	st, bk	365
		T. yunnanensis	lv, tw	425
1β-acetoxy-5α-deacetylbaccatin I	**229**	*T. mairei*	bk	203
7β-acetoxy-9-acetylspicataxine	**230**	*T. media*	rt	426

Table 14. 6/8/6-Taxanes 13: Taxanes with an Oxetane Ring

compound	no.	source	part	ref
7β-(β-D-xylopyranosyl)baccatin III	**231**	*T. yunnanensis*	bk	427
7,9,13-trideacetylbaccatin VI	**232**	*T. canadensis*	lv	407
10-deacetyl-2-debenzoyl-2-tigloyl-baccatin III	**233**	*T. baccata*	lv	428
10-deacetyl-10-oxobaccatin V	**234**	*T. chinensis*	lv, st	429
10-deacetylbaccatin III	**235**	*T. baccata*	lv	81
		T. yunnanensis	lv, st	200
		T. brevifolia	bk	338
1-dehydroxybaccatin III	**236**	*T. yunnanensis*	lv, st	200
baccatin III	**237**	*T. baccata*	bk	417
		T. baccata	hw	424
		T. wallichiana	st, rt	430
		T. wallichiana	lv, st, rt	83
		T. mairei	rt	411
1-acetyl-10-deacetylbaccatin III	**238**	*T. canadensi*	lv, st	70
baccatin V	**239**	*T. baccata*		431
taxuspine E	**240**	*T. cuspidata*	st, lv	344
10-deacetyl-10-(β-hydroxybutyryl)baccatin I	**241**	*T. baccata*	lv	432
13-deacetylbaccatin VI	**242**	*T. wallichiana*	lv	201
10-deacetyl-7-xylosylbaccatin III	**243**	*T. yunnanensi*	bk	197
(10β-*O*-acetylglycolyl)baccatin VI	**244**	*T. canadensis*	lv	86
10-deacetyl-10β-*O*-glycolylbaccatin IV	**245**	*T. canadensis*	lv	407

dx.doi.org/10.1021/cr100147u |*Chem. Rev.* 2011, 111, 7652–7709

Table 14. Continued

compound	no.	source	part	ref
1β-acetylbaccatin IV	**246**	*T. yunnanensis*	lv, st	200
7,9-deacetylbaccatinn IV	**247**	*T. canadensis*	lv	202
		T. brevifolia	bk	433
7,9,10-deacetylbaccatin VI	**248**	*T. canadensis*	lv	202
7-*epi*-9,10-deacetylbaccatin VI	**249**	*T. canadensis*	lv	202
9-dihydro-13-acetylbaccatin III	**250**	*T. canadensis*	lv	71
		T. canadensi	lv, st	70
		T. mairei	hw	434
1β-dehydroxybaccatin IV	**251**			435
		T. mairei	hw	368
baccatin IV	**252**			435
		T. chinensis	lv, tw	436
9-deacetylbaccatin VI	**253**	*T. yunnanensis*	rt	69
10-deacetylbaccatin VI	**254**	*T. yunnanensis*	rt	69
1β-dehydroxybaccatin VI	**255**	*T. mairei*	hw	368
baccatin VII	**256**			435
baccatin VI	**257**	*T. baccata*	bk	13
		T. baccata	hw	424
				435
		T. mairei	hw	368
10-hydroxyacetylbaccatin VI	**258**	*T. canadensis*	lv	202
4α,9α,10β,13α-tetraacetoxy-2α,7β-dibenzoyloxy-5β,20-epoxytax-11-en-1β-ol	**259**	*T. brevifolia*	bk	437
4α,7β,9α,13α-tetraacetoxy-2α,10β-dibenzoyloxy-5β,20-epoxytax-11-en-1β-ol	**260**	*T. brevifolia*	bk	437
4α,7β,13α-triacetoxy-2α,9α,10β-tribenzoyloxy-5β,20-epoxytax-11-en-1β-ol	**261**	*T. brevifolia*	bk	437
14β-benzoyloxybaccatin IV	**262**	*T. chinensis*	lv, st	438
13-deacetyl-14β-benzoyloxybaccatin IV	**263**	*T. chinensis*	lv, st	438
2-deacetyl-14β-benzoyloxybaccatin IV	**264**	*T. chinensis*	lv, st	438
2-deacetyl-2α,14β-dihydroxybaccatin IV	**265**	*T. chinensis*	lv, br	438
2-debenzoyl-14β-benzoyloxy-10-deacetylbaccatin III	**266**	*T. wallichiana*	lv	84
14β-hydroxy-10-deacetylbaccatin III	**267**	*T. wallichiana*	lv	439
14β-hydroxybaccatin VI	**268**	*T. chinensis*	lv, st	440
14β-hydroxy-10-deacetyl-2-*O*-debenzoylbacatin III	**269**	*T. chinensis*	lv, st	47
1β-dehydroxy-4α-deacetylbaccatin IV	**270**	*T. mairei*	st, bk	203
4-deacetylbaccatin IV	**271**	*T.* x *media*	rt	426
taxuspinanane C	**272**	*T. cuspidata*	st	441
13-oxo-7,9-bisdeacetylbaccatin VI (taxuspinanane D)	**273**	*T. cuspidata*	st	366
13-oxobaccatin III	**274**	*T. sumatrana*	tw, lv	442
19-hydroxy-13-oxobaccatin III	**275**	*T. sumatrana*	lv	443
19-hydroxybaccatin III	**276**	*T. baccata*	lv	81
		T. yunnanensis	lv, st	200
		T. wallichiana	rt, st, lv	444
7-*epi*-19-hydroxybaccatin III	**277**	*T. chinensis*	lv, st	429
9(βH)-9-dihydro-19-acetoxy-10-deacetylbaccatinIII	**278**	*T. baccata*	lv	114
13-*epi*-10-deacetylbaccatin III	**279**	*T. baccata*	lv	428
deaminoacylcinnamoyltaxol (taxuspinanane J, baccatin III 13-cinnamate)	**280**	*T. cuspidata*	st	57
		T. mairei	tw	445
		T. yunnanensis	bk	427
13-(2′,3′-dihydroxy-3′-phenylpropanoyloxy)baccatin III (yunnanxol)	**281**	*T. yunnanensis*	bk	446
taxuspine N	**282**	*T. cuspidata*	st	229

indicating that the C-10-keto group reduced the bioactivity.[86] In vitro studies of cytotoxicity to the breast adenocarcinoma cell line MCF7 revealed that **316** was cytotoxic (IC_{50} = 10 nM), similar to that of cephalomannine (IC_{50} = 6 nM), and less cytotoxic comparing to that of paclitaxel (IC_{50} = 2 nM).[86] **302**−**310** isolated first from *T. cuspidata*[87] are all bearing an *O*-linked xylosyl group at C7. And what's more, the rare 4-methylhexanoyl functional group was found (**297**) only in

dx.doi.org/10.1021/cr100147u |*Chem. Rev.* 2011, 111, 7652–7709

Table 15. 6/8/6-Taxanes 14: Taxanes with an Oxetane Ring and a Phenylisoserine Side Chain

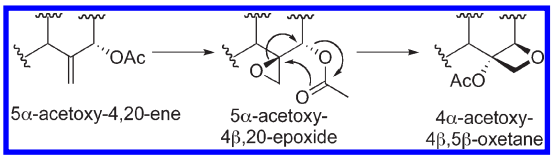
compound	no.	source	part	ref
7β-*O*-acetyl-10-deacetyltaxol	**283**	*T. canadensis*	lv	86
N-acetyl-*N*-debenzoyltaxol	**284**	*T. canadensis*	lv	407
N-debenzoyl-*N*-propanoyl-10-deacetylpaclitaxel	**285**	*T. baccata*		447
N-debenzoyl-*N*-butanoyl-10-deacetylpaclitaxel	**286**	*T. baccata*		447
10-deacetylcephalomannine (10-deacetyltaxol B)	**287**	*T. wallichiana*	rt, st, lv	444
		T. baccata	bk	417
10-deacetyltaxuyunnanine A	**288**	*T. yunnanensis*	rt	448
10-deacetyltaxol	**289**	*T. wallichiana*	rt, st, lv	444
		T. baccata	bk	417
N-debenzoyl-*N*-butanoyltaxol (taxol D, taxcultine)	**290**	*T. x media*	rt	426
cephalomannine (taxol B)	**291**	*T. baccata*	bk	417
		T. wallichiana	lv, st, rt	83, 430
		T. baccata	bk	81
N-debenzoyl-*N*-(2-methylbutyryl)taxol	**292**	*T. x media*	rt	449
taxuyunnanine (*N*-debenzoyl-*N*-hexanoyltaxol, taxol C)	**293**	*T. yunnanensis*	rt	450
		T. x media	rt	451
10-deacetyl-10-dehydro-7-acetyltaxol A	**294**	*T. x media*	rt	35
paclitaxel (Taxol)	**295**	*T. brevifolia*	bk	9
		T. wallichiana	rt, st	430
		T. wallichiana	lv, rt, st	83
		T. baccata	bk	417
		T. yunnanensis	lv, tw	420
N-methyltaxol C	**296**	*T. x media*	rt	451
taxuspinanane A	**297**	*T. cuspidata*	st	88
N-methylpaclitaxel, taxuspinanane I	**298**	*T. cuspidata*	st	57
10-(β-hydroxybutyryl)-10-deacetylcephalomannine	**299**	*T. baccata*	bk	417
N-debenzoyl-*N*-cinnamoyltaxol	**300**	*T. x media*	rt	449
10-(β-hydroxybutyryl)-10-deacetyltaxol	**301**	*T. baccata*	bk	417
7-β(β-D-xylopyranosyl)taxol D	**302**	*T. yunnanensis*	bk	452
7-β(β-D-xylopyranosyl)-*N*-methyltaxol C	**303**	*T. yunnanensis*	bk	106
7-(β-xylosyl)-10-deacetyltaxol D	**304**	*T. baccata*	bk	382
7-(β-xylosyl)-10-deacetyltaxol C	**305**	*T. baccata*	bk	417
7-(β-xylosyl)-10-deacetyltaxol	**306**	*T. baccata*	bk	417
7-(β-xylosyl)cephalomannine	**307**	*T. baccata*	bk	417
7-(β-xylosyl)taxol C	**308**	*T. baccata*	bk	417
7-(β-xylosyl)taxol	**309**	*T. baccata*	bk	417
7-*O*-β-Xylosyl-10-deacetyltaxuspinanane A	**310**	*T. cuspidata*	lv	87
10-deacetyl-10-oxo-7-*epi*-cephalomannine	**311**	*T. canadensis*	lv	86
10-deacetyl-10-oxo-7-*epi*-taxuyunnanine A	**312**	*T. yunnanensis*	rt	448
7-*epi*-10-deacetyltaxol (taxuspinanane E)				
7-*epi*-10-deacetyltaxuyunnanine A	**313**	*T. cuspidata*	st	366
		T. yunnanensis	rt	448
10-deacetyl-10-oxo-7-*epi*-taxol	**314**	*T. brevifolia*	bk	453
10-deacetyl-7-*epi*-taxol	**315**	*T. chinensis*	sd	206
7-*epi*-cephalomannine	**316**	*T. x media*	lv	454
7-*epi*-taxuyunnanine A	**317**	*T. yunnanensis*	rt	448
7-*epi*-taxol	**318**	*T. brevifolia*	bk	193
		T. yunnanensis	lv, tw	420
2′-acetoxy-7-*epi*-taxol	**319**	*T. canadensis*	lv	105
2′-acetyl-7-*epi*-cephalomannine	**320**	*T. canadensis*	lv	86
9-deoxo-9α-hydroxytaxol	**321**	*T. yunnanensis*	bk	446
2-debenzoyl-2-tigloyltaxol (*iso*-cephalomannine)	**322**	*T. x media*	rt	449
1-deoxypaclitaxel	**323**	*T. mairei*	sd	213

dx.doi.org/10.1021/cr100147u |*Chem. Rev.* 2011, 111, 7652–7709

T. cuspidata,[88] which may be the taxonomic characteristic of this species.

The committed step in the biosynthesis of paclitaxel is considered to require more than 20 enzymatic steps. Early steps proceed in sequence is the cyclization of the initial diterpenoid precursor geranylgeranyl diphosphate, catalyzed by taxadiene synthase, yielding the tricyclic taxane ring system, commonly referred to as a taxa-4,11-diene. Cyclization is then followed by hydroxylation regioselectively at the C-5α-position, with allylic migration of the C-4-double bond, to afford the second established intermediate 5α-hydroxytaxa-4(20),11-diene (Scheme 2). This parental olefin is then functionalized by a series of eight cytochrome P450-mediated oxygenations and three CoA-dependent acylations, and undergoes oxidation at C-9 and a ring expansion step to form the oxetane group en route to the late stage intermediate baccatin III, upon which the functionally important C-13α-*O*-side

Scheme 3. Proposed Biosynthetic Pathway of a C-4,20-Oxetane Ring from a C-4(20)-Double Bond



Scheme 2. Proposed Biosynthetic Pathway of Paclitaxel, Involving the Construction of Baccatin III and Final Assembly of the C-13-Side Chain

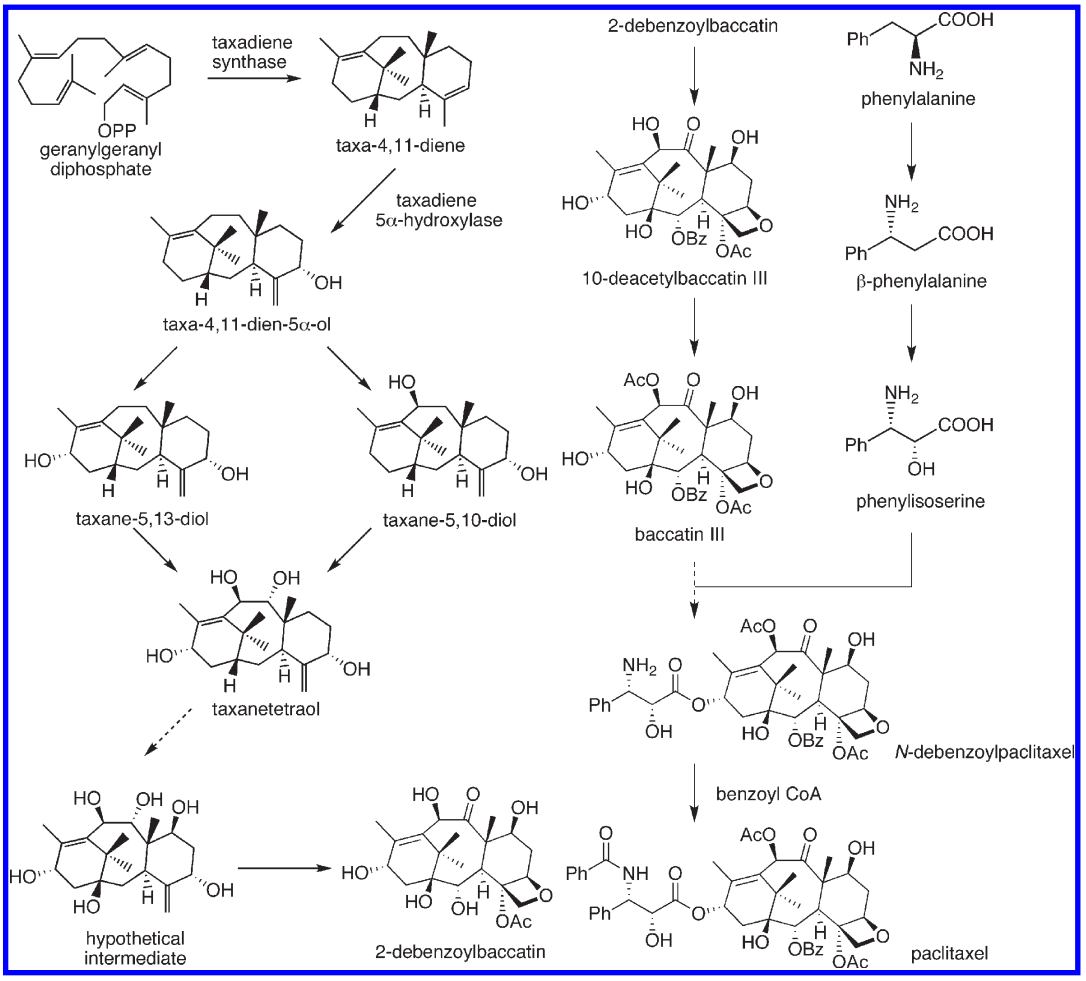


Table 16. 6/8/6-Taxanes 15: Others

compound	no.	source	part	ref
taxuyunnanine Z	**324**	*T. yunnanensis*	bk	106
taxuspine K	**325**	*T. cuspidata*	st	412
2α,10β,13α-triacetoxytaxa-4(20),5,11-trien-9-ol	**326**	*T. canadensis*	lv	53
taxezopidne B	**327**	*T. cuspidata*	sd, st	343
taxchinin N	**328**	*T. chinensis*	lv,st	108
(12αH)-2α,10β-diacetoxy-5α-cinnamoyloxy-9α,13α-epoxytax-4(20)-ene-11β,13β-diol	**329**	*T. cuspidata*	lv	96

dx.doi.org/10.1021/cr100147u |*Chem. Rev.* 2011, 111, 7652–7709

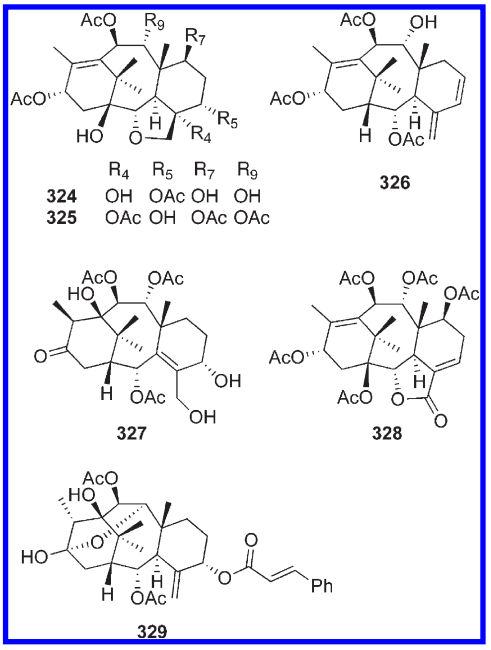


Figure 24. Other taxanes.

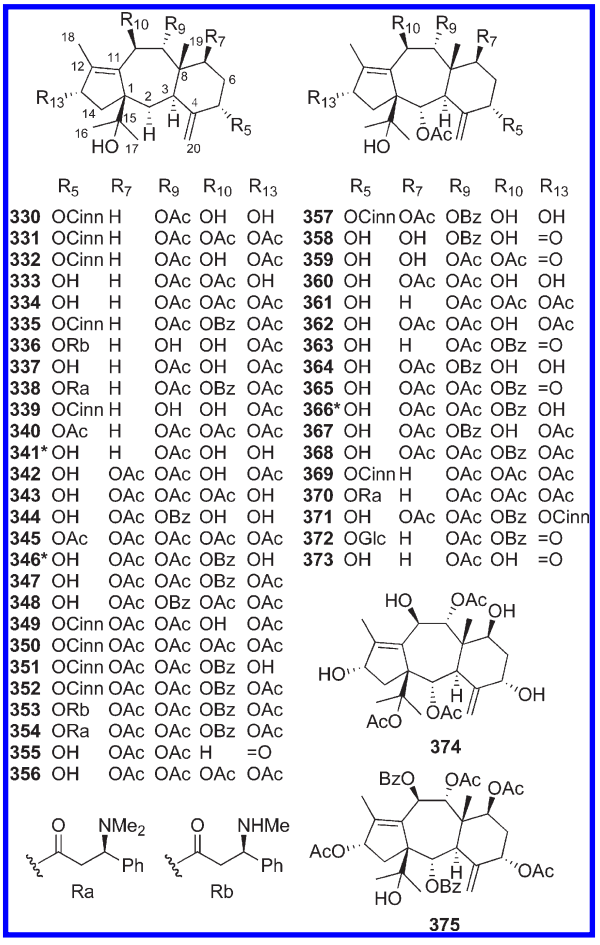


Figure 25. 11(15→1)*Abeo*taxa-4(20),11-dienes. Asterisks (*) indicate revised structures.

chain (*N*-benzoylphenylisoserine) is constructed in several additional steps to yield paclitaxel.[89−95] However, the precise

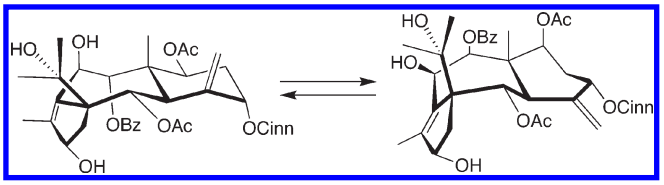


Figure 26. Two conformational isomers of **357**.

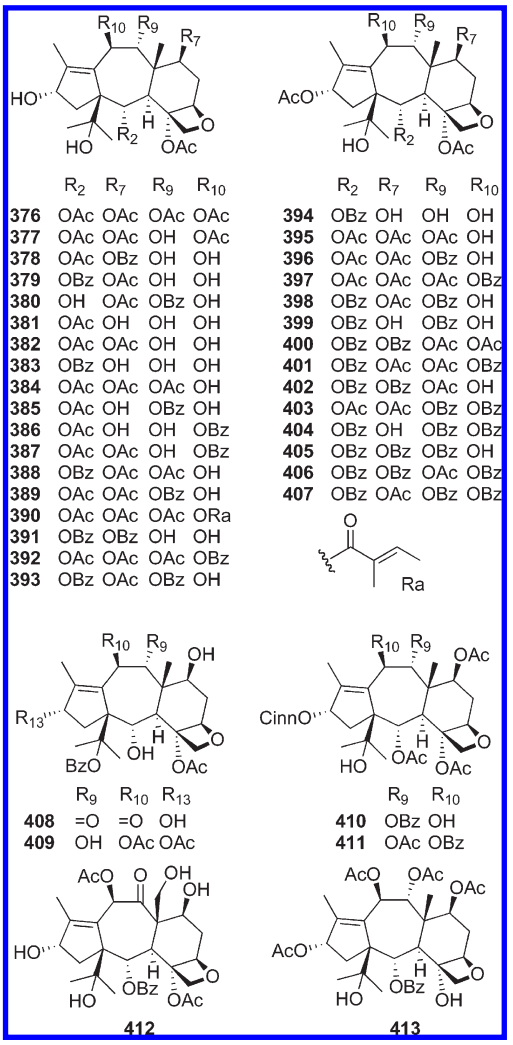


Figure 27. 11(15→1)*Abeo*taxanes with an oxetane ring.

order of hydroxylation and acetylation occurred at C-10, C-13, C-9, C7, C-2, and C-5 is uncertain.

The acetylation of the C-5α-hydroxy group is considered to be a prelude to oxetane (D-ring) formation via the sequential conversion of the 5α-acetoxy-4(20)-ene functional group to the corresponding β-epoxide, with the last step most plausibly involving intramolecular migration of the 5α-acetoxy moiety in the process of oxirane ring expansion (Scheme 3).

4.14. 6/8/6-Taxanes 15: Others (Table 16 and Figure 24)

A double bond between C-3 and C-4 was detected originally in taxezopidine B (**327**), and a tetrahydrofuran ring at C-2, C-3, C-4, and C-20 was confirmed in taxuyunnanine Z (**324**) and taxuspine K (**325**).[62] **326** is the first 6/8/6-membered normal taxane with a rare conjugated double bond between C-4(20) and

dx.doi.org/10.1021/cr100147u |*Chem. Rev.* 2011, 111, 7652–7709

Table 17. 11(15→1)*Abeo*taxanes 1:Taxanes with a C-4(20),11-Double Bonds

compound	no.	source	part	ref
chinentaxunine	**330**	*T. chinensis*	sd	206
7-deacetoxytaxuspine J	**331**	*T. cuspidata*	lv	455
9α,13α-diacetoxy-5α-cinnamoyloxy-11(15→1)*abeo*taxa-4(20),11-diene-10β,15-diol	**332**	*T. mairei*	sd	350
9α,10β-diacetoxy-11(15→1)*abeo*taxa-4(20),11-diene-5α,13α,15-triol	**333**	*T. mairei*	sd	378
9α,10β,13α-triacetoxy-11(15→1)*abeo*taxa-4(20),11-diene-5α,15-diol	**334**	*T. mairei*	sd	378
9α,13α-diacetoxy-10β-benzoyloxy-5α-cinnamoyloxy-11(15→1)*abeo*taxa-4(20),11-dien-15-ol	**335**	*T. yunnanensis*	sd	210
13α-acetoxy-5α-[(*R*)-3′-dimethylamino-3′-phenylpropanoyloxy]-11(15→1)*abeo*taxa-4(20),11-diene-9α,10β-diol	**336**	*T. yunnanensis*	sd	356
9α,13α-diacetoxy-11(15→1)*abeo*taxa-4(20),11-diene-5α,10β,15-triol	**337**	*T. yunnanensis*	sd	456
9α,13α-diacetoxy-10β-benzoyloxy-5α-[(*R*)-3′-dimethylamino-3′-phenylpropanoyloxy]-11(15→1)*abeo*taxa-4(20),11-dien-15-ol	**338**	*T. yunnanensis*	sd	456
13α-acetoxy-5α-cinnamoyloxy-11(15→1)*abeo*taxa-4(20),11-diene-9α,10β,15-triol	**339**	*T. yunnanensis*	sd	215
5α,9α,10β,13α-tetracetoxy-11(15→1)*abeo*taxa-4(20),11-dien-15-ol	**340**	*T. wallichiana*	bk	457
7-debenzoyloxy-10-deacetylbrevifoliol	**341**	*T. wallichiana*	lv	201
13-acetyl-2-deacetoxy-10-debenzoyltaxchinin A (taxawallin F)	**342**	*T. wallichiana*	lv	458
10-acetyl-2-deacetoxy-10-debenzoyltaxchinin A (taxawallin H)	**343**	*T. wallichiana*	lv	458
9-deacetyl-9-benzoyl-10-debenzoylbrevifoliol	**344**	*T. brevifolia*	bk	459
5,10,13-triacetyl-10-debenzoylbrevifoliol	**345**	*T. wallichiana*	lv	460
brevifoliol	**346**	*T. brevifolia*	lv	100
13-acetylbrevifoliol	**347**	*T. wallichiana*		201
		T. mairei	sd	406
9-benzoyl-2-deacetoxy-9-deacetyl-10-debenzoyl-10,13-diacetyltaxchinin A (taxawallin D)	**348**	*T. wallichiana*	lv	458
taxuspine M	**349**	*T. cuspidata*	st	412
taxuspine J	**350**	*T. cuspidata*	st, lv	344
taxchinin H	**351**	*T. chinensis*	st, lv	416
			lv	396
		T. wallichiana	lv	458
taxuspine A	**352**	*T. cuspidata*	st	461
		T. brevifolia	lv	100
7β,9α,13α-triacetoxy-10β-benzoyloxy-5α-(3′-methylamino-3′-phenylpropanoyloxy)-11-(15→1)*abeo*taxa-4(20),11-dien-1β-ol	**353**	*T. brevifolia*	lv	100
7β,9α,13α-triacetoxy-10β-benzoyloxy-5α-(3′-dimethylamino-3′-phenylpropanoyloxy)-11(15→1)*abeo*taxa-4(20),11-dien-1β-ol	**354**	*T. brevifolia*	lv	100
7β,9α-diacetoxy-5α,15-dihydroxy-11(15→1)*abeo*taxa-4(20),11-dien-13-one	**355**	*T. mairei*	sd	462
7β,9α,10β,13α-tetraacetoxy-11(15→1)*abeo*taxa-4(20),11-diene-5α,15-diol	**356**	*T. canadensis*	rt	103
2α,7β-diacetoxy-9α-benzoyloxy-5α-cinnamoyloxy-11(15→1)*abeo*taxa-4(20),11-diene-10β,13α,15-triol	**357**	*T. mairei*	sd	463
2α-acetoxy-9α-benzoyloxy-5α,7β,10β,15-tetrahydroxy-11(15→1)*abeo*taxa-4(20),11-dien-13-one	**358**	*T. yunnanensis*	bk	341
taxuspine O	**359**	*T. cuspidata*	st	229
10-debenzoyl-2α-acetoxybrevifoliol	**360**	*T. wallichiana*	lv	396
teixidol	**361**	*T. baccata*	lv	464
taxchinin G	**362**	*T. chinensis*		207
taxuspine Y	**363**	*T. cuspidata*	st	380
9-deacetyl-9-benzoyl-10-debenzoyltaxchinin A	**364**	*T. baccata*	bk	465
taxuspinanane B	**365**	*T. cuspidata*	st	88
taxchinin A	**366**	*T. chinensis*	lv, st	466
		T. yunnanensis	lv, tw	420
		T. baccata	sd	64
13-acetyl-9-deacetyl-9-benzoyl-10-debenzoyltaxchininA	**367**	*T. chinensis*	bk, lv	467
taxchinin D	**368**	*T. chinensis*		207
taxamedin A	**369**	*T.* x *media*	lv	468
(-)-2α-acetoxy-2′,7-dideacetoxy-1-hydroxy-11(15→1)*abeo*austrospicatine	**370**	*T. baccata*	lv	383
taxchinin E	**371**	*T. chinensis*	st, lv	416
5α-*O*-(β-D-glucopyranosyl)-10β-benzoyltaxacustone	**372**	*T. cuspidata*	lv, st	345
taxacustone	**373**	*T. cuspidata*	lv, st	345
2α,9α,15-triacetoxy-11(15→1)*abeo*taxa-4(20),11-diene-5α,7β,10β,13α-tetraol	**374**	*T. wallichiana*	bk	469
2-deacetyl-2α-benzoyl-5,13-diacetyltaxchinin A	**375**	*T. brevifolia*	bk	470

dx.doi.org/10.1021/cr100147u |*Chem. Rev.* 2011, 111, 7652–7709

Table 18. 11(15→1)*Abeo*taxanes 2: Taxanes with an Oxetane Ring

compound	no.	source	part	ref
2α-acetyl-13-deacetyl-2-debenzoyl*abeo*baccatin VI (taxayuntin H)	**376**	*T. canadensis*	lv	323
		T. yunnanensis	bk	471
taxumairol W	**377**	*T. mairei*	bk	472
2α-debenzoyl-2α-acetyltaxayuntin A (taxayuntin B)	**378**	*T. mairei*	bk	209
		T. yunnanensis	bk	473
9-deacetyltaxayuntin E (taxuspinanane F)	**379**	*T. mairei*	bk	209
		T. canadensis	lv	323
		T. cuspidata	st	366
4α,7β-diacetoxy-9α-benzoyloxy-5β,20-epoxy-11(15→1)*abeo*tax-11-ene-2α,10β,13α,15-tetraol	**380**	*T. mairei*	bk	474
taxuyunnanine M (taxumairol Q)	**381**	*T. yunnanensis*	bk	475
		T. sumatrana	lv,tw	476
tasumatrol B	**382**	*T. sumatrana*	lv,tw	477
7,13-dideacetyl-9,10-debenzoyltaxchinin C	**383**	*T. brevifolia*		459
taxacustin (10,13-deacetyl*abeo*baccatin IV)	**384**	T. cuspidata	lv,tw	203, 359
		T. wallichiana	lv	478
taxumairol K	**385**	*T. mairei*	rt	479
7,9-dideacetyltaxayuntin	**386**	*T. brevifolia*	bk	433
		T. yunnanensis	bk	480
13-decinnamoyl-9-deacetyltaxchinin B	**387**	*T. wallichiana*	bk	481
taxayuntin E	**388**	*T. yunnanensis*	lv, st	482
		T. mairei	sd	406
taxayuntin F (taxchinin L)	**389**	*T. yunnanensis*	lv, st	482
		T. chinensis	lv, st	483
taxuspine Q	**390**	*T. cuspidata*	st	399
taxayuntin A	**391**	*T. yunnanensis*	bk	473
13-deacetylbaccatin VI (taxayunnansin A, taxayuntin)	**392**	*T. wallichiana*	lv	201
		T. yunnanensis	rt	211
		T. yunnanensis	lv	212
4α,7β-diacetoxy-2α,9α-dibenzoyloxy-5β,20-epoxy-11(15→1)*abeo*taxene-10β,13α,15-triol	**393**	*T. baccata*	bk	484
7,9,10-trideacetyl*abeo*baccatin VI	**394**	*T. baccata*	lv	112
taxuyunnanine F	**395**	*T. yunnanensis*	rt	211
taxchinin M	**396**	*T. chinensis*	lv, st	483
		T. floridana	lv	485
13-acetyl-13-decinnamoyltaxchinin B	**397**	*T. baccata*	lv	486
9-*O*-benzoyl-9,10-dide-*O*-acetyl-11(15→1)*abeo*baccatinVI (taxchinin I)	**398**	*T.* x *media*	rt	487
		T. chinensis	st, lv	416
9-*O*-benzoyl-9-de-*O*-acetyl-11(15→1)*abeo*baccatin VI	**399**	*T. x media*	rt	487
4α,9α,10β,13α-tetraacetoxy-2α,7β-dibenzoyloxy-5β,20-epoxytax-11-en-1β-ol	**400**	*T. brevifolia*	bk	437
2α-deacetyl-2α-benzoyl-13α-acetyltaxayuntin (taxayuntin C)	**401**	*T. yunnanensis*	bk	473
		T. brevifolia	bk	437
2,7-dideacetyl-2,7-dibenzoyltaxayunnanine F	**402**	*T. brevifolia*	bk	470
taxchinin K	**403**	*T. chinensis*	st, lv	416
7-deacetyltaxayuntin D	**404**	*T. brevifolia*	bk	470
7-deacetyl-7-benzoyltaxchinin I	**405**	*T. brevifolia*	bk	470
7-deacetyl-7-benzoyltaxayuntin C	**406**	*T. brevifolia*	bk	470
9-deacetyl-9-benzoyltaxayuntin C (taxayuntin D, taxchinin C)	**407**	T. yunnanensis	bk	473
		T. chinensis	lv, st	429
		T. brevifolia	bk	437
15-*O*-benzoyl-10-deacetyl-2-debenzoyl-10-dehydro*abeo*baccatin III	**408**	*T. canadensis*	lv	407
7,9-di-*O*-acetyl-15-*O*-benzoyl-2-de-*O*-benzoyl-*abeo*baccatin VI	**409**	*T. canadensis*	lv	407
taxchinin J	**410**	*T. chinensis*	st, lv	416
taxchinin B	**411**	*T. chinensis*	lv, st	429
tasumatrol O	**412**	T. sumatrana	lv,tw	488
4-deacetyl-11(15→1)*abeo*baccatin VI	**413**	T. *x* media	rt	487

dx.doi.org/10.1021/cr100147u |*Chem. Rev.* 2011, 111, 7652–7709

Table 19. 11(15→1)*Abeo*taxanes 3: Taxanes with an Opened Oxetane Ring

compound	no.	source	part	ref
taxumairol U	**414**	*T. mairei*	bk	472
taxumairol V	**415**	*T. mairei*	bk	472
taxuyunnanine K	**416**	*T. yunnanensis*	bk	475
taxuyunnanine L	**417**	*T. yunnanensis*	bk	475
taxuyunnanine N	**418**	*T. yunnanensis*	bk	475
taxuyunnanine O	**419**	*T. yunnanensis*	bk	475
taxuyunnanine P	**420**	*T. yunnanensis*	bk	452
taxuyunnanine Q	**421**	*T. yunnanensis*	bk	452
taxuyunnanine R	**422**	*T. yunnanensis*	bk	452
taxuyunnanine S	**423**	*T. yunnanensis*	bk	489
taxuyunnanine T	**424**	*T. yunnanensis*	bk	489
taxuyunnanine U	**425**	*T. yunnanensis*	bk	489
taxuyunnanine V	**426**	*T. yunnanensis*	bk	489
tasumatrol E	**427**	*T. sumatrata*	lv, tw	490
tasumatrol F	**428**	*T. sumatrata*	lv, tw	490
taxayuntin G	**429**	*T. yunnanensis*	lv, st	491
			bk	452
taxayuntin J	**430**	*T. yunnanensis*	bk	471
taxumain A	**431**	*T. mairei*	tw	445
taxuchin B	**432**	*T. chinensis*	tw, lv	492
		T. yunnanensis	bk	102
taxumain B	**433**	*T. mairei*	tw	445
yunantaxusin A	**434**	*T. yunnanensis*	lv, st	493
taxuyunnanine W	**435**	*T. yunnanensis*	bk	106
taxuyunnanine X	**436**	*T. yunnanensis*	bk	106
5-*O*-acetyl-20-*O*-deacetyl-4,20-(*p*-hydroxylbenzylidenedioxy)-taxuyunnanine L	**437**	*T. chinensis*	lv, st	494

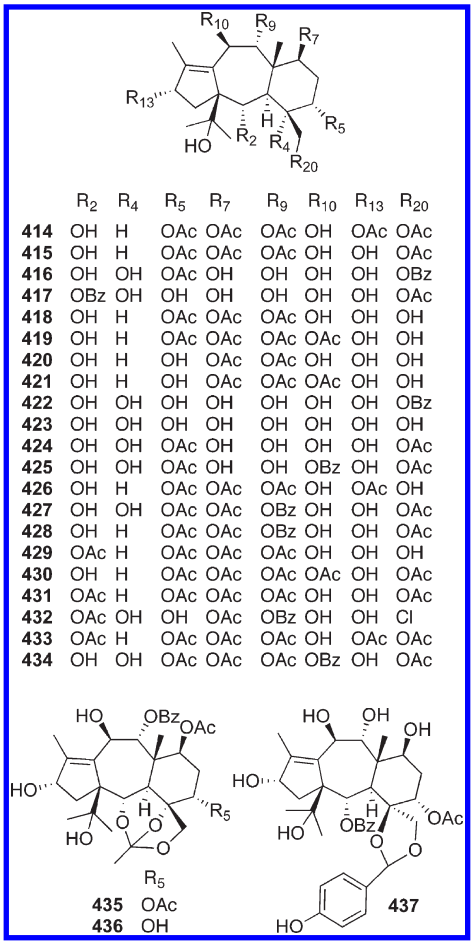


Figure 28. 11(15→1)*Abeo*taxanes with an opened oxetane ring.

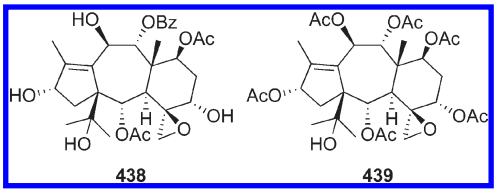


Figure 29. 11(15→1)*Abeo*taxanes with a C-4,20-epoxy ring.

C-5(6). **329** is a unique natural taxane with a C-13 and C-9-oxygen bridge to form 6-membered acetal ring.[96]

4.15. 11(15→1)*Abeo*taxanes 1: Taxanes with 4(20),11-Double Bonds (Table 17 and Figure 25)

This 11(15→1)*abeo*taxane skeleton was first encountered as a transformation product of paclitaxel,[67] then observed as naturally occurring taxane,[97,98] and the number of taxanes of this skeleton is increasing.[99] These 11(15→1)*abeo*taxanes are characterized by the presence of a C-4(20)-double bond. Esterification of the C-2 hydroxy group is normally in the form of acetate other than benzoate in this series, and both cinnamate and β-aminophenylpropionate esters are observed at C-5. Brevifoliol (**346**) was the first one isolated with this type of skeleton, but its backbone was misassigned as normal 6/8/6-membered ring system initially.[100] Actually, as a new skeleton, taxchinin A was isolated from the Chinese yew in 1992 by a Chinese group. Unfortunately it did not arose any attention due to its accessibility of the language and availability of the journal.[101] Taxuspine A (**352**) was the first correctly identified taxane structurally with an 11(15→1)*abeo*taxane skeleton from the Japanese yew.[62] Compound **356** was initially discovered as a biotransformation product[102] and later reported as a natural product.[103] **363** was the first taxane glycoside isolated from Japanese yew tree while **374** is a rare *abeo*taxane with a acetoxy group at C-15. Under acidic conditions, 10-deacetylbaccatin III derivatives can rearrange into corresponding 11(15→1)*abeo*taxane through a Wagner−Meerwein-type rearrangement (Scheme 4).[67,95,104]

11(15→1)*Abeo*taxanes usually exist as two stable conformers in solution at ambient temperature (Figure 26).

4.16. 11(15→1)*Abeo*taxanes 2: Taxanes with an Oxetane Ring (Table 18 and Figure 27)

There are some notable substitution patterns in these 11-(15→1)*abeo*taxanes such as a rare tigloyloxy group at C-10 of **390**, a cinnamoyl group at C-13 of **410** and **411** and a hydroxymethyl moiety at C-8 of **412**. It should be noted that 11-(15→1)*abeo*taxanes corresponding to paclitaxel (having a C-13-side chain), taxine B and 1-hydroxytaxinine-type taxanes (both having the C-13-oxo and C-5-side chain groups) have never been isolated as natural products. **409**[105] is an 11(15→1)*abeo*taxane with a pair of vicinal oxo groups at C-9 and C-10, and it is the first taxane having a benzoyl group attached to C-15. It was reported that 11(15→1)*abeo*taxane with two vicinal oxo groups at C-9 and C-10 could transform easily into 11(15→1),11(10→9)di*abeo*taxane such as wallifoliol (**460**).

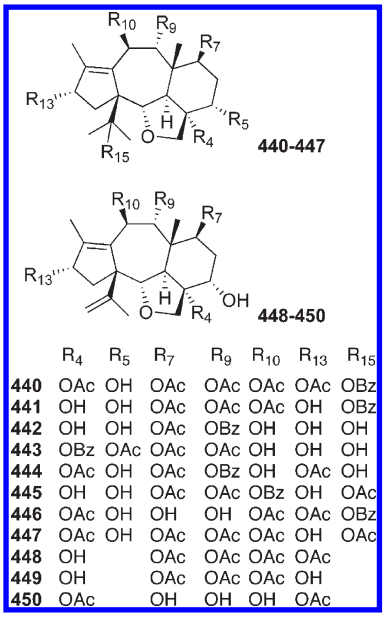
dx.doi.org/10.1021/cr100147u |*Chem. Rev.* 2011, 111, 7652–7709

Table 20. 11(15→1)*Abeo*taxanes 4: Taxanes with a C-4,20-Epoxy Ring

compound	no.	source	part	ref
2α,7β-diacetoxy-9α-benzoyloxy-4β,20-epoxy-11(15→1)*abeo*tax-11-ene-5α,10β,13α,15-tetraol	**438**	*T. mairei*	bk	209
taxuchin A	**439**	*T. chinensis*	bk	495

Table 21. 11(15→1)*Abeo*taxanes 5: Taxanes with a C-2,20-Ether Ring

compound	no.	source	part	ref
taxumairol G	**440**	*T. mairei*	rt	409
taxumairol H	**441**	*T. mairei*	rt	21
taxuyunnanine Y	**442**	*T. yunnanensis*	bk	102
tasumatrol G	**443**	*T. sumatrata*	lv, tw	490
taxuyunnanine E	**444**	*T. yunnanensis*	rt	211
10-*O*-benzoyl-15-*O*-acetyltaxumairol X	**445**	*T. chinensis*	lv, st	494
4α,10β,13α-triacetoxy-15-benzoyloxy-2α,20β-epoxy-11(15→1)*abeo*tax-11-ene-5α,7β,9α-triol	**446**	*T. canadensis*	lv	107
4α,7β,9α,10β,15-pentaacetoxy-2α,20β-epoxy-11(15→1)*abeo*tax-11-ene-5α,13α-diol	**447**	*T. canadensis*	lv	107
taxumairol I	**448**	*T. mairei*	rt	409
taxumairol J	**449**	*T. mairei*	rt	409
4α,13α-diacetoxy-2α,20-epoxy-11(15→1)-*abeo*taxa-11,15-diene-5α,7β,9α,10β-tetraol	**450**	*T. canadensis*	lv	191



	R_4	R_5	R_7	R_9	R_{10}	R_{13}	R_{15}
440	OAc	OH	OAc	OAc	OAc	OAc	OBz
441	OH	OH	OAc	OAc	OAc	OH	OBz
442	OH	OH	OAc	OBz	OH	OH	OH
443	OBz	OAc	OAc	OAc	OH	OH	OH
444	OAc	OH	OAc	OBz	OH	OAc	OH
445	OH	OH	OAc	OAc	OBz	OH	OAc
446	OAc	OH	OH	OH	OAc	OAc	OBz
447	OAc	OH	OAc	OAc	OAc	OH	OAc
448	OH		OAc	OAc	OAc	OAc	
449	OH		OAc	OAc	OAc	OH	
450	OAc		OH	OH	OH	OAc	

Figure 30. 11(15→1)*Abeo*taxanes with a C-2,20-ether ring.

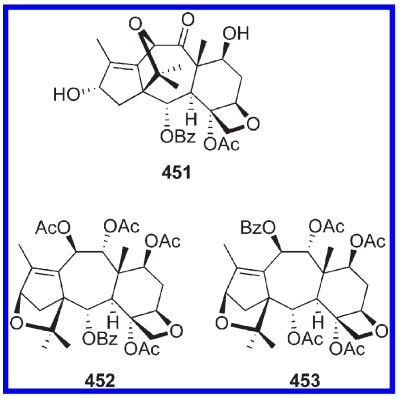


Figure 31. Other 11(15→1)*abeo*taxanes.

4.17. 11(15→1)*Abeo*taxanes 3: Taxanes with an Opened Oxetane Ring (Table 19 and Figure 28)

The 11(15→1)*abeo*taxanes undergone an oxirane or oxetane ring-opening, are observed within a group of normal taxanes. Taxuchin B (**432**), the first reported chlorine-containing taxane, was isolated from *T. chinensis*. Two orthoesterified taxanes, taxuyunnanines W (**435**) and X (**436**), were isolated from the bark of *T. yunnanensis* recently.[106] An orthoesterified taxane, 4-deacetyl-5-*epi*-20,*O*-secotaxol 4,5,20-orthoacetate, has been proposed as an intermediate of paclitaxel in its reaction with Meerwein's reagent, which led to a product with an opened oxetane ring.[67]

4.18. 11(15→1)*Abeo*taxanes 4: Taxanes with a C-4,20-Epoxy Ring (Table 20 and Figure 29)

There were two examples in the group of 11(15→1)-*abeo*taxane featured with a C-4,20-epoxy ring. They were rare rearranged baccatin II derivatives isolated from different yews with not much chemical and pharmacologic activity information available.

4.19. 11(15→1)*Abeo*taxanes 5: Taxanes with a C-2,20-Ether Ring (Table 21 and Figure 30)

All these taxanes listed in this group have a C-2,20-ether ring with **448**-**450** bearing a extra C-15(16)-double bond. Up to now, diterpenoids with the rare 2,20-ether ring system only have been isolated from five species, which may put some hint of the chemotaxonomy. Compound **446** showed weak inhibitory activity against T-98 ($IC_{50} \approx 100\ \mu M$) and MM1-CB ($IC_{50} \approx 100\ \mu M$) cells, and inactive against HeLa, HEC-1, SHIN3, HOC-21, HAC-2, HLE, U251-SP, HMV-1, and KT cells in vitro.[107]

dx.doi.org/10.1021/cr100147u |*Chem. Rev.* 2011, 111, 7652–7709

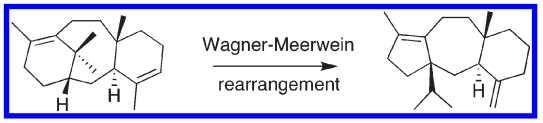
Table 22. 11(15→1)*Abeo*taxanes 6: Others

compound	no.	source	part	ref
10,15-epoxy-11(15→1)*abeo*-10-deacetylbaccatin III	**451**	*T. wallichiana*	lv	84
13-acetoxy-13,15-epoxy-11(15→1)*abeo*-13-*epi*-baccatin VI	**452**	*T.* x *media*	rt	487
13,15-epoxy-13-*epi*-taxayunnasin A	**453**	*T. chinensis*	lv, st	108

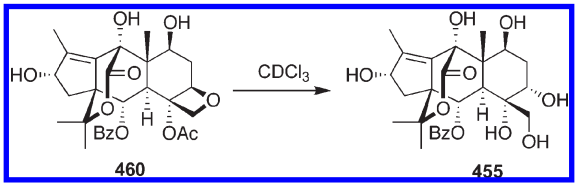
Table 23. 11(15→1),11(10→9)Di*abeo*taxanes

compound	no.	source	part	ref
20-acetoxy-2α,5α,7β,9α,13α-pentahydroxy-11(15→1),11(10→9)bis*abeo*tax-11-ene-10,15-lactone	**454**	*T. yunnansensis*	sd	215
tasumatrol H	**455**	*T. sumatrana*	lv, tw	54
tasumatrol I	**456**	*T. sumatrana*	lv, tw	54
tasumatrol R	**457**	*T. sumatrana*	lv, tw	109
13-*O*-acetylwallifoliol	**458**	*T. sumatrana*	lv, tw	476
tasumatrol J	**459**	*T. sumatrana*	lv, tw	54
wallifoliol	**460**	*T. wallichiana*	lv	496
tasumatrol A	**461**	*T. sumatrana*	lv, tw	477
tasumatrol P	**462**	*T. sumatrana*	lv, tw	109
tasumatrol T	**463**	*T. sumatrana*	lv, tw	109
tasumatrol Q	**464**	*T. sumatrana*	lv, tw	109
tasumatrol S	**465**	*T. sumatrana*	lv, tw	109

Scheme 4. Proposed Biosynthetic Pathway of 11(15→1)*Abeo*taxane



Scheme 5. Decomposition of Wallifoliol in $CDCl_3$



4.20. 11(15→1)*Abeo*taxanes 6: Others (Table 22 and Figure 31)

This group of 11(15→1)*abeo*taxanes possesses new ether rings between C-15 and C-10 or C-13. Besides isolated from the yew tree, **451** was obtained as a minor reaction product from the acidic degradation of 10-deacetylbaccatin III.[84] Chemical transformation from taxayunnansin A to **453** was conducted successfully and employed methanesulfonyl chloride pyridine with an excellent yield (99%). The mechanism of this transformation could be an intramolecular S_N2 nucleophilic substitution involving OH-15 and C-13, which might also be its biosynthetic route.[108]

4.21. 11(15→1),11(10→9)Di*abeo*taxanes (Wallifoliol Type, Table 23 and Figure 32)

This group of taxanes are often oxygenated at C-10 and esterified with a C-15-hydroxy group, sometimes with C-19-hydroxy group. Tasumatrol S (**465**) has a remarkable spiro-connected

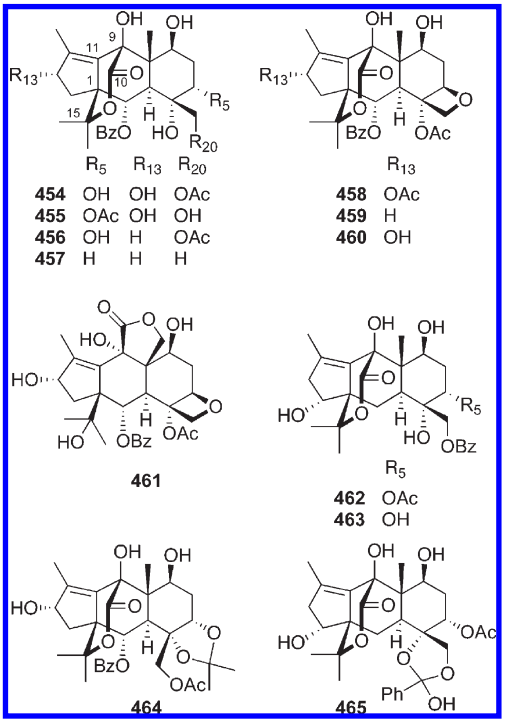


Figure 32. 11(15→1),11(10→9)di*abeo*taxanes

2-hydroxy-2-pheny-1,3-dioxolane ring.[109] This class of taxanes presumably arises from 10-dehydro-10-deacetylabeobaccatin III by benzyl−benzylic acid rearrangement of the α-dioxosystem.[110] It should be noted that compound wallifoliol (**460**) could isomerize intotasumatrol H (**455**) along with the migration of the C-4-*O*-acetyl to C-5 and hydroxylated at C-20 in $CDCl_3$ solution (Scheme 5), but it was stable in acetone-d_6 solution at ambient temperature.[111]

dx.doi.org/10.1021/cr100147u |*Chem. Rev.* 2011, 111, 7652–7709

Table 24. 2(3→20)*Abeo*taxanes

compound	no.	source	part	ref
5α-*O*-cinnamoyltaxin B	**466**	*T. canadensis*	lv	353
		T. yunnanensis	sd	195
7-deacetoxy-5-*O*-cinnamoyltaxin B	**467**	*T. canadensis*	lv	370
2α,7β,13α-triacetoxy-5α-[(2′*R*,3′*S*)-*N*,*N*-dimethyl-3′-phenylisoseryloxy]-2(3→20)*abeo*taxa-4(20),11-diene-9,10-dione	**468**	*T. cuspidata*	sd	181
2α,7β,10β,13α-tetraacetoxy-5α-[(2′*R*,3′*S*)-*N*,*N*-dimethyl-3′-phenylisoseryloxy]-2(3→20)*abeo*taxa-4(20),11-dien-9-one	**469**	*T. cuspidata*	sd	195
2-deacetyltaxuspine B	**470**	*T. cuspidata*	lv	322
5α-*O*-acetyltaxin B	**471**	*T. cuspidata*	lv	322
2α,7β,13α-triacetoxy-5α-[(2′*R*,3′*S*)-*N*,*N*-dimethyl-3′-phenylisoseryloxy]-10β-hydroxy-2(3→20)*abeo*taxa-4(20),11-dien-9-one	**472**	*T. cuspidata*	sd	456
7-*O*-acetyltaxine A	**473**	*T. baccata*		497
		T. wallichiana	lv	384
2α,5α,13α-triacetoxy-7β-hydroxy-2(3→20)*abeo*taxa-4(20),11-diene-9,10-dione	**474**	*T. mairei*	bk	498
7β,13α-diacetoxy-2α,5α,10β-trihydroxy-2(3→20)*abeo*taxa-4(20),11-dien-9-one	**475**	*T. mairei*	bk	499, 500
2α,5α,13α-triacetoxy-7β,10β-dihydroxy-2(3→20)*abeo*taxa-4(20),11-dien-9-one	**476**	*T. mairei*	bk	501
10β,13α-diacetoxy-5α-cinnamoyloxy-2α,7β-dihydroxy-2(3→20)*abeo*taxa-4(20),11-dien-9-one	**477**	*T. yunnanensis*	sd	195
7β,10β,13α-triacetoxy-5α-cinnamoyloxy-2α-hydroxy-2(3→20)*abeo*taxa-4(20),11-dien-9-one	**478**	*T. yunnanensis*	sd	195
dantaxusin A	**479**	*T. yunnanensis*	bk, lv, tw	360
2α,5α,7β,13α-tetraacetoxy-10β-hydroxy-2(3→20)*abeo*taxa-4(20),11-dien-9-one	**480**	*T. mairei*	bk	500
7β-deacetyl-5-decinnamoyltaxuspine B, deaminoacyltaxine A	**481**	*T.* x *media*	lv	502
		T. baccata	lv	112
7β,10β,13α-triacetoxy-5α-(3′-dimethylamino-3′-phenylpropanoyloxy)-2′-hydroxy-2(3→20)*abeo*taxa-4(20),11-dien-9-one	**482**	*T. canadensis*	lv	230
2-deacetyltaxin B	**483**	*T. yunnanensis*	lv, st	503
		T. mairei	sd	406
taxuspine W	**484**	*T. x media*	lv	504
		T. cuspidata	st	423
taxin B	**485**	*T. yunnanensis*	lv, st	503
taxuspinanane H (deaminoacylcinnamoyltaxine A)	**486**	*T. cuspidata*	st	57
2-deacetyltaxine A (taxine C)	**487**	*T. baccata*	lv	334, 505
taxuspine B	**488**	*T. cuspidata*	st	461
		T. mairei	bk	498
taxine A	**489**	*T. baccata*	lv	505, 506
taxezopidine P	**490**	*T. cuspidata*	sd	386
2α,10β,13α-triacetoxy-2(3→20)*abeo*taxa-4(20),11-diene-7,9-dione	**491**	*T. mairei*	bk	501
2α,13α-diacetoxy-10β-hydroxy-2(3→20)*abeo*taxa-4(20),11-diene-7,9-dione	**492**	*T. mairei*	bk	501
2α,7β,10β-triacetoxy-5α,13α-dihydroxy-2(3→20)*abeo*taxa-4(20),11-dien-9-one	**493**	*T. cuspidata*	lv	507
2α,7β-diacetoxy-5α,10β,13α-trihydroxy-2(3→20)*abeo*taxa-4(20),11-dien-9-one	**494**	*T. mairei*	bk	500
7β,10β-diacetoxy-2α,5α,13α-trihydroxy-2(3→20)*abeo*taxa-4(20),11-dien-9-one	**495**	*T. mairei*	sd	213
taxumairone A	**496**	*T. mairei*	sd	508
2 α,13α-diacetoxy-10β-hydroxy-2(3→20)*abeo*taxa-4(20),6,11-triene-5,9-dione	**497**	*T. mairei*	sd	213
2α,7β,13α-triacetoxy-5α,9α-dihydroxy-2(3→20)*abeo*taxa-4(20),11-dien-10-one	**498**	*T. yunnanensis*	sd	214
2α,7β-diacetoxy-5α,10β,13β-trihydroxy-2(3→20)*abeo*taxa-4(20),11-dien-10-one	**499**	*T. cuspidata*	lv	113
2α,7β,10α-triacetoxy-5α-hydroxy-2(3→20)*abeo*taxa-4(20),11-dien-9,13-dione	**500**	*T. sumatrana*	lv, tw	122

In addition, Tasumatrol P (**462**) showed mild cytotoxic activity against human HeLa and Daoy tumor cells.[109]

4.22. 2(3→20)*Abeo*taxanes (Table 24 and Figure 33)

Taxanes of this class are probably formed from a transannular cyclization of an intermediate verticilladiene that involved in normal taxane biosynthesis (Scheme 6).[112] The alkaloid taxine A (**489**), a component of the original "taxine," is the first member of this class isolated from *T. baccata* in 1982 and its structure was elucidated by single crystal X-ray diffractometry. The characteristics of this group are the C-4(20)-double bond, C-10-oxo and hydroxy or acetoxy substitutions at C-2, C-5, C-10 and C-13. There were three exceptions discovered so far (**496**, **497** and **498**). **496** and **497** are two 2(3→20)*abeo*taxanes with an α,β-unsaturated ketone moiety formed by the C-5-oxo and the C6-double bond, while **498** is the first example of 2(3→20)*abeo*taxane with an oxo group at C-10 instead of usual C-9, and **499** has an abnormal 13β-substituent.[113] In the molecular configuration of this group taxanes, both ring A and B were in boat conformations while ring C adopt a chair conformation with the C-4-double bond in *E*-configuration (Figure 34).

dx.doi.org/10.1021/cr100147u |*Chem. Rev.* 2011, 111, 7652–7709

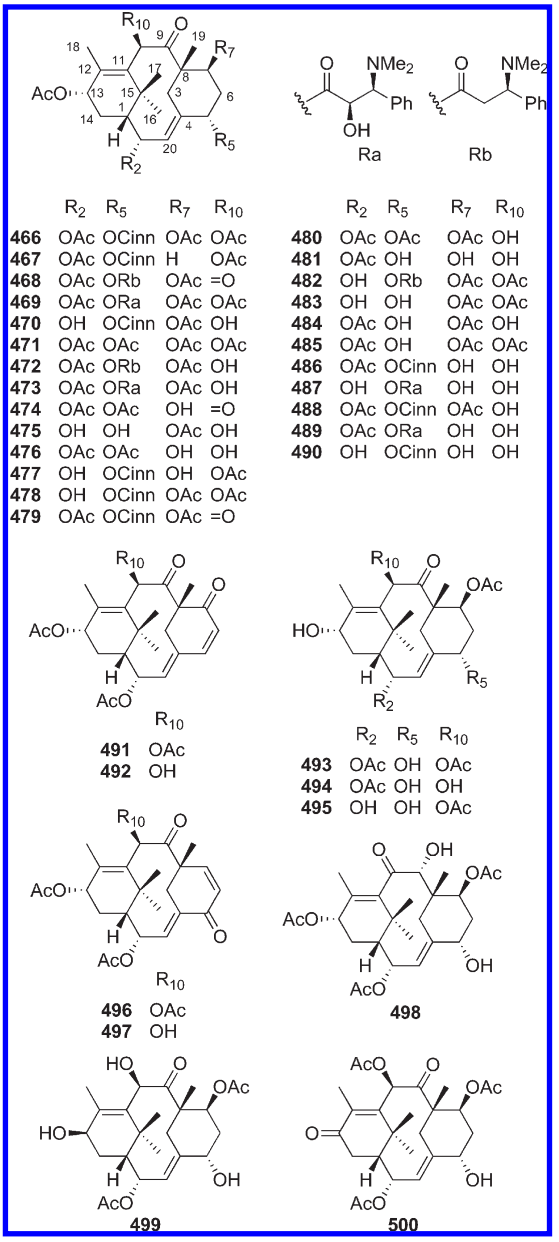


Figure 33. 2(3→20)*Abeo*taxanes.

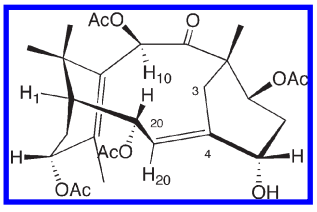


Figure 34. Stereostructure of taxin B (**485**).

4.23. 3,11-Cyclotaxanes (Table 25 and Figure 35)

All the 24 compounds in this set of taxanes have a C-13-oxo group and a C-4(20)-double bond simultaneously with the majority of them bearing a cinnamoyl moiety at C-5. Two of them have alkaloid side chains at C-5. It was initially reported that irradiation of the corresponding tax-11-en-13-ones lead to

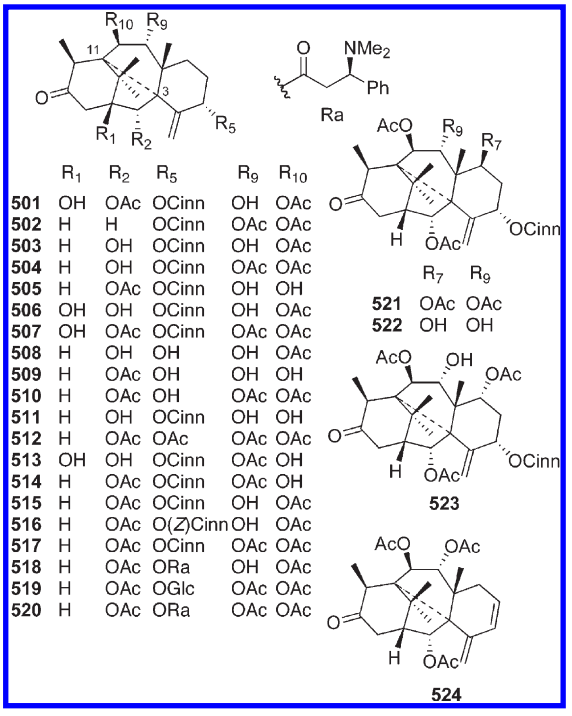
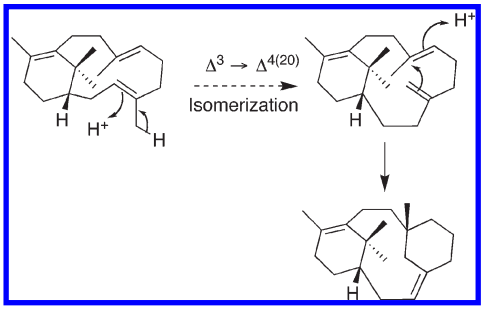


Figure 35. 3,11-Cyclotaxanes.

Scheme 6. Proposed Biosynthetic Pathway of 2-(3→20)*Abeo*taxane Skeleton



the bond formation between C-3 and C-11 but cannot get the unity optic isomer of the side chain.[114] Recently, a pair of taxanes (**515**, **516**) with optic isomer of the side chain were isolated. Taxinines K (**510**) and L (**512**) are the first two 3,11-cyclotaxanes isolated from *T. cuspidata*.[62] Compounds **521**, **522**, and **523** are three 3,11-cyclic taxanes with a rare substitution on C-7, while **524** is the only case without a substitution at C-5. Taxuspine C (**517**) exhibited remarkable multidrug-resistance (MDR)-reversing activity and enhanced the chemotherapeutic effect of VCR in P388/VCR-bearing mice.[115] 1β-Hydroxytaxuspine C (**507**) also showed remarkable activity as modulator of multidrug-resistant tumor cells.[45]

4.24. Other Cyclotaxanes (Table 26 and Figure 36)

This group of taxanes with a new skeleton was isolated from the needles of the Canadian yew, *T. canadensis*. The cross-links pulled the structures into rigid cages with a number of chiral centers. Compound **530**[116] represents the first example of the novel carbon framework with a rare 5/5/4/6/6/6-membered

dx.doi.org/10.1021/cr100147u |*Chem. Rev.* 2011, 111, 7652–7709

Table 25. 3,11-Cyclotaxanes

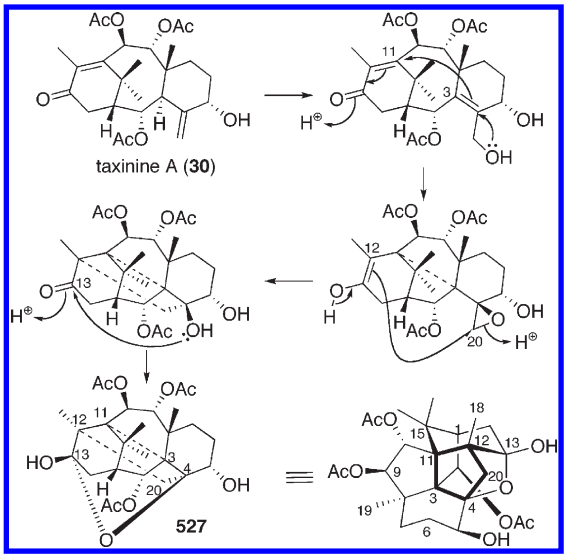
compound	no.	source	part	ref
2α,10β-diacetoxy-5α-cinnamoyloxy-1β,9α-dihydroxy-3,11-cyclotax-4(20)-en-13-one	**501**	*T. baccata*	lv	[352]
9α,10β-diacetoxy-5α-cinnamoyloxy-3,11-cyclotax-4(20)-en-13-one	**502**	*T. canadensis*	lv	326
10β-acetoxy-5α-cinnamoyloxy-2α,9α-dihydroxy-3,11-cyclotax-4(20)-en-13-one	**503**	*T. canadensis*	lv	370
9α,10β-diacetoxy-5α-cinnamoyloxy-2α-hydroxy-3,11-cyclotax-4(20)-en-13-one	**504**	*T. canadensis*	lv	370
2α-acetoxy-5α-cinnamoyloxy-9α,10β-dihydroxy-3,11-cyclotax-4(20)-en-13-one	**505**	*T. canadensis*	lv	507
10β-acetoxy-5α-cinnamoyloxy-1β,2α,9α-trihydroxy-3,11-cyclotax-4(20)-en-13-one	**506**	*T. canadensis*	rt	103
1β-hydroxytaxuspine C	**507**	T. cuspidata	lv	325
10β-acetoxy-2α,5α,9α-trihydroxy-3,11-cyclotax-4(20)-en-13-one	**508**	*T. yunnanensis*	sd	215
2α-acetoxy-5α,9α,10β-trihydroxy-3,11-cyclotax-4(20)-en-13-one	**509**	*T. yunnanensis*	sd	214
taxinine K	**510**	*T. cuspidata*	lv	16
5-cinnamoylphototaxicin II	**511**	*T. baccata*	lv	432
taxinine L	**512**	*T. cuspidata*	lv	16
5-*O*-cinnamoyl-9-*O*-acetylphototaxicin I	**513**	*T. baccata*	lv	114
2,9-diacetyl-5-cinnamoylphototaxicin II	**514**	*T. canadensis*	lv	216
2,10-diacetyl-5-cinnamoylphototaxicin II	**515**	*T. canadensis*	lv	216, 217
		T. yunnanensis	sd	215
2,10-diacetyl-5-[(*Z*)-cinnamoyl]phototaxicin II	**516**	*T. canadensis*	lv	217
taxuspine C	**517**	*T. cuspidata*	st	461
2α,10β-diacetoxy-9α-hydroxy-5α-(3′-dimetyl-amino-3′-pheylpropanoyloxy)-3,11-cyclotax-4(20)-en-13-one	**518**	*T. canadensis*	lv	230
2α,9α,10β-triacetoxy-5α-(β-D-glucopyranasyloxy)-3,11-cyclotax-11-en-13-one	**519**	*T. cuspidata*	lv, tw	417
taxuspine H	**520**	*T. cuspidata*	st, lv	344
7β-acetoxytaxuspine B	**521**	*T. canadensis*	lv	353
2,10-diacetyl-5-cinnamoyl-7β-hydroxyphototaxicin II	**522**	*T. canadensis*	lv	216
2α,7α,10β-triacetoxy-5α-cinnamoyloxy-9α-hydroxy-3,11-cyclotax-4(20)-en-13-one	**523**	*T. canadensis*	lv	325
3α,11α-cyclotaxinine NN-2	**524**	*T. cuspidata*	st	387

Table 26. Other Cyclotaxanes

compound	no.	source	part	ref
dipropellane A	**525**	*T. canadensis*	lv	218
dipropellane B	**526**	*T. canadensis*	lv	218
dipropellane C	**527**	*T. canadensis*	lv	218
2α,9α-diacetoxy-5α-cinnamoyloxy-10β,11β-dihydroxy-14β,20-cyclotax-3-en-13-one	**528**	*T. canadensis*	lv	117
canataxapropellane	**529**	*T. canadensis*	lv	219
2a,10b-diacetoxy-5a,9a,20a-trihydroxy-3a,11a;4a,12a;14a,20-tricyclotaxan-13-one	**530**	*T. canadensis*	lv	116
taxpropellane A	**531**	*T. canadensis*	lv	509

ring system, the most complex core skeleton in all the natural taxanes. Scheme 7 showed a plausible biosynthetic pathway of taxane dipropellanes **525**−**527** via intramolecular Michael addition and alkylation. Similarly, a plausible biosynthetic pathway from a taxane such as **22** to canataxpropellane was also suggested (Scheme 8).[116] It should be emphasized that structure **C** has a 6/8/6/6 tetracyclic skeleton, which showed a cage-like backbone and a similar taxane **528** has been isolated from this plant.[117] The C-3(4) and C-11(12)-double bonds were spatially closed and [2 + 2] cycloaddition could occur to form the cyclobutane ring. The coexistence of the novel type taxane **530** and **528** implied that the former should be biosynthesized from a 14,20-cyclotaxane-type precursor.

Scheme 7. Proposed Biosynthetic Pathway of 527



4.25. Bicyclic Taxanes 1: 3,8-Secotaxa-3,8,11-trienes (Table 27 and Figure 37)

Bicyclic taxanes are a group of interesting 3,8-secotaxanes comprising a 6-membered A ring and a 12-membered B-ring, and most of them possess three double bonds and a 10-acetoxy group, as well as a cinnamoyl group at C-20 in some cases.

dx.doi.org/10.1021/cr100147u |*Chem. Rev.* 2011, 111, 7652–7709

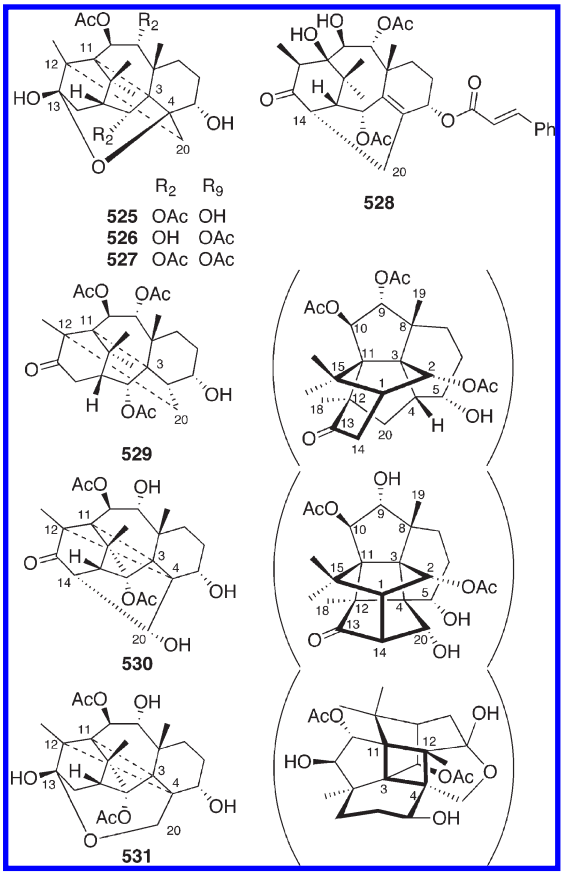


Figure 36. Other cyclotaxanes.

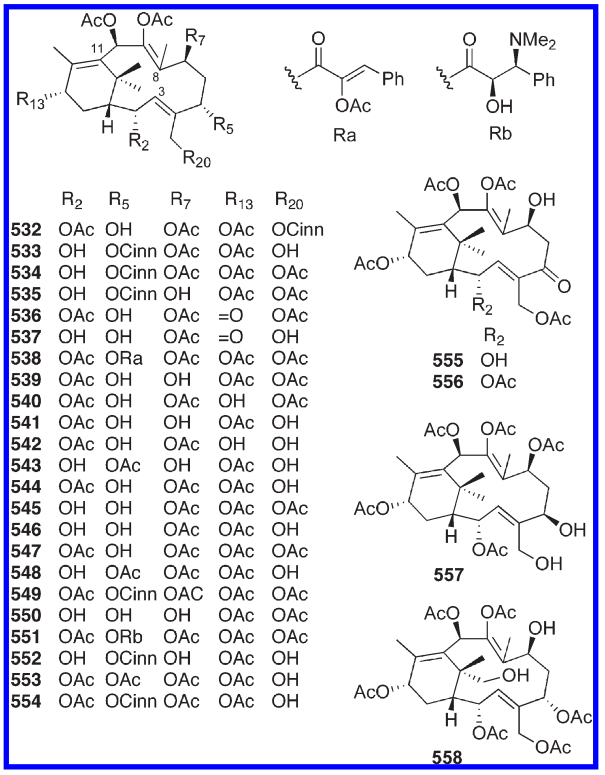


Figure 37. 3,8-Secotaxa-3,8,11-trienes.

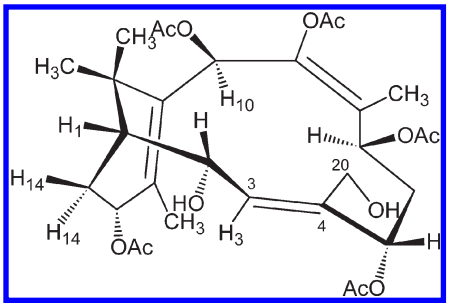


Figure 38. Stereostructure of taxachitriene B (**548**).

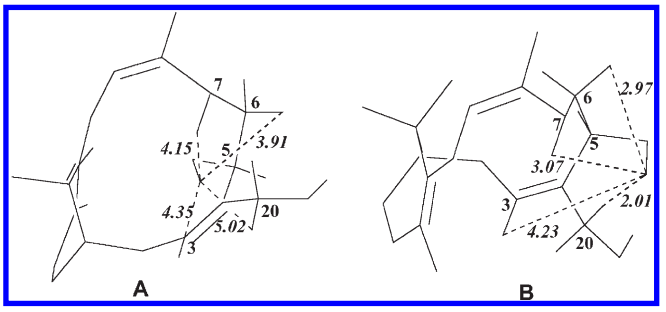
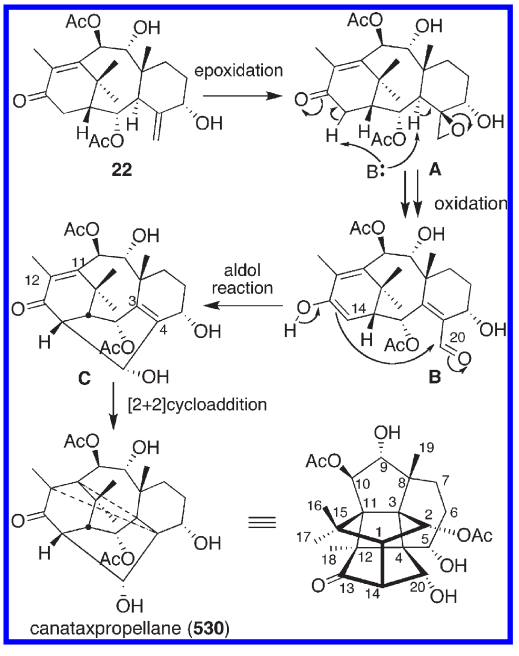


Figure 39. Molecular models of the lowest energy structure of (A) canadensene (**557**) and (B) 5-*epi*-canadensene (**544**) illustrating the distances (in Å) between the OH-5 hydrogen and the neighboring hydrogens. Reprinted with permission from ref216. Copyright 1998 Elsevier Science.

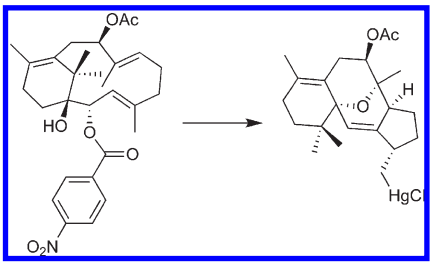
Scheme 8. Proposed Biosynthetic Pathway of Canataxpropellane (530)



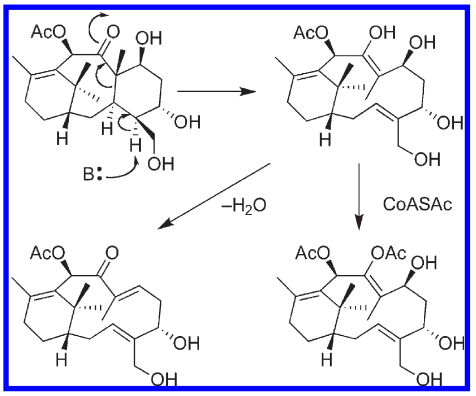
This kind of taxanes, as represented by taxachitrienes A (**547**), B (**548**, Figure 38),[118] canadensene (**557**)[119] and 5-*epi*-canadensene (**544**), was first reported by two groups simultaneously from the Chinese and Canadian yews in 1995. Up to now, bicyclic taxanes were detected mainly in the Canadian, Chinese, and Japanese

dx.doi.org/10.1021/cr100147u |*Chem. Rev.* 2011, 111, 7652–7709

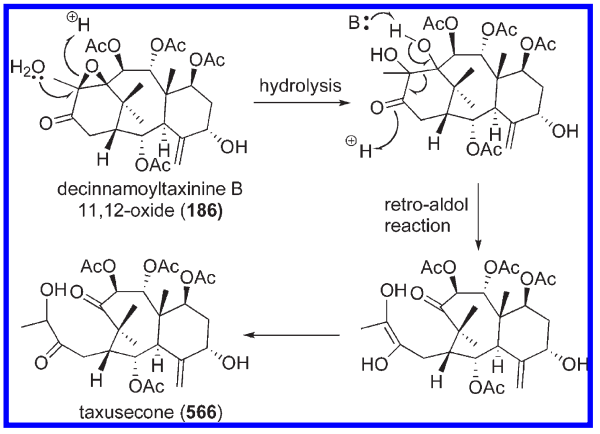
Scheme 9. Product of 3,8-Secotaxane Cyclization



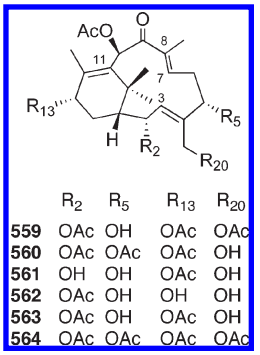
Scheme 10. Proposed Biosynthetic Pathway of Bicyclic Taxanes



Scheme 11. Proposed Biosynthetic Pathway of Taxusecone (566)



yews. Compound **537** from *T. mairei* is the only example of bicyclic taxane with a C-13-oxo group. Taxane **558** has a hydroxy substituent on the C-17-methyl group. It is of great interest that canadensene (**557**) is the first and the only bicyclic taxane with a 5β-substitution. 5-*epi*-Canadensene was originally isolated from the Chinese yew, *T. chinensis*, and was considered incorrectly to be canadensene although differences in both ^{1}H NMR and ^{13}C NMR data were observed.[120] Actually, 5β-substituted canadensene has never been isolated again. The 5-*epi*-canadensene seems to be more prone to cyclize to form an oxetane because of the



	R_2	R_5	R_{13}	R_{20}
559	OAc	OH	OAc	OAc
560	OAc	OAc	OAc	OH
561	OH	OH	OAc	OH
562	OAc	OH	OH	OH
563	OAc	OH	OAc	OH
564	OAc	OAc	OAc	OAc

Figure 40. 3,8-Secotaxa-3,7,11-trien-9-ones.

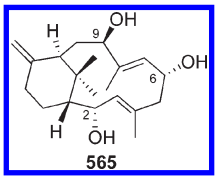


Figure 41. 3,8-Secotaxatriene-2,6,9-triol.

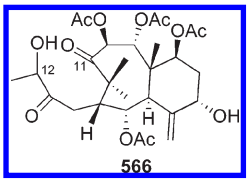


Figure 42. 11,12-Secotaxane.

proximity of the two hydroxy groups. It is tempting to assume that one of them is used for the formation of a taxane whereas the other acts as a dead-end metabolite. Preliminary studies by Zamir's group suggested that the isolation of the different stereoisomers must be dependent on the season of the plant collected. The biosynthetic puzzle is still unsolved. Why only very few yew species produce these kind of compounds? Why both C-5 stereoisomers existed only in the Canadian yew?

On the basis of molecular modeling work, distances between the oxygen atoms of 5-OH and 20-OH were measured as 4.27 Å for canadensene, which adopted a striking U-shape in the 3D-model[121] and 3.08 Å for the 5-*epi*-canadensene (Figure 39). Molecular modeling studies revealed that modified bicyclic taxanes can adopt a conformation similar to the bioactive conformation of paclitaxel and can be well accommodated within the pseudoreceptor and therefore predicted the microtubule-stabilizing activity for taxanes.[31,65] In addition, taxuspine X (**549**) indeed exhibited remarkable multidrug-resistance (MDR)-reversing activity.[61] **552** and **553** showed significant cytotoxicity against HeLa (cervical epitheloid), WiDr (colon), Daoy (medulloblastoma), and Hep2 (liver carcinoma) tumor cells.[122]

The structure diversity of compounds obtained from the Canadian yew might be a hint to two possible biosynthetic pathways of taxanes.[123] It has been considered that geranylgeranyl diphosphate first cyclized into a verticillene as a transient intermediate.[124] Initial verticillyl cation does not undergo the proton shift needed to generate the normal taxane ring system, but instead it is quenched at the bicyclic stage.

Table 27. Bicyclic Taxanes 1: 3,8-Secotaxa-3,8,11-trienes

compound	no.	source	part	ref
20-*O*-cinnamoyl-5-*epi*-canadensen	**532**	*T. canadensis*	lv	510
2,20-dideacetyltaxuspine X	**533**	*T. cuspidata*	lv	511
2-deacetyltaxuspine X	**534**	*T. cuspidata*	lv	511
2,7-dideacetyltaxuspine X	**535**	*T. cuspidata*	lv	511
(3*E*,8*E*)-2α,7β-9,10β,20-pentaacetoxy-5α-hydroxy-3,8-secotaxa-3,8,11-trien-13-one	**536**	*T. mairei*	lv	512
(3*E*,8*E*)-7β,9,10β-triacetoxy-2α,5α,20-trihydroxy-3,8-secotaxa-3,8,11-trien-13-one	**537**	*T. mairei*	lv	512
(3*E*,8*E*)-2α,7β,9,10β,13α,20-hexaacetoxy-5-[(*Z*)-2′-acetoxycinnamoyloxy]-3,8-secotaxa-3,8,11-triene	**538**	*T. mairei*	lv	220
7-deacetyltaxachitrine A	**539**	*T. mairei*	lv	513
		T. sumatrana	lv, tw	122
13-deacetyltaxachitrine A	**540**	*T. mairei*	lv	513
7-deacetylcanadensene	**541**	*T. mairei*	lv	514
		T. sumatrana	lv, tw	488
13-deacetylcanadensene	**542**	*T. mairei*	lv	514
taxuspine U	**543**	*T. cuspidata*	st	423
5-*epi*-canadensene	**544**	*T. canadensis*	lv	216
		T. mairei	sd	406
2-deacetyltaxachitriene A	**545**	*T. chinensis*	lv	515
5-deacetyltaxachitriene B	**546**	*T. chinensis*	lv	120
taxachitriene A	**547**	*T. chinensis*	lv	118
taxachitriene B	**548**	*T. chinensis*	lv	118
		T. mairei	sd	406
taxuspine X	**549**	*T. cuspidata*	st	380
tasumatrols M	**550**	*T. sumatrana*	lv, tw	488
5-[(2′*S*,3′*R*)-*N*,*N*-dimethyl-3′-phenylisoseryl]taxachitriene A	**551**	*T. chinensis*	bk, lv	467
(3*E*,8*E*)-9,10β,13α-triacetoxy-2α,7β,20-trihydroxy-5α-[(*E*)-cinnamoyloxy]-3,8-secotaxa-3,8,11-triene	**552**	*T. sumatrana*	lv, tw	122
(3*E*,8*E*)-2α,5α,7β,9,10β,13α-hexaacetoxy-20-hydroxy-3,8-secotaxa-3,8,11-triene	**553**	*T. sumatrana*	lv, tw	122
5-*epi*-*O*-cinnamoylcanadensene	**554**	*T. canadensis*	lv	105
tasumatrol N	**555**	*T. sumatrana*	lv,st	488
(3*E*,8*E*)-2α,9,10β,13α,20-pentaacetoxy-7β-hydroxy-3,8-secotaxa-3,8,11-trien-5-one	**556**	*T. sumatrana*	lv, tw	122
canadensene	**557**	*T. canadensis*	lv	119
taxumairol M	**558**	*T. mairei*	sd	516

Table 28. Bicyclic Taxanes 2: 3,8-Secotaxa-3,7,11-trien-9-ones

compound	no.	source	part	ref
(3*E*,7*E*)-2α,10β,13α,20-tetraacetoxy-5α-hydroxy-3,8-secotaxa-3,7,11-trien-9-one	**559**	*T. mairei*	lv	211
(3*E*,7*E*)-2α,5α,10$\alpha\beta$,13α-tetraacetoxy-20-hydroxy-3,8-secotaxa-3,7,11-trien-9-one	**560**	*T. mairei*	lv	211
(3*E*,7*E*)-10β,13α-diacetoxy-2α,5α,20-trihydroxy-3,8-secotaxa-3,7,11-trien-9-one	**561**	*T. mairei*	lv	211
(3*E*,7*E*)-2α,10β-diacetoxy-5α,13α,20-trihydroxy-3,8-secotaxa-3,7,11-trien-9-one	**562**	*T. chinensis*	lv	515
(3*E*,7*E*)-2α,10β,13α-triacetoxy-5α,20-dihydroxy-3,8-secotaxa-3,7,11-trien-9-one	**563**	*T. chinensis*	lv	515
(3*E*,7*E*)-2α,5α,10β,13α,20-pentaacetoxy-3,8-secotaxa-3,7,11-trien-9-one	**564**	*T. mairei*	sd	517

However, trying to close the 3,8-seco-taxane into tetracyclic taxane was failed[119] or got unexpected result (Scheme 9).[125] These results suggested another alternative pathway shown in Scheme 10.[26,62] While it is doubtful that the bicyclic taxanes originate from the opening of a full oxygenated tricyclic taxane[121] as no report is available on such transformation by chemical reactions or in vivo.

The regiochemistry of the 12-membered ring in bicyclic taxane was 3*E* and 8*E* and ring A had a boat conformation. The relative stereochemistry of ring B in bicyclic taxane like taxuspine U was 2*R**,5*S**,7*S**,10*R**.

Table 29. Bicyclic Taxanes 3: 3,8-Secotaxatriene-2,6,9-triol

compound	no.	source	part	ref
(11αH)-3,8-secotaxa-3,7,12(18)-triene-2α,6α,9β-triol	**565**	*T. mairei*	sd	126

4.26. Bicyclic Taxanes 2: 3,8-Secotaxa-3,7,11-trien-9-ones (Table 28 and Figure 40)

Bicyclic taxanes of this group were characterized by the presence of a C-9-oxo and the two double bonds at C-3 and C-7.

dx.doi.org/10.1021/cr100147u |*Chem. Rev.* 2011, 111, 7652–7709

4.27. Bicyclic Taxanes 3: 3,8-Secotaxatriene-2,6,9-triol (Table 29 and Figure 41)

Unlike other bicyclic taxanes, (11αH)-3,8-secotaxa-3,7,12(18)-triene-2,6,9-triol (**565**) has no substitution at C-5, C-10, C-13, C-20, but a 6-OH group and it was speculated to be an intermediate of bicyclic taxane biosynthesis as a least substituted taxane.[126]

Table 30. Bicyclic Taxanes 4: 11,12-Secotaxane

compound	no.	source	part	ref
taxusecone	**566**	*T. cuspidata*	lv	127

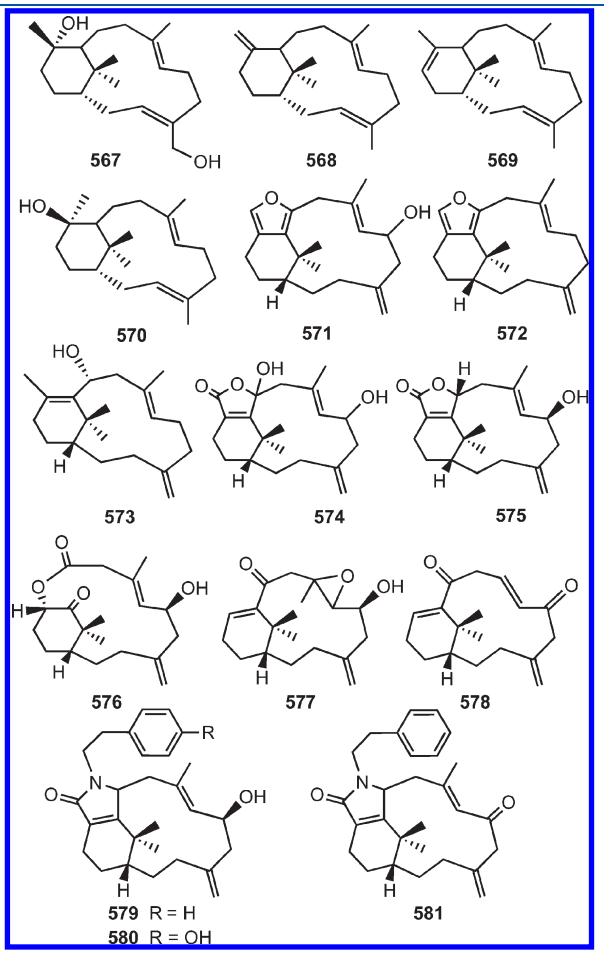


Figure 43. Bicyclic taxane analogs isolated from other sources.

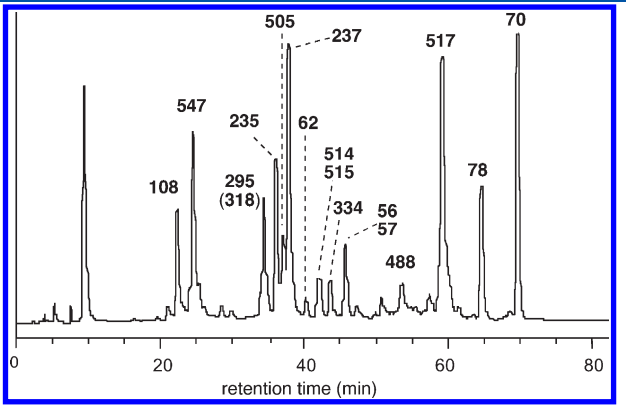


Figure 44. HPLC spectrum of taxanes eluted with a 100 min linear gradient of acetonitrile (25−100%) in water at a flow rate of 18 mL/min.

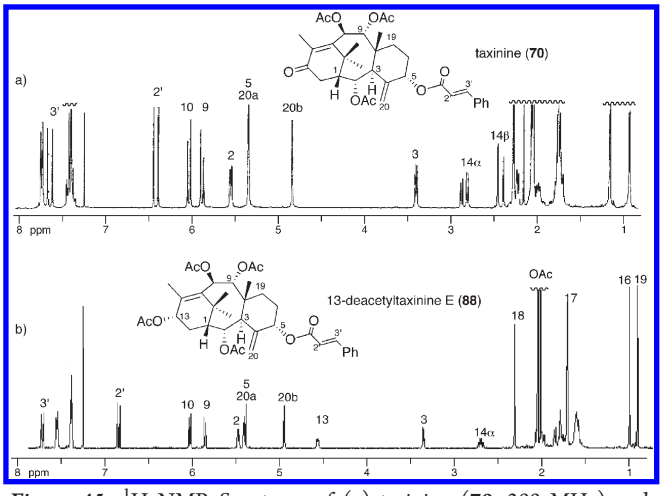


Figure 45. ^{1}H NMR Spectrum of (a) taxinine (**70**, 300 MHz) and (b) 13-deacetyltaxinine E (**88**, 500 MHz) in $CDCl_3$.

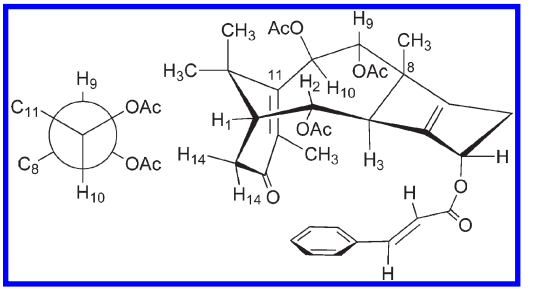


Figure 46. Newman projection along C-9 and C-10 in taxinine (**70**) and its stereostructure.

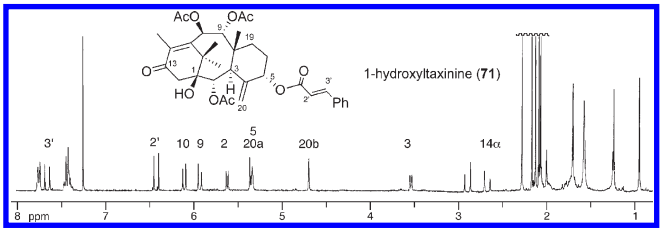


Figure 47. ^{1}H NMR spectrum of 1-hydroxytaxinine (**71**) in $CDCl_3$ (300 MHz).

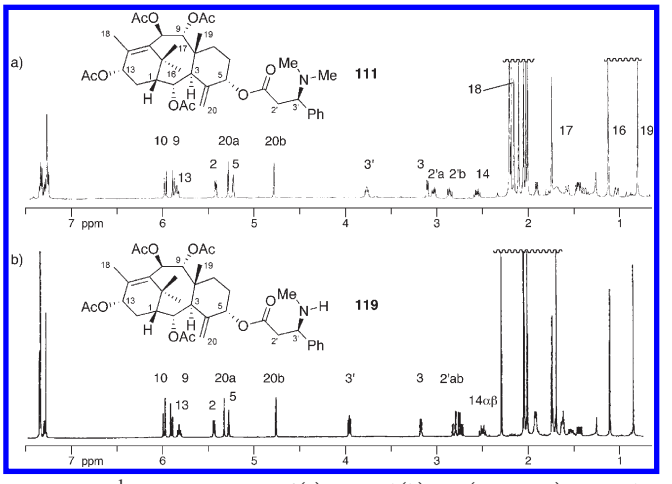


Figure 48. ^{1}H NMR spectrum of (a) **111** and (b) **119** (500 MHz) in $CDCl_3$.

dx.doi.org/10.1021/cr100147u |*Chem. Rev.* 2011, 111, 7652–7709

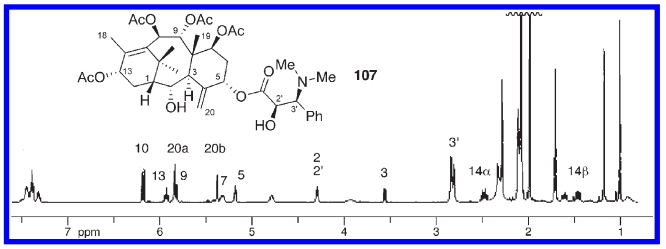


Figure 49. ^{1}H NMR spectrum of **107** in acetone-d_6 (600 MHz).

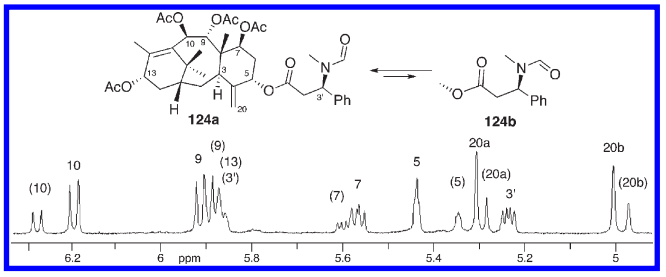


Figure 50. Part of ^{1}H NMR spectrum of **124**. Positional numbers in parentheses are of the minor rotamer.

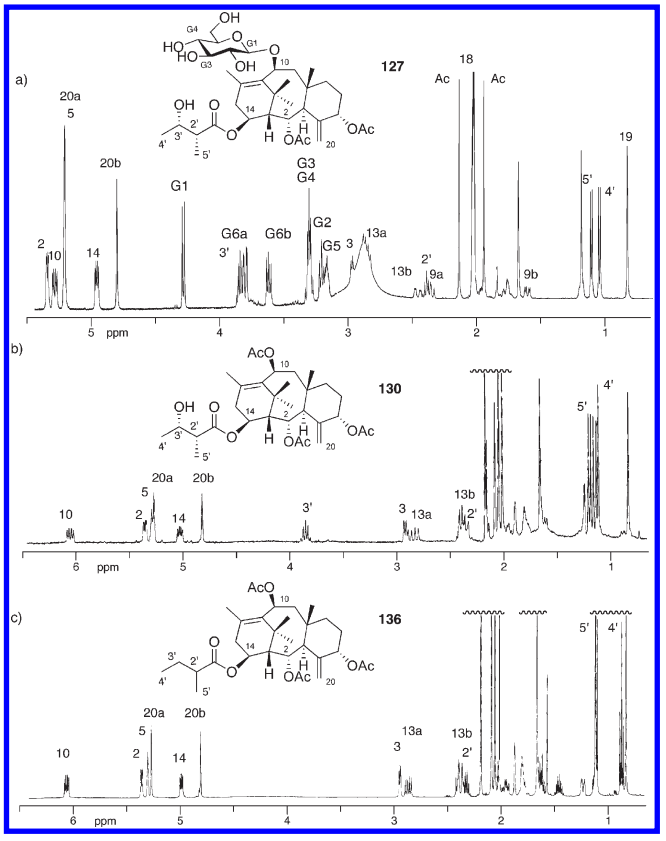


Figure 51. ^{1}H NMR spectra of (a) a taxane glycoside (**127**, acetone-d_6), (b) **130**, and (c) **136** (in $CDCl_3$).

4.28. Bicyclic Taxanes 4: 11,12-Secotaxane (Table 30 and Figure 42)

A novel 11,12-secotaxane was isolated from the needles of *T. cuspidata*, and it did not display in vitro cytotoxicity against human breast cancer MCF-7 cell line. As shown below

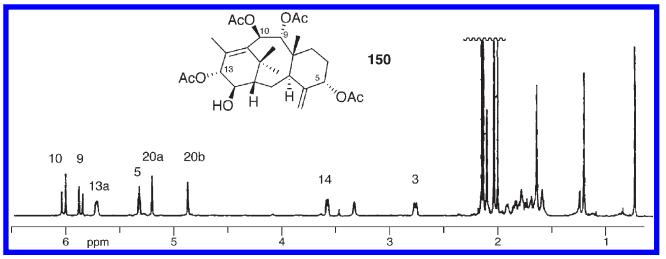


Figure 52. ^{1}H NMR spectrum of **150** with both C-13 and C-14 substitutions in $CDCl_3$.

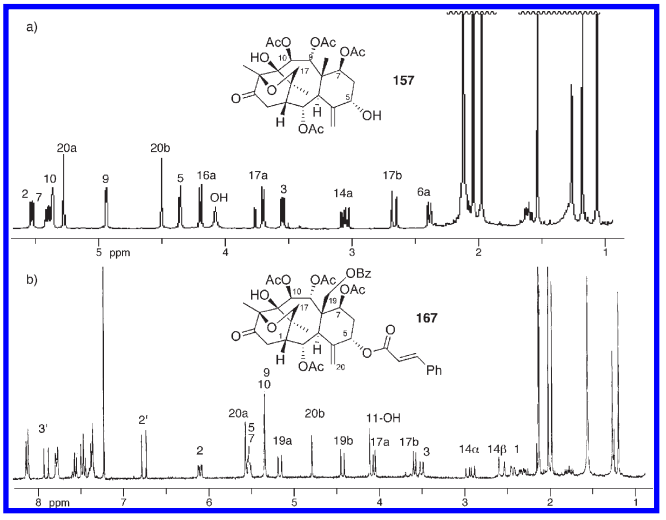


Figure 53. ^{1}H NMR spectrum of 5α-decinnamoyltaxagifine (**157**) (500 MHz) and taxacin M (**167**) (300 MHz) in $CDCl_3$.

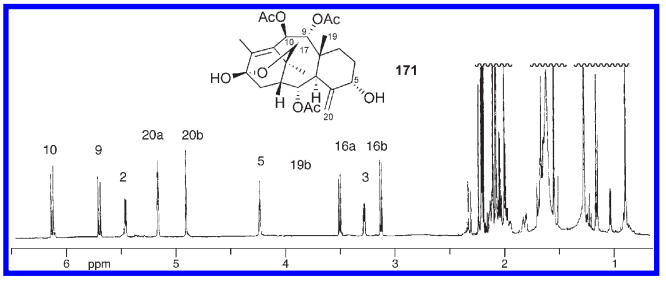


Figure 54. ^{1}H NMR spectrum of taxezopidine A (**171**) in $CDCl_3$ (300 MHz).

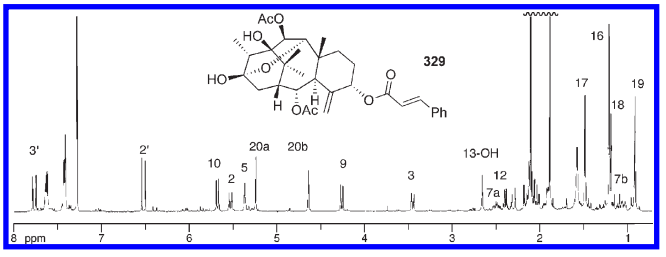


Figure 55. ^{1}H NMR spectrum of **329** in $CDCl_3$ (500 MHz).

(Scheme 11), this unique framework would be biosynthesized from decinnamoyltaxinine B 11,12-oxide (**186**).[127]

dx.doi.org/10.1021/cr100147u |*Chem. Rev.* 2011, 111, 7652–7709

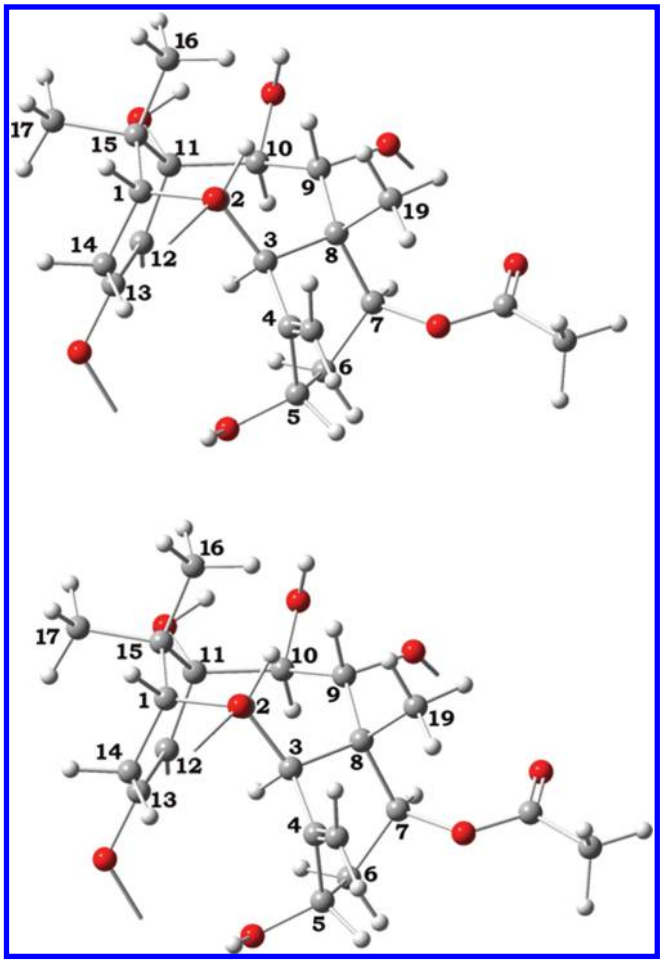


Figure 56. Optimized crown conformation (left) and boat−chair conformation (right) of taxane **175**, some nuclei of acetyl groups and Me-18 have omitted for better viewing.

5. TAXANE ANALOGS (VERTICILLENES) FROM OTHER SOURCES (FIGURE 43)

Until now, taxanes were mainly found in plants of the genera *Taxus* and *Austrotaxus*.[31] According to the view that similar chemical constituents exist in relative plant groups, much attention has been directed to several genera relative to *Taxus*. Paclitaxel was found in the stems and leaves of *Podocarpus gracilior Pilger* (Podocarpaceae) in a yield of 0.54 mg/kg,[128] but the claim was deficient as it was merely on the base of the similar retention time in HPLC and the same molecular ion peaks in MS. Luo et al.[129] found paclitaxel and its homologues from the stems and leaves of *Cephalotaxus manii, C. fortunei, C. hainannensis*, and *Podocarpus forrestii*. Chen[130] isolated 10-deacetylbaccatin III from the needles of *Pinus massoniana* and *Cephalotaxus sinensis*. Zhou et al.[131] detected paclitaxel and brevifoliol from *Pseudotaxus chienii* (Cheng) Cheng, distributed only in China, however, this result could not be repeated by other groups.[132,133]

Another source that could provide diverse taxanes is the endophytic fungus isolated from yews,[134−138] such as *Tubercularia* sp., *Pestalotiopsis* spp., *Taxomyces andreanae*, and *Pestalotiopsis microspora*. These organisms probably learned to biosynthesize paclitaxel from the tree by horizontal gene transfer.

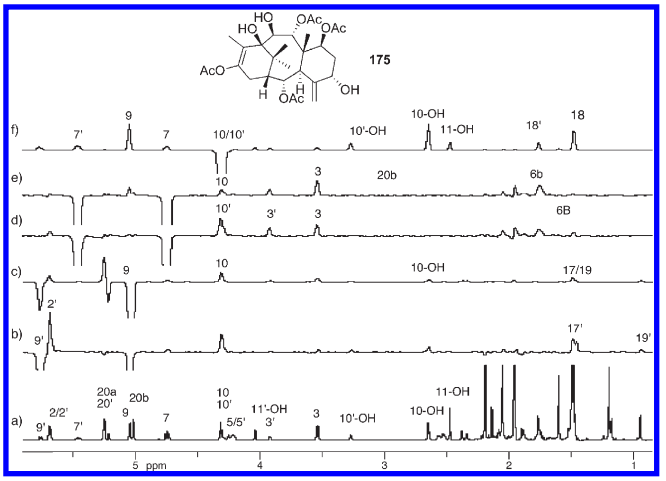


Figure 57. ^{1}H NMR spectrum of **175** in acetone-d_6 (500 MHz) and slices from the ROESY experiment with **175**: (a) normal ^{1}H NMR spectrum; (b) H-9′ slice at δ 5.76 ppm; (c) H-9 slice at δ 5.05 ppm; (d) H-7′ slice at δ 5.46 ppm; (e) H-7 slice at δ 4.74 ppm; (f) H-10/H-10′ slice at δ 4.31 ppm.

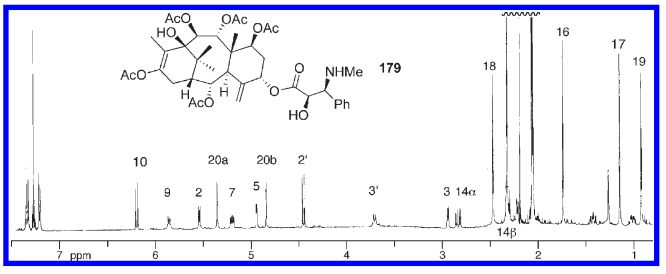


Figure 58. ^{1}H NMR spectrum of **179** with an alkaloid side chain at C-5 in $CDCl_3$ (600 MHz).

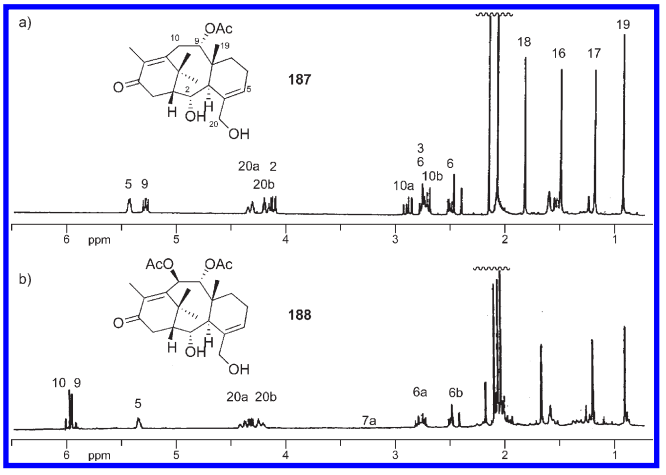


Figure 59. ^{1}H NMR spectrum of (a) **187** and (b) **188** in $CDCl_3$ (500 MHz).

Some bicyclic taxanes have been reported from other sources. Four analogs were isolated from wood of *Sciadopitys verticillata* Sieb. et Zucc.,[139] one bis-bicyclic taxane from *Hypoestes rosea*,[140] five bicyclic taxanes from Japanese liverwort *Jackiella javanica*[141] (**567**−**570**) (Figure 43), and more recently five verticillane diterpenoids from the stems of *Bursera suntui* and *Bursera*

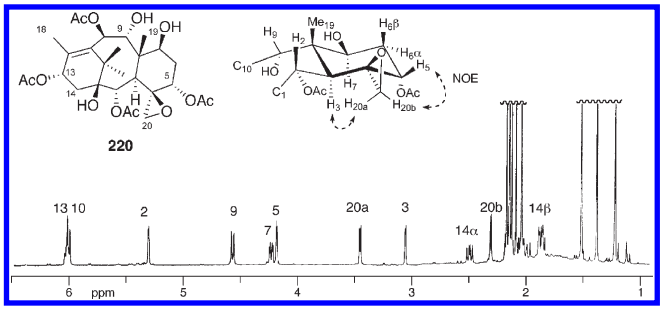


Figure 60. ^{1}H NMR spectrum of **220** with C-4,20-epoxy ring in $CDCl_3$.

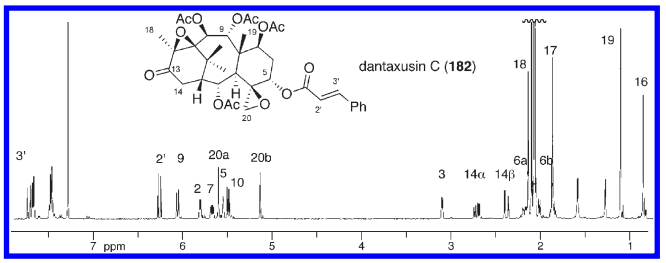


Figure 61. ^{1}H NMR spectrum of taxane with C-11,12-epoxy ring (**182**) in $CDCl_3$.

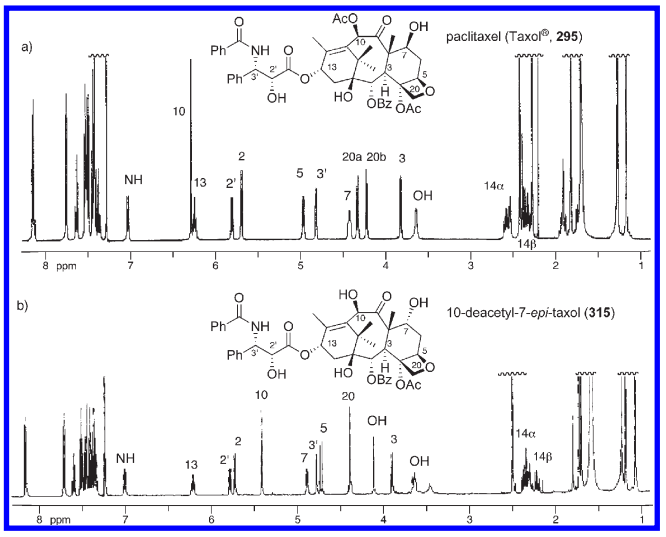


Figure 62. ^{1}H NMR spectrum of paclitaxel (**295**) (500 MHz) and 10-deaceyl-7-*epi*-taxol (**315**) in $CDCl_3$ (300 MHz).

kerberi.[142] Though bicyclic taxanes were thought to be the precursors in the biosynthesis of taxanes,[143,144] relationships between tricyclic taxanes and bicyclic taxanes were still not clear. Taxanes were also found in marine environment. Four cytotoxic diterpenes were isolated from the Formosan soft coral *Cespitularia hypotentaculata* (**571**−**574**)[145] and it is the first example of compounds with taxane skeleton found in marine origins. Recently, two more compounds were reported: a new verticillane diterpenes, cespitularins O (**575**,) and a new norditerpene, cespitularin Q (**576**), isolated from the methylene chloride solubles of the same species.[146] Shen et al. also isolated two nor-verticillane diterpenes, named cespihypotins C (**577**) and D (**578**) from soft coral *Cespitularia taeniata*.[147] In addition, three new

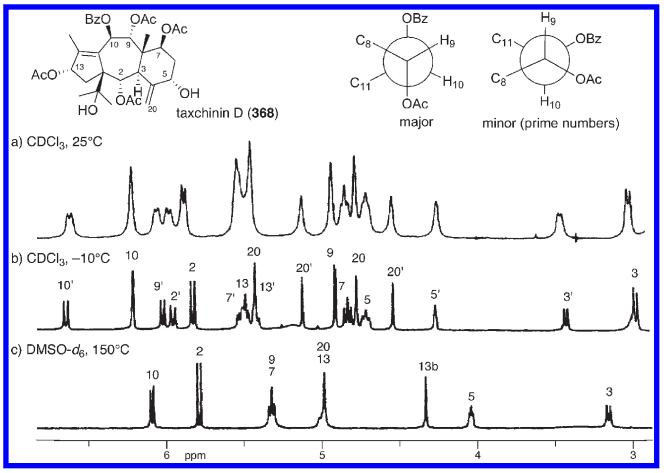


Figure 63. ^{1}H NMR spectra of taxchinin D (**368**) at different temperatures in $CDCl_3$ and DMSO-d_6 (400 MHz), and its newman projections along C-9 and C-10 in the two major conformers.

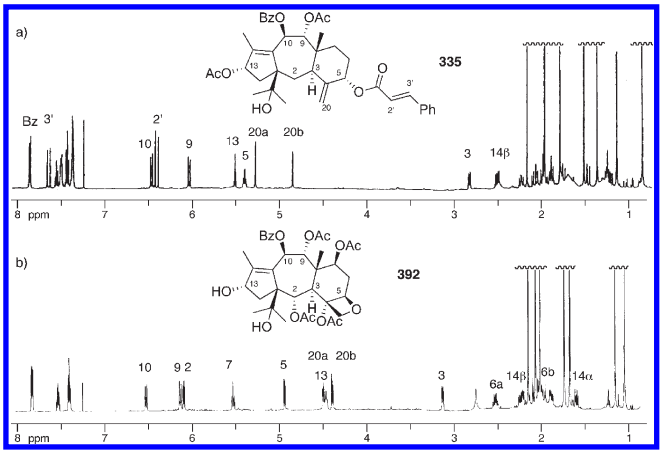


Figure 64. ^{1}H NMR spectrum of (a) **335** and (b) **392** in $CDCl_3$ (600 MHz).

nitrogen-containing verticillane diterpenoids, cepitulacames A, B and C (**579**−**581**), were isolated.[148]

6. ISOLATION AND PURIFICATION

6.1. Isolation and Purification

Taxanes have been extracted from the bark and needles of various yew species by ordinary solvent extraction. The majority of extraction processes reported in the literature have made use of MeOH as the common extraction solvent at room temperature.[149−152] However, there are also reports of extraction using other solvents, for example, MeOH−$CHCl_3$ (1:1),[153] MeOH−CH_2Cl_2 (1:1),[154,155] and 95% EtOH.[156] Supercritical fluid extraction methods exhibit high selectivity for taxanes, although organic solvents (e.g., EtOH, MeOH, and CH_2Cl_2) are required to obtain high taxane recovery.[157−160] Recently, microwave-assisted extraction has been reported as an extraction method for taxanes and found to reduce considerably both the extraction time and solvent consumption.[161]

Accelerated solvent extraction (ASE) is a new extraction method and enhances the traditional extraction process using solvent at elevated temperatures. Pressure is applied to the sample extraction cell to maintain the heated solvent in a liquid

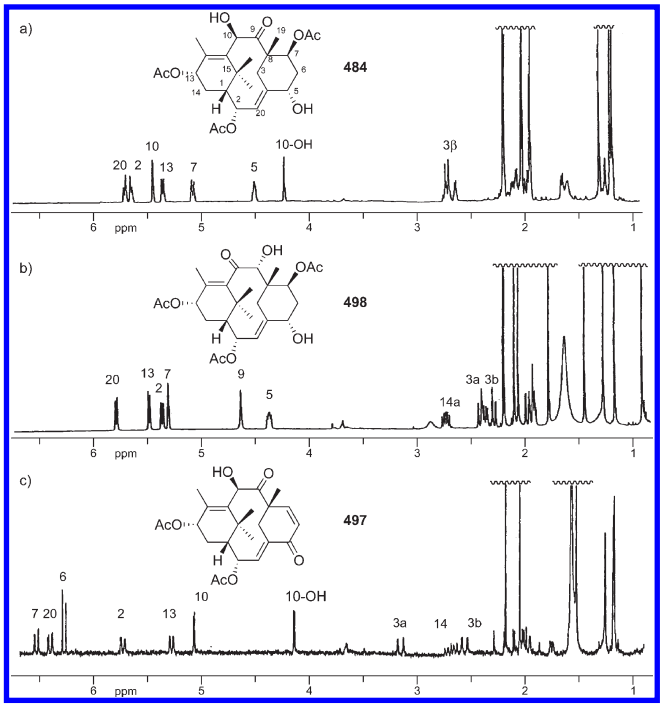


Figure 65. ^{1}H NMR spectra of 2(3→20)*abeo*taxanes: (a) **484** (300 MHz), (b) **498** (300 MHz), and (c) **497** (600 MHz) in $CDCl_3$.

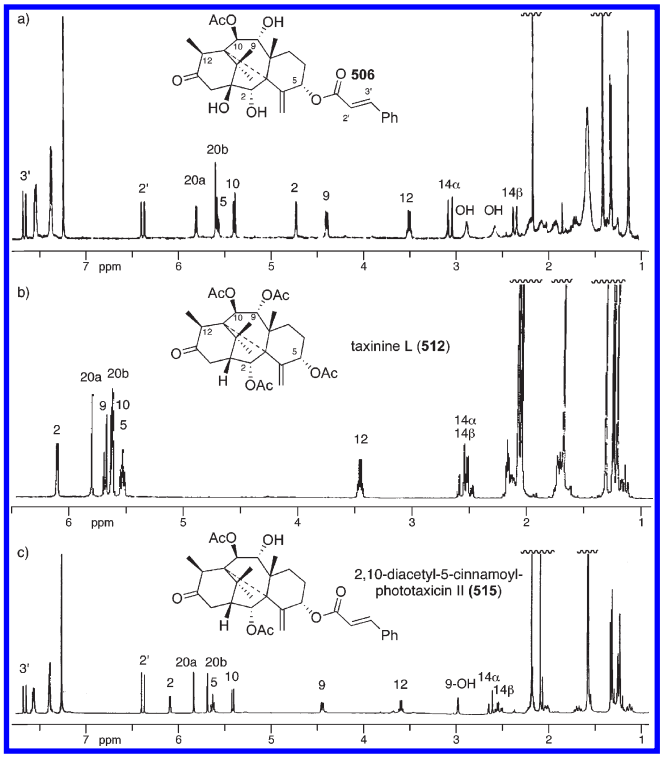


Figure 66. ^{1}H NMR spectra of (a) **506**, (b) taxinine L (**512**, 300 MHz) and (c) 2,10-diacetyl-5-cinnamoylphototaxicin II (**515**, 500 MHz) in $CDCl_3$.

state during the extraction procedure and hence augments its dissolving power.[162−164] Kawamura reported that ASE of paclitaxel, baccatin III, and 10-deacetylbaccatin III produced higher amounts of these compounds than ordinary solvent extraction at

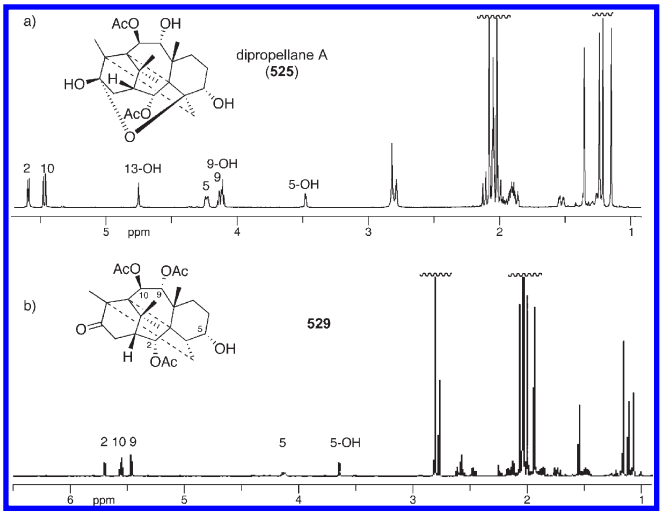


Figure 67. ^{1}H NMR spectra of (a) dipropellane A (**515**) and (b) **529** in acetone-d_6 (500 MHz).

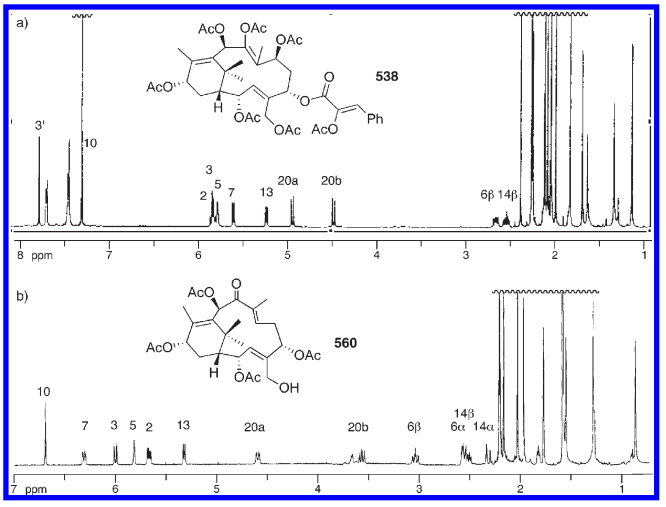


Figure 68. ^{1}H NMR spectrum of bicyclic taxanes (a) **538** (600 MHz) and (b) **560** (300 MHz) in $CDCl_3$.

room temperature. The conditions providing the highest recovery of paclitaxel were as follows: solvent, MeOH-H_2O (90:10); temperature, 150 °C; and pressure, 10.13 MPa (0.128% w/w recovery based on oven-dried sample powder). ASE does not require chlorinated solvents and can reduce solvent consumption because of its strong dissolving power. Moreover, with water alone, the recovery of paclitaxel and related compounds using ASE is much higher than with other extraction methods.[165]

Relatively crude plant extracts, generally after simple washing/extraction with hexane to remove most lipids, was subjected to partition between dichloromethane and water. Most taxanes dissolved in dichloromethane, and aqueous phase contains polar/water-soluble constituents.

The separation of taxanes is usually conducted by repeated silica gel column chromatography (sometimes using Sephadex LH-20 with CH_2Cl_2-MeCN/MeOH as eluting solvent), preparative TLC, and reversed-phase (RP) preparative HPLC.

Octadecyl, phenyl, cyano, and fluorinated phases, such as perfluorophenyl (PFP), have been used as RP-HPLC stationary

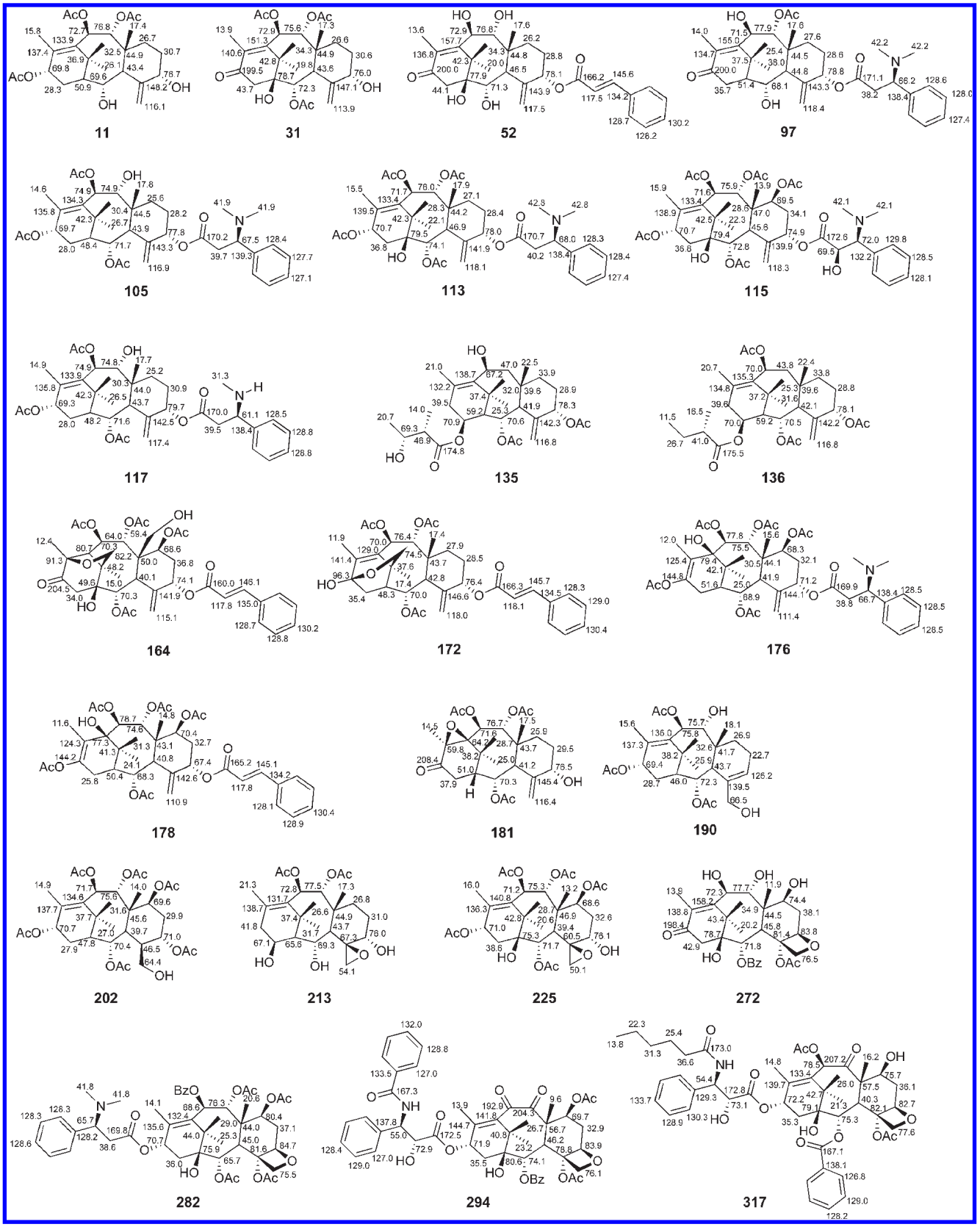


Figure 69. ^{13}C NMR chemical shift data of 6/8/6-taxanes.

phases. Octadecyl is the most used stationary phase.[150,156,166−172] Dolfinger et al. used fluorinated phases and hydrocarbonaceous phase through optimizing conditions of aqueous acetonitrile (ACN) eluent composition and temperature to separate a

dx.doi.org/10.1021/cr100147u |*Chem. Rev.* 2011, 111, 7652–7709

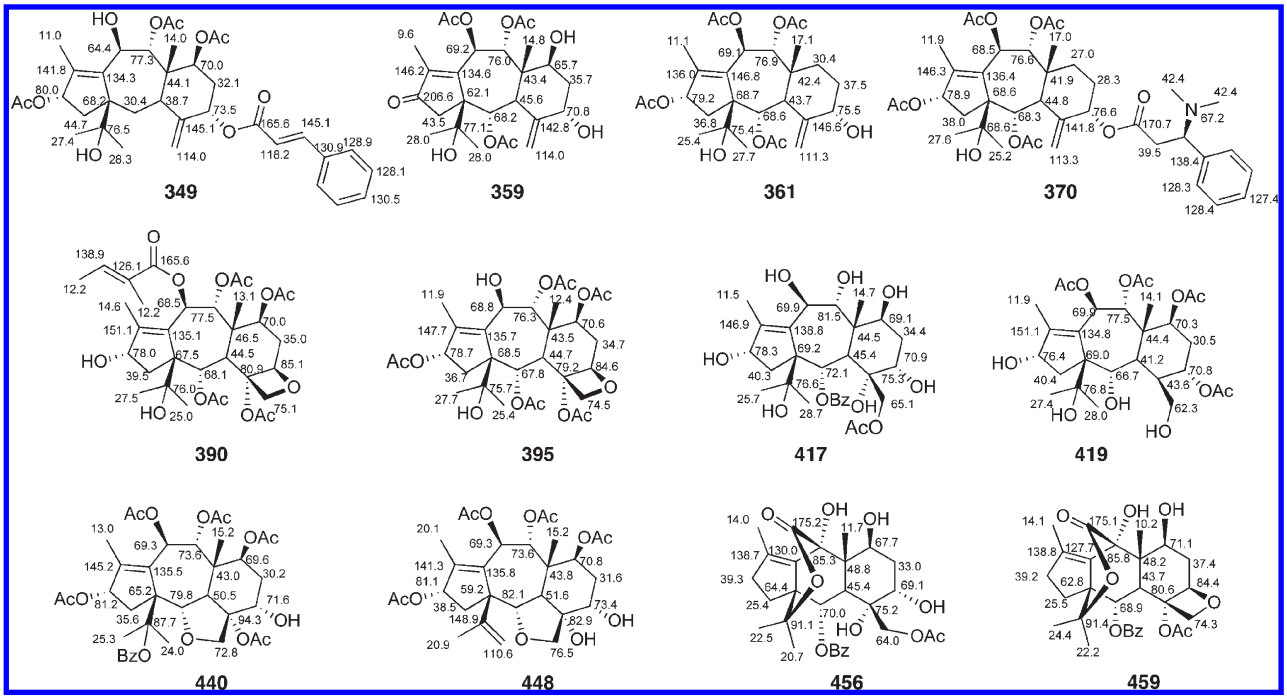


Figure 70. ^{13}C NMR chemical shift data of 11(15→1)*abeo*taxanes and 11(15→1),11(10→9)di*abeo*taxanes.

standard mixture of 15 taxanes.[173] HPLC analysis of taxanes was reviewed by Theodoridis.[174] In June 1966, separation of paclitaxel involved standard ethanol extraction, partition of the ethanolic residue between water and chloroform, followed by a large number of Craig countercurrent distribution treatments, the last of which involved a 400-tube Craig countercurrent distribution and finally approximately 0.5 g (yield 0.004%) of paclitaxel was isolated from 12 kg of air-dried stem and bark.[175]

Hexane−acetone, CH_2Cl_2−MeCN/MeOH, $CHCl_3$−MeOH, and hexane−EtOAc in different ratio are suitable solvents for developing TLC and eluting CC. Taxanes were visualized on TLC plates with 10% sulfuric acid in ethanol and heating on a hot plate, most taxanes exhibited a blue or dark blue pot, while some bicyclic taxanes showed dark green color. As for RP-HPLC, an ODS (octadecylsilyl) column is usually used and MeCN−H_2O is a good mobile phase. The retention time of taxanes usually between 18 and 70 min eluted with a 100 min linear gradient of acetonitrile (25−100%) in water at a flow rate of 3−18 mL/min (Figure 44). If it was eluted with a 50 min linear gradient of acetonitrile (25−100%) in water, the retention times of taxanes were usually between 18 (taxane glucosides) and 55 min (taxinine analogy). Although there are hundreds of taxanes in the yew trees, normal phase column chromatography and preparative TLC plus reversed-phase preparative HPLC can make all the taxanes be separated and purified. For example, the structures of paclitaxel (**295**) and 7-*epi*-taxol (**318**) were very similar, but the retention time of them were R_t = 36.0 min and R_t = 39.5 min, respectively, when they were eluted with a 50 min linear gradient of acetonitrile (25 to 100%) in water. While the retention time of taxinine (**70**), 2-deacetyltaxinine (**61**) and 9, 10-dideacetyltaxinine (**62**) were R_t = 53.2 min, 46.5 and 41.1 min, respectively, when they were eluted with a 50 min linear gradient of acetonitrile (25 to 100%) in water. The dual λ absorbance detector was set at 227 and 210 nm, and strong absorption at 278 nm would suggest the presence of a cinnamoyl substitution.

6.2. Dereplication of Taxanes

High-throughput analytical method using liquid chromatography-evaporative light scattering detection-mass spectrometry (LC-ELSD-MS) was demonstrated using fractions from the organic extract from *T. brevifolia*.[176] A *Taxus* library was produced by using a parallel four channel preparative HPLC. A total of 147 compounds were detected in the library by positive ion ESI-MS. The identification of the known taxanes was performed by ^{1}H and COSY NMR using a microcoil flow probe (5−50 μg samples in 3 μL CD_3OD) and MS. Schneider et al. reported HPLC-NMR analyses of taxanes from 500 mg of leaf samples without prior isolation.[177] They used a stopped-flow technique and acetonitrile-D_2O solvent system, and identified several known taxanes. Konishi et al. reported dereplication method of taxanes from *T. wallichiana* by using ESI-MS/MS or MS/MS/MS.[178] From EtOAc extract 57 basic taxanes including 45 new compounds were detected.

7. NMR FEATURES OF TAXANES

NMR spectra play an important role in structure elucidation of taxanes. Different backbones and substitution patterns of taxanes showed characteristic NMR features (chemical shift and splitting pattern) and provide useful information for the structure identification. Full assignment of ^{1}H and ^{13}C NMR signals can be achieved with the support of ^{1}H−^{1}H COSY, HMQC, DEPT, and HMBC spectral data.

7.1. ^{1}H NMR Features of Taxanes

Generally, proton NMR spectra of taxane diterpenoids showed much dispersed signals between 1 to 9 ppm, but different class of taxanes exhibited their own features. In 1966, Nakanishi summarized the NMR features of taxanes,[179] and this work was updated later by Miller,[20] Kingston,[22] and Appendino.[180] The proton NMR of most taxanes include four tertiary methyl signals. An angular methyl of Me-19 appeared in an upfield and a vinyl

dx.doi.org/10.1021/cr100147u |*Chem. Rev.* 2011, 111, 7652–7709

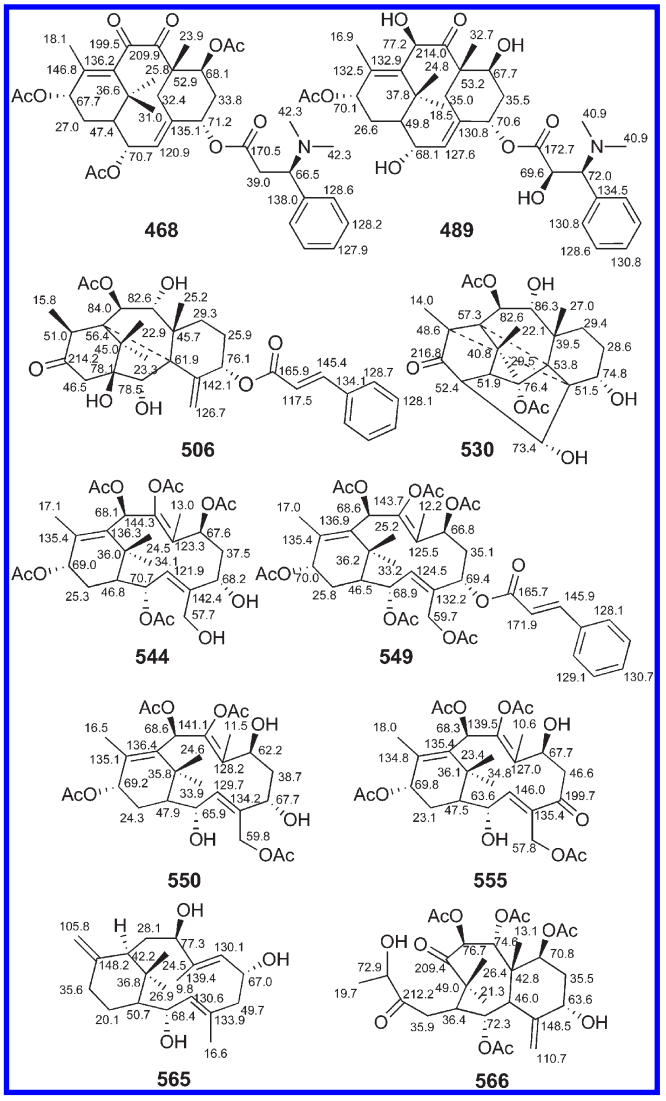


Figure 71. ^{13}C NMR chemical shift data of other taxanes.

Figure 72. Crystal structure of the β-tubulin/paclitaxel: β-tubulin (in solid ribbon), paclitaxel (in stick ball).

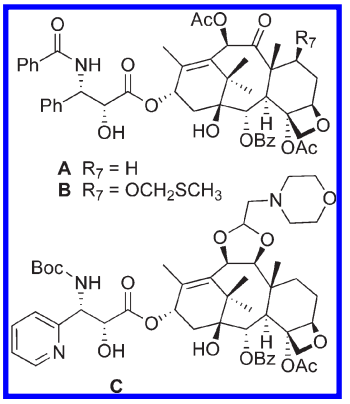


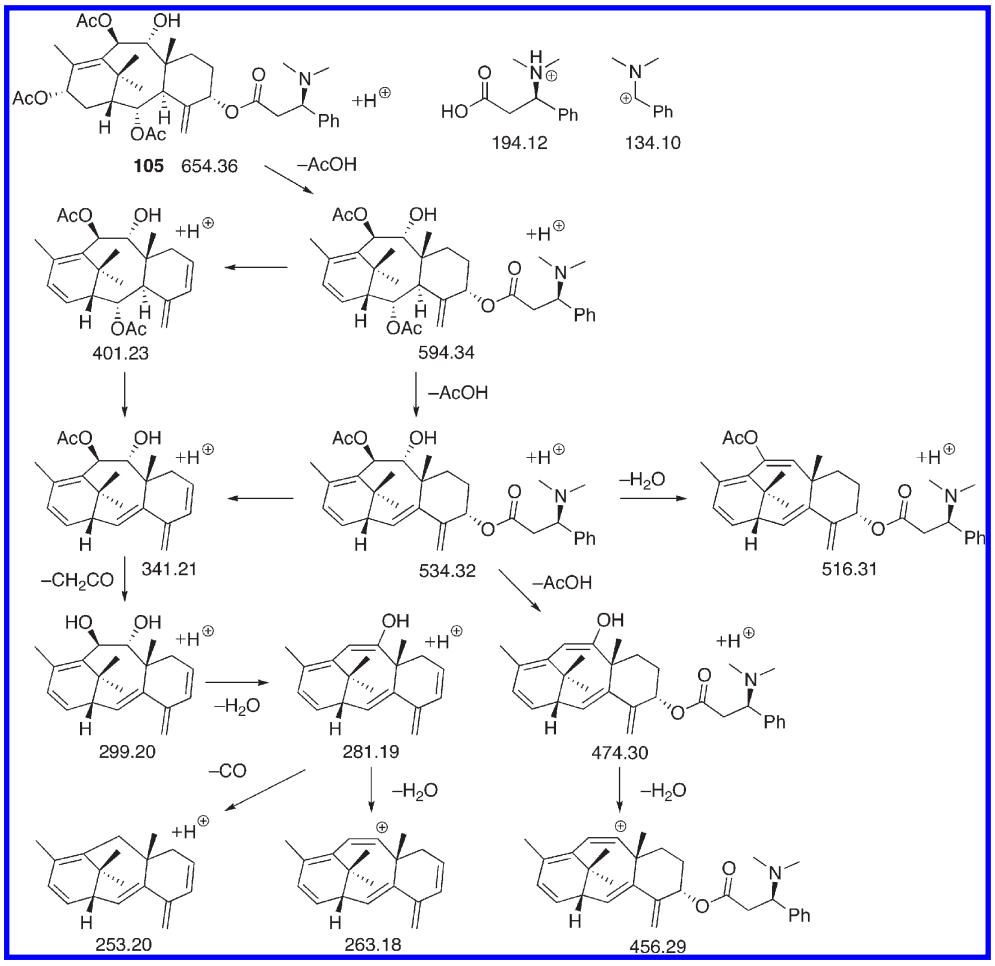
Figure 73. Modified paclitaxel.

methyl of Me-18 showed long-range coupling with H-13β generally resonating at the lowest field (usually in the range of methyl of acetyl group, but H-18 is broader and shorter than that of the acetyl methyl group). In addition, other two COSY-related geminal methyl groups on C-15 (Me-16 and Me-17) have broader peaks than the H-19 singlet signal. The methyl groups of acetyl moieties, geminal protons attached to oxygenated carbon (hydroxy or acetoxy), ring junction proton H-3, sp^2-hybrid protons of benzene ring and protons located at C-9 and C-10, which usually composed an isolated AB system, are all characteristic signals of taxanes. H-20a and H-20b are also the characteristic signals in different kind of taxanes. Protons adjacent to an acetate group are usually 1 ppm downfield than the corresponding protons adjacent to a hydroxy group. This dramatic chemical shift allows a straightforward distinction of the positions of hydroxy and acetoxy groups. Proton of hydroxy group is usually not observed in $CDCl_3$ unless forming a hydrogen bond with an adjacent keto carbonyl group, but which can be observed in acetone-d_6 or DMSO. The connectivity of the protons on the taxane skeleton can be determined by analysis of the $^1H-^1H$ COSY spectrum. The relative stereochemistry of taxanes can be defined on the basis of the NOESY/ROESY data, chemical shifts, and their coupling constants. Herein are listed some NMR spectra of different type taxanes for reference.

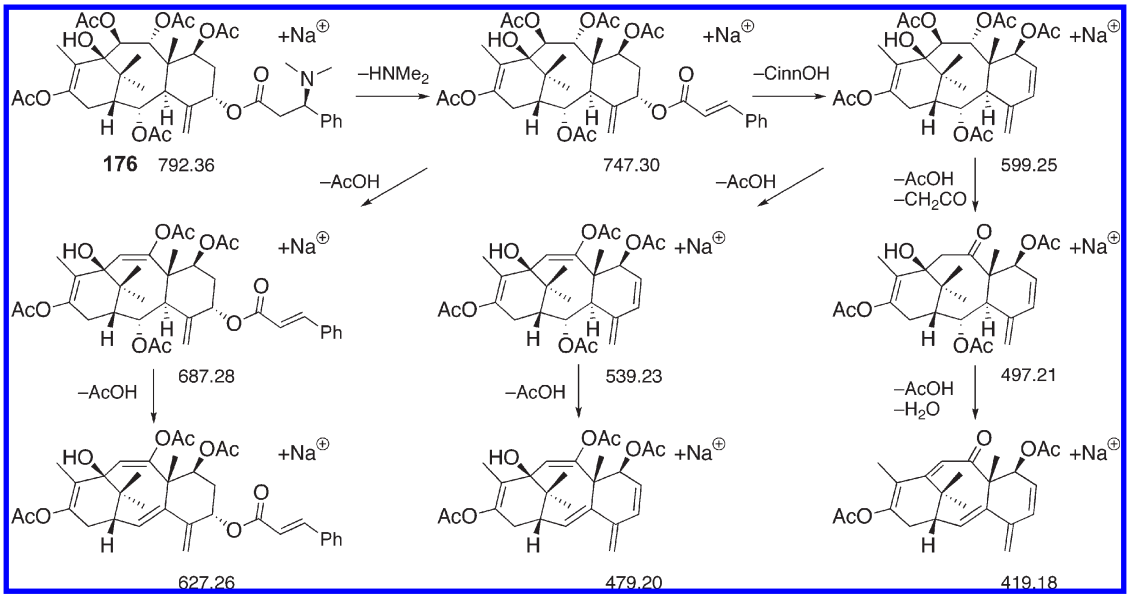
7.1.1. 6/8/6 Taxanes. *7.1.1.1. Neutral 6/8/6-Taxanes with a C-5-Cinnamoyl Group.* In stereochemistry of above two 6/8/6-membered taxanes, taxinine (**70**) and 13-deacetyltaxinine E (**88**, Figure 45),[181] oxygenic group on C-13 has a heavy influence not only on the protons of H-14α and H-14β including chemical shift and split pattern, but also the protons on the benzene ring. Because of trans-oriented configuration of H-9 and H-10 (vicinal dihedral angle ~180°, Figure 46), the vicinal coupling constant between H-9 and H-10 is large (J = ~ 10 Hz). Comparing the above two and following one spectra (Figure 44 and Figure 46), H-2′ and H-3′ of the cinnamoyl group showed different resonance. H-3′ of the cinnamoyl in taxinine (**70**) resonated between two *ortho*-phenyl hydrogen protons and H-2′ resonated at relative highfield. As for 13-deacetyltaxinine E (**88**), H-3′ of the cinnamoyl resonated beyond two *ortho*-hydrogen protons of benzene protons while the H-2′ at relative lowfield. This is presumably because the cinnamoyl residue is in the concave face of the molecule and is subjected to the anisotropic effect of C-13 carbonyl in taxinine type taxanes. However, the coupling constants of H-2′ and H-3′ were same in the two type of taxanes (J = ~ 16 Hz). If the cinnamoyl group adopts a *cis*-configuration,

dx.doi.org/10.1021/cr100147u |*Chem. Rev.* 2011, 111, 7652–7709

Scheme 12. Fragmentation Pattern of Protonated Taxane Determined by FAB-MS of Taxane 105



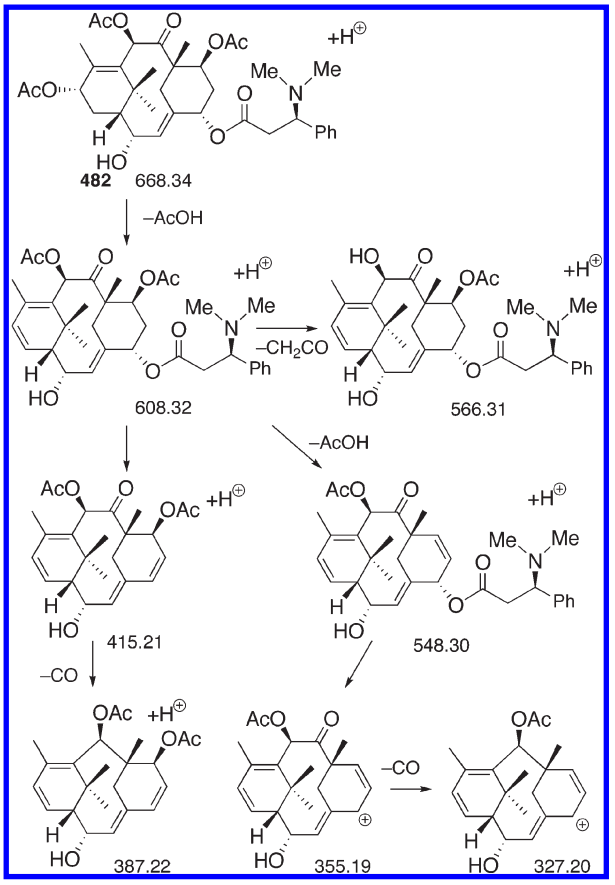
Scheme 13. Fragmentation Pattern of Sodio Taxane Determined by FAB-MS of Taxane 176



H-3′ would resonate at relatively upfield, and the coupling constant of H-2′ and H-3′ will become smaller than J = 10 Hz (as in compound **49** and **50**).[182] When a hydroxy group was located at C-1, H-14α and H-14β become a pair of doublets with

dx.doi.org/10.1021/cr100147u |*Chem. Rev.* 2011, 111, 7652–7709

Scheme 14. Fragmentation Pattern of Protonated Taxane Determined by FAB-MS of an 2(3→20)*Abeo*taxane 482



a large coupling constant J = 18 Hz. [1-hydroxytaxinine (**71**),[183] Figure 47].

7.1.1.2. 6/8/6-Taxanes with an Alkaloidal Side Chain. A methyl group attached to nitrogen resonates at downfield comparing with other methyl groups such as acetyl and methyls on the taxane skeleton (**111**,[184] Figure 48). On the other hand, the aromatic protons move to an upfield as broad singlet because the influence of a C-1′ carbonyl group on them are limited comparing with that caused by a cinnamoyl moiety (C-2′ and C-3′ are unsaturated). The proton on the nitrogen in **119**[185] cannot be observed which is different from those in a paclitaxel side chain, but the information could be obtained from the corresponding ^{13}C NMR and MS spectra (Scheme 15). In the ^{13}C NMR data, removal of one methyl from the dimethylamino group of the Winterstein's acyl moiety could result in a dramatic upfield shift (~8 ppm) of the remaining methyl group. When a hydroxy group substituted at C-2′, the chemical shifts and coupling patterns of H-2′ and H-3′ (**107**)[186] were varied dramatically as shown in Figure 49.

Of interest were **124** adopted two conformations as seen in ^{1}H NMR spectra especially for the side chain. The spectrum revealed two rotameric isomers in a ratio of approximately 2:1 (Figure 50).[52]

7.1.1.3. 6/8/6-Taxanes with a C-14-Oxygen Functional Group. There is no substitution at C-9 and C-13 in this group of taxanes (**127**,[53] **130**,[106] and **136**,[187−189] Figure 51), so both H-9 and H-13 resonated with very different resonation pattern as

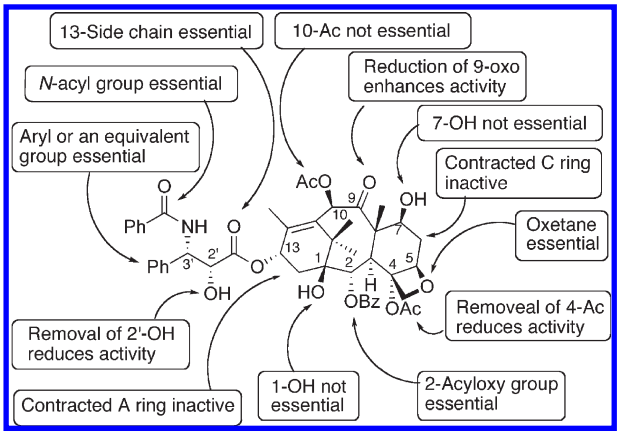


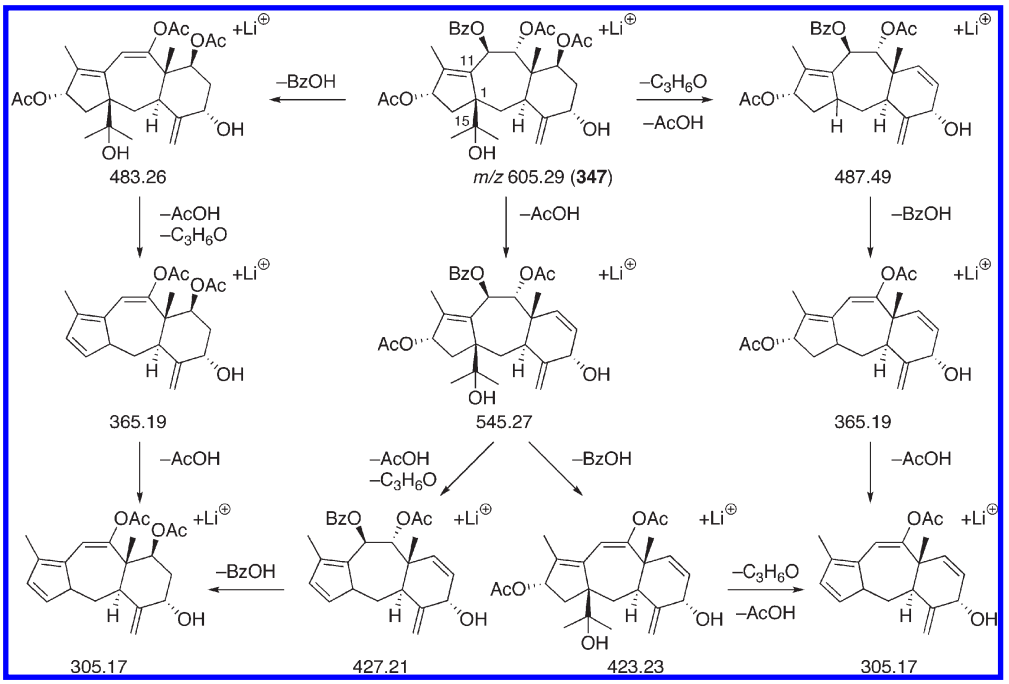
Figure 74. Brief description of structure−activity relationships of paclitaxel.

doublet of doublets. Both H-10 and H-14 resonated at downfield as doublet of doublets with coupling constants of J = 12.2, 5.6 Hz and J = 9.2, 4.8 Hz, respectively. The side chain at C-14 also showed some characters depending on whether position 3′ was substituted by a hydroxy group. Comparison of the spectroscopic data of C-13 and C-14 oxygenated taxanes revealed obvious changes of splitting patterns and coupling constants for H-13 and H-14. On the other hand, the C-1 methine carbon resonated at downfield (δ 59−65 ppm) in the C-14 oxygenated taxanes, while in the C-13 oxygenated taxane corresponding carbon resonated at δ <50 ppm. The strong NOE correlation of H-14 and H-1 and the small coupling constant between H-1 and H-14 in this class of taxanes suggested that their dihedral angle was about 90°: the C-14 side chain was β-oriented with H-14 was α-oriented. When having a hydroxy group at C-3′ (**130**), a characterized proton signal resonated at approximately δ 3.83 ppm as a multiplet. When having substitution groups at both C-13 and C-14 (**150**,[190] Figure 52), H-13 become a broad singlet and H-14 changed to a doublet with a smaller coupling constant at a relatively upfield (comparing with other protons on oxygenated carbons such as H-5, H-7 and H-9, **152**[191]).

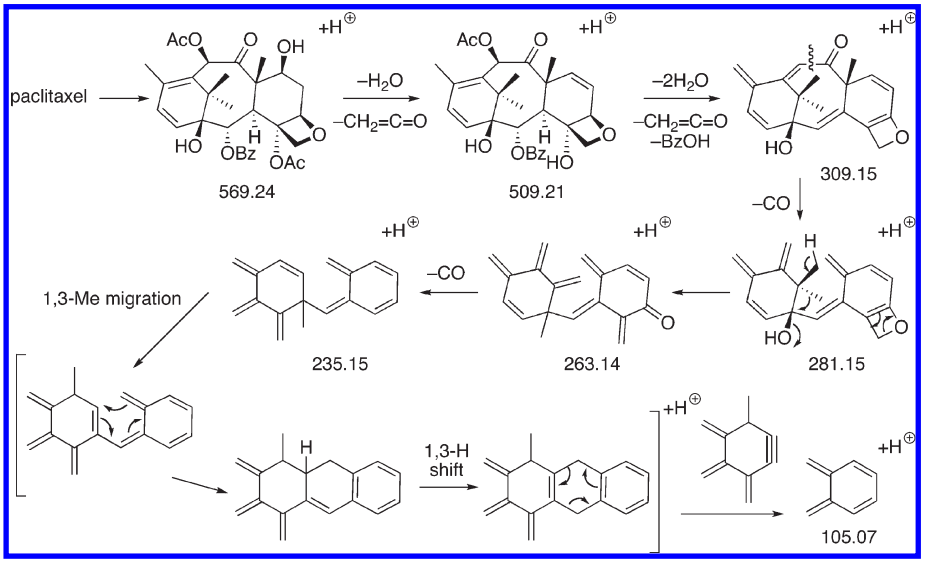
It should be noticed that when a sample of taxane glucoside was solubilized in $CDCl_3$ (2−3 mg in 0.3 mL), it solidified as a gel giving broad signals in the NMR spectrum and provided two doublets at δ 4.35 ppm (major peaks) and δ 4.42 ppm (minor peak) for the anomeric proton of the sugar. However, when the sample was dissolved in acetone, it gave sharp signals and only one peak for H-1″, which confirmed its purity.

7.1.1.4. 6/8/6-Taxanes with a C-12,17-Ether Ring. The features of taxinine M class of taxanes (**157**[192] and **167**,[193] Figure 53) are the signals of H-17 and H-19. Both of them resonate as a pair of doublets with relatively large coupling constants. C-19 oxygenated methylene has a larger coupling constant (J = 12.4 Hz) than that of C-17 oxygenated methylene (J = 8.0 Hz) because the latter accommodates in a ring. Beside protons on the benzoyl group, H-2 resonates at downfield (generally the most deshielded acyloxymethine of ring B, δ 6.18 ppm) as a doublet of doublets with a large coupling constant between H-3 and H-2 (dd, J = 10.0, 2.4 Hz, in the corresponding taxinines with C-11,12 double bond $J_{2,3}$ = ~7 Hz). As there is no double bond at position C-11,12 and a new ring formed between C-12 and C-17, the chemical shift of H-9 (δ 5.48 ppm) and H-10

Scheme 15. Fragmentation Pattern of Lithio Taxane Determined by ESI-MS/MS of Taxane 347



Scheme 16. Fragmentation Pattern of Protonated Taxanes Determined by MS/MS/MS of Paclitaxel



(δ 5.36 ppm) are very close with a small coupling constant (J = 3.2 Hz). The small value of $J_{9,10}$ = 3.2 Hz is due to an eclipsed conformation around the C-9 and C-10 bond (ϕ = 120°), that place H-9 and H-10 in an anticlinal fashion. The speculative conformation of ring B in this type of taxanes is required by the presence of the C-12, C-17 oxygen bridge. The peculiar conformation of ring B in this class of taxanes reduces the severe nonbonded interaction between H-3 and 18-methyl group. Because of an oxo group at C-13, H-14α, and H-14β also consist a pair of characteristic signals at relatively downfield as doublet (J = 18−19 Hz) and doublet of doublets (J = 18−19, 11−12 Hz).

7.1.1.5. 6/8/6-Taxanes with a C-13,17-Ether Ring. The signals of H-17 protons in this group of 6/8/6-taxanes having a C-13,17-ether ring [taxezopidine A (**171**),[194] Figure 54) resonated at δ 3.08 and 3.50 with a relatively smaller coupling constant of J = 8.1 Hz as geminal protons. Other protons on the skeleton such as H-2, H-5, H-9, and H-10 observed in the regular region with standard coupling constants as those of normal 6/8/6-taxanes. Another diagnostic signal is the hemiacetal carbon in the ^{13}C NMR data owing to the presence of a hydroxy group at C-13.

7.1.1.6. 6/8/6-Taxanes with a C-9,13-Ether Ring. The signals of H-2 and H-3 protons in these 6/8/6-taxanes with a C-9, 13-ether ring appeared in the normal region with a relatively large coupling constant of J = 11.8 Hz (**329**,[96] Figure 55). Because of the presence of the C-11 hydroxy group, H-12 resonated as a

dx.doi.org/10.1021/cr100147u |*Chem. Rev.* 2011, 111, 7652–7709

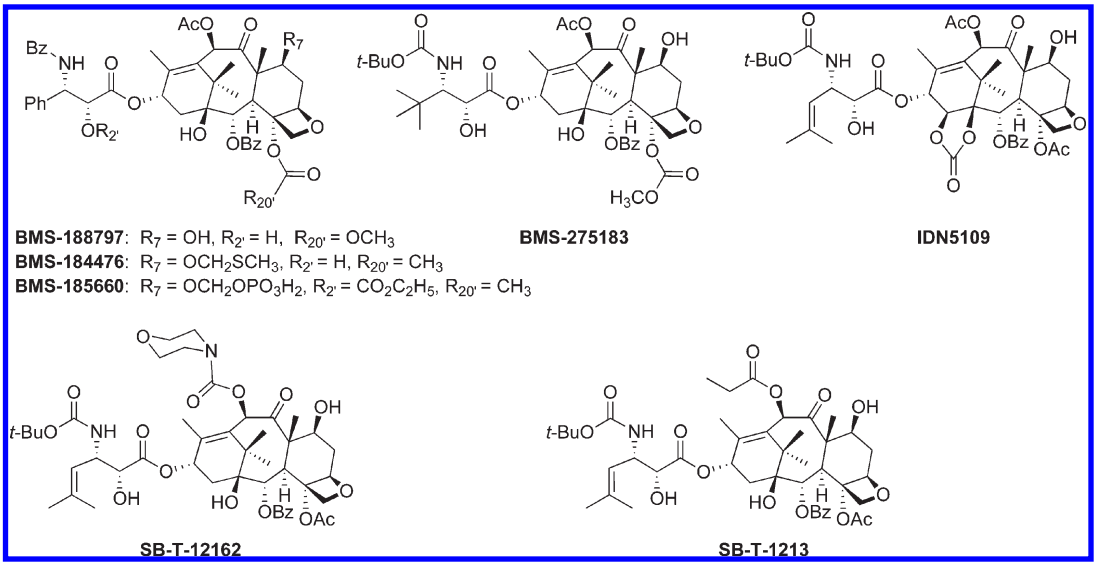
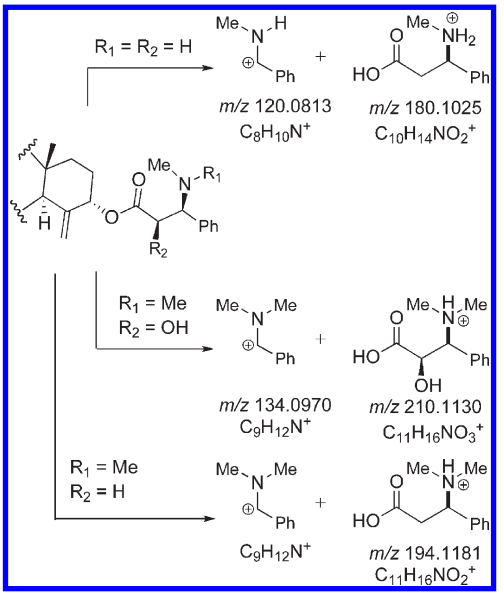


Figure 75. Second-generation derivatives of paclitaxel.

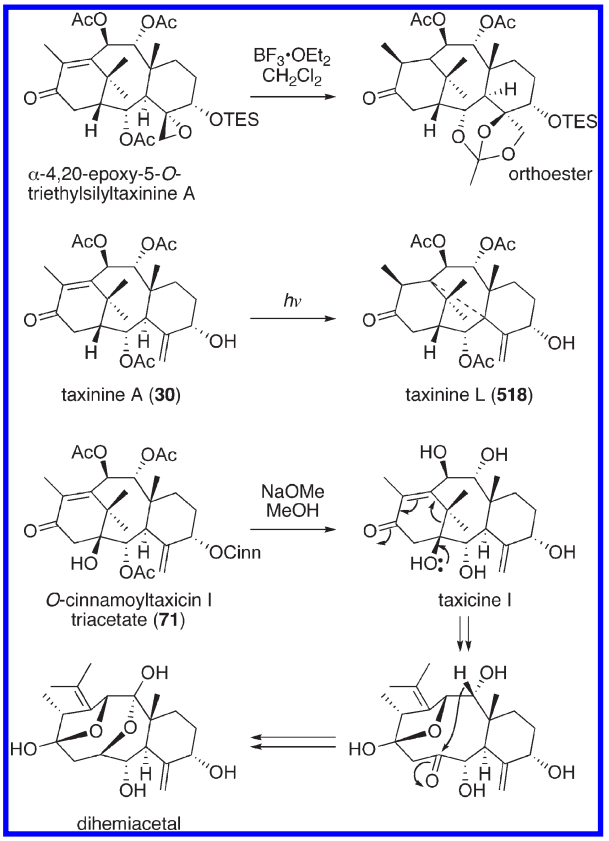
Scheme 17. Fragmentation Pattern Observed in Positive Ion FAB-MS/MS Spectra of Taxanes with Different C-5-Amino-Side Chains



quartet and H-18 as a doublet. Other protons on the skeleton including H-5, H-9, and H-10 were observed in the regular region with typical coupling constants as in common 6/8/6-membered taxanes.

7.1.1.7. 6/8/6-Taxanes with a C-12(13)-Double Bond. This class of taxanes has an unusual small coupling constant between H-9 and H-10 (J = 4.4−5.0 Hz), but H-14α and H-14β resonated at downfield (δ 2.3−2.6 ppm) as a set of doublet (J = 18.6 Hz) and doublet of doublets (J = 18.6, 8.0 Hz), respectively. The plausible two conformations of **175**[53] elucidated from ROESY experiment (Figures 56 and 57). The presence of an enol acetate moiety in ring A can be implied by the chemical shifts of the olefin carbons of C-12 and C-13, although no unambiguous HMBC correlation can be observed (**179**,[66] Figure 58).

Scheme 18. Preparation of Taxinine L (518) from Taxinine A (30)



7.1.1.8. 6/8/6-Taxanes with a C-4(5)-Double Bond. In the NMR of taxanes with C-4(5)-double bond (**187**[195] and **188**,[196] Figure 59), H-5 resonates as a broad singlet and the correlation between H-5 and C-5 in the HMQC spectrum is apparent, which suggest an endocyclic location. As shown above, both of the signal H-10a and H-10b displayed as doublet of doublet with a large coupling constant (about J = 14.3 Hz).

dx.doi.org/10.1021/cr100147u |*Chem. Rev.* 2011, 111, 7652–7709

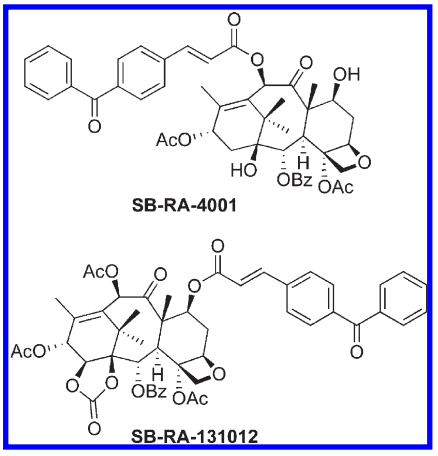


Figure 76. Taxane-based multidrug resistant (MDR) reversal agents.

7.1.1.9. 6/8/6-Taxanes with a C-4,20-Epoxy Ring. The two H-20 protons on C-4,20-epoxide ring and the H-5 in this group of taxanes are the most diagnostic features (**220**,[197] Figure 60). Although H-20a and H-20b attached to the same carbon C-20, their chemical shifts are very different (>1 ppm) as H-20a is closer to the C-2 ester carbonyl carbon than H-20b. Large separation (more than 1 ppm) of the geminal oxirane protons of H-20a and H-20b at δ 2.3 ppm and 3.6 ppm in an AX system with a coupling constant of ~5.2 Hz is a unique feature of the geminal oxirane protons with a β-oriented epoxy ring. So far, all the natural taxanes of this type bear a β-orientated oxirane ring. H-2 and H-3 resonate as a couple of doublets with relatively smaller coupling constant (J = ~3.0−4.5 Hz) comparing to the corresponding taxanes with a C-4(20)-*exo*-double bond.[68,198,199] Because of the magnetic anisotropy of the C-4,20-epoxy ring, H-5 resonated with an unusual upfield chemical shift than corresponding taxanes with a C-4(20) double bond. This peculiar feature sometimes led to incorrect assignments of H-5 by a simple inspection of the chemical shift values, whose chemical shift (4.2 ppm) was not the expected for an α-acetylated proton.[70,200,201] For example, Zamir located an acetoxy group at C-1 and a free hydroxy group at C-5.[70] Three years later, her group revised this structure as a free hydroxy group at C-1 and acetoxy group at C-15.[202] Same erroneous assignment also occurred in Liang's paper,[203] which assigned the signals according to literature report: Della Casa de Marcano and co-workers reported[204] if the C-5α-position was substituted with an acetyoxy group, the signal of H-5β appeared at 5.62 ppm. While the same position was substituted by a hydroxy group, the signal of H-5β appeared at 4.16 ppm.

7.1.1.10. 6/8/6-Taxanes with a C-11,12-Epoxy Ring. This group of taxane was characterized by the presence of a C-11,12-epoxy ring and an oxo group at C-13 (dantaxusin C (**182**),[205] Figure 61). Because of the magnetic anisotropy of the C-11,12 epoxy ring, H-9 resonated in downfield than that of H-10 when they have the same substituents, which is contrary to C-11,12 double bond taxane. Another feature is that the two ortho-protons of benzene ring shifted to upfield comparing to taxinine analogs. H-2 and H-3 also resonate as a couple of doublets with relatively smaller coupling constant (~3.0−5.1 Hz) comparing to the corresponding taxanes with an C-4(20)-*exo*-double bond, but the coupling constant of H-14α and H-14β are large as a pair of doublet (J = 20.1 Hz) and doublet of doublets (J = 20.1, 8.8 Hz).

7.1.1.11. 6/8/6-Taxanes with an Oxetane Ring. The feature of paclitaxel (**295**, Figure 62) is N−H signal at extra downfield (~7.0 ppm) as a doublet. H-20 signals of oxetane ring appeared as a couple of doublets with coupling constant about 8 Hz (the coupling constant between H-20a and H-20b would be large for the oxetane ring-open taxanes, and chemical shifts are fairly different). H-10 resonates as a singlet and H-13 as a triplet. If H-7 is epimerized [10-deacetyl-7-*epi*-taxol (**315**, Figure 62)[206]], H-20 would be a two-proton singlet. As seen from above spectra, the chemical shift and splitting pattern of H-14 depend on the functionalization of C-13. In oxetane type taxanes, the presence of the amino acid side chain at C-13 causes a marked upfield shift on H-18 (δ 2.00 ppm in baccatin III (**237**)[83] and 1.80 ppm in paclitaxel).

7.1.2. 11(15→1)*Abeo*taxanes. The NMR spectra of compounds, such as taxchinin D (**368**,[207] Figure 63), often showed broad lines or humps at ambient temperature due to fluxional behavior of the B and C ring systems, which can adopt either B-twist-boat/C-chair or B-twist-chair/C-boat conformations (the coupling constants between H-9 and H-10 mark the difference in these two conformations). If the temperature was set at below zero, this kind of taxanes usually adopts one major conformation with sharp signals in their NMR spectra.[207−209]

In fact a clear-cut distinction between C-1 hydroxylated taxanes and C-15 hydroxylated 11(15→1)*abeo*taxanes is not obvious without ^{13}C NMR or 2D NMR data to support, sometime even providing incorrect structures.[84,97] For example, the first 11(15→1)*abeo*taxane, brevifoliol (**346**),[100] was initially assigned incorrectly as a normal 6/8/6-taxane.[97] In its ^{13}C NMR, the C-1 signal of 11(15→1)*abeo*taxanes shifted to downfield comparing to those without an oxygenated carbon. It is feasible to distinguish 11(15→1)*abeo*taxane with the corresponding normal 6/8/6-taxanes with HMBC experiment. The long-range correlations between protons of Me-16, Me-17, and C-11 in the normal 6/8/6-taxanes were strong while absent in the 11(15→1)*abeo*taxanes. On the other hand, no HMBC correlations have been observed between H-14 and C-11, C-13 as well as long-range correlation between H-10 and C-1 in the normal 6/8/6-taxanes, but they could be recorded on the 11(15→1)*abeo*taxanes generally.

If having a benzoyl group at B-ring, the *ortho*-protons of benzoyl group resonated beyond 8.0 ppm in baccatin III and its analogs, but they will resonate at most 8.0 ppm or little upfield than 8.0 ppm in rearranged baccatin III and its analogs, that is, in 11(15→1)*abeo*taxanes (**335**[210] and **392**,[201,211,212] Figure 64).

7.1.3. 2(3→20)*Abeo*taxanes. The peculiarity of 2(3→20) *abeo*taxanes is H-10 and H-3 (**484**,[57] **497**[213] and **498**,[214] Figure 65). Since this kind of taxane usually has an oxo group at C-9, H-10 resonated as a singlet at ~5.4 ppm (C-10-OH), or 6.3 ppm (C-10-OAc). Although the proton of hydroxy group at C-10 is an exchangeable proton, it is still observed as a singlet around 4.2 ppm due to forming a hydrogen bond with the vicinal oxo group at C-9. Two protons at C-3 resonated as an isolated coupling system resonate at ~1.6−2.8 ppm with a large coupling constant (J = 15.0 Hz). H-2β and H-20 resonated as a pair of broad doublets at downfield because they have weak coupling with H-1 and H-5, respectively. H-7 resonated as a quartet, while H-13 resonated as a broad doublet.

7.1.4. 3,11-Cyclotaxanes. The presence of an additional transannular bond of 3,11-cyclotaxane prevents conformational mobility of the ring-B. The diagnostic features of 3,11-cyclotaxanes, **506**,[103] taxinine L (**512**),[16] and 2,10-diacetyl-5-cinnamoylphototaxicin

II (**515**)[215−217] are H-12 resonated as a quartet due to the coupling with Me-18 and consequently, Me-18 appeared as a doublet of three-protons with a coupling constant approximately J = 7.0 Hz [Figure 66b]. Because the double bond between C-11 and C-12 is saturated, the chemical shift of H-9 and H-10 is closer than that in corresponding unsaturated taxane and the coupling constants between the two protons become smaller because of the small dihedral angle between them. This kind of taxane has an oxo group at C-13, so H-14 methylene resonates at relatively downfield as a double doublets with a large coupling constant (ca. J = 20.0 Hz) when there is a proton at C-1 [(Figure 66c). When a hydroxy group substituted at C-1, H-14α and H-14β resonate as a couple of doublets of an AB system with a large coupling constant (ca. J = 20.0 Hz) [Figure 66a], but H-14β and H-2 showed as a broad doublet and a broad singlet, respectively, due to long-range coupling between them. Comparing **515** with taxinine (**70**, Figure 45), the H-3′ of the cinnamoyl group in **515** resonates beyond two *ortho*-hydrogen protons of benzene.

7.1.5. Multicyclotaxanes. The ^{1}H NMR spectra of multicyclotaxanes were simplified because the double bonds in original taxadienes are saturated by transannular C−C bond formation (**525**[218] and **529**,[219] Figure 67).

7.1.6. Bicyclic Taxanes. The signals of the bicyclic taxanes are very dispersed at downfield (**538**[220] and **560**,[221] Figure 68). Besides H-5 resonated as a broad singlet and H-10 as a singlet (even actually H-10 showed long-range couple with Me-18 and Me-19 in the ^{1}H−^{1}H COSY spectrum) resonate at most downfield among all the protons on the skeleton (sometime overlapped with the signals of $CDCl_3$ residues, for example, **538**), other oxygenated protons resonate as doublets (H-20a, H-20b, H-3, H-7, H-13) or doublet of doublets (H-2). For example, H-2 (dd, J = 11.1, 4.8 Hz) and H-3 (d, J = 11.1 Hz) consist a coupling system, the geminal protons of C-20 consist another characteristic coupling system with a large coupling constant (J = 12.9 Hz) and large separation. H-13 resonates as a doublet in this type of taxane, usually it appeared as triplets, double of doublets or multiplicity in other type of taxane except in 2(3→20)*abeo*taxane. H-13 also exhibited allylic coupling with H-18 (J = ca. 1.0 Hz) as in other type of taxanes. The geminal protons of H_2-6 resonated relatively at downfield as a pair of multiplets.

7.2. ^{13}C NMR Features of Taxanes

The ^{13}C NMR chemical shifts of representative taxanes were shown in Figures 69−71. Generally, the C-1 of 11(15→1)-*abeo*taxane and 6/8/6-taxane with C-14 acyl substituted resonated at a relatively low field. The aliphatic quaternary C-1 of 11(15→1)*abeo*taxane usually resonated between δ 60 and 70 ppm, which is diagnostic for this type of taxane. When 11-(15→1)*abeo*taxane diterpenoids with a rare 2,20-ether ring system, C-2 and C-4 also resonated at relatively downfield. C-20 of taxane with a C-4(20)-epoxy ring resonated at most upfield (δ 50 ppm). As for methyl groups on taxane skeleton, Me-18 and Me-19 usually appears at upfield (δ 11−17 ppm).

The assignments of all protonated carbons can be determined by DEPT and HMQC (or HSQC) experiments, while the assignments of quaternary carbons and the attachment of the functional groups can be achieved by interpreting multiple-bond ^{1}H−^{13}C correlations in the HMBC spectrum. Besides segment parted by quaternary carbon, HMBC experiment was also used to determine the position of all functional groups such as acetyl, benzoyl, Winterstein's acid side chain and cinnamoyl groups to the pertinent carbons and to construct the subunites derived from ^{1}H−^{1}H COSY analysis. Relative stereochemistry of taxanes can be established by analysis of NOESY or ROESY data, their chemical shifts and coupling constants (J-based Configuration Analysis). Extensive 1D- and 2D-NMR spectroscopic analysis plus literature survey can establish and verify almost all the structures of taxane, so X-ray crystallographic analysis was seldom used.

The chemical shifts of all the acetyl groups, which mostly resonated at 170 ppm for carbonyl carbon and 20 ppm for methyl carbon are omitted to improve the clarity.

8. MS FEATURES OF TAXANES

The MS features of taxane diterpenoids were reported in several papers.[178,222−227] All the taxanes can produce a relatively strong molecular ion in EI-MS or quasi-molecular ion ($[M + H]^+$, $[M + K]^+$, $[M + Na]^+$, $[M + Cu]^+$, or $[M + NH_4]^+$) in FAB-MS analysis. The molecular formula of taxanes can be corroborated by HR-FAB-MS, which can be further verified by the data from ^{1}H and ^{13}C NMR spectra. The characters of taxane MS spectra are the loss of acetates one by one and the MS can provide useful information for the structure elucidation of the side chains at C-13 and C-5 of taxanes.[85,228] Schemes 12−14 illustrated the substructure analysis of representative taxanes (**105**,[53] **176**,[229] and **482**[230]). Abliz et al. investigated MS fragmentation patterns of 11(15→1)*abeo*taxanes.[226]

Recent developments of tandem mass spectroscopy using electrospray ionization (ESI) or atmospheric pressure chemical ionization (APCI) have facilitated the identification of taxanes. Madhusudanan et al. reported the analysis of taxanes from *T. wallichiana*.[222,225,227,231] Scheme 15 illustrates the fragmentation pattern of 15(11→1)*abeo*taxane **347** with lithium cation.

ESI and APCI methods with MS/MS were compared by Ye and Guo.[232] In the positive ion mode taxanes gave prominent $[M + Na]^+$ and $[M + K]^+$ ions with ESI and $[M + NH_4]^+$ and $[M + H]^+$ ions with APCI, and the fragmentation behavior of both methods were similar.

Konishi et al. proposed the fragmentation pattern of paclitaxel by MS/MS/MS analysis (Scheme 16).[233]

Taxanes with different C-5-amino-side chains produce different fragment ions (Scheme 17).[234] The relative abundance of the molecular ion is high and sometimes displayed as the base peak. An ion peak at m/z 120 suggests that there is only one methyl group attached to the nitrogen of side chain, whereas m/z 134 suggests there are two methyl groups. Concomitantly, the former signal (m/z 120) is observed with a corresponding ion peak at m/z 180, while corresponding ion peak at m/z 194 or 210 for the latter (m/z 134), depending on whether it has a hydroxy group at C-2′ of the side chain.

9. CHEMICAL STUDIES OF PACLITAXEL DERIVATIVES

Most paclitaxel derivatives have a core structure best described as an inverted cup and this conformation could play a key role in their chemical properties. First set of reactions carried out on paclitaxel was hydrolysis for removal of the C-13-side chain on structure elucidation. Subsequent studies were mainly focused on reduction, oxidation and epimerization and found the following:

(1) The hydroxy groups of 10-deacetylbaccatin III (**235**) and baccatin III (**237**) showed weak reactivity. C-13-OH situated in the skeletal concavity hidden by C-4-OAc and a stabilizing hydrogen bond could formed between C-13-OH and C-4-OAc, thus, esterification at C-13 proved

exceedingly difficult.[235] In addition, opening of the oxetane ring did not affect the conformation of rings A, B and C.

(2) D ring (oxetane ring) of paclitaxel opened under basic conditions through intramolecular attack of the C-4-Ac, and the acetyl group immigrated to C-5.[236]

(3) The C-2-OAc group of α-4,20-epoxy-5-*O*-triethylsilyl-taxinine A attacked the epoxy ring to give an orthoester derivative under treatment with $BF_3 \cdot OEt_2$ (Scheme 18).[237] Orthoester type taxanes have been isolated from nature.

(4) 7β-OH of paclitaxel can easily epimerize into a 7α isomer presumably involving a retro-aldol processes and the reverse epimerization was also observed. Principal degradation product of paclitaxel was 7-*epi*-taxol (**318**), thermodynamically more stable.[238]

(5) Another phenomenon is intramolecular hydrogen migration: irradiation of taxinine A (**30**, Scheme 18) resulted in bond formation between C-3 and C-11, involving a hydrogen transferred from C-3 to C-12.[22] Fragmentation of the C-1/C-15 bond of *O*-cinnamoyltaxicin I triacetate (**71**) under basic conditions also involved a long-range hydride shift to give a dihemiacetal (Scheme 18).[239]

The cuplike shape could be taken into account for the above characters, at least to some degree. While Snyder suggested something interrogatory to the premise:[240] paclitaxel possesses at least seven easily rotated single bonds. Consequently, existence of only one or two paclitaxel/docetaxel conformers at 25 °C is highly unlikely. Moreover, virtual conformation was obtained based on NMR spectra. While the latter was the dynamic averages arising from rapid conformer equilibration, which illustrated that single conformation hypothesis is incomplete.

10. MECHANISM OF ACTION OF PACLITAXEL

Tubulin is the basic subunit of microtubules and one of the most highly conserved proteins in evolution.[241] Normal cell division, intracellular transport, cellular motility, cell signaling, and maintenance of cell shape are all dependent on the highly regulated dynamic instability process of the tubulin/microtubule system.[242,243] Microtubules are key actors in the cytoskeleton of eukaryotic cells where they play important roles in organizing the spatial distribution of organelles during interphase and chromosomes throughout cell division. Microtubules are hollow filaments of ~240 Å diameter comprising the 55 kD proteins α- and β-tubulin as the constituent subunits binding a molecule of GTP respectively (E-side for β-GTP, N-side for α-GTP).[244] The remainder is heterogeneous microtubule-associated proteins (MAPs). Apart from many other critical functions, they are of particular importance for the formation of the mitotic spindle, which provides the structural framework for the physical segregation of sister chromatids during cell division. First step in polymerization is the formation of a heterodimer comprising one molecule of α- and β-tubulin each (Mg^{2+} preferred, GTP existed),[245] then they bind head to tail to form nucleation center, through protofilament, finally reach the critical concentration.[246] Microtubules are not static and equilibrium are set up with constant loss and gain of subunits.[247] In this process α-GTP is nonexchangeable while β-GTP is not only exchangeable but also hydrolyzed to GDP.[248]

Interference with microtubule functionality represents an important concept in anticancer drug discovery. The microtubule-targeting drugs can be grouped into two distinct functional classes, namely, compounds which inhibit the assembly of tubulin heterodimers into microtubule polymers ("microtubule depolymerizing agents" or "tubulin polymerization inhibitors") and those which stabilize microtubules under normally destabilizing conditions ("microtubule polymerizing agents" or "microtubule stabilizers"). Paclitaxel and its analogs for more than 15 years were the only class of compounds known to act as microtubule stabilizers. Interaction between paclitaxel (microtubule polymerizing agents) and tubulin alters the normal microtubule dynamics leading finally to cell apoptosis (Scheme 17).[14,249−252]

Paclitaxel binds to β-tubulin, affects the tubulin-microtubule equilibrium, decreases the concentration of tubulin, resists to cooling and calcium ions, and dilute that could lead to depolymerize,[13] inhibits mitosis in G2/M phase. While Antonella suggested that some certain taxanes could reorganize microtubules into short fibers, unlike paclitaxel-bundled and did not always block cell-cycle in the G2/M phase.[253] The structural biology investigation into the paclitaxel-tubulin interactions has culminated in the determination of the electron crystal lographic (EC) structure of the e α/β-tubulin heterodimer bound to paclitaxel (Figure 72).[15,254] Crystallographic analysis[248] showed that paclitaxel has a T-shaped structure, optimized to a hydrophobic pocket on tubulin. C-2-Bz binds to H_7-helix, which contacted with the exchangeable nucleotide (GTP/GDP) binding site. It was supposed that paclitaxel could induce a confirmation of β-tubulin that mimics the GTP-bound tubulin and this hypothesis was supported by the fact that paclitaxel could promote tubulin assembly with GTP absent.[13] Equivalent to the pocket in β-tubulin, 8 amino acid peptide in α-tubulin formed part of S_9-S_{10} loop, which was assumed as a endogenous regulatory factor[15,255] and paclitaxel was proposed to exert activity by mimicking the function of this factor.[249] It is interesting to note that docetaxel and paclitaxel, similar in structure, compete for the same binding site[256] while microtubules induced by them are structurally different.[257] Epothilones though structurally different competitively inhibit the binding of paclitaxel to mammalian brain tubulin.[258] By far, some confusion still exists: (i) whether paclitaxel prevents microtubule from depolymerization indeed relates to mitosis inhibition. If so, whether it is just because paclitaxel mimics some endogenous factor to induce a conformational alteration. (ii) Paclitaxel could alter calcium regulation, which involves in the tubulin-microtubule equilibrium. Thus, it is reasonable to assume that paclitaxel alters calcium concentration to disrupt mitosis, or affects the cell-signaling cascade. Schiff[259] and Jordan[260] published their views on this aspect.

11. STRUCTURE−ACTIVITY RELATIONSHIPS OF PACLITAXEL DERIVATIVES

Understanding the interaction of a lead compound with its receptor on a molecular level is important for new drug development. Toward this end, extensive structure−activity studies have been performed on paclitaxel.[261−265]

Preliminary studies on paclitaxel showed that 6/8/6-membered ring and a free hydroxy group at C-2′ are important for its activity. A C-13-side chain is essential and removal of the side chain abolished its antimitotic and antimicrotubule activity completely. Functional groups at C-10 and C-7 act indirectly on tubulin,[104] so modifications at these positions have little effect on activity, while C-13, C-2, and C-4 have direct interaction with tubulin.[266] The oxetane ring was assumed to affirm a correct binding of these derivatives on tubulin.[267] However, it was not clear that the oxetane ring involves in or as a conformational lock.[268] Kingston tested the electronegativity of the heteroatom

using a thietane instead of the oxetane and the bioactivity decreased.[269] Barboni et al.[270] concluded that compounds could still be active without the D ring when substituent at C-4 have no conformational steric hindrance to the binding pocket (like 4-methyltaxol, as potent as paclitaxel at microtubule stabilization *in vitro*). 2-*Epi*-taxol was inactive in a cytotoxicity assay,[271] while modification at C-3 (*meta*) position of C-2-Bz with CN, N_3, MeO and Cl could considerably increase the anticancer activity against P-388 cell line.[264] Several *ortho*-, *meta*-substituted derivatives with smaller groups at C-2-Bz proved to be more active.[272] Compound **B** (Figure 73) modified at 7-OH was selected for clinical development.[273] Removal of the 7-OH led to compound **A**, which showed similar cytotoxicity as paclitaxel[268,274] and compound **C** modified at C-7 and C-10 showed increased anticancer activity to docetaxel.[275,276] It was notable that $CaCl_2$-induced microtubule depolymerization was inhibited by some taxanes with a C-5-cinnamoyl group but not a D-ring and C-13-side chain. The C-5-cinnamoyl group presumably plays a role like a C-13-side chain. C-10-Ac and C-11-OH act as C-4-oxetane moiety.[277] In addition, some taxoids increase VCR accumulation in MDR cells, since bulky groups at C-2, C-5, or C-13 oriented to the inside of the "cage" structure, maybe important for binding to P-glycoprotein.[62] Structure−activity relationships of paclitaxel are summerized in Figure 74.[272,278]

12. CLINICAL USE, SIDE EFFECTS, AND DEVELOPMENT

Today, paclitaxel is still the most commonly used drug to treat ovarian, breast, and other carcinomas such as nonsmall-cell lung cancer, small-cell lung cancer, squamous cancers of the head and neck, etc.[279] In 2000, it was approved for the adjuvant treatment of early stage node-positive breast carcinoma.[280] However, preclinical and clinical data are quite limited in pediatric oncology.[281] Besides great potentialities, paclitaxel has a variety of harmful side effects including: alterations in liver function, hypersensitivity reactions, cardiotoxicity, neutropenia, peripheral neuropathy, mucositis, gastrointestinal toxicities, suppression of immune system, dead sensory nerves, alopecia, arthralgias, myalgias.[282,283] Further studies on taxanes led to the discovery of advanced second generation derivatives with increased selectivity, longer efficacy, lower toxicity, potency against multidrug resistant and drug-sensitive cell lines. At least three new taxanes underwent clinical trials in 2000[284] (Figure 75): **BMS-184476** and **BMS-188797** exhibited potent activity in vitro against human tumor cell lines that are highly resistant to paclitaxel, either from overexpression of P-glycoprotein or because of specific mutations in β-tubulin. **BMS-185660**, phosphate prodrug was orally active. A 7-amino acid synthetic peptide conjugated with the paclitaxel-2′-hydroxy function by a linker, **PTXPEGBBN[7−13]**, was the first soluble tumor-directed paclitaxel prodrug.[285] The IC_{50} against NCI-H1299 human nonsmall cell lung cancer cells was 6 nM (paclitaxel: IC_{50} 15 nM). Linking antibody and a cytotoxic agent offers a mean to deliver an anticancer agent selectively to the tumor sites, for example, **SB-T-1213**, **SB-T-12162** (IC_{50} 0.18 nM and 0.09 nM against MCF7, respectively).[286] **SB-T-101131** (**IDN5109**) was the first highly promising orally active taxane anticancer agent, for it was not a substrate for P-glycoprotein[287] and with superior growth inhibition activity against P-glycoprotein-expressing MDR tumors. Additionally, **BMS-275183** showed oral efficacy in preclinical models comparable to iv-administered paclitaxel.[288]

Ojima et al. discovered taxane-based multidrug resistant (MDR) reversal agents (TRAs, such as **SB-RA-131012**, **SB-RA-4001**, etc, Figure 76), as well as paclitaxel congeners that would not be recognized by P-glycoprotein. Paclitaxel recovered 95−99.8% of its efficacy against the resistant human cancer cells when TRAs were coadministered at 1.0 μM.[289]

13. CONCLUSION

Among these natural taxanes, no one is more potential than paclitaxel. Although most of biosynthetic pathway of paclitaxel have been clarified,[290] its production by bioengeneering is still far from commercial scale. Total synthesis of paclitaxel become alternative, and many outstanding chemists devoted themselves to complete, this challenge although it was considered as a formidable task. After two decades of effort, at least six groups have achieved the total synthesis of paclitaxel. A diverse strategy and excellent approaches for the synthesis of the taxane framework[291] and for paclitaxel itself[292] were evolved. But the complexity of the fascinating structure of paclitaxel claims lengthy syntheses steps, which result in extremely low overall yields rendering total synthesis to this agent impractical for large-scale commercial preparation. The construction of the taxane framework with the oxetane ring and the homochiral ester side-chain at C-13 become challenges for synthetic chemists.

Another alternative approaches for paclitaxel production is semisynthesis from 10-deacetylbaccatin III and analogs[293] that can be isolated from the needles, a renewable resource. It has been adopted as the current commercial method for paclitaxel production. However, availability of yews is decreasing significantly due to overexploitation for medicinal/commercial purposes. A sustainable management of the resource is needed urgently; otherwise the genetic diversity and natural abundance of yew trees will be at risk. On the other hand, the in vivo productions of paclitaxel in plant tissue and cell culture have not provided economically feasible solutions to the paclitaxel supply problem.

The most challenging goals in this field at present are to discover or design molecules that possess the beneficial activities of paclitaxel but not its structural intricacy and to promote taxanes production based on biotechnology. Therefore, to fully gain command of the profile of taxane diterpenoids, a detailed understanding of the steps of taxane biosynthesis and the identification of the associated genes is essential. Actually as seen in the numerous literatures, advances in genetic engineering,[294] biotransformation of taxanes,[295−302] and cell or tissue culture[303−306] provide breakthroughs continuously for improvement of the paclitaxel production by biological methods. It is worth to note that though 3,8-*seco*-bicyclic skeleton was proposed as biosynthetic precursor for taxanes[119] and adopted a conformation similar to paclitaxel,[65,307] not enough attention has been paid to its bioactivity, synthesis and biosynthesis.[308] Anyway, advances in technology will certainly speed up the process of investigation on taxanes. As reported recently, computer-aided analysis of ^{13}C NMR spectra was applied directly to identify taxanes in different fractions of extracts from yew trees[309] and this method was reported on some clues as early as 1990s.[310,311]

Bioactivity studies of natural taxanes were carried out mostly by Kobayashi group and three comprehensive reviews have been published on these works.[61,62,312] As for the biosynthesis of paclitaxel, the groups of Croteau and William have done excellent works.[94,124,290,313−321] This review did not cover the activities, chemical synthesis and biosynthesis of taxanes. As for nontaxanes

isolated from yew trees mainly including lignans, flavonoids, ecdysteroids, sesquiterpenes and nor-sesquiterpenes, Appendino's,[23] Parmar's[25] and Gulacti's[322] reviews have described them in detail, are also beyond the scope of the review.

AUTHOR INFORMATION

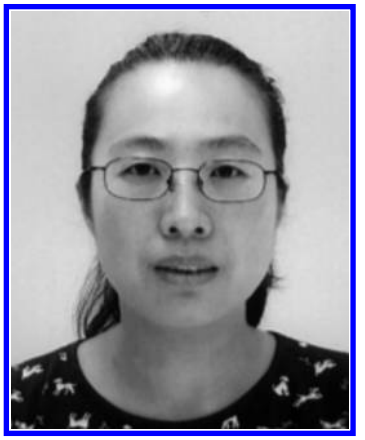
Corresponding Author

*E-mail: shiqingwen@hebmu.edu.cn (Q.W.S.); kiyota@biochem.tohoku.ac.jp (H.K.); hbydcongbin@hebmu.edu.cn (B.C.).

BIOGRAPHIES

Yu-Fang Wang (b. 1984 in Baoding, Hebei Province). She received her Bachelor and Master degrees from School of Pharmaceutical Sciences, Hebei Medical University in 2006 and 2009. Her master thesis is studies on the antitumor components of *Saussurea lappa*. Now she works in the Division of Natural Medicine of Hebei Medical University as an Assistant Professor.

Qing-Wen Shi (b. 1964 in Cangzhou, Hebei Province), Professor and Director of Division of Natural Medicine, deputy dean of School of Pharmaceutical Sciences, Hebei Medical University. He obtained his Bachelor degree from the School of Pharmaceutical Sciences, Hebei Medical University in 1985. In the same year, he assumed the position of Assistant Professor in Natural Medicine Laboratory of Hebei Medical University. He received his Master degree from Shandong Medical University in 1990, and obtained his PhD from Tohoku University, Japan, in 2000. As a postdoctoral and an associate researcher he worked in Institut National de la Recherche Scientifique, Institut Armand-Frapier, Quebec University, Canada, for 4 years. In 2004 he came back to China and was promoted to a full professor. He visited Tohoku University and McGill University as a visiting researcher in 2006, 2007, 2008, and 2009. His research interests were focused on the chemical constituents of medicinal plants and their biological activities.



Mei Dong (b. 1963 in Shijiazhuang, Hebei Province), Professor of Department of Forensic Medicine, Hebei Medical University. She got her Bachelor degree from the College of Forestry of Hebei in 1984, Master degree from Hebei Normal University in 1996, and obtained her PhD from Shinshu University, Japan, in 2000. She visited Department of Environmental Biochemistry, Graduate School of Medicine, Chiba University as a visiting researcher in 2005−2010. Her research interests are focused on the phototoxic constituents of medicinal plants and their antitumor activities.

Hiromasa Kiyota (b. 1966 in Sendai, Japan), Associate Professor of Biooganic Chemistry at Tohoku University, Japan. He received his B. S. degree (1989, soil science, Prof. Hidenori Wada) and M. S. degree (1991, organic chemistry, Prof. Kenji Mori and Associate Prof. Takeshi Kitahara) from the University of Tokyo. In 1991, he assumed the position of Assistant Professor at Prof. K. Mori's Laboratory, moved to Prof. Takayuki Oritani's Laboratory in 1994, and he was promoted to Associate Professor (Prof. Shigefumi Kuwahara) in 2002. In 1995, he received Ph. D. from the University of Tokyo (Prof. Kenji Mori) about the synthesis of optically active insect pheromones. He joined the research group of Prof. Steven V. Ley at Cambridge University,

U.K. as Visiting Academic (2001−2002). In 2003, he received The Japan Bioscience, Biotechnology and Agrochemistry Society Award for the Encouragement of Young Scientists. His research interests extend over a wide range of natural product chemistry, especially on the synthesis of biologically active compounds such as antibiotics, phytotoxins, plant hormones, insect pheromones, marine products, perfumery, etc.

Yu-Cheng Gu graduated with first honours degree in Pharmacy in 1984 at the Hebei Medical University and obtained his MSc on natural products at the Institute of Materia Medica, China Academy of Traditional Chinese Medicine in 1989. He worked for five years as an assistant professor in the China Japan Friendship Institute of Clinical Medical Sciences in Beijing. In 1998, he received his PhD in natural products at the Edinburgh Napier University followed by two years of postdoctoral work at Huddersfield University. He joined Syngenta at its Jealott's Hill International Research Centre as a natural products chemist in 2002 and is now principal scientist. His research interests are natural product from terrestrial and marine organisms, bioactive compound application in agrichemical and pharmaceutical areas, and polysaccharide chemistry. From 2004, he received honorary professorships from the Hebei Medical University, Wuhan Polytechnic University and visiting professorships from the Peking Union Medical College, Chinese Academy of Medical Sciences, Central China Normal University, Hubei Academy of Agricultural Sciences, Shanghai Southern Pesticide Research Centre, and Jilin University of China.

Bin Cong (born in 1957, Qiqihar, Heilongjiang Province), Professor of Department of Forensic Medicine, Hebei Medical University. He got his Bachelor degree from Hebei Medical University in 1983, and Master degree from Xi'an Medical University in 1989, and in 1998 he obtained his PhD from Hebei Medical University. He had been in Shinshu University (Japan) as a visiting scholar in 1994. His research field is concentrated on the phototoxic constituents of medicinal plants and their antitumor activities.

ACKNOWLEDGMENT

We are grateful for the financial supports from National Natural Science Foundation of China (81072551), Scientific Research Foundation for the Returned Overseas Chinese Scholars of Hebei Province and Scientific Research Foundation of Hebei Province (08B032 and C-2010000489). We also wish to extend our sincere thanks for the financial support of Syngenta Ltd. (2011-Hebei Medical University-Syngenta-03). We would like to thank Dr. John Clough at Syngenta Jealott's Hill International Research Centre for his contributions to the preparation and proofreading of the manuscript.

REFERENCES

(1) Ettouati, L.; Ahond, A.; Convert, O.; Poupat, C.; Potier, P. *Bull. Soc. Chim. Fr.* **1989**, *5*, 687.
(2) Ettouati, L.; Ahond, A.; Convert, O.; Laurent, D.; Poupat, C.; Potier, P. *Bull. Soc. Chim. Fr.* **1988**, *4*, 749.
(3) Lucas, H. *Arch. Pharm.* **1856**, *135*, 145.
(4) Bryan-Brown, T. *J. Pharm. Pharmacol.* **1932**, *5*, 205.
(5) Panter, K. E.; Molyneux, R. J.; Smart, R. A.; Mitchell, L.; Hansen, S. *J. Am. Vet. Med. Assoc.* **1993**, *202*, 1476.
(6) Jenniskens, L. H. D.; van Rosendaal, E. L. M.; van Beek, T. A. *J. Nat. Prod.* **1996**, *59*, 117.
(7) Lythgoe, R. *The Alkaloids: Chemistry and Physiology*; Academic Press: New York, 1967; Vol. 10, p 597.
(8) Lythgoe, B.; Harrison, J. W. *J. Chem. Soc. C* **1966**, 1932.
(9) Wani, M. C.; Taylor, H. L.; Wall, M. E.; Coggon, P.; McPhail, A. T. *J. Am. Chem. Soc.* **1971**, *93*, 2325.
(10) Patel, R. N. *Annu. Rev. Microbiol.* **1998**, *98*, 361.
(11) Fuchs, D. A.; Johnson, R. K. *Cancer Treat. Rep.* **1978**, *62*, 1219.
(12) Horwitz, S. B. *J. Nat. Prod.* **2004**, *67*, 136.
(13) Schiff, P. B.; Fan, J.; Horwitz, S. B. *Nature* **1979**, *277*, 665.
(14) Schiff, P. B.; Horwitz, S. B. *Proc. Natl. Acad. Sci. U.S.A.* **1980**, *77*, 1561.
(15) Nogales, E.; Wolf, S. G.; Downing, K. H. *Nature* **1998**, *391*, 199.
(16) Chiang, H. C.; Woods, M. C.; Nakadaira, Y.; Nakanishi, K. *Chem. Commun.* **1967**, *23*, 1201.
(17) Woods, M. C.; Chiang, H. C.; Nakadaira, Y.; Nakanishi, K. *J. Am. Chem. Soc.* **1968**, *90*, 522.
(18) Eyre, D. H.; Harrison, J. W.; Scrowston, R. M.; Lythgoe, B. *Proc. Chem. Soc.* **1963**, *9*, 271.
(19) (a) Kurono, M.; Nakadaira, Y.; Onuma, S.; Sasaki, K.; Nakanishi, K. *Tetrahedron Lett.* **1963**, *30*, 2153. (b) Ueda, K.; Uyeo, S.; Yamamoto, Y.; Maki, Y. *Tetrahedron Lett.* **1963**, *30*, 2167.
(20) Miller, R. W. *J. Nat. Prod.* **1980**, *43*, 425.
(21) Chen, W. M. *Acta Pharmacol. Sin. (Yaoxue Xuebao)* **1990**, *25*, 227.
(22) Kingston, D. G. I.; Molinero, A. A.; Rimoldi, J. M. In *Progress in the Chemistry of Organic Natural Products*; Herz, W., Kirby, G. W., Moore, R. E., Steglich, W., Tamm, C. H., Eds.; Springer-Verlag: Wien, Austria, 1993; Vol. 61, p 1.
(23) Appendino, G. *Nat. Prod. Rep.* **1995**, *12*, 349.
(24) Zhang, J. Z. *Acta Pharmacol. Sin.* **1995**, *30*, 862.
(25) Parmer, V. S.; Jha, A.; Bish, K. S.; Taneja, P.; Sight, S. K.; Kumar, A.; Poonam, J. R.; Olsen, C. E. *Phytochemistry* **1999**, *50*, 1267.
(26) Baloglu, E.; Kingston, D. G. I. *J. Nat. Prod.* **1999**, *62*, 1448.
(27) Shi, Q. W.; Kiyota, H. *Chem. Biodiversity* **2005**, *2*, 1597.
(28) Hilger, A.; Brande, F. *Ber. Dtsch. Chem. Ges.* **1890**, *23*, 464.
(29) Graf, E. *Angew. Chem.* **1956**, *68*, 249.

(30) Graf, E.; Boeddecker, H. *Arch. Pharm.* **1956**, *289*, 364.
(31) Krüssman, G. In *Handbuch der Nadelgehölze*; Paul Parey: Berlin, 1983; pp 317−333.
(32) Rozendaal, E. L. M.; Kurstjens, S. J. L.; Beek, T. A.; Berg, R. G. *Phytochemistry* **1999**, *52*, 427.
(33) Shar, A.; Li, D.-Z.; Möller, M.; Gao, L.-M.; Hollingsworth, M. L.; Gibby, M. *Taxon* **2008**, *57*, 211.
(34) Topcu, G.; Sultana, N.; Akhtar, F.; Habib-ur-Rehman; Hussain, T.; Choudharis, M. I.; Atta-ur-Rahman *Nat. Prod. Lett.* **1994**, *36*, 987.
(35) Gabetta, B.; Peterlongo, F.; Zini, G.; Barboni, L.; Rafaiani, G.; Ranzuglia, P.; Torregiani, E.; Appendino, G.; Cravotto, G. *Phytochemistry* **1995**, *40*, 1825.
(36) Appendino, G.; Gariboldi, P.; Pisetta, A.; Bombardelli, E.; Gabetta, B. *Phytochemistry* **1992**, *31*, 4253.
(37) Tong, X. J.; Fang, W. S.; Zhou, J. Y.; He, C. H.; Chen, W. M.; Fang, Q. C. *Acta Pharmacol. Sin. (Yaoxue Xuebao)* **1994**, *29*, 55.
(38) Yoshizaki, F.; Takahashi, N.; Hisamichi, S. *Annu. Rep. Tohoku Coll. Pharm.* **1987**, *34*, 107. *Chem. Abstr.* **1989**, *110*, 121510.
(39) Yoshizaki, F.; Madarame, M.; Takahashi, C.; Hisamichi, S. *Shoyakugaku Zasshi* **1986**, *40*, 429. *Chem. Abstr.* **1987**, *107*, 130861.
(40) Kondo, H.; Takahashi, T. *Yakugaku Zasshi* **1925**, *45*, 861.
(41) Shiro, M.; Sato, T.; Koyama, H.; Maki, Y.; Nakanishi, K.; Uyeo, S. *Chem. Commun.* **1966**, *4*, 97.
(42) Shiro, M.; Koyama, H. *J. Chem. Soc. B* **1971**, *1*, 1342.
(43) Horiguchi, T.; Cheng, Q.; Oritani, T. *Tetrahedron* **2001**, *41*, 3907.
(44) Fukushima, M.; Fukamiya, N.; Okano, M.; Nehira, T.; Tagahara, K.; Zhang, S. X.; Zhang, D. C.; Tachibana, Y.; Bastow, K. F.; Le, K. H. *Cancer Lett.* **2000**, *158*, 151.
(45) Kosugi, K.; Sakai, J. Y.; Zhang, S. J.; Watanabe, Y.; Sasaki, H.; Suzuki, T.; Hagiwara, H.; Hirataa, N.; Hirose, K.; Ando, M.; Tomida, A.; Tsuruo, T. *Phytochemistry* **2000**, *54*, 839.
(46) Tong, J.; Lu, J. C.; Zhang, N.; Chi, H. D.; Yamashita, K.; Manabe, M.; Kodama, H. *Planta Med.* **2009**, *75*, 814.
(47) Xia, Z. H.; Peng, L. Y.; Zhao, Y.; Xu, G.; Zhao, Q. S.; Sun, H. D. *Chem. Biodivers.* **2005**, *2*, 1316.
(48) Ettouati, L.; Ahond, A.; Poupat, C.; Potier, P. *J. Nat. Prod.* **1991**, *54*, 1455.
(49) Ettouati, L.; Ahond, A.; Poupat, C.; Potier, P. *Tetrahedron* **1991**, *47*, 9823.
(50) Wiegerinck, P. H. G.; Fluks, L.; Hammink, J. B.; Mulders, S. J. E.; Groot, F. M. H.; Rozendaal, H. L. M.; Scheeren, H. W. *J. Org. Chem.* **1996**, *61*, 7092.
(51) Alloattil, G.; Pennal, C.; Levil, R. C.; Gallol, M. P.; Appendino, G.; Fenoglio, I. *Life Sci.* **1996**, *58*, 845.
(52) Zhang, M. L.; Dong, M.; Li, X. N.; Li, L. G.; Sauriol, F.; Huo, C. H.; Shi, Q. W.; Gu, Y. C.; Kiyota, H.; Cong, B. *Tetrahedron Lett.* **2008**, *49*, 3405.
(53) Shi, Q. W.; Sauriol, F.; Mamer, O.; Zamir, L. O. *J. Nat. Prod.* **2003**, *66*, 1480.
(54) Shen, Y. C.; Lin, Y. S.; Cheng, Y. B.; Cheng, K. C.; Khalil, A. T.; Kuo, Y. H.; Chien, C. T.; Lin, Y. C. *Tetrahedron* **2005**, *61*, 1345.
(55) Banskota, A. H.; Usia, T.; Tezuka, Y.; Kouda, K.; Nguyen, N. T.; Kadata, S. *J. Nat. Prod.* **2002**, *65*, 1700.
(56) Dong, M.; Zhang, M. L.; Wang, Y. F.; Zhang, X. P.; Li, C. F.; Shi, Q. W.; Cong, B.; Kiyota, H. *Biosci. Biotechnol. Biochem.* **2007**, *71*, 2087.
(57) Morita, H.; Gonda, A.; Wei, L.; Yamamura, Y.; Wakabayashi, H.; Takeya, K.; Itokawa, H. *Phytochemistry* **1998**, *48*, 857.
(58) Kobayashi, J.; Hosoyama, H.; Wang, X. X.; Shigemori, H.; Koiso, Y.; Iwasaki, S.; Sasaki, T.; Naito, M.; Tsuruo, T. *Bioorg. Med. Chem. Lett.* **1996**, *7*, 393.
(59) Morita, H.; Machida, I.; Hirasawa, Y.; Kobayashi, J. *J. Nat. Prod.* **2005**, *68*, 935.
(60) Kobayashi, J.; Hosoyama, H.; Koiso, Y.; Iwasaki, S. *Experientia* **1995**, *51*, 592.
(61) Kobayashi, J.; Shigemori, H. *Med. Res. Rev.* **2002**, *22*, 305.
(62) Shigemori, H.; Kobayashi, J. *J. Nat. Prod.* **2004**, *67*, 245.
(63) Shi, Q. W.; Sauriol, F.; Park, Y.; Smith, V. H., Jr.; Lord, G.; Zamir, L. O. *Magn. Reson. Chem.* **2005**, *43*, 798.
(64) Appendino, G.; Tagliapietra, S.; Ozen, H. C.; Gariboldi, P.; Gabetta, B.; Bombardelli, E. *J. Nat. Prod.* **1993**, *56*, 514.
(65) Wu, J. H.; Zamir, L. O. *Anti-Cancer Drug Des.* **2000**, *15*, 73.
(66) Zhang, M. L.; Huo, C. H.; Dong, M.; Li, L. G.; Sauriol, F.; Shi, Q. W.; Gu, Y. C.; Kiyota, H.; Cong, B. *Z. Naturforsch.* **2008**, *63B*, 1005.
(67) Samaranayake, G.; Magri, N. F.; Jitrangsri, C.; Kingston, D. G. I. *J. Org. Chem.* **1991**, *56*, 5114.
(68) Chu, A.; Davin, L. B.; Zajicek, J.; Lewis, N. G.; Croteau, R. *Phytochemistry* **1993**, *34*, 473.
(69) Zhang, H. J.; Mu, Q.; Sun, H. D.; Yoshio, T. *Phytochemistry* **1997**, *44*, 911.
(70) Zamir, L. O.; Nedea, M. E.; Belair, S.; Sauriol, F.; Mamer, O.; Jacqmain, E.; Jean, F. I.; Garneau, F. *Tetrahedron Lett.* **1992**, *33*, 5173.
(71) Gunawardana, G. P.; Premachandran, U.; Burres, N. S.; Whittern, D. N.; Henry, R.; Spanton, S.; McAlpine, J. B. *J. Nat. Prod.* **1992**, *55*, 1686.
(72) Zhang, S.; Chen, W. M.; Chen, Y. H. *Acta Pharmacol. Sin.* **1992**, *27*, 268.
(73) Nikolakakis, A.; Caron, G.; Cherestes, A.; Sauriol, F.; Mamerc, O.; Zamira, L. O. *Bioorg. Med. Chem.* **2000**, *8*, 1269.
(74) DeMattei, J. A.; Leanna, M. R.; Li, W. K.; Nichols, P. J.; Rasmussen, M. W.; Morton, H. E. *J. Org. Chem.* **2001**, *66*, 3330.
(75) Clein, L.; Li, L.; Maring, C. J.; Yeung, C. M.; Thomas, S. A.; Grampovnik, D. J.; Plattner, J. J. *J. Med. Chem.* **1995**, *38*, 1482.
(76) Klein, L. *Tetrahedron Lett.* **1993**, *34*, 2047.
(77) Chen, S. H.; Wei, J. M.; Farina, V. *Tetrahedron Lett.* **1993**, *34*, 3205.
(78) Chen, S. H.; Farina, V.; Wei, J. M.; Long, B.; Fairchild, C.; Mamber, S. W.; Kadow, J. F.; Vyas, D.; Doyle, T. W. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 479.
(79) Georg, G. I.; Cheruvallath, Z. S.; Vander Velde, D. G. *Tetrahedron Lett.* **1995**, *36*, 1783.
(80) Kant, I.; Farina, V.; Fairchild, C.; Kadow, J. F.; Langley, D. R.; Long, B. H.; Rose, W. C.; Vyas, D. M. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 1565.
(81) Chauviere, G.; Guenard, D.; Picot, F.; Senilh, V.; Potier, P. *C. R. Acad. Sci. Paris, Ser. II* **1981**, *293*, 501.
(82) Appendino, G.; Varese, M.; Garibaldi, P.; Gabetta, B. *Tetrahedron Lett.* **1994**, *35*, 2217.
(83) Miller, R. W.; Powell, R. G.; Smith, C. R., Jr.; Arnold, E.; Clardy, J. *J. Org. Chem.* **1981**, *46*, 1469.
(84) Appendino, G.; Ozen, H. C.; Gariboldi, P.; Torregiani, E.; Gabetta, B.; Nizzola, R.; Bombardelli, E. *J. Chem. Soc., Perkin Trans. 1* **1993**, *14*, 1563.
(85) Ma, W.; Park, G. L.; Gomez, G. A.; Nieder, M. H.; Adams, T. L.; Aynsley, J. S.; Sahai, O. P.; Smith, R. J.; Stahlhut, R. W.; Hylands, P. J.; Bitsch, F.; Shackleton, C. *J. Nat. Prod.* **1994**, *57*, 116.
(86) Zhang, Z.; Sauriol, F.; Mamer, O.; You, X.; Alaoui-Jamali, M. A.; Batist, G.; Zamir, L. O. *J. Nat. Prod.* **2001**, *64*, 450.
(87) Huo, C. H.; Zhang, X. P.; Li, C. F.; Wang, Y. F.; Shi, Q. W.; Kiyota, H. *Biochem. System. Ecol.* **2007**, *35*, 704.
(88) Morita, H.; Gonda, A.; Wei, L.; Yamamura, Y.; Takeya, K.; Itokawa, H. *J. Nat. Prod.* **1997**, *60*, 390.
(89) Croteau, R.; Ketchum, R. E. B.; Long, R. M.; Kaspera, R.; Wildung, M. R. *Phytochem. Rev.* **2006**, *5*, 75.
(90) Jennewein, S.; Wildung, M. R.; Chau, M.; Walker, K.; Croteau, R. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 9149.
(91) Jennewein, S.; Long, R. M.; Williams, R. M.; Croteau, R. *Chem. Biol.* **2004**, *11*, 375.
(92) Kingston, D. G. I.; Jagtop, P. G.; Yuan, H.; Samala, L. *Fortschr. Chem. Org. Naturst.* **2002**, *84*, 53.
(93) Chau, M. D.; Jennewein, S.; Walker, K.; Croteau, R. *Chem. Biol.* **2004**, *11*, 663.
(94) Wildung, M. R.; Croteau, R. *J. Biol. Chem.* **1996**, *271*, 9201.
(95) Gueritte-Voegelein, F.; Guenard, D.; Potier, P. *J. Nat. Prod.* **1987**, *50*, 9.
(96) Zhang, M. L.; Shi, Q. W.; Dong, M.; Wang, Y. F.; Huo, C. H.; Gu, Y. C.; Cong, B.; Kiyota, H. *Tetrahedron Lett.* **2008**, *49*, 1180.

(97) Appendino, G.; Barboni, L.; Gariboldi, P.; Bombardelli, E.; Gabetta, B.; Viterbo, D. *J. Chem. Soc., Chem. Commun.* **1993**, *20*, 1587.
(98) Chu, A.; Furlan, M.; Davin, L. B.; Zajicek, J.; Towers, G. H. N.; Soucy-Breau, C. M.; Rettig, S. J.; Croteau, R.; Lewis, N. G. *Phytochemistry* **1994**, *36*, 975; for the structure revision, see ref 97.
(99) Das, B.; Rao, S. P.; Das, R. *Planta Med.* **1995**, *61*, 393.
(100) Balza, F.; Tachibana, S.; Barrios, H.; Towers, G. H. N. *Phytochemistry* **1991**, *30*, 1613;for the structure revision, see ref 97.
(101) Liu, X. K.; Wu, D. G.; Wang, Z. Y. *Kexue Tongbao* **1992**, *37*, 2186.
(102) Sun, D. A.; Sauriol, F.; Mamer, O.; Zamir, L. O. *Can. J. Chem.* **2001**, *79*, 1381.
(103) Petzke, T. L.; Shi, Q. W.; Sauriol, F.; Mamer, O.; Zamir, L. O. *J. Nat. Prod.* **2004**, *67*, 1864.
(104) Suffness, M. *Annu. Rep. Med. Chem.* **1993**, *28*, 305.
(105) Zhang, Z.; Sauriol, F.; Mamer, O.; Zamir, L. O. *J. Nat. Prod.* **2000**, *63*, 929.
(106) Li, S. H.; Zhang, H. J.; Niu, X. M.; Yao, P.; Sun, H. D.; Fong, H. H. S. *Tetrahedron* **2003**, *59*, 37.
(107) Zhang, M. L.; Zhang, J.; Dong, M.; Feng, S. H.; Huo, C. H.; Sauriol, F.; Shi, Q. W.; Gu, Y. C.; Kiyota, H.; Cong, B. *Z. Naturforsch.* **2009**, *64C*, 43.
(108) Zhao, Y.; Wang, F. S; Peng, L. Y.; Li, X. L.; Xu, G.; Luo, X. X.; Lu, Y.; Wu, L.; Zheng, Q. T.; Zhao, Q. S. *J. Nat. Prod.* **2006**, *69*, 1813.
(109) Shen, Y. C.; Lin, Y. S.; Hsu, S. M.; Khalil, A. T.; Wang, S. S.; Chien, C. T.; Kuo, Y. H.; Chou, C. H. *Helv. Chim. Acta* **2007**, *90*, 1319.
(110) Appendino, G.; Jakupovic, J.; Varese, M.; Bombardelli, E. *Tetrahedron Lett.* **1996**, *37*, 727.
(111) Li, L. G.; Tu, G. Z.; Cao, C. M.; Zhang, M. L.; Shi, Q. W. *Chin. Trad. Herb. Drugs* **2006**, *37*, 1454.
(112) Appendino, G.; Cravotto, G.; Enriu, R.; Jakupovic, J.; Gariboldi, P.; Gabetta, B.; Bombardelli, E. *Phytochemistry* **1994**, *36*, 407.
(113) Huo, C. H.; Su, X. H.; Li, X.; Zhang, X. P.; Li, C. F.; Wang, Y. F.; Shi, Q. W; Kiyota, H. *Magn. Reson. Chem.* **2007**, *45*, 527.
(114) Appendino, G.; Ozen, H. C.; Gariboldi, P.; Gabetta, B.; Bombardelli, E. *Fitoterapia* **1992**, *64*, 47.
(115) Kobayashi, J.; Hosoyama, H.; Wang, X. X.; Shigemori, H.; Sudo, Y.; Tsuruo, T. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1555.
(116) Huo, C. H.; Su, X. H.; Wang, Y. F.; Zhang, X. P.; Shi, Q. W.; Kiyota, H. *Tetrahedron Lett.* **2007**, *48*, 2721.
(117) Shi, Q. W.; Sauriol, F.; Mamer, O.; Zamir, L. O. *Tetrahedron Lett.* **2002**, *43*, 6869.
(118) Fang, W. S.; Fang, Q. C.; Liang, X. T.; Lu, Y.; Zheng, Q. T. *Tetrahedron* **1995**, *51*, 8483.
(119) Zamir, L. O.; Zhou, Z. H.; Caron, G.; Nedea, M. E.; Sauriol, F.; Mamer, O. *J. Chem. Soc., Chem. Commun.* **1995**, *5*, 529.
(120) Fang, W. S.; Fang, Q. C.; Liang, X. T. *Planta Med.* **1996**, *62*, 567.
(121) Boulanger, Y.; Khiat, A.; Zhou, Z. H.; Caron, G.; Zamir, L. O. *Tetrahedron* **1996**, *52*, 8957.
(122) Luh, L. J.; Abd El-Razek, M. H.; Liaw, C. C.; Arthur Chen, C. T.; Lin, Y. S.; Kuo, Y. H.; Chien, C. T.; Shen, Y. C. *Helv. Chim. Acta* **2009**, *92*, 1349.
(123) Zamir, L. O; Nedea, M. E.; Garneau, F. X. *Tetrahedron Lett.* **1992**, *33*, 5235.
(124) Hezari, M.; Croteau, R. *Planta Med.* **1997**, *63*, 291.
(125) Nishizawa, M.; Imagawa, H.; Hyodo, I.; Takeji, M.; Morikuni, E.; Asoh, K.; Yamada, H. *Tetrahedron Lett.* **1998**, *39*, 389.
(126) Shi, Q. W.; Li, L. G.; Li, Z. P.; Cao, C. M.; Kiyota, H. *Tetrahedron Lett.* **2005**, *46*, 6301.
(127) Yu, S. H.; Ni, Z. Y.; Zhang, J.; Dong, M.; Sauriol, F.; Huo, C. H.; Shi, Q. W.; Gu, Y. C.; Kiyota, H.; Cong, B. *Biosci. Biotechnol. Biochem.* **2009**, *73*, 756.
(128) Stahlhut, R.; Park, G.; Petersen, R.; Ma, W. W.; Hylands, P. *Biochem. Syst. Ecol.* **1999**, *27*, 613.
(129) Luo, S. D.; Ning, B. M.; Yuan, D. C. *J. Plant Resour. Environ. (Zhiwu Ziyuan Yu Huanjing)* **1994**, *3*, 31.
(130) Chen, C.; Luo, S. Q. *Chin. J. Pharm.* **1997**, *28*, 37.
(131) Zhou, R. H.; Zhu, D. N.; Gao, S. L; Cai, C. H. *J. Chin. Pharm. University (Zhongguo Yaoke Daxue Xuebao)* **1994**, *25*, 259.
(132) Zhang, J. Z.; Fang, Q. C.; Liang, X. T. *J. Chin. Med. Mater. (Zhiwu Xuebao)* **1996**, *38*, 399.
(133) Ma, Z. W.; He, G. F.; Yin, W. F. *J. Chin. Med. Mater. (Zhiwu Xuebao)* **1982**, *24*, 554.
(134) Wang, J. F.; Li, G. L.; Lu, H. Y.; Zheng, Z. H.; Huang, Y. J.; Su, W. J. *FEMS Microbiol. Lett.* **2000**, *193*, 249.
(135) Pulici, M.; Sugawara, F.; Koshino, H.; Okada, G.; Esumi, Y.; Uzama, J.; Yoshida, S. *Phytochemistry* **1997**, *46*, 313.
(136) Stierle, A.; Strobel, G.; Stierle, D. *Science* **1993**, *260*, 214.
(137) Strobel, G.; Yang, X. S.; Sears, J.; Kramer, R.; Sidhu, R. S.; Hess, W. M. *Microbiology* **1996**, *142*, 435.
(138) Wang, J. F.; Lu, H. Y.; Huang, Y. J.; Zheng, Z. H.; Su, W. J. *J. Xiamen Univ. (Nat. Sci.)* **1999**, *38*, 485.
(139) Karlsson, B.; Pilotti, A. M.; Soderholm, A. C. *Tetrahedron* **1978**, *34*, 2349.
(140) Adesomoju, A. A.; Okogun, J. I. *J. Nat. Prod.* **1984**, *47*, 308.
(141) Nagashima, F.; Tamada, A.; Fuji, N.; Asakawa, Y. *Phytochemistry* **1997**, *46*, 1203.
(142) Hernández-Hernández, J. D.; Román-Marín, L. U.; Cerda-García-Rojas, C. M.; Joseph-Nathan, P. *J. Nat. Prod.* **2005**, *68*, 1598.
(143) Jackson, C. B.; Pattenden, G. *Tetrahedron Lett.* **1985**, *26*, 3393.
(144) Begley, M. J.; Jackson, C. B.; Pattenden, G. *Tetrahedron* **1990**, *46*, 4907.
(145) Duh, C. Y.; El-Gamal, A. A. H.; Wang, S. K.; Dai, C. F. *J. Nat. Prod.* **2002**, *65*, 1429.
(146) Duh, C. Y.; Li, C. H.; Wang, S. K.; Dai, C. F. *J. Nat. Prod.* **2006**, *69*, 1188.
(147) Shen, Y. C.; Lin, J. J.; Wu, Y. R.; Chang, J. Y.; Duh, C. Y.; Lo, K. L. *Tetrahedron Lett.* **2006**, *47*, 6651.
(148) Shen, Y. C.; Lin, J. J.; Kuo, Y. H.; Cheng, Y. B. *Tetrahedron Lett.* **2005**, *46*, 7893.
(149) Wickremesinhe, E. R. M.; Arteca, R. N. *J. Liq. Chromatogr.* **1993**, *16*, 3263.
(150) Witherup, K. M.; Look, S. A.; Stasko, M. W.; McCloud, T. G.; Issaq, H. J.; Muschik, G. M. *J. Liq. Chromatogr.* **1989**, *12*, 2117.
(151) Castor, T. P.; Tyler, T. A. *J. Liq. Chromatogr.* **1993**, *16*, 723.
(152) Mattina, M. J. I.; MacEachern, G. J. *J. Chromatogr. A* **1994**, *679*, 269.
(153) Fang, W.; Wu, Y.; Zhou, J.; Chen, W.; Fang, Q. *J. Chin. Pharm. Sci.* **1995**, *4*, 47.
(154) Fang, W.; Wu, Y.; Zhou, J.; Chen, W.; Fang, Q. *Phytochem. Anal.* **1993**, *4*, 115.
(155) Neto, A. G. F.; DiCosmo, F. *Planta Med.* **1992**, *58*, 464.
(156) Kopycki, W. J.; El Sohly, H. N.; McChesney, J. D. *J. Liq. Chromatogr.* **1994**, *17*, 2569.
(157) Jennings, D. W.; Deutsh, H. M.; Leon, H. Z.; Amyn, S. T. *J. Supercrit. Fluids* **1992**, *5*, 1.
(158) Heaton, D. M.; Bartle, K. D.; Rayner, C. M.; Clifford, A. A. *J. High Resolut. Chromatogr.* **1993**, *16*, 666.
(159) Chun, M.-K.; Shin, H.-W.; Lee, H. *J. Supercrit. Fluids* **1996**, *9*, 192.
(160) Vandana, V.; Teja, A. S.; Zalkow, L. H. *Fluid Phase Equilib.* **1996**, *116*, 162.
(161) Mattina, M. J. I.; Berger, W. A. I.; Denson, C. L. *J. Agric. Food Chem.* **1997**, *45*, 4691.
(162) Björklund, E.; Järemo, M.; Mathiasson, L.; Karlsson, L.; Strode, J. T., III; Eriksson, J.; Torstensson, A. *J. Liq. Chromatogr., Relat. Technol.* **1998**, *21*, 535.
(163) Richter, B. E.; Jones, B. A.; Ezzell, J. L.; Porter, N. L.; Avdalovie, N.; Pohl, C. *Anal. Chem.* **1996**, *68*, 1033.
(164) Schafer, K. *Anal. Chim. Acta* **1998**, *358*, 69.
(165) Kawamura, F.; Kikuchi, Y.; Ohira, T.; Yatagai, M *J. Nat. Prod.* **1999**, *62*, 244.
(166) Shao, L. K.; Locke, D. C. *Anal. Chem.* **1997**, *69*, 2008.
(167) Reichheimer, S. L.; Tinnermeier, D. M.; Timmons, D. W. *Anal. Chem.* **1992**, *64*, 2323.

(168) Liu, J.; Volk, K. J.; Mata, M. J.; Kerns, E. H.; Lee, M. S. *J. Pharm. Biomed. Anal.* **1997**, *18*, 1729.
(169) Theodoridis, G.; Laskaris, G.; de Jong, C. F.; Hofte, A. J. P.; Verpoorte, R. *J. Chromatogr., A* **1998**, *802*, 297.
(170) Wu, Y.; Zhu, W. *J. Liq. Chromatogr., Relat. Technol.* **1997**, *20*, 3147.
(171) Harvey, S. D.; Campbell, J. A.; Kelsey, R. G.; Vance, N. C. *J. Chromatogr.* **1991**, *587*, 300.
(172) Ketchum, R. E. B.; Gibson, D. M. *J. Liq. Chromatogr.* **1993**, *16*, 2519.
(173) Dolfinger, R.; Locke, D. C. *Anal. Chem.* **2003**, *75*, 1355.
(174) Theodoridis, G. A. *Encyclopedia of Chromatography*, 3rd ed.; CRC Press: Boca Raton, FL, 2010; pp 2274−2280.
(175) Wall, M. E. *Med. Res. Rev.* **1998**, *18*, 299.
(176) Eldridge, G. R.; Vervoort, H. C.; Lee, C. M.; Cremin, P. A.; Williams, C. T.; Hart, S. M.; Goering, M. G.; O'Neil-Johnson, M.; Zeng, L. *Anal. Chem.* **2002**, *74*, 3963.
(177) Schneider, B.; Zhao, Y.; Blitzke, T.; Shmitt, B.; Nookandeh, A.; Sun, X.; Stöckigt, J. *Phytochem. Anal.* **1998**, *9*, 237–244.
(178) Stefanowicz, P.; Prasain, J. K.; Yeboah, K. F.; Konishi, Y. *Anal. Chem.* **2001**, *73*, 3583.
(179) Woods, M. C.; Nakanishi, K. *Tetrahedron* **1966**, *22*, 243.
(180) Appendino, G. In *Taxol: Science and Applications*; Farina, V., Ed.; Elsevier: Amsterdam, 1995; Vol. 22, p 1.
(181) Shi, Q. W.; Oritan, T.; Zhao, D.; Murakami, R.; Yamada, T. *Planta Med.* **2000**, *66*, 294.
(182) Shi, Q. W.; Petzke, T. L.; Sauriol, F.; Mamer, O.; Zamir, L. O. *Can. J. Chem.* **2003**, *81*, 64.
(183) Baxter, J. N.; Lythgoe, B.; Scales, B.; Scrowston, R. M.; Trippett, S. *J. Chem. Soc.* **1962**, *1*, 2964.
(184) Chen, Y. J.; Chen, C. Y.; Shen, Y. C. *J. Nat. Prod.* **1999**, *62*, 149.
(185) Shi, Q. W.; Oritani, T.; Sugiyama, T.; Yamada, T. *Phytochemistry* **1999**, *52*, 1571.
(186) Appendino, G.; Ozen, H. C.; Fenoglio, I.; Gariboldi, P.; Gabetta, B.; Bombardelli, E. *Phytochemistry* **1993**, *33*, 1521.
(187) Shi, Q. W.; Li, Z. P.; Zhao, D.; Gu, J. S.; Kiyota, H. *Nat. Prod. Res.* **2006**, *20*, 47.
(188) Sugiyama, T.; Oritani, T.; Oritani, T. *Biosci. Biotechnol. Biochem.* **1994**, *58*, 1923.
(189) Topcu, G.; Sultana, N.; Akhtar, F.; Habib-ur-Rehman; Hussain, T.; Choudhary, M. I.; Atta-ur-Rahman *Nat. Prod. Lett.* **1994**, *4*, 93.
(190) Shi, Q. W.; Oritani, T.; Kiyota, H. *Nat. Prod. Lett.* **1998**, *12*, 85.
(191) Shi, Q. W.; Dong, M.; Huo, C. H.; Su, X. H.; Li, C. F.; Zhang, X. P.; Wang, Y. F.; Kiyota, H. *Biosci. Biotechnol. Biochem.* **2007**, *71*, 1777.
(192) Zhang, Z.; Jia, Z.; Zhu, Z.; Cui, Y.; Cheng, J.; Wang, Q. *Planta Med.* **1990**, *56*, 293.
(193) Yoshizaki, F.; Fuduka, M.; Hisamichi, S.; Ishida, T.; In, Y. *Chem. Pharm. Bull.* **1988**, *36*, 2098.
(194) Wang, X. X.; Shigemori, H.; Kobayashi, J. *Tetrahedron Lett.* **1997**, *38*, 7587.
(195) Shi, Q. W.; Oritani, T.; Sugiyama, T.; Murakami, R.; Wei, H. *J. Nat. Prod.* **1999**, *62*, 1114.
(196) Shi, Q. W.; Oritani, T.; Sugiyama, T.; Cheng, Q. *Nat. Prod. Lett.* **1999**, *13*, 305.
(197) Chen, W. M.; Zhang, P. L.; Zhou, J. Y. *Acta Pharmacol. Sin. (Yaoxue Xuebao)* **1994**, *29*, 207.
(198) Viterbo, D.; Milanesio, M.; Appendino, G.; Chattopadhyay, S. K.; Saha, G. C. *Acta Crystallogr.* **1997**, *CS3*, 1687.
(199) Barboni, L.; Lambertucci, C.; Gariboldi, P.; Appendino, G. *Phytochemistry* **1997**, *46*, 179.
(200) Zhang, Z.; Jia, Z. *Phytochemistry* **1990**, *29*, 3673.
(201) Barboni, L.; Pierluigi, G.; Torregiani, E.; Appendino, G.; Gabetta, B.; Zini, G.; Bombardelli, E. *Phytochemistry* **1993**, *33*, 145; structure should be revised to the corresponding 11(15→1)*abeo*taxane.
(202) Zamir, L. O.; Nedea, M. E.; Zhou, Z. H.; Belair, S.; Caron, G.; Sauriol, F.; Jacomain, E.; Jean, F. I.; Garneau, F. X.; Mamer, O. *Can. J. Chem.* **1995**, *73*, 655.
(203) Lian, J. Y.; Min, Z. D.; Mizuno, M.; Tanaka, T.; Iinuma, M. *Phytochemistry* **1988**, *27*, 3674.
(204) Della Casa de Marcano, D. P.; Halsall, T. G. *J. Chem. Soc. D* **1969**, *21*, 1282.
(205) Shinozaki, Y.; Fukamiya, N.; Fukushima, M.; Okano, M.; Nehira, T.; Tagahara, K.; Zhang, S. X.; Zhang, D. C.; Lee, K. H. *J. Nat. Prod.* **2002**, *64*, 371.
(206) Shen, Y. C.; Chen, Y. J.; Chen, C. Y. *Phytochemistry* **1999**, *52*, 1565.
(207) Li, B.; Tanaka, K.; Fuji, K.; Sun, H.; Taga, T. *Chem. Pharm. Bull.* **1993**, *41*, 1672.
(208) Fuji, K.; Tanaka, K.; Li, B.; Shingu, T.; Yokoi, T.; Sun, H. D.; Taga, T. *Tetrahedron* **1995**, *51*, 10175.
(209) Shi, Q. W.; Oritani, T.; Sugiyama, T.; Kiyota, H.; Horiguchi, T. *Heterocycles* **1999**, *51*, 841.
(210) Shi, Q. W.; Horiguchi, T.; Oritani, T.; Zhao, D. *Biosci. Biotechnol. Biochem.* **2000**, *64*, 869.
(211) Zhang, H.; Tadeda, Y.; Sun, H. *Phytochemistry* **1995**, *39*, 1147.
(212) Rao, C.; Zhou, J. Y.; Chen, W. M.; Lu, Y.; Zheng, Q. T. *Chin. Chem. Lett.* **1993**, *4*, 693.
(213) Shi, Q. W.; Zhao, Y. M.; Si, X. T.; Li, Z. P.; Yamada, T.; Kiyota, H. *J. Nat. Prod.* **2006**, *69*, 280.
(214) Shi, Q. W.; Oritani, T.; Kiyota, H.; Zhao, D. *Phytochemistry* **2000**, *54*, 829.
(215) Kiyota, H.; Shi, Q. W.; Oritani, T.; Li, L. *Biosci. Biotechnol. Biochem.* **2001**, *65*, 35.
(216) Zamir, L. O.; Zhang, J.; Kutterer, K.; Sauriol, F.; Mamer, O.; Khiat, A.; Boulanger, Y. *Tetrahedron* **1998**, *54*, 15845.
(217) Yang, C.; Wang, J. S.; Luo, J. G.; Kong, L. Y. *J. Asian Nat. Prod. Res.* **2009**, *11*, 534.
(218) Shi, Q. W.; Sauriol, F.; Lesimple, A.; Zamir, L. O. *Chem. Commun.* **2004**, *5*, 544.
(219) Shi, Q. W.; Sauriol, F.; Mamer, O.; Zamir, L. O. *Chem. Commun.* **2003**, *1*, 68.
(220) Shi, Q. W.; Oritani, T.; Horiguchi, T.; Sugiyama, T.; Yamada, T. *Biosci. Biotechnol. Biochem.* **1999**, *63*, 756.
(221) Shi, Q. W.; Oritani, T.; Sugiyama, T. *Planta Med.* **1999**, *65*, 356.
(222) Madhusudanan, K. P.; Chattopadhyay, S. K.; Tripathi, V. K.; Sashidhara, K. V.; Kukreja, A. K.; Jain, S. P. *Biomed. Chromatogr.* **2002**, *16*, 343.
(223) Hoke, S. H.; Wood, J. M.; Cooks, R. G.; Li, X. H.; Chang, C. J. *Anal. Chem.* **1992**, *64*, 2313.
(224) Madhusudanan, K. P.; Chattopadhyay, S. K.; Saha, G. C.; Kulshrestha, M.; Sharma, R. P.; Sushil, K. *J. Mass Spectrom.* **1997**, *32*, 216.
(225) Madhusudanan, K. P.; Chattopadhyay, S. K.; Srivastava, S. *J. Mass Spectrom.* **2002**, *37*, 91.
(226) Chang, Y.; Abliz, Z.; Li, L. J.; Fang, Q. C.; Takayama, M. *J. Mass Spectrom.* **2000**, *35*, 1207.
(227) Joshi, B. S.; Roy, R.; Chattopadhyay, S. K.; Madhusudanan, K. P. *J. Mol. Struct.* **2003**, *645*, 235.
(228) Bitsch, V.; Shackleton, C.; Ma, W.; Park, G. L.; Nieder, M. *Rapid. Commun. Mass. Spectrom.* **1993**, *7*, 891.
(229) Kobayashi, J.; Hosoyama, H.; Katsui, T.; Yoshida, N.; Shigemori, H. *Tetrahedron* **1996**, *52*, 5391.
(230) Shi, Q. W.; Si, X. T.; Zhao, Y. M.; Su, X. H.; Li, X.; Zamir, L. O.; Yamada, T.; Kiyota, H. *Biosci. Biotechnol. Biochem.* **2006**, *70*, 732.
(231) Madhusudanan, K. P.; Chattopadhyay, S. K.; Tripathi, V. K.; Sashidhara, Kumar, S. *Phytochem. Anal.* **2002**, *13*, 18.
(232) Ye, M.; Guo, D.-A. *Rapid Commun. Mass Spectrom.* **2005**, *19*, 818.
(233) Konishi, Y.; Kiyota, T.; Draghici, C.; Gao, J.-M.; Yeboah, F.; Acoca, S.; Jarussophon, S.; Purisima, E. *Anal. Chem.* **2007**, *79*, 1187.
(234) Shi, Q. W.; Ji, X.; Lesimple, A.; Sauriol, F.; Zamir, L. O. *Phytochemistry* **2004**, *65*, 3097.
(235) Denis, J. N.; Greene, A. E. *J. Am. Chem. Soc.* **1988**, *110*, 5917.
(236) Chen, S. H.; Huang, S.; Wei, J. M.; Farian, V. *Tetrahedron* **1993**, *49*, 2805.

(237) Hosoyama, H.; Shigemori, H.; Kobayashi, J. *J. Chem. Soc., Perkin Trans. 1* **2000**, *3*, 449.
(238) MacEachern-Keith, G. J.; Wagner Butterfield, L. J.; Incorvia Mattina, M. J. *Anal. Chem.* **1997**, *69*, 72.
(239) Appendino, G.; Fenoglio, I. *J. Nat. Prod.* **1997**, *60*, 464.
(240) James, P. S.; Neysa, N.; Daniel, O. C.; Johanna, J. *J. Am. Chem. Soc.* **2000**, *122*, 724.
(241) Downing, K. H.; Nogales, E. *Curr. Opin. Struct. Biol.* **1998**, *8*, 785.
(242) Jordan, M. A. *Curr. Med. Chem. Anticancer Agents* **2002**, *2*, 1.
(243) Hamel, E. *Med. Res. Rev.* **1996**, *16*, 207.
(244) Sullivan, K. F. *Annu. Rev. Cell Biol.* **1988**, *4*, 687.
(245) Bershadsky, A. D.; Vasiliev, J. M. *Cytoskeleton*; Plenum: New York, 1989, 100.
(246) Purich, D. L.; Kristofferson, D. *Adv. Protein Chem.* **1984**, *36*, 133.
(247) (a) Haimo, L. T. *Methods Cell Biol.* **1982**, *24*, 189. (b) Burton, P. R.; Hims, R. H. *J. Cell Biol.* **1978**, *77*, 120. (c) Mandelkow, E. M.; Mandelkow, E. *J. Mol. Biol.* **1979**, *129*, 135.
(248) Lifeng, H.; George, A. O.; Susan, B. H. *DDT* **2001**, *6*, 1153.
(249) Parness, J.; Horwitz, S. B. *J. Cell Biol.* **1981**, *91*, 479.
(250) Manfredi, J. J.; Parness, J.; Horwitz, S. B. *J. Cell Biol.* **1982**, *94*, 688.
(251) Horwitz, S. B. *Trends Pharmacol. Sci.* **1992**, *13*, 134.
(252) Manfredi, J. J.; Horwitz, S. B. *Pharmacol. Ther.* **1984**, *25*, 83.
(253) Antonella, M.; Claudia, B.; Ludovica, G. *Chem.-Biol. Interact.* **2002**, *139*, 283.
(254) Loewe, J.; Li, H.; Downing, K. H.; Nogales, E. *J. Mol. Biol.* **2001**, *313*, 1045.
(255) Amos, L. A.; Lowe, J. *Chem. Biol.* **1999**, *6*, 65.
(256) Diaz, J. F.; Andreu, J. M. *Biochemistry* **1993**, *32*, 2747.
(257) Fromes, V.; Guonon, P.; Bissery, M. C.; Fellous, A. *Proc. Am. Assoc. Cancer Res.* **1992**, *33*, 511.
(258) Claudia, J. B.; Mohan, L. G., Jr.; Emily, A. R.; Kathy, A. S.; Gunda, I. G.; Richard, H. H. *Biochemistry* **2002**, *41*, 3870.
(259) Schiff, P. B.; Horwitz, S. B. *Biochemistry* **1981**, *20*, 3247.
(260) Jordan, M. A.; Toso, R. J.; Wilson, L. *Proc. Natl. Acad. Sci. U.S.A.* **1993**, *90*, 9552.
(261) Kingston, D. G. I. *J. Nat. Prod.* **2000**, *63*, 726.
(262) Georg, G. I.; Harriman, G. C. B.; Vandervelde, D. G.; Boge, T. C.; Cheruvallath, Z. S.; Datta, A.; Hepperle, M.; Park, H.; Himes, R. H.; Jayasinghe, L. In *Taxane Anticancer Agent*; Georg, G. I., Chen, T. T., Ojima, I., Vyas, D. M., Eds.; ACS Symposium Series 583; American Chemical Society: Washington, DC, 1995; p 217.
(263) Kingston, D. G. I. *Pharmacol. Ther.* **1991**, *52*, 1.
(264) Kingston, D. G. I. In *Taxane Anticancer Agent*; Georg, G. I., Chen, T. T., Ojima, I., Vyas, D. M., Eds.; ACS Symposium Series 583; American Chemical Society: Washington, DC, 1995; p 203.
(265) Guenard, D.; Gueritte-Voegelein, F.; Potier, P. *Acc. Chem. Res.* **1993**, *26*, 160.
(266) (a) *Taxol, Science and Applications*; Suffness, M., Ed., CRC: Boca Raton, FL, 1995. (b) *Taxane Anticancer Agent*; Georg, G. I., Chen, T. T., Ojima, I., Vyas, D. M., Eds.; ACS Symposium Series 583; American Chemical Society: Washington, DC, 1995. (c) *Taxol: Science and Applications*; Farina, V., Ed.; Elsevier: Amsterdam, 1995; Vol. 22.
(267) Kingston, D. G. I.; Magri, N. F.; Jitrangsri, C. *Nat. Prod. Chem.* **1986**, *26*, 219.
(268) Braga, S. F.; Galvão, D. S. *J. Mol. Graphics Modell.* **2002**, *21*, 57.
(269) Gunatilaka, A. A. L.; Ramdayal, F. D.; Sarragiotto, M. H.; Kingston, D. G. I.; Sackett, D. L.; Hamel, E. *J. Org. Chem.* **1999**, *64*, 2694.
(270) Barboni, L.; Giarlo, G.; Ricciutelli, M.; Ballini, R.; Georg, G. I.; Vander Velde, D. G.; Himes, R. H.; Wang, M. M.; Lakdawala, A.; Snyder, J. P. *Org. Lett.* **2004**, *6*, 461.
(271) Chordia, M. D.; Kingston, D. G. I. *J. Org. Chem.* **1996**, *61*, 799.
(272) Kingston, D. G. I. *Pure Appl. Chem.* **1998**, *70*, 331.
(273) Kadow, J. F.; Chen, S. H.; Dextraze, P.; Fairchild, C. R.; Golik, J.; Hansel, S. B.; Johnston, K. A.; Kramer, R. A.; Lee, F. Y.; Long, B. H.; Ouellet, C.; Perrone, R. K.; Rose, W. C.; Schulze, G. E.; Xue, M.; Wei, J. M.; Wittman, M. D.; Wong, H.; Wright, J. J. K.; Zoeckler, M. E.; Vyas, D. M. Presented at the 219th ACS National Meeting, San Francisco, CA, 2001, Abstr. MEDI 298.
(274) Chaudhary, A. G.; Rimoldi, J. M.; Kingston, D. G. I. *J. Org. Chem.* **1993**, *58*, 3798.
(275) Ishiyama, T.; Iimura, S.; Ohsuki, S.; Uoto, K.; Terasawa, H.; Soga, T. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1083.
(276) Takeda, Y.; Uoto, K.; T.; Chiba, J.; Horiuchi, T.; Iwahana, M.; Atsumi, R.; Ono, C.; Terasawa, H.; Soga, T. *Bioorg. Med. Chem.* **2003**, *11*, 4431.
(277) Kobayashi, J. H. H.; Wang, X. X.; Shigemori, H.; Koiso, Y. I. S.; Sasaki, T.; Naito, M.; Tsuruo, T. *Bioorg. Med. Chem. Lett.* **1977**, *7*, 393.
(278) Kingston, D. G. I. *Phytochemistry* **2007**, *68*, 1844.
(279) Eisenhauer, E. A.; Vermorken, J. B. *Drugs* **1998**, *55*, 5.
(280) Crown, J.; O'Leary, M. *The Lancet* **2000**, *355*, 1176.
(281) Nicolas, A.; Christophe, M. *Cancer Treat. Rev.* **2006**, *32*, 65.
(282) Gotaskie, R. E.; Andreassi, B. F. *Cancer Pract.* **1994**, *2*, 27.
(283) Nicolaou, K. C.; Guy, R. K.; Potier, P. *Sci. Am.* **1996**, *6*, 94.
(284) Altmann, K. H. *Curr. Opin. Chem. Biol.* **2001**, *5*, 424.
(285) Safavy, A.; Raisch, K. P.; Khazaeli, M. B.; Buchsbaum, D. J.; Bonner, J. A. *J. Med. Chem.* **1999**, *42*, 4919.
(286) Ojima, I.; Geney, R.; Ungureanu, I. M.; Li, D. *IUBMB Life* **2002**, *53*, 269.
(287) Distefano, M.; Scambia, G.; Ferilini, C.; Gaggini, C.; De Vincenzo, R.; Riva, A.; Bombardelli, E.; Ojima, I.; Fattorossi, A.; Bennedetti Panici, P.; Mancuso, S. *Int. J. Cancer* **1997**, *72*, 844.
(288) Mastalerz, H.; Cook, D.; Fairchild, C. R.; Hansel, S.; Johnson, W.; Kadow, J. F.; Long, B. H.; Rose, W. C.; Tarrant, J.; Wu, M. J.; Xue, M. Q.; Zhang, G. F.; Zoeckler, M.; Vyas, D. M. *Bioorg. Med. Chem.* **2003**, *11*, 4315.
(289) Ojima, I.; Bounaud, P. Y.; Bernacki, R. J. *CHEMTECH* **1998**, *28*, 31.
(290) Jennewein, S.; Croteau., R. *Appl. Microbiol. Biotechnol.* **2001**, *57*, 13.
(291) Swindell, C. S. *Org. Prep. Proced. Int.* **1991**, *23*, 465.
(292) (a) Holton, R. A.; Somoza, C.; Kim, H. B.; Liang, F.; Biediger, R. J.; Boatman, D.; Shindo, M.; Smith, C. C.; Kim, S.; Nadizadeh, H.; Suzuki, Y.; Tao, C.; Vu, P.; Tang, S.; Zhang, P.; Murthi, K. K.; Gentile, L. S.; Liu, J. H. *J. Am. Chem. Soc.* **1994**, *116*, 1597. (b) Holton, R. A.; Somoza, C.; Kim, H. B.; Liang, F.; Biedige, R. J.; Boatman, D.; Shindo, M.; Smith, C. C.; Kim, S.; Nadizadeh, H.; Suzuki, Y.; Tao, C.; Vu, P.; Tang, S.; Zhang, P.; Murthi, K. K.; Gentile, L. S.; Liu, J. H. *J. Am. Chem. Soc.* **1994**, *116*, 1599. (c) Nicolaou, K. C.; Nantermet, P. G.; Ueno, H.; Guy, R. K.; Coulandouros, E. A.; Sorensen, E. J. *J. Am. Chem. Soc.* **1995**, *117*, 624. (d) Nicolaou, K. C.; Liu, J. J.; Yangh, H.; Claiborne, C. F.; Hwang, C. K.; Nakada, M.; Nantermet, P. G.; Ueno, H.; Guy, R. K.; Sorensen, E. J. *J. Am. Chem. Soc.* **1995**, *117*, 634. (e) Nicolaou, K. C.; Liu, J. J.; Yangh, H.; Claiborne, C. F.; Renaud, J.; Nantermet, P. G.; Guy, R. K.; Shibayama, K. *J. Am. Chem. Soc.* **1995**, *117*, 645. (f) Nicolaou, K. C.; Ueno, H.; Liu, J. J.; Yangh, H.; Renaud, J.; Nantermet, P. G.; Paulvannan, K.; Chadha, R. *J. Am. Chem. Soc.* **1995**, *117*, 653. (g) Danishefsky, S. J.; Masters, J. J.; Young, W. B.; Link, J. T.; Snyder, L. B.; Magee, T. B.; Jung, D. K.; Isaacs, R. C. A.; Bornman, W. G.; Alaimo, C. A.; Coburn, C. A.; DiGrandi, M. J. *J. Am. Chem. Soc.* **1996**, *118*, 2843. (h) Wender, P. A.; Badham, N. F.; Conway, S. P.; Floreancig, P. E.; Glass, T. E.; Granicher, C.; Houze, J. B.; Janichen, J.; Lee, D.; Marquess, D. G.; McGrane, P. L.; Meng, W.; Mucciaro, T. P.; Muhlebach, M.; Natchus, M. G.; Paulsen, H.; Rawlins, D. B.; Satkofsky, J.; Shuker, A. J.; Sutton, J. C.; Taylor, R. E.; Tomooka, K. I. *J. Am. Chem. Soc.* **1997**, *119*, 2755. (i) Wender, P. A.; Badham, N. F.; Conway, S. P.; Floreancig, P. E.; Glass, T. E.; Houze, J. B.; Krauss, N. E.; Lee, D.; Marquess, D. G.; McGrane, P. L.; Meng, W.; Natchus, M. G.; Shuker, A. J.; Sutton, J. C.; Taylor, R. E. *J. Am. Chem. Soc.* **1997**, *119*, 2757. (j) Mukaiyama, T.; Shiina, I.; Iwadare, H.; Saitoh, M.; Nishimura, T.; Ohkawa, N.; Sahoh, H.; Nishimura, K.; Tani, Y.; Hasegawa, M.; Yamada, K.; Saitoh, K. *Chem.—Eur. J.* **1999**, *5*, 121. (k) Kusama, H.; Hara, R.; Kawahara, S.; Nishimori, T.; Kashima, H.; Nakamura, N.; Morihira, K.; Kuwajima, I. *J. Am. Chem. Soc.* **2000**, *122*, 3811.
(293) Nicolaou, K. C.; Dai, W. M.; Guy, R. K. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 15.

(294) Huang, Q.; Roessner, C. A.; Croteau, R.; Scott, A. I. *Bioorg. Med. Chem.* **2001**, *9*, 2237.
(295) Dai, J. G.; Ye, M.; Guo, H. Z.; Zh, W. H.; Zhang, D. Y.; Hu, H.; Zheng, J. H.; Guo, D. A. *Tetrahedron* **2002**, *58*, 5659.
(296) Dai, J. G.; Zhang, S. J.; Sakai, J. I.; Bai, J. *Tetrahedron Lett.* **2003**, *44*, 1091.
(297) Zhang, J. Z.; Zhang, L. H.; Wang, X. H.; Qiu, D. Y.; Sun, D. A.; Gu, J. Q.; Fang, Q. C. *J. Nat. Prod.* **1998**, *61*, 497.
(298) Zhang, S. J.; Wang, J. L.; Hirose, K.; Ando, M. *J. Nat. Prod.* **2002**, *65*, 1786.
(299) Sun, D. A.; Sauriol, F.; Mamer, O.; Zamir, L. O. *Bioorg. Med. Chem.* **2001**, *9*, 793.
(300) Sun, D. A.; Nikolakakis, A.; Sauriol, F.; Mamer, O.; Zamir, L. O. *Bioorg. Med. Chem.* **2001**, *9*, 1985.
(301) Hu, S. H.; Tian, X. F.; He, W. Y.; Kong, M.; Sun, D. A.; Fang, Q. C. *Chin. Chem. Lett.* **1998**, *9*, 39.
(302) Shen, Y. C.; Lo, K. L.; Lin, C. L.; Chakraborty, R. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 4493.
(303) Ketchum, R. E. B.; Rithner, C. D.; Qiu, D. Y.; Kim, Y. S.; Williams, R. M.; Croteau, R. B. *Phytochemistry* **2003**, *62*, 901.
(304) Menhard, B.; Eisenreich, W.; Hylands, P. J.; Bacher, A.; Zenk, M. H. *Photochemistry* **1998**, *49*, 113.
(305) Vanĕk, T.; Mala, J.; Saman, D.; Silhava, I. *Planta Med.* **1999**, *65*, 275.
(306) Srinivasan, V.; Pestchanker, L.; Moser, S. *Biotechnol. Bioeng.* **1995**, *47*, 666.
(307) Renzulli, M. L.; Rocheblave, L.; Avramova, S.; Corelli, F.; Botta, M. *Tetrahedron Lett.* **2004**, *45*, 5155.
(308) Gutta, P.; Tantillo, D. J. *Org. Lett.* **2007**, *9*, 1069.
(309) Duquesnoy, E.; Paoli, M.; Castola, V.; Bighelli, A.; Casanova, J. *Phytochem. Anal.* **2009**, *20*, 246.
(310) Castola, V.; Bighelli, A.; Casanova, J. *Appl. Spectrosc.* **1999**, *53*, 344.
(311) Tomi, F.; Bradesi, P.; Bighelli, A.; Casanova, J. *J. Magn. Reson. Anal.* **1995**, *1*, 25.
(312) Kobayashi, J.; Shigemori, H. *Heterocycles* **1999**, *52*, 1111.
(313) Horiguchi, T.; Rithner, C. D.; Croteaub, R.; Williams, R. M. *Tetrahedron* **2003**, *59*, 267.
(314) Horiguchi, T.; Rithner, C. D.; Croteaub, R.; Williams, R. M. *J. Org. Chem.* **2002**, *67*, 4901.
(315) Vazquez, A.; Williams, R. M. *J. Org. Chem.* **2000**, *65*, 7865.
(316) Walker, K.; Croteau, R. *Phytochemistry* **2001**, *58*, 1.
(317) Walker, K.; Croteau, R. *Proc. Natl. Acad. Sci. U.S.A.* **2000**, *97*, 583.
(318) Walker, K.; Schoendorf, A.; Croteau, R. *Arch. Chem. Biophys.* **2000**, *374*, 371.
(319) Williams, D. C.; Wildung, M. R.; Jin, A. Q.; Dalal, D.; Oliver, J. S.; Coates, R. M.; Croteau, R. *Arch. Biochem. Biophys.* **2000**, *379*, 137.
(320) Ketchum, R. E. B.; Horiguchi, T.; Qiu, D.; Williams, R. M.; Croteau, R. *Phytochemistry* **2007**, *68*, 335.
(321) Li, H.; Horiguchi, T.; Croteau, R.; Williams, R. M. *Tetrahedron* **2008**, *64*, 6561 and references cited therein.
(322) Topcu, G.; Demirkiran, O. *Top. Heterocycl. Chem.* **2007**, *11*, 103.
(323) Shi, Q. W.; Oritani, T.; Sugiyama, T.; Kiyota, H. *Nat. Prod. Lett.* **2001**, *15*, 55.
(324) Zamir, L. O.; Zhang, J.; Wu, J.; Sauriol, F.; Mamer, O. *J. Nat. Prod.* **1999**, *62*, 1268.
(325) Shi, Q. W.; Oritani, T.; Horiguchi, T.; Sugiyama, T.; Murakami, R.; Yamada, T. *Biosci. Biotechnol. Biochem.* **1999**, *63*, 924.
(326) Shi, Q. W.; Sauriol, F.; Mamer, O.; Zamir, L. O. *J. Nat. Prod.* **2003**, *66*, 470.
(327) Erdtman, H.; Tsuno, K. *Phytochemistry* **1969**, *8*, 931.
(328) Liu, C. L.; Lin., Y. C.; Lin, Y. M.; Chen, F. C. *Taiwan Kexue* **1984**, *38*, 119.
(329) Ho, T. I.; Lee, G. H.; Peng, S. M.; Yeh, M. K.; Chen, F. C.; Yang, W. L. *Acta Crystallogr. Sect. C* **1987**, *43*, 1378.
(330) Miyazaki, M.; Kazumasa, S.; Mishima, H.; Kurabayashi, M. *Chem. Pharm. Bull.* **1968**, *16*, 546.
(331) Zhang, H.; Takeda, Y.; Minami, Y.; Yoshida, K.; Matsumoto, T.; Xiang, W.; Mu, O.; Sun, H. *Chem. Lett.* **1994**, *5*, 957.
(332) Zhang, Z. P.; Wiedenfeld, H.; Roder, E. *Phytochemistry* **1995**, *38*, 667.
(333) Yang, S. J.; Fang, J. M.; Cheng, Y. S. *Phytochemistry* **1996**, *43*, 839.
(334) Barboni, L.; Gariboldi, P.; Appendino, G.; Enriu, R.; Gabetta, B.; Bombardelli, E. *Liebigs Ann.* **1995**, *2*, 345.
(335) Zhang, J. Z.; Fang, Q. C.; Liang, X. T.; Kong, M.; He, W. Y. *Chin. Chem. Lett.* **1995**, *6*, 967.
(336) Chattopadhyay, S. K.; Sharma, R. P. *Phytochemistry* **1995**, *39*, 935.
(337) Yeh, M. K.; Wang, J. S.; Lui, L. P.; Chen, F. C. *J. Chin. Biochem. Soc.* **1988**, *35*, 309.
(338) Kingston, D. G. I.; Hawkins, D. R.; Ovington, L. *J. Nat. Prod.* **1982**, *45*, 466.
(339) Jia, Z. J.; Zhang, Z. P. *Chin. Sci. Bull.* **1991**, *36*, 1174. Structure revision to the corresponding 11(15→1)*abeo*-taxoid has been suggested: Huang, K.; Liang, J.; Gunatilaka, A. A. L. *J. Chin. Pharm. Univ. (Zhongguo Yaoke Daxue Xuebao)* **1998**, *29*, 259.
(340) Chattopadhyay, S. K.; Pal, A.; Maulik, P. R.; Kaur, T.; Garga, A.; Khanuja, S. P. S. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2446.
(341) Nguyen, N. T.; Banskota, A. H.; Tezuka, Y.; Nobukawa, T.; Kadota, S. *Phytochemistry* **2003**, *64*, 1141.
(342) Li, L. G.; Cao, C. M.; Huo, C. H.; Zhang, M. L.; Shi, Q. W.; Kiyota, H. *Magn. Reson. Chem.* **2005**, *43*, 475.
(343) Wang, X. X.; Shigemori, H.; Kobayashi, J. *J. Nat. Prod.* **1998**, *61*, 474.
(344) Kobayashi, J.; Inubushi, A.; Hosoyama, H.; Yoshida, N.; Sasaki, T.; Shigemori, H. *Tetrahedron* **1995**, *51*, 5971.
(345) Tong, X. J.; Fang, W. S.; Zhou, J. Y.; He, C. H.; Chen, W. M.; Fang, Q. C. *J. Nat. Prod.* **1995**, *58*, 233.
(346) Li, Z. P.; Wang, C. L.; Gu, J. S.; Shi, Q. W. *Chin. J. Chin. Mater. Med. (Zhongguo Zhongyao Zazhi)* **2005**, *30*, 1260.
(347) Li, Z. P.; Shi, Q. W. *Chin. Tradit. Herb. Drugs (Zhongcaoyao)* **2000**, *31*, 490.
(348) Chiang, H. C. *Shih Ta Hsueh Pao* **1975**, *20*, 147.
(349) Tong, X. J.; Liu, Y. C.; Chang, C. J. *Nat. Prod. Lett.* **1995**, *6*, 197.
(350) Shi, Q. W.; Oritani, T.; Gu, J.; Meng, Q.; Liu, R. *J. Asian. Nat. Prod. Res.* **1999**, *2*, 311.
(351) Chan, W. R.; Halsall, T. G.; Hornby, G. M.; Oxford, A. W.; Sabel, W.; Bjamer, K.; Ferguson, G.; Robertson, J. M. *Chem. Commun.* **1966**, *24*, 923.
(352) Shi, Q. W.; Lederman, Z.; Sauriol, F.; McCollum, R. S.; Zamir, L. O. *J. Nat. Prod.* **2004**, *67*, 168.
(353) Zamir, L. O.; Zhang, J.; Wu, J.; Sauriol, F.; Mamer, O. *Tetrahedron* **1999**, *55*, 14323.
(354) Sakai, J.; Sasaki, H.; Kosugi, K.; Zhang, S.; Hirata, N.; Hirose, K.; Tomida, A.; Tsuruo, T.; Ando, M. *Heterocycles* **2001**, *54*, 999.
(355) Cheng, Q.; Oritani, T.; Horiguchi, T. *Biosci. Biotechnol. Biochem.* **2000**, *64*, 894.
(356) Shi, Q. W.; Oritani, T.; Sugiyama, T.; Murakami, R.; Yamada, T. *J. Asian. Nat. Prod. Res.* **1999**, *2*, 71.
(357) Shrestha, T. B.; Chetri, S. K. K.; Banskota, A. H.; Manandhar, M. D. *J. Nat. Prod.* **1997**, *60*, 820.
(358) Dukes, M.; Etre, D. H.; Harrison, J. W.; Scrowston, R. M.; Lythgoe, B. *J. Chem. Soc. C* **1967**, *1*, 448.
(359) Tong, X. J.; Fang, W. S.; Zhou, J. Y.; He, C. H.; Chen, W. M.; Fang, Q. C. *Chin. Chem. Lett.* **1993**, *4*, 887.
(360) Shinozaki, Y.; Fukamiya, N.; Fukushima, M.; Okano, M.; Nehira, T.; Tagahara, K.; Zhang, S. H.; Zhang, D. C.; Lee, K. H. *J. Nat. Prod.* **2001**, *64*, 1073.
(361) Liang, J. Y.; Huang, K. S.; Gunatilaka, A. A. L. *Planta Med.* **1998**, *64*, 187.
(362) Yeh, M. K.; Wang, J. S.; Liu, L. P.; Chen, F. C. *Phytochemistry* **1988**, *27*, 1534.
(363) Zhang, Z.; Jia, Z. *Phytochemistry* **1991**, *30*, 2345.
(364) Liang, J.; Min, Z.; Niwa, M. J. *Huaxue Xuebao* **1988**, *46*, 1053.

(365) Mao, S. L.; Chen, W. S.; Liao, S. X. *J. Chin. Med. Mate. (Zhongyaocai)* **1999**, *22*, 346.
(366) Morita, H.; Gonda, A.; Wei, L.; Yamamura, Y.; Wakabayashi, H.; Takeya, K.; Itokawa, H. *Planta Med.* **1998**, *64*, 183.
(367) Zhang, J. Z.; Fang, Z. C.; Liang, X. T.; He, C. H.; Kong, M.; He, W. Y.; Jin, X. L. *Phytochemistry* **1995**, *40*, 881.
(368) Min, Z. D.; Jiang, H.; Liang, J. Y. *Acta Pharmacol. Sin. (Yaoxue Xuebao)* **1989**, *24*, 673.
(369) Liang, J. Y.; Huang, K. S.; Gunatilaka, A. A. L.; Yang, L. *Phytochemistry* **1998**, *47*, 69.
(370) Shi, Q. W.; Sauriol, F.; Mamer, O.; Zamir, L. O. *Bioorg. Med. Chem.* **2003**, *11*, 293.
(371) Zhang, Z. P.; Jia, Z. J.; Zhu, Z. Q.; Cui, Y. X.; Cheng, J. L.; Wang, Q. G. *Acta Chim. Sin.* **1991**, *49*, 1023.
(372) Revision of this stucture to the corresponding 11(15→1)-*abeo*taxoid skeleton has been suggested: Huang, K.; Liang, J.; Gunatilaka, A. A. L. *J. Chin. Pharm. University (Zhongguo Yaoke Daxue Xuebao)* **1998**, *29*, 259.
(373) Shi, Q. W.; Oritani, T.; Sugiyama, T.; Yamada, T. *Nat. Prod. Lett.* **2000**, *14*, 265.
(374) Called taxine I by the original authors: Baxter, J. N.; Lythgoe, B.; Scales, B.; Trippett, S. *Proc. Chem. Soc.* **1958**, *1*, 9. For Structure revision, see: Ettouati, L.; Ahond, A.; Poupat, C.; Potier, P. *J. Nat. Prod.* **1991**, *54*, 1455.
(375) Graf, E. *Arch. Pharm. (Weinheim, Ger.)* **1958**, *291*, 443.
(376) Graf, E.; Weinandy, S.; Koch, B.; Breitmaier, E. *Liebigs Ann. Chem.* **1986**, *7*, 1147.
(377) Ando, M.; Sakai, J.; Zhang, S.; Watanabe, Y.; Kosugi, K.; Suzuki, T.; Hagiwara, H. *J. Nat. Prod.* **1997**, *60*, 499.
(378) Shi, Q. W.; Oritani, T.; Sugiyama, T.; Zhao, D.; Murakami, R. *Planta Med.* **1999**, *65*, 767.
(379) Zhang, J. Z.; Fang, Q. C.; Liang, X. T.; He, C. H. *Chin. Chem. Lett.* **1994**, *5*, 497.
(380) Shigemori, H.; Wang, X. X.; Yoshida, N.; Kobayashi, J. *Chem. Pharm. Bull.* **1997**, *45*, 1205.
(381) Chattopadhyay, S. K.; Kulshrestha, M. K.; Saha, G. C.; Sharma, R. P.; Kumar, S. *Indian J. Chem.* **1996**, *35B*, 508.
(382) Guo, Y.; Diallo, B.; Jaziri, M.; Vanhalen-Fastre, R.; Vanhalen, M.; Ottinger, R. *J. Nat. Prod.* **1995**, *58*, 1906.
(383) Doss, R. P.; Carney, J. R.; Shanks, C. H. J.; Williamson, R. T.; Chamberlain, J. D. *J. Nat. Prod.* **1997**, *60*, 1130.
(384) Prasain, J. K.; Stefanowicz, P.; Kiyota, T.; Habeichi, F.; Konishi, Y. *Phytochemistry* **2001**, *58*, 1167.
(385) Shi, Q. W.; Oritani, T.; Sugiyama, T.; Yamada, T. *Nat. Prod. Lett.* **1999**, *13*, 179.
(386) Ishiyama, H.; Kakuguchi, Y.; Arita, E.; Kobayashi, J. *Heterocycles* **2007**, *73*, 341.
(387) Wang, L.; Bai, L.; Tokunaga, D.; Watanabe, Y.; Sakai, J.; Tang, W.; Bai, Y.; Hirose, K.; Ando, M. *Heterocycles* **2008**, *75*, 911.
(388) Zhang, H.; Sun, H.; Takeda, Y. *J. Nat. Prod.* **1995**, *58*, 1153.
(389) Erdemoglu, N.; Sener, B.; Ide, S. *J. Mol. Struct.* **2001**, *559*, 227.
(390) Chattopadhyay, S. K.; Kulshrestha, M.; Saha, G. C.; Sharma, R. P.; Kumar, S. *Planta Med.* **1996**, *62*, 482.
(391) Yeh, M. K.; Wang, J. S.; Yang, W. L.; Chen, F. C. *Proc. Natl. Sci. Counc. Repub. China, Part A: Phys. Sci. Eng.* **1988**, *12*, 89.
(392) Ho, T. I.; Lin, Y. C.; Lee, G. H.; Peng, S. M.; Yeh, M. K.; Chen, F. C. *Acta Crystallogr. Sect. C* **1987**, *43*, 1380.
(393) Shen, Y. C.; Ko, C. L.; Cheng, Y. B.; Chiang, M. I.; Khalil, A. T. *J. Nat. Prod.* **2004**, *67*, 2136.
(394) Shen, Y. C.; Prakash, C. V. S.; Hung, M. C. *J. Chin. Chem. Soc.* **2000**, *47*, 1125.
(395) Zhang, Z. P.; Jia, Z. J. *Chin. Chem. Lett.* **1990**, *1*, 91.
(396) Barboni, L.; Gariboldi, P.; Torregiani, E.; Appendino, G.; Varese, M.; Gabetta, B.; Bombardelli, E. *J. Nat. Prod.* **1995**, *58*, 934.
(397) Beutler, J. A.; Chmurny, G. M.; Look, S. A.; Witherup, K. M. *J. Nat. Prod.* **1991**, *54*, 893.
(398) Chauviere, G.; Guenard, D.; Pascard, C.; Picot, F.; Potier, P.; Prange, T. *J. Chem. Soc., Chem. Commun.* **1982**, *9*, 495.
(399) Wang, X. X.; Shigemori, H.; Kobayashi, J. *Tetrahedron* **1996**, *52*, 12159.
(400) Fukushima, M.; Takeda, J.; Fukamiya, N.; Okano, M.; Tagahara, K.; Zhang, S. X.; Zhang, D. C.; Lee, K. H. *J. Nat. Prod.* **1999**, *62*, 140.
(401) Shigemori, H.; Sakurai, C. A.; Hosoyama, H.; Kobayashi, A.; Kajiyama, S.; Kobayashi, J. *Tetrahedron* **1999**, *55*, 2553.
(402) Murakami, R.; Shi, Q. W.; Oritani, T. *Phytochemistry* **1999**, *52*, 1577.
(403) Wang, C. L.; Zhang, M. L.; Cao, C. M.; Shi, Q. W.; Kiyota, H. *Heterocycl. Commun.* **2005**, *11*, 211.
(404) Shi, Q. W.; Cao, C. M.; Gu, J. S.; Kiyota, H. *Nat. Prod. Res.* **2006**, *20*, 173.
(405) Yue, Q.; Fang, Q. C.; Liang, X. T. *Phytochemistry* **1996**, *43*, 639.
(406) Li, Z. P.; Hu, C. H.; Zhang, M. L.; Shi, Q. W. *Chin. Tradit. Herb. Drugs (Zhongcaoyao)* **2006**, *37*, 175.
(407) Zhang, J.; Sauriol, F.; Mamer, O.; Zamir, L. O. *Phytochemistry* **2000**, *54*, 221.
(408) Shen, Y. C.; Lo, K. L.; Chen, C. Y.; Kuo, Y. H.; Hung, M. C. *J. Nat. Prod.* **2000**, *63*, 720.
(409) Shen, Y. C.; Chang, Y. T.; Lin, Y. C.; Lin, C. L.; Kuo, Y. H.; Chen, C. Y. *Chem. Pharm. Bull.* **2002**, *50*, 781.
(410) Liang, J. Y.; Bao, G. H.; Chen, P. D. *Straight Pharm. J. (Haixia Yaoxue)* **2000**, *12*, 47.
(411) Shen, Y. C.; Chen, C. Y. *Phytochemistry* **1997**, *44*, 1527.
(412) Wang, X. X.; Shigemori, H.; Kobayashi, J. *Tetrahedron* **1996**, *52*, 2337.
(413) Liang, J.; Kingston, D. G. I. *J. Nat. Prod.* **1993**, *56*, 594.
(414) Cao, C. M.; Zhang, M. L.; Wang, Y. F.; Shi, Q. W.; Yamada, T.; Kiyota, H. *Chem. Biodiversity* **2006**, *3*, 1153.
(415) Shen, Y. C.; Tai, H. R.; Chen, C. Y. *J. Nat. Prod.* **1996**, *59*, 173.
(416) Tanaka, K.; Fuji, K.; Yokoi, T.; Shingu, T.; Li, B.; Sun, H. *Chem. Pharm. Bull.* **1994**, *42*, 1539.
(417) Senilh, V.; Blechert, S.; Colin, M.; Guenard, D.; Picot, F.; Potier, P.; Varenne, P. *J. Nat. Prod.* **1984**, *47*, 131.
(418) Shen, Y. C.; Chen, C. Y. *Planta Med.* **1997**, *63*, 569.
(419) Wang, F. S.; Peng, L. Y.; Zhao, Y.; Gu, K.; Zhao, Q. S.; Sun, H. D. *Yunnan Zhiwu Yanjiu* **2003**, *25*, 507.
(420) Liang, J. Y.; Yang, L.; Cheng, Q. L.; Zheng, F. M.; Wei, X. L.; Zhang, Y. *Chin. Tradit. Herb. Drugs (Zhongcaoyao)* **2002**, *33*, 294.
(421) Wiedenfeld, H.; Knoch, F.; Zhang, Z. P. *Acta Crystallogr. Sect. C: Cryst. Struct. Commun.* **1995**, *C51*, 2184.
(422) Della Casa de Marcano, D. P.; Halsall, T. G. *J. Chem. Soc. D* **1970**, *21*, 1381.
(423) Hosoyama, H.; Inubushi, A.; Katasui, T.; Shigemori, H.; Kobayashi, J. *Tetrahedron* **1996**, *52*, 13145.
(424) Küpeli, E.; Erdemoglü, N.; Yesilada, E.; Sener, B. *J. Ethnopharmacol.* **2003**, *89*, 265.
(425) Xiao, C.; Zhou, J. Y.; Chen, W. M.; Lv, Y.; Zheng, Q. T. *Acta Pharm. Sin. (Yaoxue Xuebao)* **1994**, *29*, 355.
(426) Appendino, G.; Cravotto, G.; Enriu, R.; Gariboldi, P.; Barboni, L.; Torregiani, E.; Gabetta, B.; Zini, G.; Bombardelli, E. *J. Nat. Prod.* **1994**, *57*, 607.
(427) Li, S.; Zhang, H.; Yao, P.; Sun, H. *Chin. Chem. Lett.* **1998**, *9*, 1017.
(428) Gabetta, B.; de Bellis, P.; Pace, R.; Appendino, G.; Barboni, L.; Torregiani, E.; Gariboldi, P.; Viterbo, D. *J. Nat. Prod.* **1995**, *58*, 1508.
(429) Fuji, K.; Tanaka, K.; Li, B.; Shingu, T.; Sun, H.; Taga, T. *J. Nat. Prod.* **1993**, *56*, 1520.
(430) Powell, R. G.; Miller, R. W.; Smith, C. R., Jr. *J. Chem. Soc., Chem. Commun.* **1979**, *3*, 102.
(431) Della Casa de Marcano, D. P.; Halsall, T. G.; Castellano, E.; Hodder, O. J. R. *J. Chem. Soc. D* **1970**, *21*, 1382.
(432) Soto, J.; Castedo, L. *Phytochemistry* **1998**, *47*, 817.
(433) Rao, K. V.; Bhakuni, R. S.; Hanuman, J. B.; Davies, R.; Johnson, J. *Phytochemistry* **1996**, *41*, 863.
(434) Zhou, X. T.; Yu, F.; Zeng, Q. *Zhongyao Xinyao Linchuang Yaoli* **2002**, *13*, 317.

(435) Della Casa de Marcano, D. P.; Halsall, T. G. *J. Chem. Soc., Chem. Commun.* **1975**, *9*, 365.
(436) Wang, F. S.; Peng, L. Y.; Zhao, Y.; Zhao, Q. S.; Gu, K.; Sun, H. D. *Chin. Chem. Lett.* **2004**, *15*, 307.
(437) Chu, A.; Zajicek, J.; Davin, L. B.; Lewis, N. G.; Croteau, R. B. *Phytochemistry* **1992**, *31*, 4249. Structure revision to the corresponding 11(15→1)*abeo*taxoid has been suggested: Huang, K.; Liang, J.; Gunatilaka, A. A. L. *J. Chin. Pharm. University (Zhongguo Yaoke Daxue Xuebao)* **1998**, *29*, 259.
(438) Wang, F. S.; Peng, L. Y.; Zhao, Y.; Xu, G.; Zhao, Q. S.; Sun, H. D. *J. Nat. Prod.* **2004**, *67*, 905.
(439) Appendino, G.; Gariboldi, P.; Gabetti, B.; Pace, P.; Bombardelli, E.; Viterbo, D. *J. Chem. Soc., Perkin Trans. 1* **1992**, *21*, 2925.
(440) Wang, F. S.; Peng, L. Y.; Zhao, Y.; Gu, K.; Zhao, Q. S.; Sun, H. D. *Yunnan Zhiwu Yanjiu* **2003**, *25*, 369.
(441) Morita, H.; Wei, L.; Gonda, A.; Takeya, K.; Itokawa, H. *Phytochemistry* **1997**, *46*, 583.
(442) Huang, C. J. Master Thesis, National Cheng Kung University, Chinese Taiwan, 2008 (etd.lib.nsysu.edu.tw)
(443) Kitagawa, I.; Mahmud, T.; Kobayashi, M.; Roemantyo; Shibuya, H. *Chem. Pharm. Bull.* **1995**, *43*, 365.
(444) McLaughlin, J. L.; Miller, R. W.; Powell, R. G.; Smith, C. R., Jr. *J. Nat. Prod.* **1981**, *44*, 312.
(445) Yang, S. J.; Fang, J. M.; Cheng, Y. S. *Phytochemistry* **1999**, *50*, 127.
(446) Chen, W. M.; Zhou, J. Y.; Zhang, P. L.; Fang, Q. C. *Chin. Chem. Lett.* **1993**, *4*, 699.
(447) Gabetta, B.; Orsini, P.; Peterlongo, F.; Appendino, G. *Phytochemistry* **1998**, *47*, 1325.
(448) Zhang, H.; Takeda, Y.; Matsumoto, T.; Minami, Y.; Yoshida, K.; Xiang, W.; Mu, Q.; Sun, H. *Heterocycles* **1994**, *38*, 975.
(449) Gabetta, B.; Fuzzatti, N.; Orsini, P.; Peterlongo, F.; Appendino, G.; Vander Velde, D. G. *J. Nat. Prod.* **1999**, *62*, 219.
(450) Zhang, H. J.; Takeda, Y.; Minami, Y.; Yoshida, K.; Unemi, N.; Mu, Q.; Xiang, W.; Matsumoto, T.; Sun, H. D. *Yunnan Zhiwu Yanjiu* **1993**, *15*, 424.
(451) Barboni, L.; Gariboldi, P.; Torregiani, E.; Appendino, G.; Gabetta, B.; Bombardelli, E. *Phytochemistry* **1994**, *36*, 987.
(452) Li, S.; Zhang, H.; Yao, P.; Sun, H.; Fong, H. H. S. *Phytochemistry* **2001**, *58*, 369.
(453) Huang, C. H. O.; Kingston, D. G. I.; Magri, N. F.; Samaranayake, G. *J. Nat. Prod.* **1986**, *49*, 665.
(454) De Bellis, P.; Lovati, M.; Pace, R.; Peterlongo, F.; Zini, G. F. *Fitoterapia* **1995**, *66*, 521.
(455) Murakami, R.; Shi, Q. W.; Horiguchi, T.; Oritani, T. *Biosci. Biotechnol. Biochem.* **1999**, *63*, 1660.
(456) Shi, Q. W.; Oritani, T.; Sugiyama, T.; Horiguchi, T.; Murakami, R.; Zhao, D.; Oritani, T. *Tetrahedron* **1999**, *55*, 8365.
(457) Habib-ur-Rehman; Atta-ur-Rahman; Choudhary, M. L. *J. Chem. Soc. Pakistan* **2004**, *26*, 302.
(458) Zhang, J. Z.; Fang, Q. C.; Liang, X. T.; Kong, M.; Yi, He, W. *Chin. Chem. Lett.* **1995**, *6*, 971.
(459) Chen, R.; Kingston, D. G. I. *J. Nat. Prod.* **1994**, *57*, 1017.
(460) Chattopadhyay, S. K.; Tripathi, V.; Sharma, R. P.; Shawl, A. S.; Joshi, B. S.; Roy, R. *Phytochemistry* **1999**, *50*, 131.
(461) Kobayashi, J.; Ogiwara, A.; Hosoyama, H.; Shigemori, H.; Yoshida, N.; Sasaki, T.; Li, Y.; Iwasaki, S.; Naito, M.; Tsuruo, T. *Tetrahedron* **1994**, *50*, 7401.
(462) Huo, C. H.; Wang, Y. F.; Zhang, X. P.; Li, C. F.; Shi, Q. W.; Kiyota, H. *Chem. Biodivers.* **2007**, *4*, 84.
(463) Shi, Q. W.; Oritani, T.; Sugiyama, T.; Kiyota, H.; Horiguchi, T. *Nat. Prod. Lett.* **1998**, *12*, 67.
(464) Soto, J.; Fuentes, M.; Castedo, L. *Phytochemistry* **1996**, *43*, 313.
(465) Guo, Y.; Diallo, B.; Jaziri, M.; Vanhaelen-Fastre, R.; Vanhaelen, M. *J. Nat. Prod.* **1996**, *59*, 169.
(466) Fuji, K.; Tanaka, K.; Li, B.; Shingu, T.; Sun, H.; Taga, T. *Tetrahedron Lett.* **1992**, *33*, 7915.
(467) Shi, Q. W.; Oritani, T.; Sugiyama, T.; Kiyota, H. *Planta Med.* **1998**, *64*, 766.
(468) Gao, Y. L.; Zhou, J. Y.; Ding, Y.; Fang, Q. C. *Chin. Chem. Lett.* **1997**, *8*, 1057.
(469) Choudhary, M. I.; Khan, A. M.; Habib-Ur-Rehman; Atta-Ur-Rahman; Ashraf, M. *Chem. Pharm. Bull.* **2002**, *50*, 1488.
(470) Rao, K. V.; Juchum, J. *Phytochemistry* **1998**, *47*, 1315.
(471) Zhou, J. Y.; Zhang, P. L.; Chen, W. M.; Fang, Q. C. *Phytochemistry* **1998**, *48*, 1387.
(472) Shen, Y. C.; Prakash, C. V. S.; Chen, Y. J.; Hwang, J. F.; Kuo, Y. H.; Chen, C. Y. *J. Nat. Prod.* **2001**, *64*, 950.
(473) Chen, W. M.; Zhou, J. Y.; Zhang, P. L.; Fang, Q. C. *Chin. Chem. Lett.* **1993**, *4*, 695.
(474) Shi, Q. W.; Oritani, T.; Sugiyama, T. *Nat. Prod. Lett.* **1999**, *13*, 105.
(475) Li, S. H.; Zhang, H. J.; Yao, P.; Sun, H. D.; Fong, H. H. S. *J. Nat. Prod.* **2000**, *63*, 1488.
(476) Shen, Y. C.; Wang, S. S.; Pan, Y. L.; Lo, K. L.; Chakraborty, R.; Chien, C. T.; Kuo, Y. H.; Lin, Y. C. *J. Nat. Prod.* **2002**, *65*, 1848.
(477) Shen, Y. C.; Pan, Y. L.; Lo, K. L.; Wang, S. S.; Chang, Y. C.; Wang, L. T.; Lin, Y. C. *Chem. Pharm. Bull.* **2003**, *51*, 867.
(478) Chattopadhyay, S. K.; Sharma, R. P.; Appendino, G.; Gariboldi, P. *Phytochemistry* **1995**, *39*, 869.
(479) Shen, Y. C.; Chen, C. Y.; Kuo, Y. H. *J. Nat. Prod.* **1998**, *61*, 838.
(480) Zhong, S. Z.; Hua, Z. X.; Fan, J. S. *J. Nat. Prod.* **1996**, *59*, 603.
(481) Chattopadhyay, S. K.; Saha, G. C.; Sharma, R. P.; Kumar, S.; Roy, R. *Phytochemistry* **1996**, *42*, 787.
(482) Yue, Q.; Fang, Q. C.; Liang, X. T.; He, C. H. *Phytochemistry* **1995**, *39*, 871.
(483) Tanaka, K.; Fuji, K.; Yokoi, T.; Shingu, T.; Li, B.; Sun, H. *Chem. Pharm. Bull.* **1996**, *44*, 1770.
(484) Guo, Y.; Vanhaelen-Fastre, R.; Diallo, B.; Vanhaelen, M.; Jaziri, M.; Homes, J.; Ottinger, R. *J. Nat. Prod.* **1995**, *58*, 1015.
(485) Rao, K. V.; Johnson, J. H. *Phytochemistry* **1998**, *49*, 1361.
(486) Das, B.; Rao, S. P.; Srinivas, K. V. N. S.; Yadav, J. S.; Das, R. *Phytochemistry* **1995**, *38*, 671.
(487) Barboni, L.; Gariboldi, P.; Torregiani, E.; Appendino, G.; Cravotto, G.; Bombardelli, E.; Gabetta, B.; Viterbo, D. *J. Chem. Soc, Perkin Trans. 1* **1994**, *21*, 3233.
(488) Shen, Y. C.; Hsu, S. M.; Lin, Y. S.; Cheng, K. C.; Chien, C. T.; Chou, C. H.; Cheng, Y. B. *Chem. Pharm. Bull.* **2005**, *53*, 808.
(489) Li, S. H.; Zhang, H. J.; Niu, X. M.; Yao, P.; Sun, H. D.; Fong, H. H. S. *Planta Med.* **2002**, *68*, 253.
(490) Shen, Y. C.; Cheng, K. C.; Lin, Y. C.; Cheng, Y. B.; Khalil, A. T.; Guh, J. H.; Chien, C. T.; Teng, C. M.; Chang, Y. T. *J. Nat. Prod.* **2005**, *68*, 90.
(491) Yue, Q.; Fang, Q. C.; Liang, X. T. *Chin. Chem. Lett.* **1995**, *6*, 225.
(492) Fang, W. S.; Fang, Q. C.; Liang, X. T.; Lu, Y.; Wu, N.; Zheng, Q. T. *Chin. Chem. Lett.* **1997**, *8*, 231.
(493) Zhang, S.; Lee, C. T. L.; Kashiwada, Y.; Chen, K. *J. Nat. Prod.* **1994**, *57*, 1580.
(494) Xia, Z. H.; Peng, L. Y.; Li, R. T.; Zhao, Q. S.; Sun, H. D. *Heterocycles* **2005**, *65*, 1403.
(495) Zhang, S.; Lee, C. T. L.; Kashiwada, Y.; Zhang, D. C.; McPhail, A. T.; Lee, K. H. *J. Chem. Soc., Chem. Commun.* **1994**, *12*, 1561.
(496) Vander Velde, D. G.; Georg, G. I.; Gollapudi, S. R.; Jampani, H. B.; Liang, X. Z.; Mitscher, L. A.; Ye, Q. M. *J. Nat. Prod.* **1994**, *57*, 862.
(497) Graf, E.; Bertholdt, H. *Pharmazeut. Zent.* **1957**, *96*, 385.
(498) Shi, Q. W.; Oritani, T.; Sugiyama, T. *Nat. Prod. Lett.* **1999**, *13*, 113.
(499) Shi, Q. W.; Oritani, T.; Horiguchi, T.; Sugiyama, T. *Biosci. Biotechnol. Biochem.* **1998**, *62*, 2263.
(500) Shi, Q. W.; Oritani, T.; Sugiyama, T. *Phytochemistry* **1999**, *52*, 1559.
(501) Shi, Q. W.; Oritani, T. *Nat. Prod. Lett.* **2000**, *14*, 273.
(502) Hall, A. M.; Tong, X.; Chang, C. *Nat. Prod. Lett.* **1997**, *10*, 165.

(503) Yue, Q.; Fang, Q. C.; Liang, X. T.; He, C. H.; Jing, X. L. *Planta Med.* **1995**, *61*, 375.
(504) Rao, K. V.; Reddy, G. C.; Juchum, J. *Phytochemistry* **1996**, *43*, 439.
(505) Poupat, C.; Ahond, A.; Potier, P. *J. Nat. Prod.* **1994**, *57*, 1468.
(506) Graf, E.; Kirfel, A.; Wolff, G. J.; Breitmaier, E. *Liebigs Ann. Chem.* **1982**, *2*, 376.
(507) Shi, Q. W.; Li, Z. P.; Zhao, D.; Gu, J. S.; Oritani, T.; Kiyota, H. *Biosci. Biotechnol. Biochem.* **2004**, *68*, 1584.
(508) Shen, Y.; Chen, C.; Hung, M. *Chem. Pharm. Bull.* **2000**, *48*, 1344.
(509) Zhang, M. L.; Dong, M.; Huo, C. H.; Li, L. G.; Sauriol, F.; Shi, Q. W.; Gu, Y. C.; Makabe, H.; Kiyota, H. *Eur. J. Org. Chem.* **2008**, *32*, 5414.
(510) Shi, Q. W.; Nikolakakis, A.; Sauriol, F.; Mamer, O.; Zamir, L. O. *Can. J. Chem.* **2003**, *81*, 406.
(511) Shi, Q. W.; Oritani, T.; Sugiyama, T.; Murakami, R.; Horiguchi, T. *J. Asian Nat. Prod. Res.* **1999**, *2*, 63.
(512) Shi, Q. W.; Oritani, T.; Sugiyama, T.; Yamada, T. *Nat. Prod. Lett.* **1999**, *13*, 171.
(513) Shi, Q. W.; Oritani, T.; Horiguchi, T.; Sugiyama, T.; Cheng, Q. *Chin. Chem. Lett.* **1999**, *10*, 481.
(514) Shi, Q. W.; Oritani, T.; Sugiyama, T. *Phytochemistry* **1999**, *50*, 633.
(515) Shi, Q. W.; Oritani, T.; Sugiyama, T.; Kiyota, H. *J. Nat. Prod.* **1998**, *61*, 1437.
(516) Shen, Y. C.; Chen, C. Y.; Chen, Y. J. *Planta Med.* **1999**, *65*, 582.
(517) Shi, Q. W.; Oritani, T.; Sugiyama, T. *Nat. Prod. Lett.* **1999**, *13*, 81.
(518) Zhou, J. L.; Zhang, P. L.; Chen, W. M.; Fang, Q. C. *Phytochemistry* **1998**, *48*, 1387.