Diterpenoids from *Isodon* species and their biological activities†

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Isodon species (Labiatae) are widely distributed plants, many of which are used in folk medicine. Over the past twenty years, they have received considerable phytochemical and biological attention. The structures of their many diterpenoids constituents, especially those with an *ent*-kaurane skeleton, have been elucidated. The significant phytochemical and pharmacological diterpenoids form the subject of this review. There are 290 references.

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1 Introduction

Isodon (formally *Rabdosia*) is a cosmopolitan and important genus of the Labiatae (= Lamiaceae) family. About 150 species of undershrubs, subundershrubs, or perennial herbs are found throughout the world mainly in tropical and subtropical Asia.[1,2] The use of *Isodon* species in Chinese popular folk medicine has a long tradition. For example, the leaves of *I. rubescens*, which is the most studied species and is known in China by the name, "*donglingcao*", are still used by the local people in Henan province for the treatment of respiratory and gastrointestinal bacterial infections, inflammation, and cancer. In 1977, the standard extract of this plant was successfully developed into a drug product which was used in treating sore throats and inflammation in the People's Republic of China.[3] In Yunnan province, *I. eriocalyx* has been used in the form of a crude drug (Yanshukang) as an antibacterial and anti-inflammatory agent. Clinical trials showed that this crude drug had excellent efficiency for the treatment of sore throats and inflammation. In addition, the aerial parts of *I. ternifolia*, *I. lophanthoides*, and *I. megathyrsa* are empirically employed as antimalarial and anti-inflammatory agents and also for the treatment of enteritis and jaundice.[2] The leaves of *I. amethystoides*, commonly known as "*wangzaozi*", are reputed for their efficacy for the treatment of pneumonia in local folk medicine in Anhui province. The herb *I. serra*, distributed mainly over southeast China, is said to have hepatoprotective and anti-inflammatory activities.[1] In Japan, the leaves of *I. japonica* and *I. trichocarpa* have been used since ancient times as a remedy for gastrointestinal disorders under the name of "*enmei-so*", which means a grass effective for the prolongation of human life.[4,5]

The first investigation on *Isodon* diterpenoids can be traced back to 1910. Yagi isolated a crystalline bitter principle named plectranthin from "*enmei-so*".[6] In 1958, three Japanese research groups isolated enmein independently from *I. japonica* as the major bitter principle. The structure of enmein was firstly elucidated as a 6,7-seco-*ent*-kuaranoid by X-ray crystallography in 1966.[7] During the mid 1970s, some diterpenoids isolated from *I. japonica* were found to possess highly selective anti-bacterial and anti-cancer activities.[8] Since then, a highlight of the research into *Isodon* diterpenoids has been the work of several Japanese scientists in their isolation, structural elucidation, biogenesis, and chemical synthesis. E. Fujita was an outstanding chemist who spent the majority of his professional career investigating the *Isodon* diterpenoids and

Han-Dong Sun was born in Baoshan county, Yunnan province, P.R. China in 1939 and received his PhD from the Faculty of Pharmaceutical Sciences at Kyoto University, Japan in 1988. He was appointed as a professor in 1989 at the Kunming Institute of Botany (KIB), Chinese Academy of Sciences (CAS). In 2003, He became an Academician of the CAS. At present, he works as a research professor at the CAS-affiliated KIB and serves as the vice director of the academic committee of the State Key Laboratory of Phytochemistry and Plant Resource in West China. During his three decades of research life, more than 200 plants belonging to Labiatae, Taxaceae, Schisandraceae, Umbelliferae and Lauraceae families have been phytochemically investigated by his research group, and about 2200 compounds including 700 new ones have been isolated and characterized. He has published over 500 scientific papers in international journals. He is the author of three books and also one of the inventors for 16 patents. Professor Sun has received 21 awards and recognition for his contribution to the development of natural medicines and perfume in China. He is currently a member of the editorial boards of three international journals, i.e. Planta Medica, Fitoterapia *and* Journal of Asian Natural Products Research. *His current research interests involve the activity directed isolation, structure elucidation and the structure–activity relationship of natural products from medically important plants.*

Sheng-Xiong Huang was born in Sichuan province of P.R. China in 1978, studied chemistry from 1997 to 2001 at Shaanxi Normal University and obtained his MS in 2004 at the Chengdu Institute of Biology, Chinese Academy of Sciences. He is currently carrying out doctoral research with Professor Han-Dong Sun at the Kunming Institute of Botany, Chinese Academy of Sciences, studying the isolation, chemical modification, and structure–activity relationship of bioactive natural products. Further interests include the MS analysis of natural products and stereochemistry determination of natural products using spectroscopic methods.

Quan-Bin Han was born in 1974 in Henan province, P.R. China. He obtained his PhD in 2003 under the guidance of Professor Han-Dong Sun at Kunming Institute of Botany, Chinese Academy Sciences and was presented the "President Award" by the Academy. Since 2004, he has worked as a scientist at the Hong Kong Jockey Club Institute of Chinese Medicine. His research is focused on biologically active natural products, and the chemistry and authentication of traditional Chinese medicine

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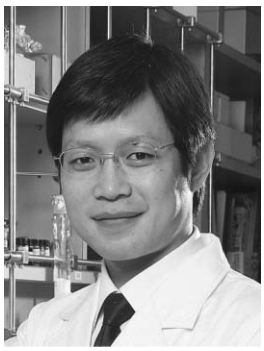


Quan-Bin Han

published many important articles on this topic.[4] At the same time (in 1976), our group began phytochemical investigations of this genus. Given the important bioactivities, structural complexity, and interesting chemical diversity of the composition of this genus, our group has phytochemically investigated more than 50 *Isodon* species distributed in China. About 500 new diterpenoids (mainly *ent*-kauranoids) with different oxygenations and cleavage patterns have been isolated and characterized, comprising more than 60% of the literature in this field.[9] Most importantly, a number of those isolated diterpenoids have been found to have potent antitumour activities with low toxicity. They are therefore promising candidates for anticancer drugs, and are being studied in our laboratory. Another achievement of our studies is the discovery of many interesting novel compounds such as 1 : 1 complexes of natural *ent*-kauranoids (Diter-Complex-RA),[10] a natural equimolecular mixture of two epimeric *ent*-kauranoids (irroratin A),[11] 8,15-*seco*-*ent*-kauranoids (rubescensin U),[12] 6,7:8,15-*seco*-*ent*-kauranoids (laxiflorins F and G),[13] 15,16-*seco*-*ent*-kauranoid (rubescensin S),[14] 20-*nor*-*ent*-kauranoid (rubescensin N),[15] symmetric and asymmetric *ent*-kauranoid dimers (maoecrystal M, enanderinanin J, xindongnins M–O, and lushanrubescensin J),[16–19] novel *ent*-abietanoids (laxiflorins N–O, micranthin C),[20,21] and 6,7-seco-6-nor-15(8→9)-*abeo*-5,8-epoxy-*ent*-kauranoid (maoecrystal V).[22] Because of these discoveries, a new wave of *Isodon* diterpenoid research has been developing

Some 20 years ago, Professor E. Fujita and M. Node gave an excellent review about the structures, synthesis, and biological activities of diterpenoids from *Isodon* species.[4] Since then, several other authors reviewed this group of diterpenoids.[5,23] However, no extensive review has appeared since 1984. Considering the recent flurry of reports in this area, here we review systematically all the papers that have appeared in the literature from 1984 until 2005, concerning the isolation, structural elucidation, and biological evaluations of *Isodon* diterpenoids.

2 The categories of diterpenoids

The criteria for the structural classification of *Isodon* diterpenoids had depended on the number of known compounds. In 1984, E. Fujita classified this group of diterpenoids into four groups: *ent*-kauranes, 6,7-*seco*-*ent*-kauranes, 8,9-*seco*-*ent*-kauranes, and others, on the basis of the limited number of diterpenoids isolated at that time.[4] When the number of diterpenoids increased to 303

in 1995, the *Isodon* diterpenoids were divided into nine groups by Y. Takeda and H. Otsuka.[5] For clarity and in order to maintain this nomenclature, we classified the *Isodon* diterpenoids into 11 groups including five subgroups on the basis of the structures of diterpenoids isolated from *Isodon* species during the period 1984–2005.

2.1 C-20 non-oxygenated *ent*-kauranes

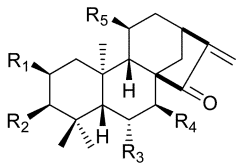
Out of 610 known *Isodon* diterpenoids, 212 found in 36 *Isodon* species belong to the C-20 non-oxygenated *ent*-kauranes, and 190 of them have been identified since 1984 (Table 1). This is the largest group of known *Isodon* diterpenoids, and appears to be the most widely distributed. In this group, carbon C-20 is always an isolated methyl and C-15 is generally functionalized by a ketone or hydroxyl group. Interestingly, only carbon C-5 and C-9 (except for shikoccidin) have never been functionalized.

The most representative species that produced this type of diterpenoid is *I. angustifolius* subsp. *glabrescens.* From this species, 25 diterpenoids with highly oxygenated structures, glabcensins A–Y (**1–10**, **30–33**, **72**, **73**, **11**, **76–79**, **12–14**, and **34**), in addition to four previous known ones, 7-acetyl-lushanrubesceusin A, lushanrubescensins A and B, and rabdoforrestin A, were isolated by our group.[24–28] All of these diterpenoids share very similar structures with an oxygen function at C-2, 3, 6, 7, 11, and 15. Glabcensin U is the sole example of an *Isodon* diterpenoid with an epoxide function between C-6 and C-7. Due to the structural similarities of glabcensin to 7-acetyl-lushanrubescesins A, lushanrubescensins A and B, and rabdoforrestin A, reinvestigation of their structures was performed. This showed that the earlier structure assignments were incorrect and they were epimers at C-11.[24] In 1998 and 1999, our group published two papers on *I. melissiodes*, reporting melissoidesins A–G (**43**, **44**, **81**, **99**, **35**, **36**, and **15**).[29,30] More recently, extensive reinvestigations on this species collected from a different region led to the isolation of 14 new analogues, melissoidesins I–K (**111–113**) and M–W (**37**, **16**, **17**, **38**, **39**, **40**, **45**, **82**, **83**, **114**, and **115**).[31–33] The cytotoxicity of some of these diterpenoids was examined. Melissiodesin N (**17**) demonstrated strong inhibitory activity against BGC-823 cells with an IC_{50} value of 0.036 μg mL^{-1}.[32] Adenanthin A (**46**), as one of the chief constituents of *I. adenantha*, was first isolated in 1987. Its structure was established mainly by NMR experiments on an oxidation product, and the absolute *ent*-kaurane configuration was determined by application of the CD exciton chirality rule to the *p*-bromobenzoate derivative.[34] A series of derivatives of adenanthin A, adenanthins B–K (**84**, **47**, **100**, **85**, **48**, **49**, **86**, **50**, **87**, and **101**) and N–P (**18–20**),[35,36] were then isolated by repeated phytochemical investigations on *I. adenantha.* Extraction of the aerial parts of *I. calcicola* from Yunnan province afforded five new diterpenoids, calcicolins A–E (**51–53**, **88**, and **102**),[37] along with two known ones, nervosanin (**103**) and weisiensin A (**54**) (originally from *I. nervosa* and *I. weisiensis*, respectively). They are very similar to adenanthin A, differing only in their substituents. It should be noted that the structure of weisiensin A was revised by comparison of the spectroscopic data with those of known diterpenoids and by chemical transformation.[38] The leaves of *I. lungshengensis*, *I. gesneroides*, *I. dawoensis* and *I. forrestii* were systematically investigated by our group during the period 1988–1999. Twenty-one new diterpenoids, lungshengenins A–G (**116**, **117**, **21**, **120**, **121**, **118**, and **119**) (from *I. lungshengensis*),[39–42] gesneroidins A–E (**22**, **23**, **55**, **104**, and **89**) (from *I. gesneroides*),[43,44] dawoensin A (**24**) (from *I. dawoensis*),[45] forrestins A–G (**105**, **90**, **91**, **106**, **107**, **126**, and **127**) and rabdoforrestin A (**25**) (from *I. forrestii*),[46,47] were isolated. Their structures were determined mainly by spectroscopic means and in the case of gesneroidin B (**23**) by X-ray crystallography analysis.[43] Only three compounds, rabyuennanes A–C (**108**, **109**, and **128**),[48] were reported from *I. yuennanensis.* Their structures are very similar, in which every molecule have an acetoxyl group at C-3, 7, and 15, respectively. Ding and coworkers published two papers on *I. leucophylla* from Sichuan province of China, reporting the isolation and identification of leucophyllins A–F (**56**, **57**, **92**, **58**, **122**, and **123**).[49,50] It is of interest to note that reinvestigations of this species collected from Yunnan province, gave other structure types of *ent*-kauranoids.[51,52] From a chemotaxonomic point of view, it should be pointed out that the secondary metabolites of this species change in different ecological environments.

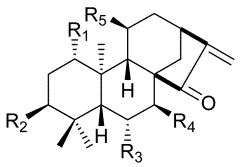
Interestingly, we found that all of those C-20 non-oxygenated *ent*-kauranes isolated from the species mentioned above, bear similar oxidation patterns.

Investigation of the leaves of *I. liangshanica* gave seven new C-20 non-oxygenated *ent*-kauranes, liangshanins A–G (**129–134**, and **41**).[53,54] Liangshanins A–D (**129–132**), having an α,β-unsaturated ketone in A ring, and differ in the functionalities at C-7, 14, and 15. Liangshanin G (**41**) was the first example isolated from genus *Isodon*, having an 11β,16β ether ring.[53] Taketa and his coworkers had systematically studied the chemical constituents of *I. inflexa* collected in Japan. Twelve new diterpenoids, inflexanin A (**59**) and inflexarabdonins A–K (**93**, **94**, **26**, **110**, **60**, **95**, **61–63**, **96**, and **135**), were isolated,[55–60] and their structures were established by spectroscopic methods including 1D and 2D NMR analysis. The structures of the three previously misidentified diterpenoids, inflexin (**64**), inflexinol (**65**), and inflexanin B (**66**), were unambiguously revised by spectroscopic means and comparison with their analogues.[60] Further investigation on the same species collected in China was undertaken and only one C-20 non-oxygenated *ent*-kauranes, rabdoinflexin B (**136**), was isolated.[61] Sculponeatin L (**145**) and a related acetonide derivative, sculponeatin M (**146**), isolated from *I. sculponeata*, were detected as the sole examples of *Isodon* diterpenoids with a phenylacetyl substitution group.[62] The four new diterpenoids, isodopharicins A (**151**), B (**152**), D (**153**), and F (**154**)[63,64] from *I. pharicus*, possess an α-orientated hydroxyl group at C-13 similar to rosthornins A–C (**147–149**) (from *I. rosthornii*).[65,66] The structure of rosthornin A was confirmed by X-ray analysis. Glaucocalyxin C (**150**),[67] isolated from *I. japonica* subsp. *glaucocalyx*, was structurally very interesting. It had an unusual α-orientated hydroxyl group at C-15 and a β-orientated hydroxyl group at C-14. These rare substitution patterns provide a sterically hindered environment for H-7, OH-15, and OH-14. Liangshanin D (**132**) (from *I. liangshanica*) was another example with a rare substitution pattern.[53] Xindongnins A–L (**155**, **67**, **68**, **97**, **98**, **69**, **157**, **70**, **71**, **156**, **74**, and **75**),[68–70] suimiyain A (**158**),[71] and taibairubescensins A and B (**80** and **159**) (from *I. rubescens*),[72] and lushanrubescensins A–E (**27–29**, **124**, and **125**) (from *I. rubescens* subsp. *lushanensis*)[73–75] were isolated by several research groups. The most recent products isolated are weisiensins B (**160**) and D (**172**),[76] which occur in *I. weisiensis* collected from Gansu province of China. The structure of weisiensin

Table 1 Structures of C-20 non-oxygenated *ent*-kauranes (**1–190**)



	R_1	R_2	R_3	R_4	R_5	Ref.
1	OH	OAc	OAc	OAc	OAc	25
2	OAc	OH	OAc	OAc	OAc	25
3	OH	OAc	OH	OAc	OAc	25
4	OAc	OH	OAc	OH	OAc	25
5	OH	OAc	OAc	OAc	OH	25
6	OAc	OH	OAc	OAc	OH	25
7	OAc	OAc	OH	OAc	OH	25
8	OAc	OH	OH	OAc	OH	25
9	OH	OAc	OH	OAc	OH	25
10	OH	OH	OAc	H	OH	25
11	OH	OAc	=O	OAc	OAc	26
12	H	OAc	OH	OAc	OH	27,28
13	H	OAc	OAc	OAc	OAc	27
14	H	OH	=O	OAc	OAc	27
15	H	OAc	OAc	OH	OH	30
16	H	OH	OAc	H	OH	32
17	H	OAc	OAc	H	OH	32
18	OAc	OAc	OH	OH	OH	36
19	OH	OAc	OH	H	OH	36
20	OAc	OH	OH	H	OH	36
21	OAc	OAc	OAc	H	OH	41
22	H	H	OAc	H	OH	43
23	H	H	OAc	H	=O	43
24	H	OAc	OAc	OAc	OH	45
25	OAc	OAc	OAc	OAc	OH	47
26	H	OAc	=O	H	OH	56
27	OAc	OAc	OAc	OH	OAc	74
28	OAc	OAc	OAc	OH	OH	73
29	OAc	OAc	OAc	H	OAc	73



	R_1	R_2	R_3	R_4	R_5	Ref.
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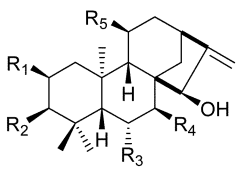
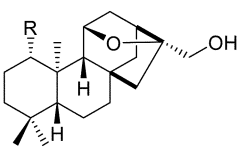
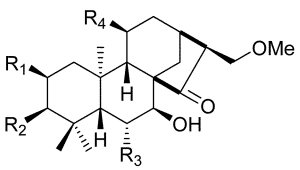
44	OH	OAc	OAc	OAc	OH	29
45	OH	OAc	OAc	H	OH	32
46	OAc	OH	=O	OAc	OAc	34
47	OAc	OH	H	OAc	OAc	35
48	OH	OAc	H	OAc	OH	35
49	OH	OH	H	OAc	OAc	35
50	OH	OAc	OH	OAc	OH	35
51	OAc	OH	OAc	OAc	OAc	37
52	OH	OH	=O	OAc	OAc	37
53	OAc	OH	OH	H	OAc	37
54	OAc	OH	OH	OAc	OAc	38,102
55	OH	OAc	OAc	OAc	OAc	43
56	OH	OAc	=O	OAc	OAc	49
57	OH	OAc	=O	OAc	OH	49
58	OAc	OAc	OH	OAc	OH	49
59	H	OAc	OH	H	OH	57,60
60	OH	OAc	=O	H	OH	56
61	OH	OAc	H	H	OAc	58
62	OAc	OAc	=O	H	OH	58
63	H	=O	OH	H	OH	59
64	OH	OAc	=O	H	OAc	60
65	OH	OAc	OH	H	OAc	60
66	OH	OAc	OH	H	OH	60
67	H	OH	OAc	OH	OH	68
68	H	OH	OAc	OAc	OH	69
69	H	OAc	OH	OH	OH	69
70	H	OAc	=O	OH	OH	70
71	H	OH	=O	OH	OH	70



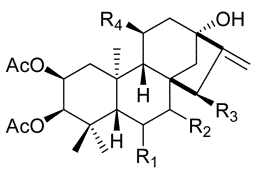
	R_1	R_2	R_3	R_4	R_5	Ref.
30	OH	OAc	OH	OAc	OH	25
31	OH	OAc	OH	OAc	OAc	25
32	OH	OAc	OAc	OAc	OH	25
33	OAc	OAc	OAc	OAc	OAc	25
34	H	OH	=O	OAc	OAc	27
35	H	OAc	OAc	OH	OH	30
36	H	OAc	OAc	H	OH	30
37	H	OH	OAc	H	OH	32
38	H	OH	OAc	OH	OH	32
39	H	OH	OAc	OAc	OH	32
40	H	OAc	OAc	OAc	OH	32



41 R = H Ref. 53
42 R = OH Ref. 85

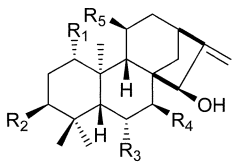


	R_1	R_2	R_3	R_4	Ref.
72	OAc	OAc	OAc	OAc	17
73	OH	OAc	OAc	OAc	17
74	H	OH	=O	OH	70
75	H	OAc	=O	OH	70

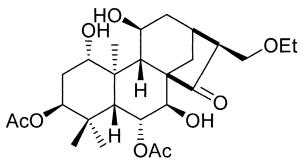


	R_1	R_2	R_3	R_4	Ref.
76	=O	β-OAc	=O	OAc	26
77	α-OAc	β-OAc	=O	OAc	26
78	α-OAc	β-OAc	OH	OAc	26
79	α-O		OH	OAc	26
80	H	H	=O	OH	72

Table 1 (*Contd.*)



	R_1	R_2	R_3	R_4	R_5	Ref.
81	OH	OAc	OAc	OH	OH	29
82	OH	OAc	OAc	H	OH	32
83	OAc	OAc	OAc	H	OH	32
84	OAc	OH	H	OAc	OAc	35
85	OH	OAc	H	OAc	OH	35
86	OAc	OH	H	OAc	OH	35
87	OAc	OH	=O	OAc	OAc	35
88	OAc	OH	OAc	OAc	OAc	37
89	OAc	OAc	OAc	OAc	OAc	44
90	OH	OAc	OH	OAc	OH	46
91	OAc	OH	OH	OAc	OAc	46
92	OH	OAc	=O	OAc	OH	49
93	OH	OAc	OH	H	OAc	55
94	OH	OAc	=O	H	OAc	55
95	OH	OAc	OH	H	OH	56
96	H	=O	H	H	OH	59
97	H	OAc	OAc	OAc	OH	69
98	H	OAc	OH	OAc	OH	69



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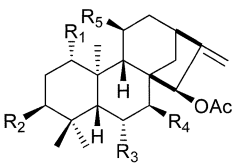
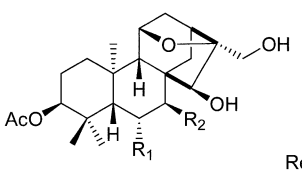
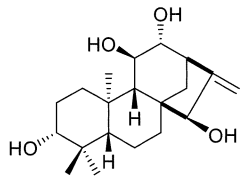


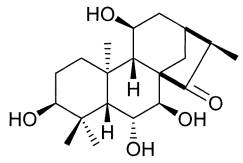
	R_1	R_2	R_3	R_4	R_5	Ref.
100	OAc	OH	H	OAc	OAc	35
101	OAc	OH	=O	OH	OAc	35
102	OAc	OH	OAc	OH	OAc	37
103	OAc	OH	=O	OAc	OAc	37
104	H	OAc	=O	OAc	OAc	44
105	OAc	OH	OAc	OAc	OAc	46
106	OH	OH	OAc	OAc	OAc	46
107	OH	OH	OH	OAc	OAc	46
108	H	OAc	OAc	OAc	=O	48
109	H	OAc	OH	OAc	=O	48
110	OH	OAc	OH	H	OH	56



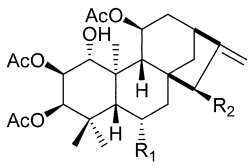
			Ref.
111	R_1 = OH,	R_2 = H	31
112	R_1 = OAc,	R_2 = H	31
113	R_1 = OAc,	R_2 = OH	31



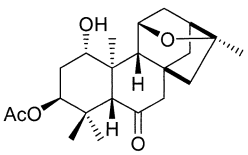
114 Ref. 33



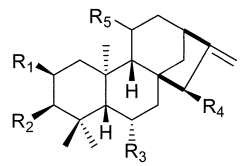
115 Ref. 33



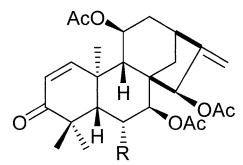
			Ref.
116	R_1 = OH,	R_2 = =O	39,40
117	R_1 = =O,	R_2 = OAc	41
118	R_1 = H,	R_2 = =O	42
119	R_1 = =O,	R_2 = =O	40



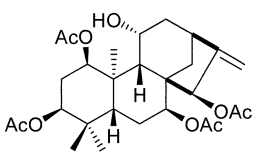
120 Ref. 42



	R_1	R_2	R_3	R_4	R_5	Ref.
121	OAc	OAc	=O	OAc	β-OAc	40
122	OAc	OAc	OH	=O	α-OH	50
123	OAc	OAc	=O	=O	α-OH	50
124	OH	OAc	OH	=O	α-OH	74
125	OH	OAc	OAc	=O	α-OH	75

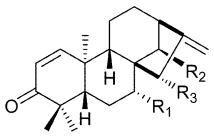


126 R = OAc Ref. 46
127 R = H Ref. 46

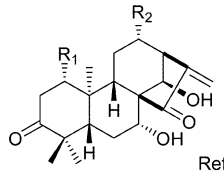


128 Ref. 48

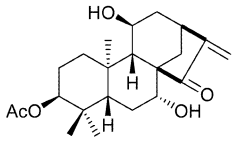
Table 1 (*Contd.*)



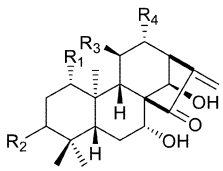
	R_1	R_2	R_3	Ref.
129	OH	OH	=O	53
130	OH	OAc	=O	53
131	OAc	OH	=O	53
132	OH	OH	OH	53



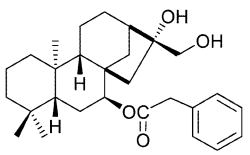
	R_1	R_2	Ref.
133	OAc,	H	53,54
134	H,	OAc	53



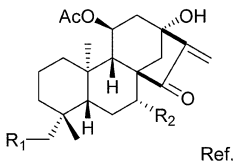
135 Ref. 59



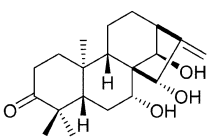
	R_1	R_2	R_3	R_4	Ref.
136	OH	H	OH	H	61
137	OAc	α-OH	H	H	91
138	H	H	OH	OH	92,93
139	H	α-OH	H	H	54
140	H	α-OH	H	OH	54
141	H	β-OAc	H	=O	54
142	OH	β-OAc	H	=O	96
143	H	β-OH	H	=O	97
144	H	H	OAc	OH	66



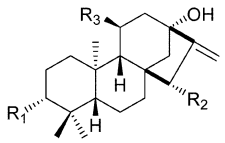
145	R_1 = OH, R_2 = OH	Ref.	62
146	Acetonide of **145**	Ref.	62



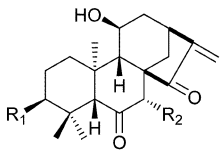
	R_1	R_2	Ref.
147	OH,	H	65
148	OAc,	OH	65
149	OH,	OH	66



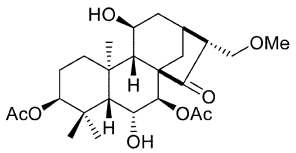
150 Ref. 67



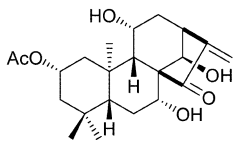
	R_1	R_2	R_3	Ref.
151	OH	=O	OAc	63
152	OAc	=O	OAc	63
153	OH	=O	OH	64
154	OGlc	OH	OH	64



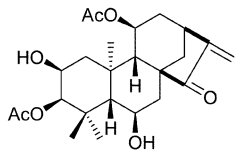
	R_1	R_2	Ref.
155	OAc,	OAc	68
156	OH,	OH	70



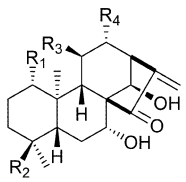
157 Ref. 69



158 Ref. 71

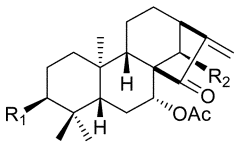


159 Ref. 72

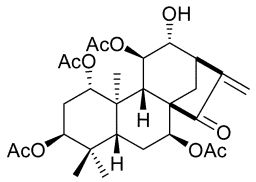


	R_1	R_2	R_3	R_4	Ref
160	OH	CHO	H	H	76
161	H	CH_2OAc	H	OH	77
162	H	COOH	H	OH	80
163	H	CH_2OH	H	H	82
164	OH	CH_2OAc	H	H	83
165	OH	CH_2OH	H	H	84
166	H	CH_2OH	=O	H	86,87
167	H	CH_2OH	H	OH	90
168	H	CH_2OH	OH	H	90
169	H	CH_2OH	OH	OH	90
170	H	CH_2OH	=O	OH	92
171	H	CHO	=O	OH	94

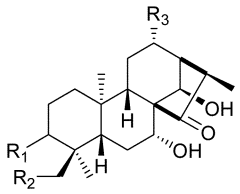
Table 1 (*Contd.*)



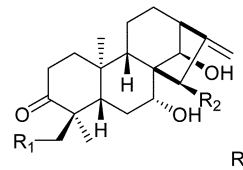
				Ref.
172	R_1 = OAc,	R_2 = OAc		76
173	R_1 = =O,	R_2 = OH		89



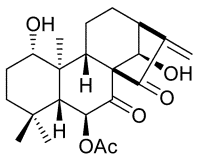
174 Ref. 78,79



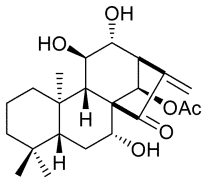
				Ref.
175	R_1 = H	R_2 = OH	R_3 = OH	80
178	R_1 = =O	R_2 = H	R_3 = H	89



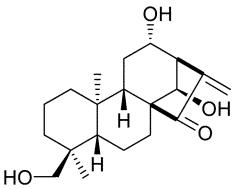
				Ref.
176	R_1 = OH,	R_2 = =O		81
177	R_1 =H,	R_2 = OH		88



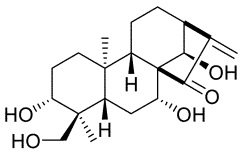
179 Ref. 85



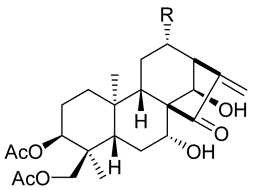
180 Ref. 90



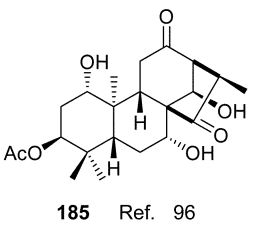
181 Ref. 90



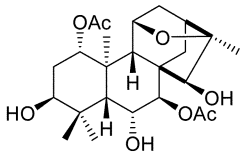
182 Ref. 95



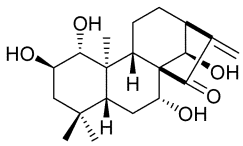
183	R = =O	Ref.	96
184	R = OH	Ref.	96



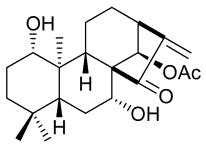
185 Ref. 96



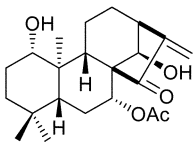
186 Ref. 98



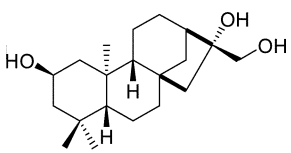
187 Ref. 99



188 Ref. 100



189 Ref. 100



190 Ref. 101

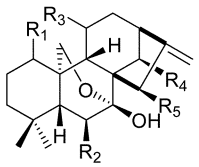
B was established through a single crystal X-ray diffraction analysis.

Many other C-20 non-oxygenated *ent*-kauranes were also identified from different species, such as albopilosin A (**161**) (from *I. albopilosus*),[77] bulleyanin (**174**) (from *I. bulleyana*),[78,79] coetsanoic acid (**162**) and dihydrorabdokunmin C (**175**) (from *I. coetsa*),[80] excisoidesin (**176**) (from *I. excisoides*),[81] excisanins C and D (**163** and **164**)[82,83] and K (**165**)[84] (from *I. excisa*), isodoglutinosins A and B (**179** and **42**) (from *I. glutinosa*),[85] 4-epi-henryine (**166**) (from *I. henryi*),[86,87] rabdosinatol (**177**) (from *I. japonica*),[88] glaucocalyxins D and E (**173** and **178**) (from *I. japonica* subsp. *glaucocalyx*),[89] rabdokunmins A–E (**180**, **181**, and **167–169**) (from *I. kunmingensis*),[90] reniformin B (**137**) (from *I. latifolia*),[91] rabdoloxins A and B (**170** and **138**) (from *I. loxothyrsa*),[92,93] macrocalyxin E (**171**) (from *I. macrocalyx*),[94] parvifoline A (**182**) (from *I. parvifolia*),[95] pseuratas A–G (**139–141**, **183**, **184**, **142**, and **143**) and dihydropseurata F (**185**) (from *I. pseudo-irrorata*),[54,96–97] rosthornin D (**144**) (from *I. rosthornii*),[66] tenuifolin A (**186**) (from *I. tenuifolia*),[98] umbrosianin (**187**), 14-acetyl-kamebanin (**188**), and 7-acetyl-kamebanin (**189**) (from *I. umbrosa*),[99,100] siegesbeckiol (**190**) (from *I. flavidus*),[101] and weisiensin A (**54**) (from *I. weisiensis*).[102]

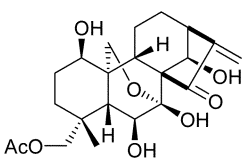
2.2 C-20 oxygenated *ent*-kauranes

The number of naturally occurring C-20 oxygenated *ent*-kauranes from *Isodon* species reported to the end of 2005 is 200. Of these, 160 have been discovered since 1984 (Table 2). In contrast to the C-20 non-oxygenated *ent*-kauranes, C-20 of this group is usually an oxymethylene, oxymethine, or carbonyl group. This group is also widely distributed in the genus *Isodon*, and can be divided

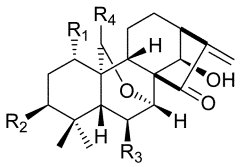
Table 2 Structures of C-20 oxygenated *ent*-kauranes (**191–351**)



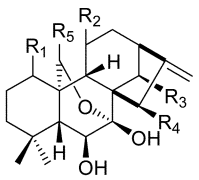
	R_1	R_2	R_3	R_4	R_5	Ref.
191	α-OH	OH	H	OH	=O	103
192	β-OH	OH	H	H	=O	110
193	H	OH	β-OAc	OH	=O	110
194	=O	OAc	H	H	OAc	117
195	α-OAc	OH	H	H	OH	117
196	α-OAc	OAc	H	H	OH	119
197	H	OAc	H	H	OH	119
198	=O	OH	H	H	OAc	122
199	α-OH	OAc	H	H	OAc	123
200	α-OH	OH	β-OGlc	H	OH	126
201	α-OH	OH	α-OAc	H	=O	132
202	α-OH	H	β-OH	H	=O	134
203	α-OAc	H	H	OH	=O	135
204	α-OH	H	β-OAc	H	=O	135
205	α-OAc	H	H	OH	OH	139
206	α-OH	OAc	β-OH	H	OH	144
207	H	OH	α-OH	OH	=O	148
208	α-OAc	OAc	H	H	=O	151
209	α-OAc	OAc	H	OH	OH	152
210	α-OH	H	H	OH	=O	157
211	α-OH	H	β-OH	H	OH	158
212	α-OH	OH	α-OH	H	OH	161
213	H	OH	β-OH	OH	=O	107
214	H	OH	β-OCH	OH	OH	165
215	H	OAc	H	OH	OH	166
216	β-OH	OAc	H	OH	OAc	166
217	α-OAc	OH	α-OAc	H	OH	168
218	H	OAc	H	OH	OAc	112
219	H	OAc	β-OH	OH	OH	169
220	α-OH	OAc	β-OAc	H	OH	170
221	H	OAc	α-OAc	H	OAc	171
222	H	OH	α-OAc	H	OH	171



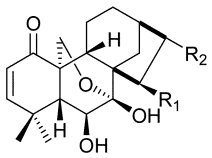
223 Ref. 110



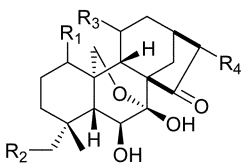
	R_1	R_2	R_3	R_4	Ref.
224	H	OH	H	(*S*) OMe	113
225	H	OH	OH	(*S*) OMe	113
226	H	OH	H	(*S*) OEt	113
227	H	OH	OH	(*S*) OH	113
228	H	OH	OH	(*R*) OH	113
229	OH	H	H	(*S*) OMe	114
230	OH	H	H	(*R*) OMe	116
231	OH	H	H	(*R*,*S*) OH	100
232	OH	H	H	(*S*) OEt	91



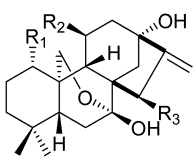
	R_1	R_2	R_3	R_4	R_5	Ref.
233	α-OAc	H	OH	=O	(*R*) OH	110
234	H	β-OH	OH	OH	=O	111
235	H	β-OAc	OH	OH	=O	111
236	H	H	OH	=O	=O	111
237	H	H	OH	OH	=O	112
238	α-OH	H	OH	OH	=O	112
239	α-OH	H	OH	OH	(*R*) OMe	15
240	α-OH	H	OH	=O	(*R*) OMe	169
241	α-OH	H	OH	=O	(*S*) OMe	169
242	α-OH	β-OH	H	=O	(*S*) OMe	169



	R_1	R_2	Ref.
243	= OAc,	R_2 = $=CH_2$	118
244	R_1 = OH,	R_2 = $=CH_2$	117
245	R_1 = =O,	R_2 = β-CH_2OMe	122
246	R_1 = =O,	R_2 = α-CH_2OMe	124
247	R_1 = =O,	R_2 = α-CH_2OH	140

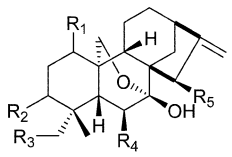


	R_1	R_2	R_3	R_4	Ref.
248	H	OAc	α-OAc	β-CH_2OMe	133
249	α-OH	OAc	α-OH	$=CH_2$	133
250	H	OAc	α-OH	β-CH_2OMe	133
251	H	H	α-OAc	β-CH_2OMe	133
252	α-OAc	H	β-OH	β-CH_2OMe	133
253	β-OH	OAc	α-OAc	$=CH_2$	136
254	β-OH	OAc	α-OH	$=CH_2$	136
255	β-OH	OAc	H	$=CH_2$	137
256	β-OH	OAc	H	β-CH_2OMe	138
257	α-OAc	OAc	α-OAc	$=CH_2$	52
258	α-OAc	H	α-OAc	β-CH_2OEt	52
259	α-OAc	H	α-OAc	α-CH_2OEt	52
260	H	H	α-OAc	β-CH_2OEt	147
261	α-OH	H	H	β-CH_2OMe	160
262	α-OH	H	β-OH	β-CH_2OH	164
263	α-OH	H	β-OH	β-CH_2OMe	167

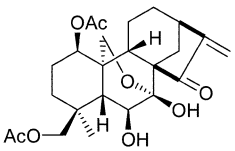


	R_1	R_2	R_3	Ref.
264	R_1 = OH	R_2 =OAc	R_3 = =O	139
265	R_1 = OAc	R_2 = H	R_3 = =O	139
266	R_1 = OAc	R_2 = H	R_3 = OH	139

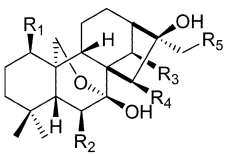
Table 2 (*Contd.*)



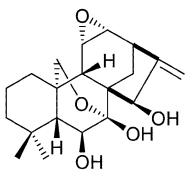
	R_1	R_2	R_3	R_4	R_5	Ref.
267	β-OH	β-OH	OAc	OH	=O	120
268	H	β-OAc	OAc	OH	=O	120
269	H	β-OH	OH	OH	OH	121
270	H	β-OH	OGlc	OH	OH	121
271	β-OH	β-OH	OGlc	OH	OH	121
272	=O	α-OH	H	OH	OAc	140
273	β-OH	β-OH	H	OAc	OAc	150
274	=O	β-OH	H	OAc	OAc	159
275	α-OH	H	OAc	OH	OH	162
276	H	β-OH	OAc	OH	=O	172



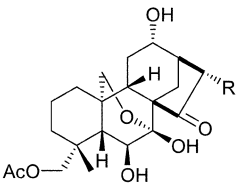
277 Ref. 122



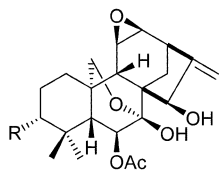
	R_1	R_2	R_3	R_4	R_5	Ref.
278	OH	OAc	H	OH	OAc	141
279	OH	OAc	H	OAc	OH	142
280	H	OAc	H	OH	OAc	143
281	H	OH	OH	OH	OAc	153
282	OH	OH	H	OH	OAc	154
283	H	OAc	OH	OH	OAc	156



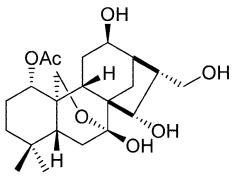
284 Ref. 127



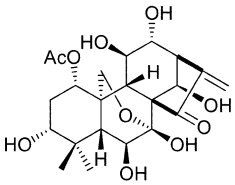
285 R = $=CH_2$ Ref. 127
286 R = CH_2OMe Ref. 127



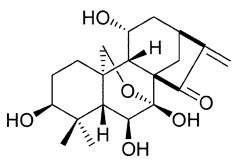
287 R = H Ref. 128
288 R = OH Ref. 129



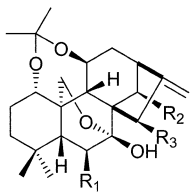
289 Ref. 130



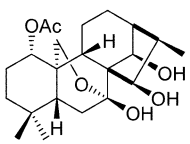
290 Ref. 131



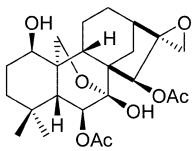
291 Ref. 132



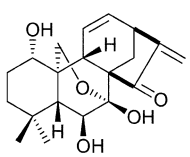
	R_1	R_2	R_3	Ref.
292	OAc	H	OAc	122
293	OH	H	OH	127
294	H	H	OH	135
295	OH	OH	=O	138
296	OAc	H	OH	144



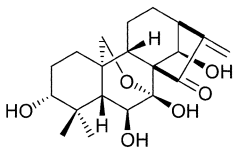
297 Ref. 139



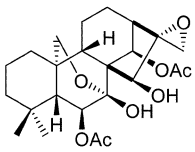
298 Ref. 142



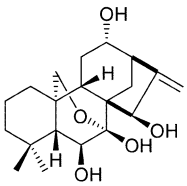
299 Ref. 145



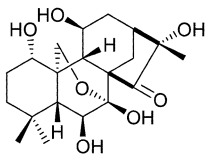
300 Ref. 146



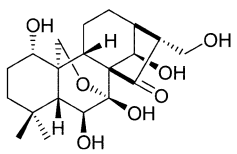
301 Ref. 155



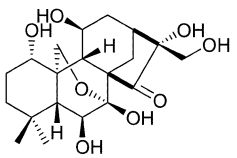
302 Ref. 128



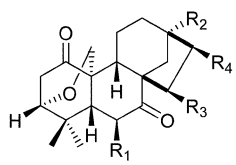
303 Ref. 163



304 Ref. 164

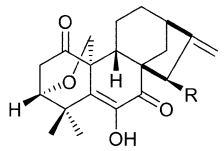


305 Ref. 167

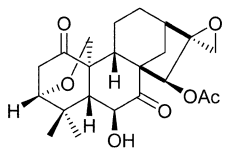


	R_1	R_2	R_3	R_4	Ref.
306	OAc	H	OAc	$=CH_2$	174
307	OH	H	OAc	$=CH_2$	117
308	OAc	H	OH	$=CH_2$	124
309	OH	H	=O	$=CH_2$	177
310	OH	H	=O	CH_2OH	177
311	OH	H	OH	$=CH_2$	177
312	OH	OH	OAc	$=CH_2$	177

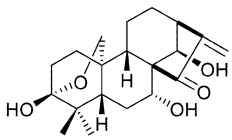
Table 2 (*Contd.*)



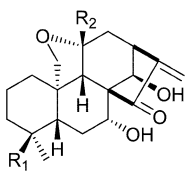
313 R = OAc Ref. 176
314 R = =O Ref. 176



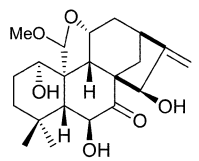
315 Ref. 123



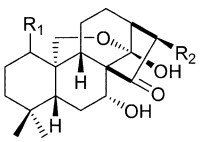
316 Ref. 113



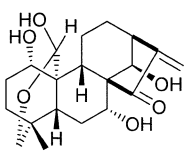
	R_1	R_2	Ref.
317	CHO	OMe	156
318	CHO	OH	95
319	CH_3	OH	178



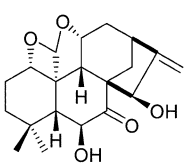
320 Ref. 179



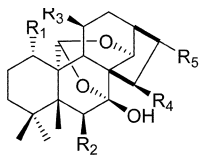
	R_1	R_2	Ref.
321	α-OH	$=CH_2$	84
322	α-OH	CH_3	180
323	β-OH	CH_3	180



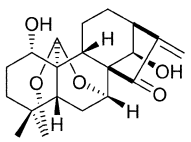
324 Ref. 61



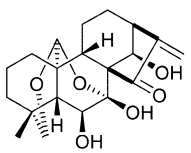
325 Ref. 179



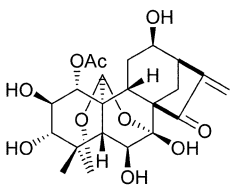
	R_1	R_2	R_3	R_4	R_5	Ref.
326	H	OH	OAc	=O	$=CH_2$	183
327	H	OH	H	=O	$=CH_2$	183
328	OH	OH	H	=O	α-CH_3	183
329	H	OH	OH	=O	$=CH_2$	184
330	H	OAc	OAc	=O	$=CH_2$	185
331	H	OH	OH	OAc	$=CH_2$	146



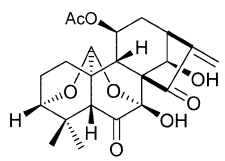
332 Ref. 186



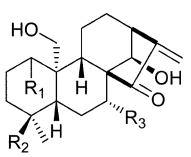
333 Ref. 187



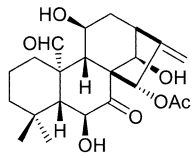
334 Ref. 130



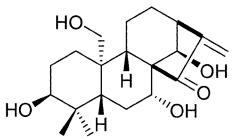
335 Ref. 188



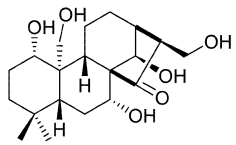
	R_1	R_2	R_3	Ref.
336	α-OH	CH_2OH	OH	76
337	α-OH	CH_2OAc	OH	83
338	α-OH	CHO	OH	190
339	H	CH_2OH	OH	84
340	H	CHO	OH	193
341	β-OH	CH_3	OH	195
342	OH	CH_3	OAc	100



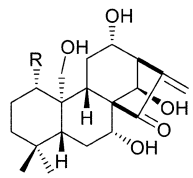
343 Ref. 189



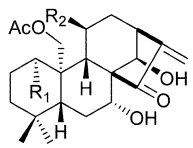
344 Ref. 113



345 Ref. 190



346 R = H Ref. 84
347 R = OH Ref. 194



	R_1	R_2	Ref.
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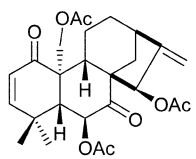
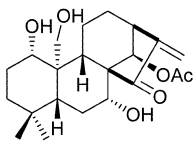
349	OH	H	116



350 Ref. 192

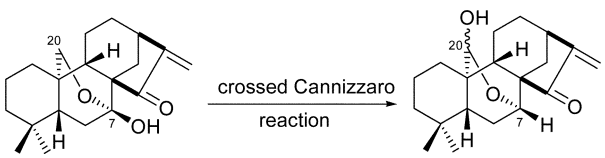


351 Ref. 100

into nine subgroups, depending on the number of epoxy rings with C-20 and the position of the C–O–C_{20} bond.

2.2.1 Monoepoxy-*ent*-kauranes.

2.2.1.1 7,20-Epoxy-ent-*kauranes.* One of the known 7,20-epoxy-*ent*-kauranes, oridonin (**191**), is a typical compound in this subgroup.[103–105] Oridonin has been isolated from several species[106–109] and found to have broad spectrum anti-tumour and anti-bacterial activities *in vitro* and *in vivo* (this will be discussed later more in detail in section **3.2**).[8,9] *Ent*-kauranoids like oridonin in which carbon C-6 is an oxymethine and carbon C-7 is a hemiketal group, are the most common examples of 7,20-epoxy-*ent*-kauranes, and are exemplified by xerophilusins G (**223**) and I–N (**192**, **233**, **193**, and **234–236**), isolated from *I. xerophilus* by our group.[110,111] The structure of xerophilusin J (**233**) was confirmed by X-ray analysis. Xerophilusins L–N (**234–236**) possessing a carbonyl group at carbon C-20 are rare among the C-20 oxygenated *ent*-kauranes. Only two other compounds, rabdoternins A and B (**237** and **238**) (from *I. ternifolia*),[112] have been reported. Interestingly, cytotoxicity testing showed that **236** with an active center (cyclopentanone conjugated with an exo-methylene group) was less active than other analogues, which suggests that the lactone group present in the molecules resulted in the decline of cytotoxicity.[111] The five 7,20-epoxy-*ent*-kauranes (**224–228**) isolated from *I. coetsoides* were structurally very unusual.[113] Coetsoidins C–G (**224–228**) also have a 7,20-epoxy-*ent*-kaurane core, but with a methine group at carbon C-7 rather than a hemiketal. In addition, all these compounds bear the same structural features: one β-hydroxyl group at carbons C-3 and C-14, respectively, an α,β-unsaturated ketone group at carbon C-15, and a hemiacetal or acetal group at carbon C-20. The only difference among them is the substituent at carbons C-20 and C-6. Coetsoidins C and E are devoid of the β-orientated hydroxyl group at C-6, whose configurations of carbon C-20 were determined by the downfield shift of carbon C-11 due to the δ-*syn*-axial effect between C-20 methoxyl and carbon C-11. It is notable that all the 7,20-epoxy-*ent*-kauranes which lack a hemiketal function at carbon C-7, isolated so far from the genus *Isodon*, always have an additional hemiacetal or acetal group at carbon C-20. These are exemplified by kamebacetals A and B (**229** and **230**) (from *I. umbrosa* var. *leucantha* f. *kameba*),[114–116] demethylkamebacetal (**231**) (from *I. umbrosa*),[100] and reniformin C (**232**) (from *I. latifolia*).[91] These structural features suggest that this type of 7,20-epoxy *ent*-kauranes are biosynthesized from the "oridonin type", having an oxymethylene at C-20 and a hemiketal at C-7, *via* an intramolecular crossed Cannizzaro reaction between C-7 and C-20 (Scheme 1).



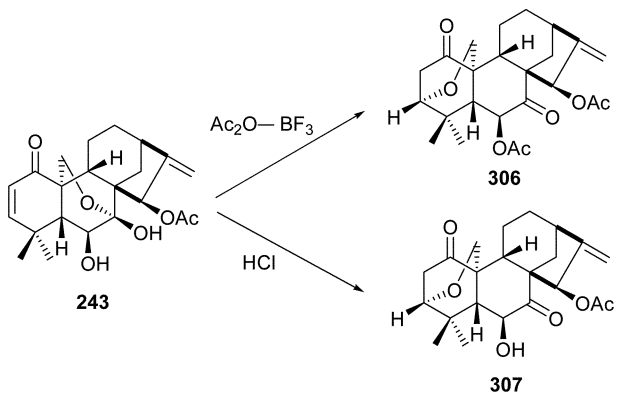
Scheme 1

Extensive research on *I. eriocalyx* by our group has revealed that this species is a prolific source of new and biologically active diterpenoids. Seventeen new C-20 oxygenated *ent*-kauranes, maoecrystals B–G (**243**, **244**, and **194–197**),[117–119] I–K (**267–269**),[120–121] and Q–T (**245**, **277**, **198**, and **292**),[122] eriocalyxin D (**199**),[123] epi-maoecrystal P (**246**),[124,125] and rabdosides **1** and **2** (**270** and **271**),[121] were isolated and characterized. Among them, rabdosides **1** and **2** are very similar, both containing a β-D-glucopyranoside moiety at carbon C-19, the only difference being the presence of an additional β-hydroxyl group at C-1 in the former. Parvifoliside (**200**) (from *I. parvifolia*) is another example of diterpene glucoside.[126] Compounds **200**, **270**, and **271** are three of only five *ent*-kauranoids isolated from *Isodon* which bear a β-D-glucopyranosyl function in the molecule. Wikstroemioidins A–D (**284**, **293**, **285**, and **286**) were isolated from the leaves of *I. wikstroemioides* growing in Yunnan province,[127] and their structures were determined by extensive spectroscopic means. Wikstroemioidin A is the first report of an *Isodon* diterpenoid with an epoxide group between C-11 and C-12. Two recent analogues of wikstroemioidin A, oreskaurin B (**287**)[128] and phyllostachysin C (**288**) (originally from *I. phyllostachys*)[129] were isolated from the 70% aq. acetone extract of the leaves of *I. oresbius.* These two compounds share structural similarities, in which phyllostachysin C possesses an additional hydroxyl group at carbon C-3. Both compounds were evaluated for their cytotoxicity against several cancer cell lines, and yet, both were completely inactive, which suggests that the epoxide group present in each of these molecules is not related to the cytotoxicity of *ent*-kauranes. In studies by Li, four 7,20-epoxy-*ent*-kauranes, taibaijaponicains C and E (**289** and **290**),[130,131] and taibaihenryiins A and B (**201** and **291**),[132] were identified from two species of *Isodon* collected from Taibai mountain, *I. japonica* and *I. henryi*, respectively. It is interesting to note that taibaijaponicain C with a β-orientated hydroxyl group at carbon C-12 is rare in *Isodon* diterpenoids, and taibaijaponicain E is one of the most highly oxygenated in naturally occurring *ent*-kauranes. Recently, further examination of *I. japonica* has yielded maoyecrystal J (**299**),[145] having an unusual double bond between C-11 and C-12.

Other members belonging to the 7,20-epoxy-*ent*-kauranes include adenolins A–E (**248–252**),[133] (from *I. adenoloma*), rabdocoetsins A–D (**202**, **203**, **294**, and **204**),[134,135] (from *I. coetsa*), enanderianins A–C (**253–255**)[136,137] G (**256**), H (**295**)[138] and K–O (**264–266**, **205**, and **297**)[139] (from *I. enanderianus*), laxiflorins H and I (**272** and **247**) (from *I. eriocalyx* subsp. *laxiflora*),[140] maoyerabdosin (**278**),[141] maoyecrystals A–C (**279**, **298**, and **280**),[142,143] F (**206**)[144] and the acetonide of maoyecrystal F (**296**)[144] (from *I. japonica*), baiyecrystals A, C and E (**257**, **258** and **300**),[52,146] and epi-baiyecrystal C (**259**)[52] (from *I. leucophylla*), lihsienin A (**260**) (from *I. lihsienensis*),[147] longikaurin G (**207**),[148,149] rabdolongin A (**273**),[150] and rabdokaurins A and C (**208** and **209**)[151,152] (from *I. longituba*), macrocalyxins G and H (**281** and **282**) (from *I. macrocalyx*),[153,154] jiuhuanin A (**301**) (from *I. macrocalyx* subsp. *jiuhua*),[155] rabdophyllin H (**283**) (from *I. macrophylla*),[156] megathyrins A and B (**210** and **211**) (from *I. megathyrsus*),[157,158] ganervosin A (**274**)[159] Zentralbl Bakterioland nervosanins A and B (**261** and **212**) (from *I. nervosa*),[160,161] neoangustifolin (**275**)[162] and oreskaurin C (**302**) (from *I. oresbius*),[128] parvifolin (**303**) (from *I. parvifolia*),[163] rosthorin A (**213**) (from *I. rosthornii*),[107] rubescensins F–H (**262**, **304**, and **214**),[164,165] O (**239**),[15] Q (**215**), and R (**216**) (from *I. rubescens*),[166] lushanrubescensins F and G (**263** and **305**) (from *I. rubescens* subsp. *lushanensis*),[167] rabdosichuanin D (**217**) (from *I. setschwanensis*),[168] rabdoternins C–G (**218**, **219**, **240**, **241**, ; and **242**),[112,169] ternifolin (**220**),[170] isodoternifolins A and B (**221**

and **222**) (from *I. ternifolia*),[171] and trichoranin (**276**)[172] (from *I. trichocarpa*).

2.2.1.2 3,20-Epoxy-ent-*kauranes.* The first 3,20-epoxy-*ent*-kaurane found in *Isodon* species was neorabdosin (**306**) isolated from *I. nervosa.*[173,174] Its structure was established by spectroscopic means and chemical evidence, and finally confirmed by X-ray analysis.[175] In this subgroup, positions C-1, C-3, C-6, C-7, and C-15 are commonly oxygenated, and carbons C-1 and C-7 are always a ketone group. New examples are coetsoidin A (Wang) (**313**) (from *I. coetsoides*),[176] eriocalyxin C (**315**)[123] and maoecrystals A (**307**),[117] P (**314**),[176] and U (**308**),[124,125] (from *I. eriocalyx*), laxiflorins J–M (**309–312**)[177] (from *I. eriocalyx* subsp. *laxiflora*). These compounds may be biosynthesized from 7,20-epoxy-*ent*-kauranoids with an α,β-unsaturated ketone group at carbon C-1 *via* an intramolecular Michael addition. This assumption was confirmed by the chemical transformation (Scheme 2).[117] But coetsoidin A (Huang) (**316**) isolated from *I. coetsoides* is a sole special case. It lacks any oxygenation at C-1 and C-6, and contains a hemiketal group at C-3 and an α-hydroxyl instead of a ketone group at C-7.[113] The absolute configuration of coetsoidin A (Huang) was determined by its dihydro-derivative, which showed a negative ORD effect in methanol. The cytotoxic activities of the compounds **307**, **314**, and **309–312** isolated from *I. eriocalyx* subsp. *laxiflora* were tested against the human tumour line K562, A549, and T24 cells. Laxiflorins J (**309**) and maoecrystal P (**314**) demonstrated significant cytotoxicities toward T24 cells, with IC_{50} values of 0.314 μg mL^{-1} and 0.051 μg mL^{-1}, respectively.[177] The stronger activity of **314** than **309** could be explained by the existence of an additional double bond between C-5 and C-6 in maoecrystal P, leading to the formation of a second α,β-unsaturated ketone moiety in the B-ring.



Scheme 2

2.2.1.3 11,20-Epoxy-ent-*kauranes.* In this subgroup, only four compounds, macrocalyxin B (**317**),[156] parvifoline B (**318**),[95] pseudoirroratin A (**319**),[178] and rubescensin W (**320**),[179] have been found in four different species, *I. macrocalyx*, *I. parvifolia*, *I. pseudo-irrorata*, and *I. rubescens*, respectively. Compound **319** showed broad spectrum cytotoxicities against the Lu1, SW626, LNCaP, KB, and HOS cancer cell lines.[178]

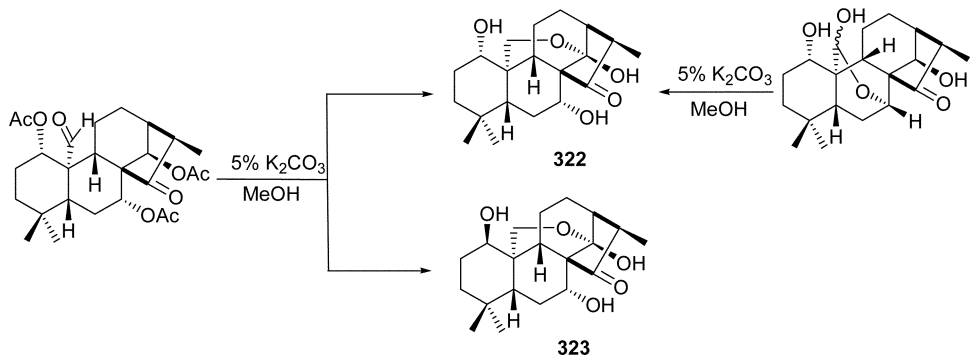
2.2.1.4 14,20-Epoxy-ent-*kauranes.* Excisanin H (**321**),[84] isolated from *I. excisa*, is the only example in this subgroup. Based on the structure of **231**, the 14,20-epoxy ring of excisanin H may be formed from **231** *via* an intramolecular crossed Cannizzaro reaction between C-20 and C-14. Two other hemisynthetic compounds **322** and **323** (Scheme 3),[180] provide important support to this biosynthetic assumption.

2.2.1.5 19,20-Epoxy-ent-*kauranes.* This subgroup is rare in genus *Isodon*, only rabdoinflexin A (**324**) has been isolated from *I. inflexa*.[61]

2.2.2 Diepoxy-*ent*-kauranes.

2.2.2.1 1,20:11,20-Diepoxy-ent-*kauranes.* Maoyecrystal I (**325**) isolated from *I. japonicus*,[179] is the only example of this subgroup. In our studies, **325** without any substructure of α,β-unsaturated ketone, exhibited a comparable inhibitory effect toward K562 cells, while **320** was completely inactive. The unusual oxetane group in the former was the only difference between the structures of **325** and **320**. This was therefore suggested to be a new bioactive moiety in this class of natural products. Many biologically natural products containing the oxetane moiety have been found, such as the antiviral oxetanocin A, the antibacterial oxetin, and thromboxane A_2 (TXA_2) being highly active against aggregation of blood platelets.[181] The oxetane moiety in Taxol is especially necessary for its strong cytotoxicity.[182]

2.2.2.2 7,20:14,20-Diepoxy-ent-*kauranes.* In studies by our group, three new compounds, xerophilusins A–C (**326–328**),[183] along with a known one, macrocalin B (**329**)[184] (originally from *I. macrocalyx*), were isolated from *I. xerophilus.* Compounds **326–329**, but not **328**, showed cytotoxicities in the K562, HL-60, and MKN-28 cells culture assay, with **327** being the most potent. Rugosinin (**330**),[185] isolated from the leaves of *I. rugosus* of Pakistani origin, exhibited DNA-damaging activity in an assay which employed DNA-repair deficient (RAD52Y) and repair proficient (RAD^+) yeast strains. The structure of rugosinin was



Scheme 3

established by X-ray analysis. Baiyecrystal D (**331**) was recently isolated from the leaves of *I. leucophyllus*.[146]

2.2.2.3 7,20:19,20-Diepoxy-ent-*kauranes.* Rabdoserrin A (**332**),[186] the first one belonging to this subgroup, was obtained from the aerial parts of *I. serra* in 1985. Following that, only two analogues, xerophilusin D (**333**)[187] (from *I. xerophilus*) and taibaijaponicain D (**334**)[130] (from *I. japonica*), have been reported. Compound **334** has two rare structural features. It is one of the most highly oxygenated *ent*-kauranes in nature, and furthermore it is one of the only two *ent*-kauranoids (**234** and **334**) isolated from genus *Isodon*, which bears a β-hydroxyl group at C-12 in the molecule.

2.2.2.4 3,20:7,20-Diepoxy-ent-*kauranes.* Xerophilusin E (**335**) (from *I. xerophilus*) was the sole example of this subgroup detected in genus *Isodon*, whose structure was established using extensive spectroscopic methods and X-ray analysis. It was cytotoxic against K562, HL-60, and MKN-28 human tumour cell lines.[187,188]

2.2.3 C-20 oxygenated non-epoxy ring *ent*-kauranes. Eighteen diterpenoids belong to this subgroup, 16 have been discovered since 1984. This subgroup is characterized by an isolated oxygen-containing methylene carbon at C-20, and with an oxygen function at C-7, C-14, and C-15, respectively, as in weisiensin C (**336**)[76] isolated recently from *I. weisiensis.* The only exception is phyllostachysin B (**343**) isolated from *I. phyllostachys*,[189] which bears special structural features, with an aldehyde group at C-20, a ketone group at C-7, and a hydroxyl at C-6. Biogenetically, compounds with such a substitution patterns are likely to form an epoxy ring between C-7 and C-20, and are usually considered to be artefacts formed during the extraction and isolation. However, phyllostachysin B could be a natural product since the unusual α-orientated acetoxyl group at C-15 can sterically hinder the β-orientated hydroxyl group at C-7, preventing the formation of 7,20-epoxy ring. Other examples of this subgroup are coetsoidin B (**344**) (from *I. coetsoides*),[113] excisanins E–G (**337**, **338**, and **345**)[83,190] and I–J (**346** and **339**)[84] (from *I. excisa*), flexicaulin A (**348**) (from *I. flexicaulis*),[191] henryin (**349**) (from *I. henryi*),[116] longirabdosin (**350**) (from *I. longituba*),[192] macrocalyxin D (**340**) (from *I. macrocalyx*),[193] rabdoserrins B (**347**) and D (**341**) (from *I. serra*),[194,195] and 7-acetyl-kamebakaurin (**342**) and 14-acetyl-kamebakaurin (**351**) (from *I. umbrosa*).[100]

2.3 6,7-Seco-*ent*-kauranes

This group is also a large group, comprising 105 of the 610 *Isodon* diterpenoids. Of these, 88 have been identified since 1984 (Table 3).

This group of compounds can be regarded as the products of the oxidative cleavage of the C_6–C_7 bond of the 7,20-epoxy-*ent*-kaurane precursors. According to their structure, this group is further classified into two subgroups, enmein type (1,7-lactone type) and spiro-lactone type (7,20-lactone type). From the biosynthetic point of view, if no substituent is present at C-1, the oxidative cleavage must give the 7,20-lactone type, but if an α-orientated hydroxyl group is present at C-1, relactonization generally occurs to produce the 1,7-lactone type.

2.3.1 Enmein type (1,7-lactone type). A major constituent of the leaves of "*enmei-so*" belonging to this subgroup, designated as enmein (**352**), were isolated about 40 years ago and characterized by a combination of spectral measurements, chemical correlation, and X-ray analysis.[7] Since then, a series of enmein type diterpenoids have been isolated from "*enmei-so*". Enmein consists of five characteristic rings, with ring B being a 1,7-lactone and ring E being a C_6–C_{20} hemiacetal. Macrocalyxin A (**366**)[155,196] (from *I. macrocalyx*), nervosin (**353**)[173] and ganervosin B (**354**)[197] (from *I. nervosa*), rugosanin (**355**), dihydrorugosanin (**356**), dihydroisodocarpin (**357**), and dihydrocarpalasionin (**358**) (from *I. rugosa*),[198] rabdosichuanin C (**359**) (from *I. setschwanensis*),[168,199] irroratin A (**371**) (from *I. irrorata*),[11] taibaijaponicains A (**360**) and B (**361**),[200] and maoyecrystals D (**362**)[143] and K (**363**)[145] (from *I. japonica*), baiyecrystal B (**367**) (from *I. leucophylla*),[51,52] longirabdolides C (**364**) and D (**368**) (from *I. longituba*),[201,202] and sculponeatins E–G (**369–370**, and **365**) (from *I. sculponeata*),[203,204] are a series of derivatives of the enmein core structure. Irroratin A (**371**) isolated from the leaves of *I. irrorata*, was a very interesting compound. It was shown to be an equimolecular mixture of two C-20 epimers both in the crystalline state and pyridine solution on the basis of X-ray analysis and NMR experiments. Two epimers were bonded together by hydrogen bonds, and when in chloroform and methanol solution, the 20*S* epimer predominates.[11]

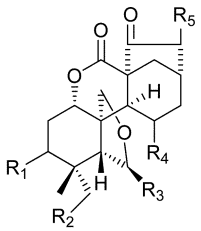
An investigation on *I. japonica* subsp. *glaucocalyx* afforded a very special diterpenoid, glaucocalactone (**372**).[205] It contains an isolated aldehyde group at C-20 instead of an oxymethylene or acetal group, and an additional lactone ring between C-6 and C-11. Macrocalyxoformins A (**373**) and B (**374**) with a (6*S*)-6,20-epoxy structure, were isolated from the leaves of *I. macrocalyx.* Hara form.[206–208] The oxygen bridge connects C-19 with the hemiacetal carbon C-6, thus forming an additional tetrahydrofuran ring structural element. Recently, five newly examples, ludongnins C–E (**375–377**) (from *I. rubescens* subsp. *lushiensis*)[209] and sculponeatins H (**378**) and I (**379**) (from *I. sculponeata*),[204] were reported by our group. Enanderinanin F (**380**),[138] isolated from *I. enanderianus*, had a unique structural feature since carbon C-11 formed an oxygen bridge with hemiacetal hydroxyl group at C-6.

2.3.2 Spiro-lactone type (7,20-lactone type). During the 1970s and the early 1980s, discrimination between the enmein type and spiro-lactone type was very difficult due to the lack of modern 2D NMR methods. For this reason, some spiro-lactone type compounds were misidentified as enmein type, such as isodonal (**381**), isodonal acid (**382**), trichodonin (= trichorabdal H) (**383**), isodonoiol (**384**), rabdosin B (**385**), and rabdolasional (**386**). Based on X-ray analysis and modern 2D NMR experiments mainly including HMBC and NOESY spectra, their structures were revised (Scheme 4).[9,210]

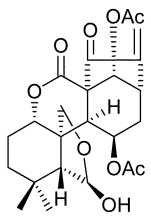
During the studies on trichorabdals, a Japanese group found an interesting phenomenon. If C-6 is an aldehyde group and the A-ring does not have any other large substituent, there are two possible chair conformation in ring A of the spiro-6,7-seco-*ent*-kaurane nucleus. One has the C-9 axial and C-20 equatorial orientation, the other a C-9 equatorial and C-20 axial one.[211] In addition, we found that the C-9 axial and C-20 equatorial conformations are commonly predominant in different solutions (Scheme 5).[211]

This is also an abundant subgroup, which includes 62 compounds. Biogenetically, diterpenoids of this subgroup should have an aldehyde group at C-6, although in many members of this subgroup, the aldehyde has subsequently been reduced, oxidized, or

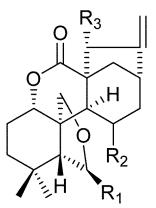
Table 3 Structures of 6,7-seco-*ent*-kauranes (**352–446**)



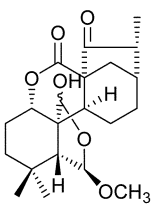
	R_1	R_2	R_3	R_4	R_5	Ref.
352	β-OH	H	OH	H	$=CH_2$	7
353	H	H	OMe	β-OH	$=CH_2$	173
354	H	H	OEt	β-OH	$=CH_2$	197
355	H	OAc	OH	H	$=CH_2$	198
356	H	OAc	OH	H	α-CH_3	198
357	H	H	OH	H	α-CH_3	198
358	H	OAc	OH	β-OH	α-CH_3	198
359	H	H	OH	α-OH	α-CH_3	199
360	H	H	OH	α-OH	α-CH_2OMe	200
361	β-OAc	H	OH	α-OH	α-CH_2OMe	200
362	H	H	OH	α-OH	α-CH_2OH	143
363	H	H	OH	α-OH	β-CH_2OMe	145
364	β-OH	H	OH	β-OH	$=CH_2$	201
365	H	OAc	OH	H	α-CH_2OEt	204



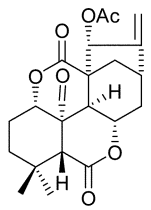
366 Ref. 196



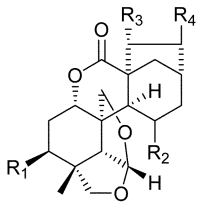
				Ref.
367	R_1 = OAc	R_2 = α-OH	R_3 = OH	51
368	R_1 = OAc	R_2 = β-OH	R_3 = OAc	202
369	R_1 = OH	R_2 = α-OH	R_3 = OAc	203
370	R_1 = OH	R_2 = α-OH	R_3 = OH	204



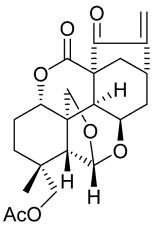
371 Ref. 11



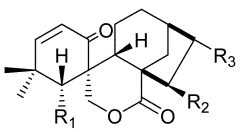
372 Ref. 205



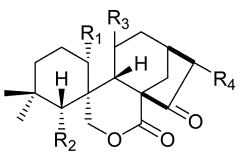
	R_1	R_2	R_3	R_4	Ref.
373	H	H	OH	$=CH_2$	206
374	H	H	=O	$=CH_2$	208
375	H	H	=O	α-CH_3	209
376	H	H	=O	β-CH_3	209
377	H	β-OH	=O	α-CH_3	209
378	H	α-OH	=O	$=CH_2$	204
379	OH	H	=O	$=CH_2$	204



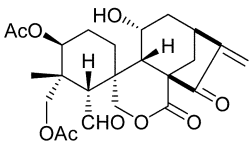
380 Ref. 138



				Ref.
387	R_1 = CHO	R_2 = =O	R_3 = α-CH_3	212
388	R_1 = CHO	R_2 = OAc	R_3 = $=CH_2$	123
389	R_1 = CHO	R_2 = =O	R_3 = β-CH_3	212
390	R_1 = COOH	R_2 = =O	R_3 = α-CH_3	212
391	R_1 = CH_2OH	R_2 = OH	R_3 = $=CH_2$	214
392	R_1 = CH_2OH	R_2 = =O	R_3 = $=CH_2$	214
393	R_1 = CH_2OH	R_2 = =O	R_3 = β-CH_3	214
394	R_1 = CHO	R_2 = OH	R_3 = $=CH_2$	140
395	R_1 = CH_2OH	R_2 = =O	R_3 = α-CH_3	140



	R_1	R_2	R_3	R_4	Ref.
396	OAc	CHO	H	α-CH_3	213
397	OAc	COOH	H	α-CH_3	212
398	OAc	CH_2OH	α-OH	$=CH_2$	143
399	OAc	CH_2OAc	β-OAc	$=CH_2$	218
400	OH	CH_2OH	H	$=CH_2$	220
401	OH	CH_2OAc	H	$=CH_2$	220
402	OAc	CHO	β-OH	β-CH_3	168
403	H	CHO	α-OH	β-CH_3	168
404	OAc	CH_2OH	H	$=CH_2$	222
405	OAc	CH_2OH	H	$=CH_2$	167



406 Ref. 215

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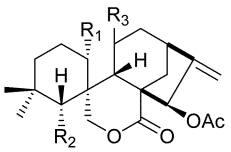
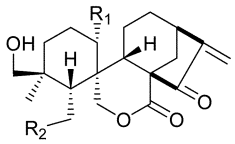
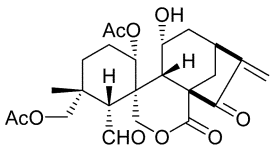


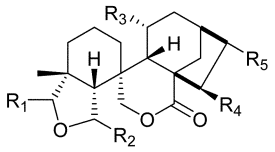
				Ref.
407	R_1 = OAc	R_2 = CH_2OAc	R_3 = α-OAc	216
408	R_1 = OAc	R_2 = CH_2OAc	R_3 = β-OAc	88
409	R_1 = OH	R_2 = CHO	R_3 = β-OH	167



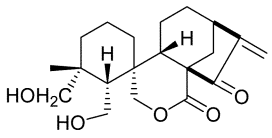
			Ref.
410	R_1 = OAc,	R_2 = OAc	151
411	R_1 = OAc,	R_2 = OH	152
412	R_1 = H,	R_2 = OH	219



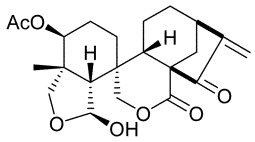
413 Ref. 221



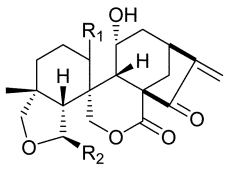
	R_1	R_2	R_3	R_4	R_5	Ref.
414	H	=O	OH	OH	$=CH_2$	226
415	H	=O	H	=O	β-CH_3	227
416	H	=O	OH	=O	β-CH_3	227
417	H	=O	OH	=O	β-CH_2OH	227
418	H	α-OH	H	=O	β-CH_3	227
419	H	β-OH	H	=O	β-CH_3	227
420	H	β-OH	OH	OH	$=CH_2$	227
421	β-OMe	H	H	=O	β-CH_3	227
422	H	=O	OH	=O	$=CH_2$	228
423	H	=O	H	=O	β-CH_3	229
424	H	α-OMe	H	=O	β-CH_3	230
425	H	α-OMe	H	=O	α-CH_3	230
426	H	β-OMe	H	=O	α-CH_3	230
427	H	β-OMe	H	=O	β-CH_3	230
428	H	α-OMe	H	=O	$=CH_2$	230
429	H	OH	OH	=O	$=CH_2$	224
430	H	β-OMe	OH	=O	$=CH_2$	232
431	H	α-OMe	OH	=O	$=CH_2$	138
432	=O	H	H	=O	$=CH_2$	233
433	OH	H	H	=O	$=CH_2$	233
434	H	α-OH	H	=O	$=CH_2$	207



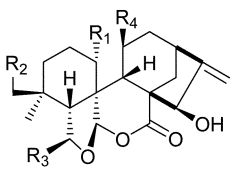
435 Ref. 225



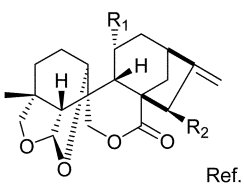
436 Ref. 231



			Ref.
437	R_1 = α-OAc,	R_2 = OMe	215
438	R_1 = β-OH,	R_2 = OAc	128



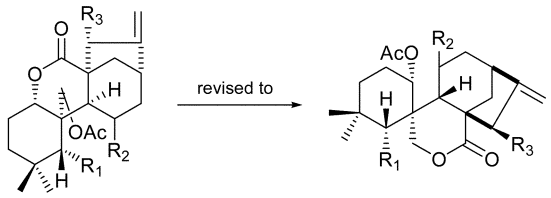
	R_1	R_2	R_3	R_4	Ref.
439	OH	H	OH	H	234
440	OH	H	OMe	H	235
441	OH	H	OEt	H	236
442	H	H	OH	H	207
443	OH	OH	OH	OH	237



			Ref.
444	R_1 = OH,	R_2 = =O	238
445	R_1 = H,	R_2 = =O	239
446	R_1 = H,	R_2 = OH	239

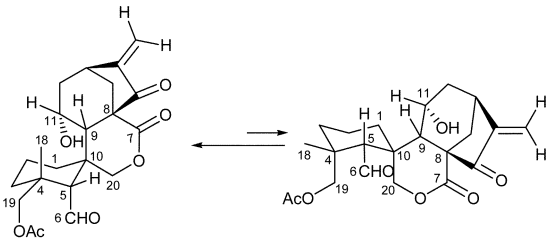
otherwise modified. This subgroup can further divided into three sets having four-ring, five-ring or six-ring skeletons, depending on whether C_6–O–C_{19}, C_6–O–C_{20}, or C_6–O–C_1 bonds have been made or not.

Ericalyxins A (**387**)[212] and E (**388**),[123] epi-eriocalyxin A (**389**),[212] maoecrystals L (**396**),[213] N (**390**),[212] and O (**397**)[212] were all isolated from *I. eriocalyx*. They possess the common four-ring substructure and an aldehyde carboxyl group at C-6. Among them, compounds **387**, **388**, and **389** having an α,β-unsaturated ketone in A-ring, are very similar to laxiflorins A–E (**391–395**) isolated from the subspecies of *I. eriocalyx*, *I. eriocalyx* subsp. *laxifloria*.[140,214] The only difference is whether the aldehyde at C-6, the ketone at C-15, and the double bond between C-16 and C-17 have been reduced or not. Many other four-ring analogues have been isolated from different species, such as coetsin B (**406**) (from *I. coetsa*),[215] inflexusin (**407**) (from *I. inflexa*),[216] rabdosinate (**408**),[88]



	R_1	R_2	R_3	R_1	R_2	R_3
381	CHO	α-OH	=O	CHO	β-OH	=O
382	COOH	α-OH	=O	COOH	β-OH	=O
383	CHO	β-OH	=O	CHO	α-OH	=O
384	CH_2OH	α-OH	=O	CH_2OH	β-OH	=O
385	CH_2OAc	α-OH	=O	CH_2OAc	β-OH	=O
386	CHO	α-OH	OH	CHO	β-OH	OH

Scheme 4

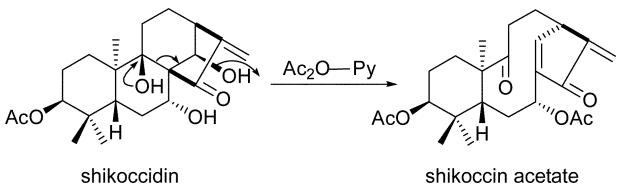


Scheme 5

isodonoiol (**384**),[217] and maoyecrystal E (**398**) (from *I. japonica*),[143] acetylexidonin (**399**) (from *I. japonica* subsp. *glaucocalys*),[218] rabdokaurins B (**410**)[151] and D (**411**),[152] isolongirabdiol (**412**),[219] and longirabdolides E (**400**) and F (**401**) (from *I. longituba*),[220] loxothyrin A (**413**) (from *I. loxothyrsa*),[221] rabdosichuanins A (**402**) and B (**403**) (from *I. setschwanensis*),[168] rabdoternin H (**404**) (from *I. ternifolia*),[222] trichorabdal H (trichodonin) (**383**) (from *I. trichocarpa*),[223,224] macrocalyxoformin D (**435**) (from *I. macrocalyx* Hara. form),[225] and lushanrubescensins H (**405**) and I (**409**) (from *I. rubescens* subsp. *lushanensis*).[167] Eight new spiro-lactone type diterpenoids with an additional C_6–O–C_{19} moiety, guidongnins A–H (**414–421**),[226,227] have been isolated from the leaves of *I. rubescens* collected from Taihang mountain. Among them, guidongnins A–D (**414–417**) exhibited considerable similarities to guidongnins E–G (**418–420**), and the major difference is the presence of a γ-lactone ring between C-6 and C-19 in the former instead of a hemiacetal ring. Thus, the former compounds may be obtained biogenetically by the oxidation of hemiacetal hydroxyl of guidongnins E–G. Ludongnins A (**422**),[228] B (**423**)[229] and F–J (**424–428**)[230] (from *I. rubescens* subsp. *lushiensis*), trichorabdals F (**429**)[224] and G (**436**)[231] (from *I. trichocarpa*), coetsin A (**437**) (from *I. coetsa*),[215] angustifolin (**430**) (from *I. angustifolia*),[232] 6-epi angustifolin (**431**) (from *I. enanderianus*),[138] longirabdolactone (**432**) and longirabdacetal (**433**) (from *I. longituba*),[233] macrocalyxoformin C (**434**) (from *I. macrocalyx*),[207] and oreskaurin A (**438**) (from *I. oresbius*),[128] are the other members containing the C_6–O–C_{19} bonds. Rabdonervosins A–C (**439–441**) (from *I. nervosa*),[234–236] macrocalyxoformin E (**442**) (from *I. macrocalyx.* form),[207] and sculponeatin D (**443**) (from *I. sculponeata*),[237] also have an additional ring formed in the case by an oxygen atom linking C-6 and C-20. Sculponeatins C (**444**),[238] J (**445**) and K (**446**)[239] isolated from *I. sculponeata*, contained a complex ring system with two additional tetrahydrofuran rings formed by the condensation reaction of aldehyde group at C-6 with OH-1 and OH-19. The structure of sculponeatin K was confirmed by X-ray analysis.

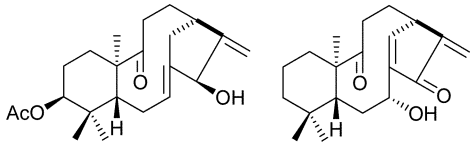
2.4 8,9-Seco-*ent*-kauranes

The 8,9-seco-*ent*-kauranes are thought to be derived biosynthetically from an *ent*-kaurane diterpenoid with a hydroxyl at C-9 by a retro-aldol reaction leading to the cleavage of the C-8,9 bond and loss of H_2O to give the C-8,14 or C-7,8 double bond. For example, acetylation of shikoccidin with a mixture of acetic anhydride and pyridine gave shikoccin acetate as shown in Scheme 6.[240] The reverse C-8,9 cyclization has also been achieved by Backhaus and Paquette,[241] as an adjunct to their synthesis of 8,9-seco-*ent*-kauranes.[242]



Scheme 6

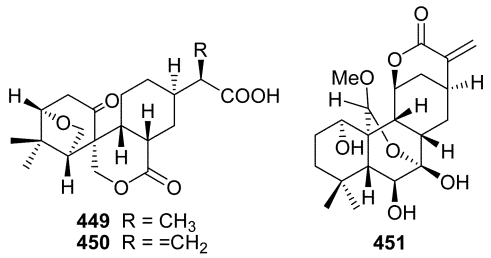
Since 1984, only two compounds, rabdohakusin (**447**)[243] (from *I. umbrosa* subsp. *hakusanensis*) and rabdoumbrosanin (**448**)[99] (from *I. umbrosa*), have been described. Interestingly, all the compounds in this group were isolated from species collected in Japan. The only other reported source of 8,9-seco-*ent*-kauranes is the structurally simplest terrestrial plants, liverwort.[244,245] From a New Zealand liverwort, *Lepidolaena taylorii*, eight 8,9-seco-*ent*-kauranes were identified.[245] To our surprise, their structures bear nearly identical oxygen patterns with those isolated from genus *Isodon.* In our opinion, the 8,9-seco-*ent*-kauranes are not directly produced by the plant itself, but may be derived from a type of fungus that inhabits the plants, since both species of *Isodon* produced this type of compounds and the liverwort always grow in wet environment.



2.5 8,15-Seco-*ent*-kauranes and 15,16-seco-*ent*-kauranes

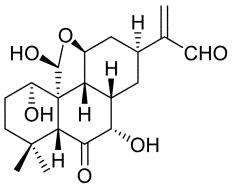
All compounds in the 8,15-seco-*ent*-kaurane series can be viewed as being derived from the 15-hydroxy-7-oxo or hemiketal *ent*-kauranoids *via* a retro-aldol reaction between C-8 and C-15. In fact, the planar structure of this type of compound is identical with that of *ent*-abietanoid, and the key difference is the reverse orientation of H-8. There are only four compounds, laxiflorins F (**449**) and G (**450**) and rubescensins T (**451**) and U (**452**), belonging to this group. Laxiflorins F and G, with a 7,20-spiro-lactone moiety, were isolated from *I. eriocalyx* subsp. *laxifloria.*[13] It is of interest to note that laxiflorins F and G are the only examples possessing an unprecedented oxygen bridge between C-3 and C-6 in natural *ent*-kauranoids. The structure of laxiflorin F was

established by comprehensive NMR analysis and confirmed by single-crystal X-ray diffraction analysis. Rubescensins T[14] and U[12] were isolated from *I. rubescens.* The structure of **452** was also supported by X-ray analysis.



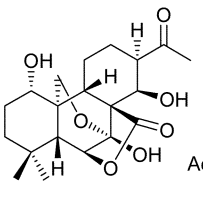
449 R = CH_3
450 R = $=CH_2$

451

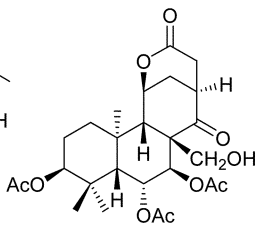


452

Rubescensin S (**453**) and gesneroidin G (**454**) are included in the 15,16-seco-*ent*-kauranes. Rubescensin S was isolated from *I. rubescens*,[14] and it may be biosynthesized from the typical 7,20-epoxy-*ent*-kauranoid, oridonin, by a key oxidation cleavage of the C_{15}–C_{16} bond and loss of H_2O to form a ketone at C-16 and a γ-lactone between C-15 and C-6. Rubescensin S (**453**) showed moderate cytotoxic activity against K562 cells. Gesneroidin G was isolated from *I. gesneroides.*[246]



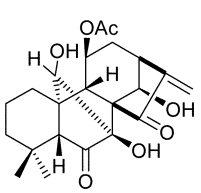
453



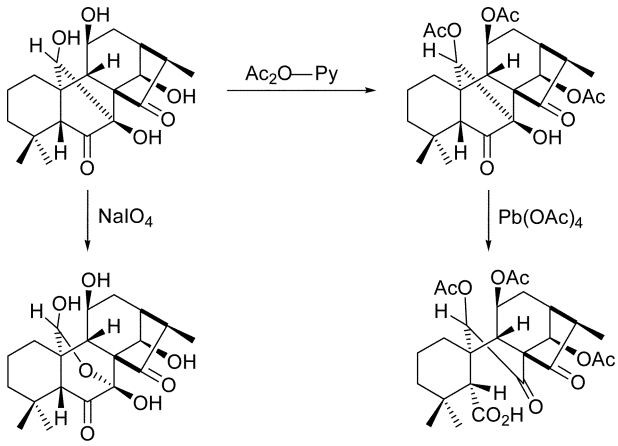
454

2.6 7,20-Cyclo-*ent*-kauranes

Since 1984, only one compound, xerophilusin F (**455**) (from *I. xerophilusa*), has been reported having an unusual 7,20-cyclo-*ent*-kaurane nucleus.[188] Xerophilusin F exhibited a significant cytotoxicity against HL-60 and MKN-28 human tumour cells with IC_{50} values of 0.44 and 2.19 μg mL^{-1}, respectively. This type of *ent*-kaurane is rare. They are characterized by a ketone at C-6 and a hydroxyl group at C-7 and C-20, respectively. Based on this structural feature, the chemical conversion of 7,20-cyclo-*ent*-kauranes into 7,20-epoxy-*ent*-kauranes and 6,7-seco-*ent*-kauranes was investigated (Scheme 7).[247]



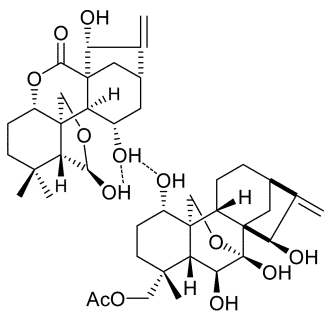
455



Scheme 7

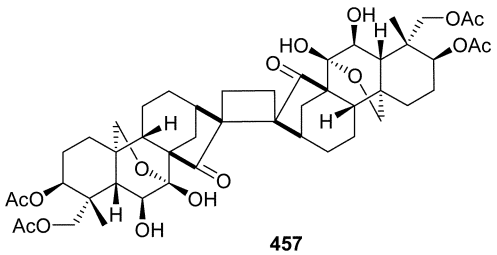
2.7 *ent*-Kaurane dimers

Diterp-Complex-RA (DCRA) (**456**) obtained from *I. angustifolia*, was a unique, inseparable, natural hydrogen-bonded 1 : 1 complex consisting of neoangustifolin (**284**) and epinodosinol.[10] The structure and the binding mode of the complex were elucidated through NMR methods and X-ray crystallography. The different diterpene substructures are bonded together by an intermolecular hydrogen bond and the very strong hydrophobic close approach of mutual matching surfaces. In addition, the intramolecular hydrogen bonds contribute to the stabilization of the complex. DCRA is extremely stable under different conditions. Decomposition does not occur even at melting (215 °C). The TLC chromatographic pattern remained the same, and the FABMS was identical to the isolated starting material.



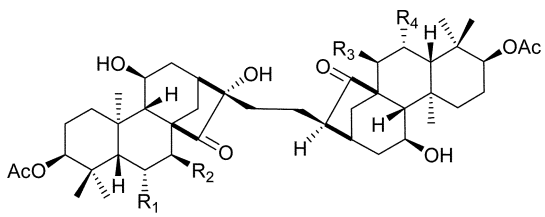
456

Maoecrystal M (**457**) is the only example of a naturally occurring symmetric *ent*-kaurane dimer in genus *Isodon.*[16] The two diterpene moieties of maoecrystal M are linked through an unusual four-membered ring formed by the condensation between the olefin group of C-16 and C-17 *via* a [2 + 2] cycloaddition reaction. The structure was determined by the extensive 2D NMR

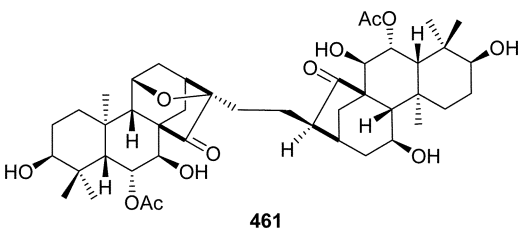


457

experiments and chemical transformation. Four novel asymmetric *ent*-kaurane dimers, xindongnins M–P (**458–461**), were isolated from *I. rubescens* by our group.[18] They possessed the rare linkage of a single carbon bond between two structural subunits, and are believed to be formed *via* two key steps. One is the intermolecular Diels–Alder cycloaddition between the olefin group of diterpene and the α,β-unsaturated ketone group of another one, leading to the formation of a six-membered dihydropyran ring. The other is the hydrolysis of the dihydropyran ring. Two other *ent*-kaurane dimers, isodopharicin E (**462**)[248] and eanderianin J (**463**)[17] with the key six-membered dihydropyran ring, isolated from *I. pharicus* and *I. enanderianus*, provide important support for the proposed biotransformation route. More recently, two new dimers, lushanrubescensin J (**464**)[19] (from *I. rubescens* subsp. *lushanensis*) and taihangjaponicain A (**465**)[249] (from *I. japonica*), have also been reported. We note that the synthesis of this type of dimer may be catalyzed by a Diels–Alderase in *Isodon* species. In recent years, considerable efforts have been made to prove and to identify the enzymatic Diels–Alder reaction in the biosynthesis of secondary natural products.[250] Several natural Diels–Alderases such as solanapyrone synthase,[251] lovastatin nonaketide synthase,[252] and macrophomate synthase,[253] have been purified and characterized. Thus, the function and catalytic mechanism of Diels–Alderases in *Isodon* species are another interesting topic to be investigated.



458 R_1 = OAc, R_2 = OH, R_3 = OH, R_4 = OAc
459 R_1 = OAc, R_2 = OH, R_3 = OAc, R_4 = =O
460 R_1 = =O, R_2 = OAc, R_3 = OH, R_4 = OAc



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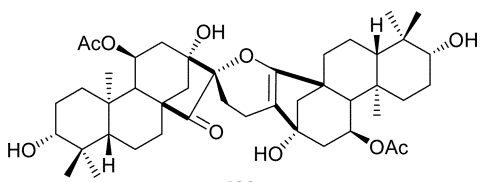

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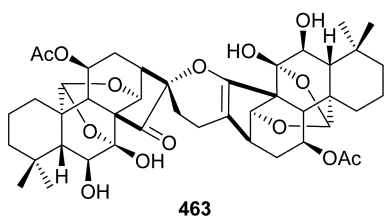

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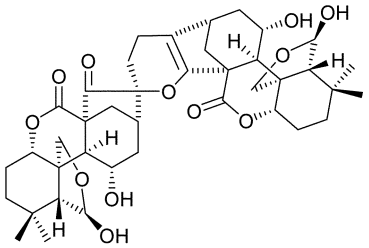
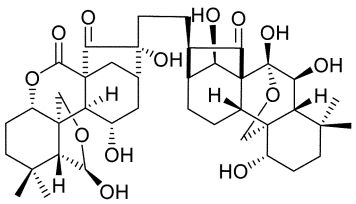


464

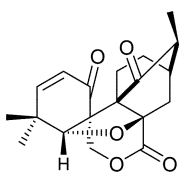


465

2.8 Miscellaneous *ent*-kauranes

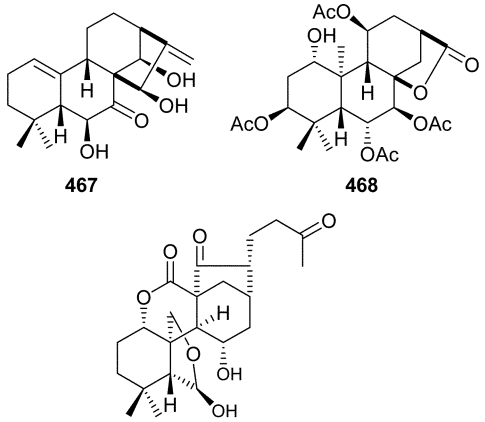
This group includes all of the *Isodon ent*-kauranoids that do not belong in any of the aforementioned groups. Four diterpenoids are included in this group.

The first compound to be introduced is maoecrystal V (**466**), and it is extremely unusual and interesting.[22] About 11 years ago, we investigated the leaves of *I. eriocalyx* collected from Yunnan province, which led to the isolation a number of new spiro-lactone type *ent*-kauranoids. Among them, maoecrystal V was not published due to the failure to elucidate its structure. In 2004, a single crystal of it was obtained and X-ray analysis was successfully performed, which revealed the unusual structure of this compound. It possesses an unprecedented 6,7-seco-6-nor-15(8→9)-*abeo*-5,8-epoxy-*ent*-kaurane skeleton, which is by far the most modified naturally occurring *ent*-kauranoid. Maoecrystal V was evaluated for its cytotoxicity towards five human tumor cell lines, K562, A549, BGC-823, CNE, and HeLa. Interestingly, it only exhibited remarkable inhibitory activity against HeLa cells with $IC_{50} = 0.02\ \mu g\ mL^{-1}$, indicating that its cytotoxicity is highly selective.



466

Rubescensin N (**467**) (from *I. rubescens*) is the sole example of the naturally occurring C-20-nor-*ent*-kaurane diterpenoid from the *Isodon* genus plants.[15] Gesneroidin H (**468**) isolated from the leaves of *I. gesneroides*, is a bisnor-*ent*-kaurane diterpenoid, in which the carbonyl group at C-16 and the C-8 form a γ-lactone ring.[246] This is the second report of 15,17-nor-8,16-olide-*ent*-kaurane in nature. The first one is mikanialactone obtained from *Mikania hirsutissima*.[254] A rare *ent*-kauranoid derivative, taihangjaponicain B (**469**),[249] was isolated from *I. japonica* collected from southwest of Taihang mountain. It was composed of a

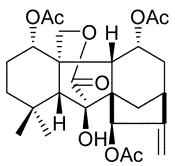


467 **468** **469**

C_{23} carbon skeleton. But in our opinion, this compound may be an artefact formed in the course of extraction and separation by a Michael addition between the olefin group at C-17 and acetone.

2.9 *ent*-Gibberellane

Rabdoepigibberellolide (**470**) is the only compound in this group. It was first obtained from *I. shikokiana* collected in Japan, and its structure was confirmed by X-ray analysis.[255] Our group also isolated it from the leaves of *I. japonica* from China.[256]

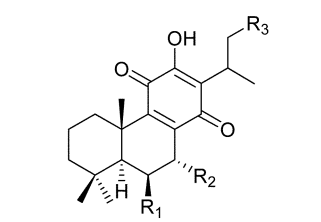


470

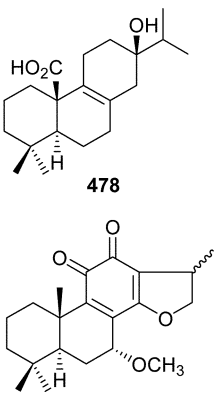
2.10 Abietanes and *ent*-abietanes

In 1987, 16-acetoxy-7α-methoxyroyleanone (**471**) was reported to be the first diterpenoid constituent of *I. stracheyi* having an abietane nucleus.[257] Following that report, 15 abietanoids were isolated from several species of *Isodon*. *I. lophanthoides* is a rich source of abietanoids, and ten new compounds including lophanthoidins A–F (**472–477**),[258] lophanic acid (**478**),[259] and micrathins A–C (**479–481**)[21,260] have been reported from this species. Among them, compound **481** has a novel 13(12→11)-*abeo*-abietane sub-skeleton. Its structure and relative stereochemistry was determined by an X-ray diffraction study.[21] Based on the extensive spectroscopic experiments, isodoforrestin (**482**), which was obtained from *I. forrestii*, was elucidated as a diterpene glucoside with a 20(10→9)-*abeo*-abietane skeleton.[261] The other four members belonging to abietane diterpenoids are gerardianins A (**483**) and B (**484**) (from *I. lophanthoides* subsp. *gerardiana*),[262] atuntzensin A (**485**) (from *I. grandifolia* subsp. *atuntzensis*),[263] and 16-acetoxy-7α-ethoxyroyleanone (**486**) (from *I. serra*).[264]

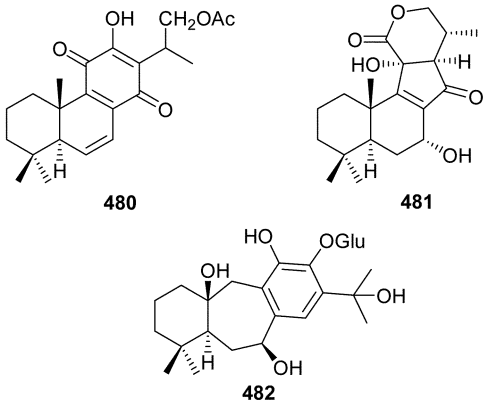
Whereas *ent*-kauranoids in which ring B has been cleaved are well known in this series, a number of compounds that have been



471 R_1= H, R_2 = OMe, R_3 = OAc
472 R_1= OH, R_2 = OMe, R_3 = OAc
473 R_1= OH, R_2 = OAc, R_3 = OAc
474 R_1= OH, R_2 = OAc, R_3 = OH
475 R_1= OH, R_2 = OEt, R_3 = OH
476 R_1= OH, R_2 = OH, R_3 = OAc
477 R_1= OH, R_2 = OEt, R_3 = OAc
483 R_1= H, R_2 = OAc, R_3 = OAc
486 R_1= H, R_2 = OEt, R_3 = OAc

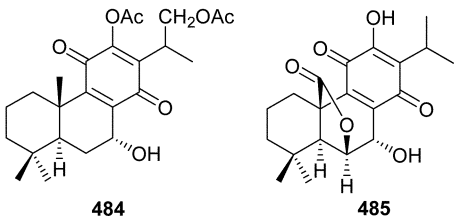


478 **479**



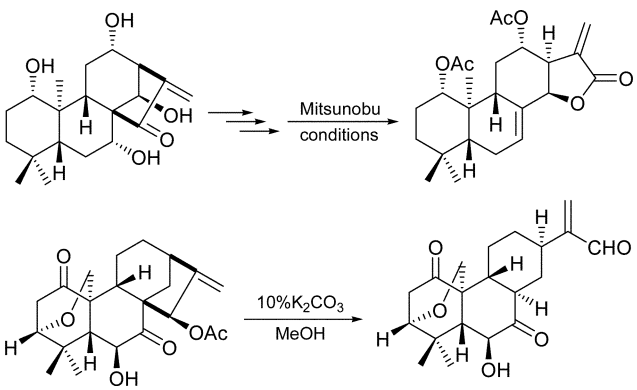
480 **481**

482

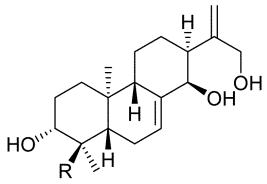


484 **485**

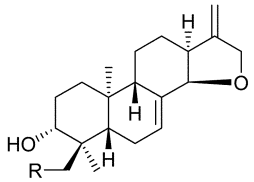
isolated have ring D cleaved. These include compounds **487–503**. This cleavage has the effect of generating the *ent*-abietane skeleton. Recently, the cleavage of *ent*-kauranes under Mitsunobu[265] or basic conditions[266] to form *ent*-abietanes has been investigated (Scheme 8).



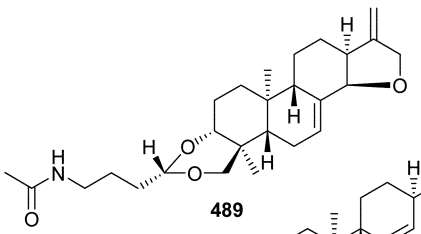
Scheme 8



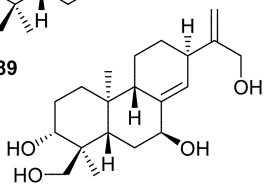
487 R = CH_2OH
496 R = CHO



488 R = OH
490 R = OGlu



489



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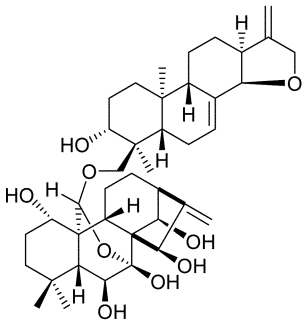

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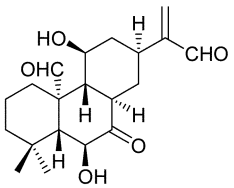

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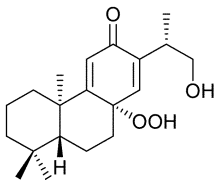

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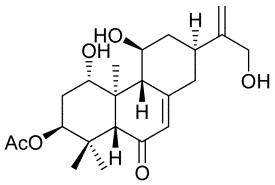

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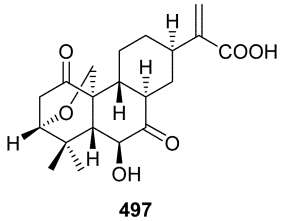

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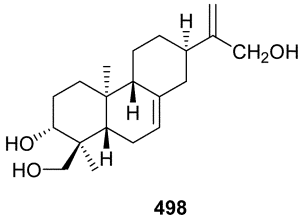

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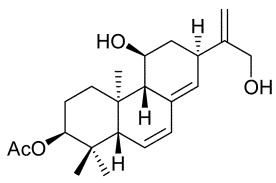

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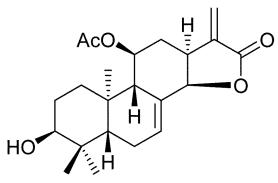
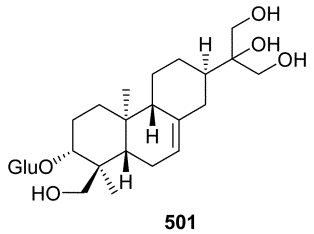


500

Rubescensins I–M (**487–491**),[267] P (**492**)[267] and V (**493**)[12] were isolated by our group from the leaves of *I. rubescens.* Among them, rubescensin K (**489**) was the only N-containing diterpenoid found in genus *Isodon*, and rubescensin M (**491**) is a novel dimeric diterpenoid in which the hydroxyl at C-18 of rubescensin J (**488**) forms an ether linkage with a 7,20-epoxy-*ent*-kaurane diterpenoid. Glutinosin C (**494**), isolated from *I. glutinosa*,[268]



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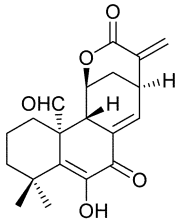

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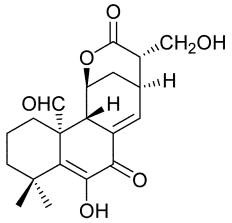
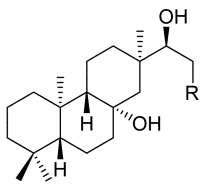


503

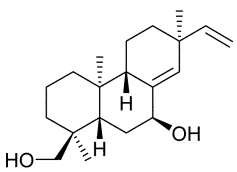
possesses a unique α-orientated hydroperoxyl group at C-8. Its structure and relative stereochemistry were elucidated by X-ray analysis. Other *ent*-abietanoids include adenanthin L (**495**) (from *I. adenantha*),[35] enanderianin P (**496**) (from *I. enanderianus*),[139] laxiflorins N (**497**) and O (**498**) (from *I. eriocalyx* subsp. *laxifolia*),[20] melissiodesin L (**499**) (from *I. melissiodes*),[31] taibaihenryiin C (**500**) (from *I. henryi*),[269] eriocaside A (**501**) from (*I. eriocalyx*),[270] and xerophilusins R (**502**) and S (**503**) (from *I. xerophilus*).[271]

2.11 Other tricyclic and bicyclic diterpenes

On biogenetic grounds, the tri- and tetracyclic diterpenoids, such as pimarane and kaurane, are clearly biosynthetically related, in which *ent*-pimarane is considered as the precursor of *ent*-kaurane. Thus, the pimaranes isolated from genus *Isodon* should share an absolute *ent*-pimarane configuration. For example, forrestins H (**504**) and I (**505**) (from *I. forrestii*),[272] lophanthins A (**506**) and B (**507**)[273] and *ent*-11β-hydroxyisopimara-8(9),15-diene-3-one (**508**)[259] (from *I. lophanthoides* subsp. *gerardiana*), *ent*-3β-acetoxyisopimar-15-en-8β-ol (**509**)[274] and *ent*-isopimar-15-en-6β,7β,8β-triol (**510**)[274] (from *I. parvifolia*). Interestingly, flavidusins



504 R = OH
505 R = OAc



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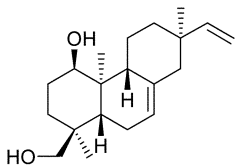

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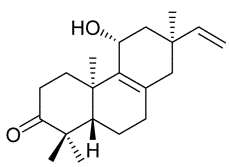

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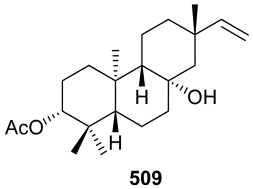

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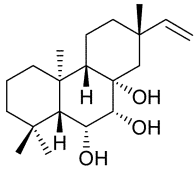
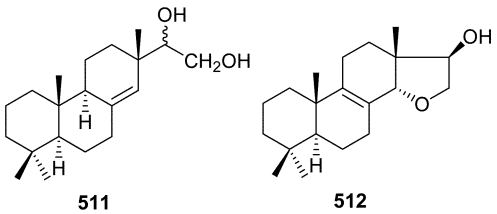
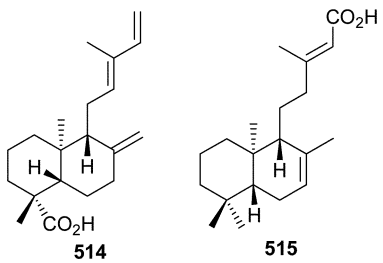


510

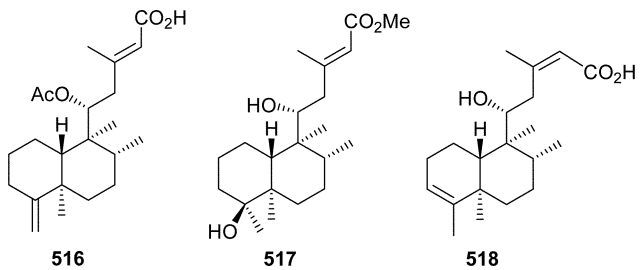
A (**511**)[101] and B (**512**),[101] and glutinosin B (**513**)[108] (originally from *I. glutinosa*), which were isolated from *I. flavidus*, are the exceptions. The absolute configuration of them was determined to be isopimarane type rather than the *ent*-isopimarane type on the basis of chemical correlation with (+)-isopimara-8(9),15-diene.



The *ent*-labdanes are rare in *Isodon* diterpenoids. Only two previously known compounds, (12*E*)-*ent*-labda-8(17),12,14-trien-18-oic acid (**514**)[259] (from *I. lophanthoides* subsp. *gerardiana*) and (13*E*)-*ent*-labda-7,13-dien-15-oic acid (**515**)[275] (from *I. scoparius*), were isolated.



Only three *ent*-clerodanes, isocoparins A–C (**516–518**) from *I. scoparius*, were found in genus *Isodon*.[275]



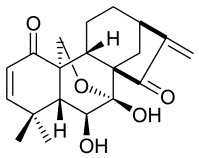
3 Biological activities of *ent*-kauranoids

Isodon diterpenoids have attracted considerable attention as antibacterial, antitumour, anti-inflammatory, and anti-feeding agents. Many natural *Isodon* diterpenoids from different species, as well as hemisynthetic derivatives, have been tested in laboratory assays. A few have shown very potent activity against bacteria and tumour cell lines, but whether these activities will be retained under field conditions is still unknown. The present review is a concise summation of the biological activities of *ent*-kauranoids from genus *Isodon*.

3.1 Antibacterial activity

Studies on the antibacterial activity of *Isodon* constituents began in 1954, when the discovery of a crystalline substance (enmein) isolated from the ethanolic extract of *I. japonica*, inhibited the growth of Gram-positive bacteria.[276] Then, T. Arai and his coworkers found that the antibacterial activity was due to enmein, and dihydroenmein was completely inactive, whilst the 3,6-diacetylenmein remained active.[277] Therefore, the antibacterial active site of enmein was suggested to be the cyclopentanone conjugated with an exo-methylene unit. Later, two Japanese groups studied the bacterial activity of a number of *ent*-kauranoids isolated from different *Isodon* species, and found that all of the diterpenoids with the α-methylenecyclopentanone moiety exhibited some activity.[8] Hence, it was further confirmed that the α-methylenecyclopentanone moiety was absolutely essential for the activity, the activity being attributed to a Michael addition of a sulfhydryl enzyme of bacteria to this function.

E. Fujita *et al.* examined the antibacterial activity of a series of 7,20-epoxy-*ent*-kauranoids, and found that this type of *ent*-kauranoid with a 6β-OH group had stronger activity against *Sarcina lutea*.[8b] Therefore, they presumed that the greater activity was attributed to the hydrogen-bonding between the 6β-OH and ketone group at C-15. Our group systematically investigated the antibacterial activity of the major constituent of *I. eriocalyx*, eriocalyxin B (Table 4), and found that this compound showed significant inhibitory activity against Gram-positive bacteria.[9] There are two key aspects to the highly antibacterial activity of eriocalyxin B. One is the presence of hydrogen-bonding between 6β-OH and the C-15 ketone group in the molecule. In addition, the α,β-unsaturated ketone group in ring A of the molecule forms an additional active center.



eriocalyxin B

Recently, rosthornins A–D (**127–129** and **185**) were reported to exhibit antibacterial activity against Gram-positive bacteria, among which *Propionibacterium acnes* was noted to be the most susceptible. But none of rosthornins tested had any activity against a Gram-negative bacterium, *Helicobacter pylori*.[278] Interestingly, S. Kadota *et al.* reported that a 6,7-seco-*ent*-kauranoid, trichorabdal A, exhibited remarkable antibacterial activity against a Gram-negative bacterium, *Helicobacter pylori*, and oridonin (**191**) had moderate antibacterial activity against this bacterium.[279]

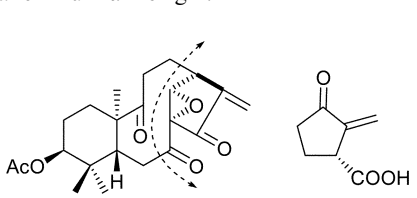
Table 4 Antibacterial activity of eriocalyxin B

Categories	Name	MIC/μg mL^{-1}
Gram-positive bacteria	*Staphylococcus aureus*	31
	Staphylococcus epidermidis	62
	Streptococcus sanguis	62
Gram-negative bacteria	*Escherichia coli*	500
	Enterobacter gergoviae	2000
Microzyme	*Candida albicans*	62
Epiphyte	*Zygosaccharomyces bailii*	63

3.2 Cytotoxicity and antitumour activity

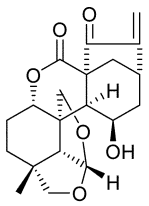
3.2.1 Structure–activity relationship. In 1961, Professor T. Arai and his coworkers first reported the antitumour activity of a crystalline substance (enmein) isolated from *I. trichocarpa.*[280] Although the structure of enmein at that time had not yet been determined, the antitumour activity of enmein was assumed to be attributed to the α-methylenecyclopentanone. Subsequently, Professor E. Fujita and his coworkers examined the *in vivo* antitumour activity of a series of *ent*-kauranoids from *I. japonica* and *I. trichocarpa* against Ehrlich ascites carcinoma in the mouse.[8c] The results further supported the idea that the α-methylenecyclopentanone system was an essential active centre for the antitumour activity. The antitumour mechanism may be due to the facile addition of soft nucleophiles, such as alkanethiols and L-cysteine, to the α,β-unsaturated ketone moiety in a 1,4 addition fashion, leading to the deactivation of SH-enzymes or SH-coenzymes. The studies by Fujita also showed that oridonin had a higher activity and lower toxicity than enmein. They assumed that the enhanced activity of oridonin was attributed to hydrogen-bonding between 6β-OH and ketone group at C-15, and that the 7β-OH and 14β-OH played a role as a binding site to specific enzymes in the tumour cells.[8b,8c]

Since the 1970s, a number of novel diterpenoids, such as spiro-lactone type *ent*-kauranoids and 8,9-seco-*ent*-kauranoids, have been isolated from the genus *Isodon.* The cytotoxicity and antitumour activity of them and their chemically modified derivatives were tested against Hela and P-388 human cancer cells and Ehrlich ascites carcinoma cells in mouse. As a result, it was found that an additional active site, such as an aldehyde at C-6, a spiro-lactone, or an epoxyketone group, in addition to the presence of α-methylenecyclopentanone moiety, acts as an active centre, giving rise to a synergistic enhancement of the antitumour activity.[211] Shikoccin isolated from *I. shikokiana* subsp. *accidentalis*, only showed a moderate antitumour activity against Ehrlich ascites carcinoma cells in mouse, but the oxidation product of shikoccin, epoxyketoshikoccin, exhibited greatly increased activity compared with that of shikoccin.[281] The only structural difference between these two compounds is the presence of an epoxyketone group in epoxyketoshikoccin rather than a hydroxyl in shikoccin. Thus, the epoxyketone group may be a second active centre of epoxyketoshikoccin. It was suggested that the increase of antitumour activity of epoxyketoshikoccin is due to the synergism between α,β-unsaturated ketone and epoxyketone group in the molecule. Interestingly, the active unit of epoxyketoshikoccin is structurally extremely similar to that of sarkomycin (Scheme 9), which was a well known antitumour agent used in Japan during the 1980s. T. Fujita and our group examined the *in vitro* and *in vivo* antitumour activities of sculponeatins A–C isolated from *I. sculponeta* of Yunnan origin.[282] Due to the lack of an α,β-unsaturated ketone, sculponeatin B exhibited weak activity both *in vitro* and *in vivo.* Sculponeatin A and C (**444**) are approximately equally potent *in vitro*, but when tested *in vivo*, **444** showed a marked increase of antitumour activity. This indicated that the complex ring system in sculponeatin C might play an important role in enhancing the antitumour activity.

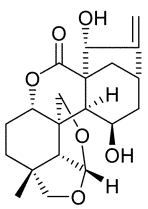


epoxyketoshikoccin sarkomycin

Scheme 9



sculponeatin A



sculponeatin B

3.2.2 Cytotoxicity and its mechanism. Recent work by our group with eriocalyxin B showed that this compound may be a promising candidate as an antitumour agent. Eriocalyxin B exhibited broad spectrum cytotoxicity against K562, HL-60, A549, MKN-28, HCT, and CA with IC_{50} values of 0.45, 0.46, 0.24, 0.22, 0.34, and 2.15 μM, respectively.[9] In addition, we found that it would inhibit the proliferation on leukemic K562 cells significantly and the suppression was dose-dependent. The telomerase activity of K562 detected by TRAP-ELISA decreased significantly after exposure to eriocalyxin B, the higher the eriocalyxin B concentration, the lower the telomerase activity in K562 cells (with 1 μM and 0.1 μM of the compound, the inhibitory rate is 86.7% and 75.8%, respectively).[9] Angiogenesis is considered as a potential target for anticancer chemotherapy. One useful *in vivo* system that has been used extensively in angiogenesis research is the highly vascularized chorioallantoic membrane (CAM) of the chicken embryo. The eriocalyxin B tested was applied to the CAM and after 7 days the CAM was photographed. The vessel area/area (VA/A) values of the compound (10 μg mL^{-1}) were significantly lower than that of NS group ($P < 0.05$). The results further confirm its antiangiogenic activity.

Oridonin and ponicidin, two major constituents of *I. rubescens*, are the most frequently studied compounds among the *Isodon* diterpenoids. Recently, both oridonin and ponicidin were reported to have significant antiangiogenic activity at subcytotoxic concentrations, suggesting that they may strongly contribute to the demonstrated clinical efficacy as a treatment for advanced prostate cancer.[283] Additionally, the inhibitory effect of oridonin on the proliferation of several human cancer cells and its mechanisms have also been described recently.[284–287]

The transcription factor NF-κB plays a critical role in controlling inflammatory and immune response and cell proliferation. The development of specific inhibitors that can block NF-κB activation is believed to hold great potential in suppressing certain types of tumour growth as well as improving cancer therapy. More recently, four *ent*-kauranoids isolated from *I. rubescens* including oridonin, ponicidin, and xindongnin A, were found to be potent inhibitors of NF-κB transcription activity and the expression of its downstream targets, COX-2 and the inducible nitric-oxide synthase.[288] The mechanism of action of diterpenoids against NF-κB are similar, but significant differences were also identified. All of the diterpenoids directly interfere with the DNA-binding activity of NF-κB to its response DNA sequence. Oridonin and ponicidin

have an additional impact on the translocation of NF-κB from the cytoplasm to nuclei without affecting lκB-α phosphorylation and degradation. The effect of these compounds on the interaction of NF-κB with consensus DNA sequence is unique. Different inhibitory effects were observed when NF-κB bound to various DNA sequences. Both p65/p65 and p50/p50 homodimers, as well as p65/p50 heterodimer association with their responsive DNA, were inhibited. Kinetic studies on the NF-κB–DNA interaction indicate that the diterpenoids decrease the $B_{\max app}$ but have no effect on $K_{d app}$. This suggests that this class of compounds interacts with both p65 and p50 subunits at a site other than the DNA binding site and subsequently modulates the binding affinity of the transcription factor toward DNA with different NF-κB binding sequences. This study could partly explain the use of *I. rubescens* for the treatment of cancer and inflammation in Chinese medicine. Most importantly, it reveals that *ent*-kauranoids are a novel and new class of NF-κB inhibitors that interfere with the binding between NF-κB and DNA with a unique sequence by a distinct mechanism.

3.3 Other activities

In 2000, Hayashi reported that ponicidin potentiates the cell-killing activity of antiherpes prodrugs acyclovir (ACV) and ganciclovir (GCV) in human cancer cells expressing herpes simplex virus thymidine kinase (HSV-TK).[289] A few years later, the *in vivo* experiment was performed and the results further proved the ability of ponicidin to pharmacologically enhance HSV-TK/ACV- and HSV-TK/GCV-mediated tumour cell and bystander killing, and showed that it may have an important therapeutic effect in tumours with a low efficiency of gene transfer.[290]

4 Acknowledgements

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