Triterpenoids from the Schisandraceae family

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Over the past 30 years, the family Schisandraceae has received considerable attention in chemical and biological studies. In particular, the discovery of a series of highly oxygenated triterpenoids with different skeletons has further increased the interest in this family. This review covers the structures, proposed biosynthetic pathways, total synthesis and biological activities of these and other triterpenoids from the plants of the family Schisandraceae. There are 100 references.

1 Introduction

The economically and medicinally important family Schisandraceae, a family of climbing plants, contains the genera *Schisandra* and *Kadsura*. There are about 50 species in total in the world, and these are mainly distributed in southeast Asia and in North America. In China, there are 29 species of this family distributed throughout the country, primarily in the southwest regions. Many species have a long history of use as folk medicines in China. The most famous is *Schisandra chinensis*, which is widely distributed in northeastern China, Russian, Korea, and Japan, and is known in China by as "*wu-wei zi*". Its fruits have been used as sedative and tonic agents and for the treatment of hepatitis for over 2000 years in China.

Because of their remarkable medicinal functions, plants of the family Schisandraceae have been a hot topic within the medicinal chemistry and drug discovery community since the 1970's. Modern phytochemical and pharmacological studies have shown that this family is a rich sources of lignans[1–7] and lanostane- and cycloartane-type triterpenoids,[8–13] which possess various beneficial pharmacological effects such as antihepatitis,[1–3] antitumor,[4,5] and anti-HIV-1[4,8,9] bioactivities. Interestingly, some species of this family have not only been used as traditional Chinese medicines, but also more recently as an important material for the food and drink industries, having been used in products such as wine,[14] fruit juice and jelly,[15–17] and as foods for health maintenance.[18,19] Over the past ten years or so, considerable efforts from our group have been devoted to the discovery of bioactive and novel triterpenoids from the species of the family Schisandraceae. One of the most distinguishing features of *Schisandra* and *Kadsura* species studied recently was the discovery of more than 70 highly oxygenated triterpenoids endowed with different oxygenated skeletons, such as schiartane,[20] 18-norschiartane,[21,22] 18(13→14)-*abeo*-schiartane,[23] schisanartane,[24] pre-schisanartane,[25] wuweiziartane,[26] and kadlongilactone.[27] The schisanartane skeleton triterpenoids are representative of these series of novel triterpenoids because of their octacyclic backbone, which includes a 7/8/5 fused carbocycle and more than 12 chiral centers. This unusual ring system and highly oxygenated structural features make it distinctive from other naturally occurring triterpenoids. As a consequence, these structurally complex molecules have brought great interests and challenges for phytochemists, synthetic chemists, and pharmacologists.

In 2000, Dr L. Li and co-authors provided a review of Schisandraceae triterpenoids and their spectroscopic properties.[28] In 2001, Prof. Y. G. Chen also reviewed triterpenoid constituents of this family,[29] followed in 2007 by a review on the bioactivity and constituents of the *Kadsura* genus.[30] In addition, the lignan constituents of this family have been frequently reviewed by several authors.[4,31–38] Considering the recent flurry of reports on triterpenoids, here we review systematically the isolation, structural elucidation, biological evaluations and total synthesis of triterpenoids from the Schisandraceae family, covering the literature from 1973 until January 2008. The biosynthetic relationships between these triterpenoids are also discussed.

2 The categories of triterpenoids

Triterpenoids from the Schisandraceae family can be classified into three groups on the basis of their different carbon frameworks: lanostane (**A**), cycloartane (**B**), and *Schisandra* nortriterpenoids (**C**). From the biosynthetic point of view, lanostane and cycloartane are both derived from 2,3-oxidosqualene under the action of oxidosqualene cyclases.[39] According to the different oxygenated patterns and structure characterization, both can be divided into several sub-types, respectively.

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Schisandra nortriterpenoids represent a series of recently discovered novel nortriterpenoids from the Schisandraceae family, and can be deduced to derive biosynthetically from cycloartane. This group can be further divided into schisanartane (**C1**), schiartane (**C2**), 18-norschiartane (**C3**), 18(13→14)-*abeo*-schiartane (**C4**), pre-schisanartane (**C5**), and wuweiziartane (**C6**) types (Fig. 1).

2.1 Lanostane-type triterpenoids

2.1.1 Intact lanostanes. This group is characterized by a hydroxyl group or ketone at C-3 and comprises 15 new members with the majority having a ketone at C-3. Among them, there are only four members belonging to the C-3 hydroxyl substitution series, including anwuweizic acid (**1**) from *Schisandra sphenanthera*,[40] epianwuweizic acid (**2**) from the fruits of *Kadsura longipedunculata*[41] and the stems of *K. angustifolia*,[42] isoanwuweizic acid (**3**) from the roots of *K. heteroclita*,[43] and schisanol (**4**) from the fruits of *S. sphenanthera*.[44] The eleven other members all have a ketone at C-3, and are anwuweizonic acid (**5**) from the roots and stems of *S. propinqua*[45] and the stems of *K. heteroclita*,[12] 12α-acetoxy-3-oxolanosta-8,24-dien-26-oic acid (**6**) and the corresponding acetate (**7**) from *K. longipedunculata*,[11] (24*E*)-3-oxo-8,24-dien-26-oic acid (**8**) from the stems of *K. ananosma*,[46] coccinic acid (**9**) from the roots and stems of *K. coccinea*[10] and its

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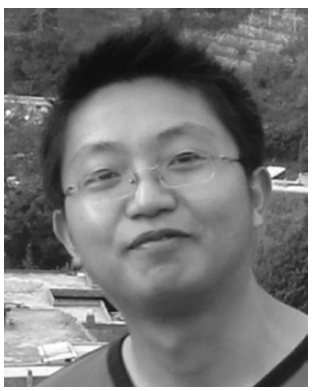
Wei-Lie Xiao obtained his Ph.D. in 2005 at Kunming Institute of Botany, CAS, under the guidance of Prof. Han-Dong Sun. He was presented with "The Tenth Young Medicinal Chemist Award" by the Chinese Pharmaceutical Association and the Servier Company in 2007. His current research is focused on the isolation and structure–activity relationships of bioactive natural products from Traditional Chinese Medicine.

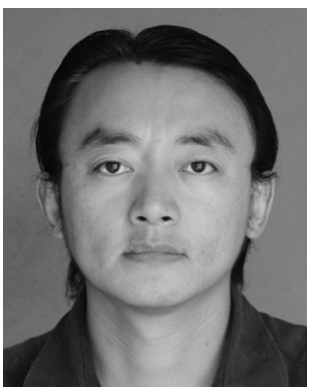
Rong-Tao Li

Rong-Tao Li received her Ph.D. in 2004 at Kunming Institute of Botany, CAS, under the guidance of Prof. Han-Dong Sun. She was presented the with a "National Excellent Doctoral Dissertation of P. R. China" award in 2006. She has been a professor at Kunming University of Science and Technology since 2005. The main focus of her current research is biologically active natural products and the utilization of plant resources.



Sheng-Xiong Huang

Sheng-Xiong Huang joined Prof. Han-Dong Sun's group at the Kunming Institute of Botany, CAS, for doctoral studies in 2004. He is currently working as a postdoc in Prof. Ben Shen's group at the School of Pharmacy, University of Wisconsin. His current research mainly focuses on investigations into the biosynthetic pathways of bioactive natural products, and hence the understanding of enzymatic mechanisms.



Jian-Xin Pu

Jian-Xin Pu studied natural products chemistry at the Kunming Institute of Botany, CAS, where he received his doctoral degree in 2007. After finishing his Ph.D., he joined the group of Prof. Han-Dong Sun. His current interests include stereochemical determination of natural products using spectroscopic and computational methods, and natural product medicines research and development.

Han-Dong Sun

Han-Dong Sun received his Ph.D. at Kyoto University, Japan, in 1988. In 2003, he became an Academician of CAS. He has phytochemically studied about 230 plants, published 16 patents and over 540 scientific papers, and received 21 awards. His current research interests involve the activity-directed isolation, structure elucidation and the structure–activity relationships of natural products from medically important plants.

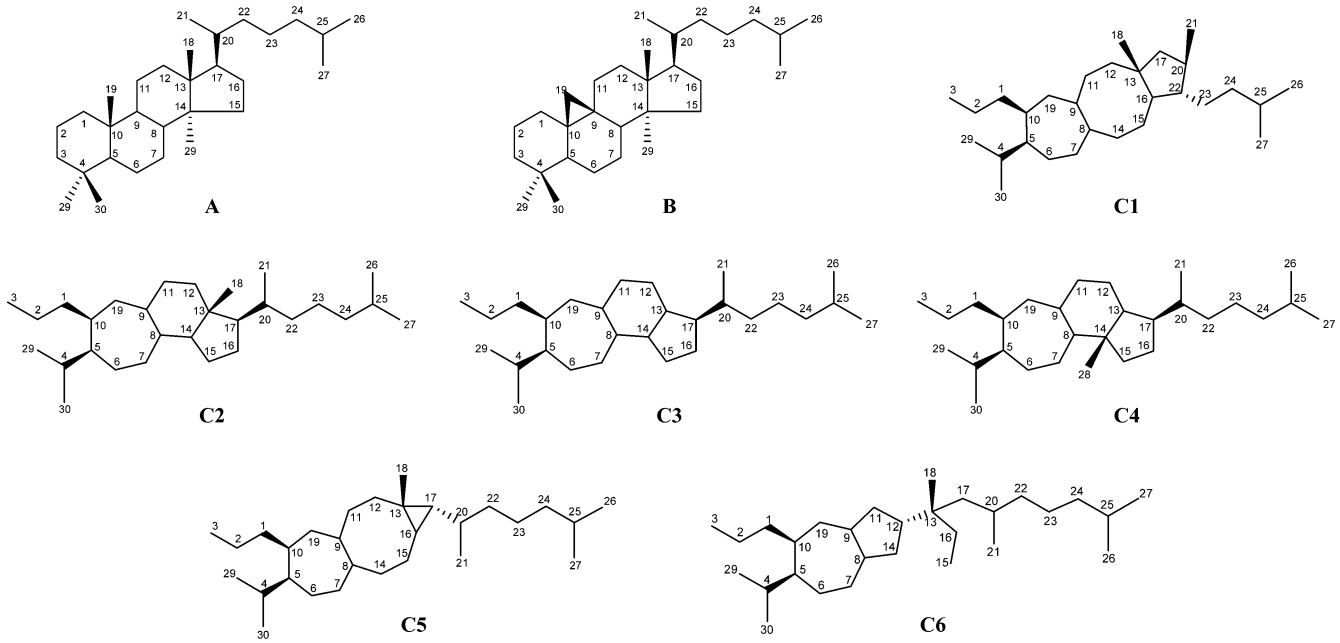
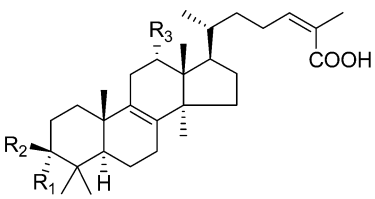
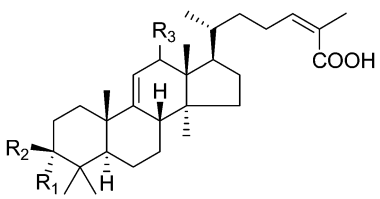


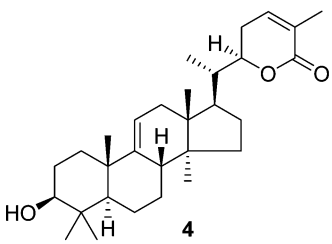
Fig. 1 Basic skeletons of triterpenoids from the Schisandraceae family.



1 R_1 = OH, R_2 = H, R_3 = H
2 R_1 = H, R_2 = OH, R_3 = H
5 R_1 = R_2 = O, R_3 = H
6 R_1 = R_2 = O, R_3 = OAc
7 R_1 = R_2 = O, R_3 = OH



3 R_1 = OH, R_2 = H, R_3 = H
9 R_1 = R_2 = O, R_3 = H
10 R_1 = R_2 = O, R_3 = β-OAc
11 R_1 = R_2 = O, R_3 = β-OH
12 R_1 = R_2 = O, R_3 = α-OAc
13 R_1 = R_2 = O, R_3 = α-OH



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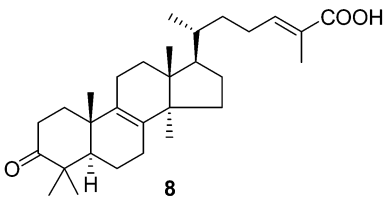

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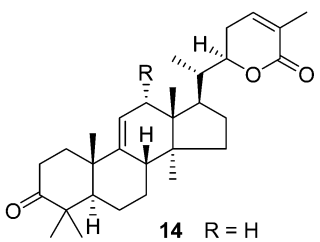
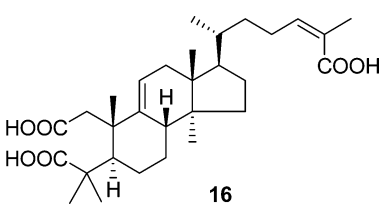


14 R = H
15 R = OH

four 12-acetoxy and 12-hydroxy derivatives (**10–13**) from the stems of *K. heteroclita*,[47] and schisanlactone D (**14**) and E (**15**) from the fruits of an unidentified *Schisandra* species.[48] Among these compounds, **4**, **14** and **15** have a 26,22-lactone.

2.1.2 2,3-Seco-lanostanes. Lanopropic acid (**16**),[49] recently isolated from the stems of *S. propinqua*, is the only 2,3-seco-lanostane triterpenoid from the Schisandraceae. Its structure was elucidated on the basis of spectroscopic techniques and further confirmed by X-ray diffraction studies.



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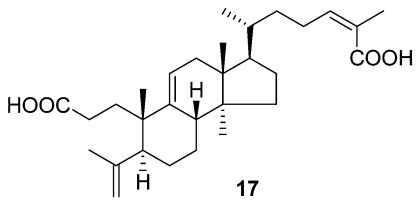
2.1.3 3,4-Seco-lanostanes. There are only three 3,4-seco-lanostane type triterpenoids. Early in 1976, the first, kadsuric acid (**17**), was isolated from *K. japonica* and its structure was elucidated on the basis of spectroscopic data and chemical transformations.[50] Manwuweizic acid (**18**) was isolated from both the roots and stems of *S. propinqua*[45] and the stems of *K. heteroclita*,[13] is an inhibitor of cholesterol biosynthesis and shows significant inhibitory activity against Lewis lung cancer, brain tumor-22, and solid hepatoma in mice, but exhibits no cytotoxic action *in vitro*.[51] Schisanlactone F (**19**), an anti-leukemia P-388 triterpenoid, was isolated from *K. longipedunculata*.[41]



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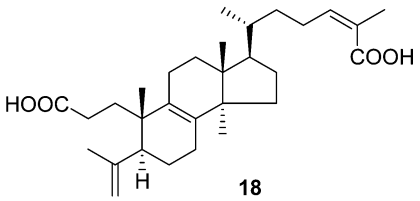

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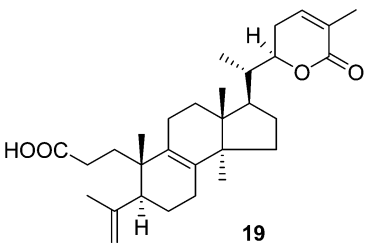

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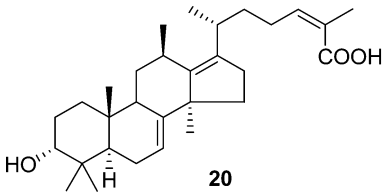
2.1.4 18(13→12)-*abeo*-Lanostanes. The first example of the 18(13→12)-*abeo*-lanostane group was ananosic acid A (**20**),[7] which was isolated from the stem bark of *K. ananosma* collected from Mengna County, Yunnan Province, China. Its structure was elucidated by extensive spectral studies and further confirmed by single crystal X-ray diffraction analysis. Further phytochemical studies on the same plants led to the discovery of ananosic acid B–D (**21**–**23**).[46,52] Ananosic acids B (**21**) and C (**22**) were elucidated by spectral studies and chemical transformation. Both were evaluated for cytotoxicity against CCRF-CEM leukemia cells and HeLa cells *in vitro*, toward CCRF-CEM leukemia cells, with IC_{50} values of 49.6 and 45.2 μg mL^{-1}, respectively, and toward HeLa cells, with IC_{50} values of 0.54 and 0.48 μg mL^{-1}, respectively.

2.1.5 14(13→12)-*abeo*-Lanostanes. Neokadsuranic acid A (**24**),[12] the first compound with a 14(13→12)-*abeo*-lanostane skeleton, was isolated from the stems of *K. heteroclita*. It was found to be effective in inhibiting the biosynthesis of cholesterol with 19.2 and 35.9% inhibition at 5 μg mL^{-1} and 25 μg mL^{-1}, respectively.[53] From the same plant, seco-neokadsuranic acid A (**25**),[13] was found to show cholesterol biosynthesis inhibition activity with 25.8% inhibition at 25 μg mL^{-1}.[54] Following the



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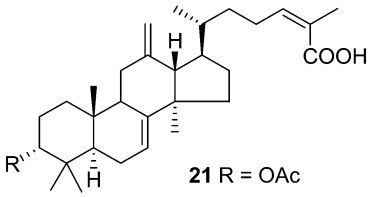
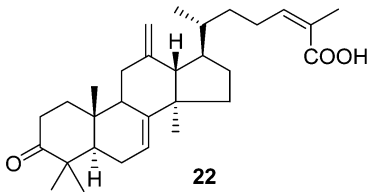


21 R = OAc
23 R = OH



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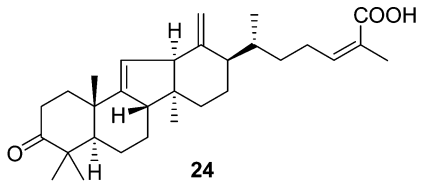

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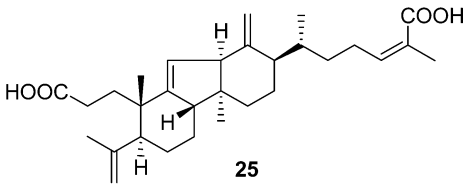

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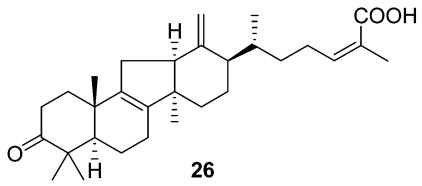

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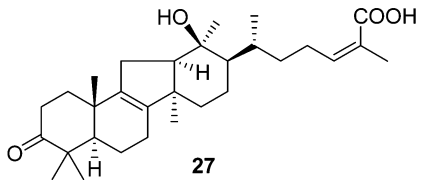

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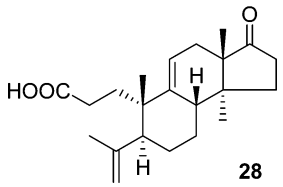

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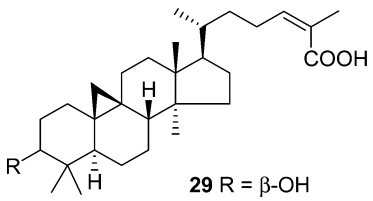
discovery of **24** and **25**, other two analogs, neokadsuranic acids B (**26**) and C (**27**), were isolated from the stems of *K. longipedunculata*,[11] and both are useful as anticholesteremics.[55]

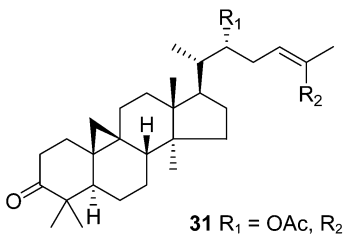
2.1.6 Norlanostanes. Only one norlanostane has been found in the plants of the Schisandraceae family, namely micranoic acid A (**28**) from the leaves and stems of *S. micrantha*.[56] This compound features an unusual octanortriterpenoid backbone degraded by the oxidative fission of the C-17–C-20 bond.

2.2 Cycloartane-type triterpenoids

2.2.1 Intact cycloartanes. This class of cycloartane-type triterpenoids features a hydroxyl group or a ketone at C-3. There are only two C-3 hydroxyl-substituted members. One is schizandrolic acid (**29**),[57] which was isolated from the wood of *Schisandra nigra*, and the other is isoschizandrolic acid (**30**),[58] isolated from an unidentified species of the Schisandraceae family collected from Lichuan Prefecture, Hubei Province, China. Bioactivity studies showed that both showed moderate cytotoxicity against several cell lines.[59] Three C-3 ketone members, named heteroclic acid (**31**),[60] cycloartenone (**32**)[60] and schizandronic acid (**33**),[60] were isolated from the stems of *Kadsura heteroclita*, which is a well known traditional Chinese medicine used in southern China. From the woody part of *S. nigra*, schizandronic acid (**33**) was found,[61] which showed weak cytotoxic activity against four cancer cell lines including Bel-7402, BGC-823, MCF-7 and HL-60. However, heteroclic acid (**31**) and cycloartenone (**32**) showed no activity against the four cell lines.[60] Another three, named schisandraflorin (**34**),[62] 24-methylenecycloartenone (**35**)[10] and kadsulactone (**36**),[11] were isolated from the whole plant of *S. grandiflora*, the roots and stems of *K. coccinea*, and the stems of *K. longipedunculata*, respectively.

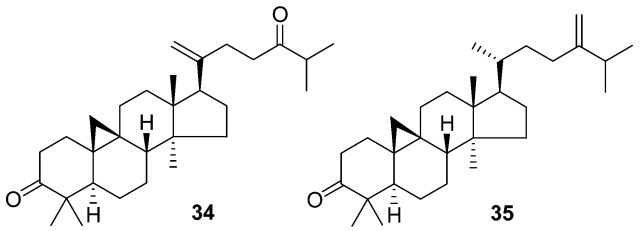


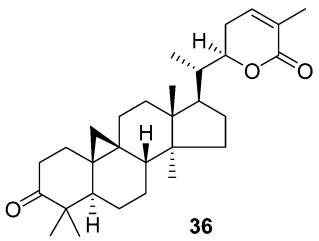
29 R = β-OH
30 R = α-OH



31 R_1 = OAc, R_2 = COOH
32 R_1 = H, R_2 = CH_3
33 R_1 = H, R_2 = COOH

2.2.2 3,4-Seco-cycloartanes. These are abundant in the plants of Schisandraceae family: out of the total 166 triterpenoids from this family, 46 belong to this group. The first representative of this group is nigranoic acid (**37**), which was isolated from *S. nigra* in 1973.[63] Its structure elucidation and NMR spectral assignment were achieved by the combination of 1D- and 2D-NMR





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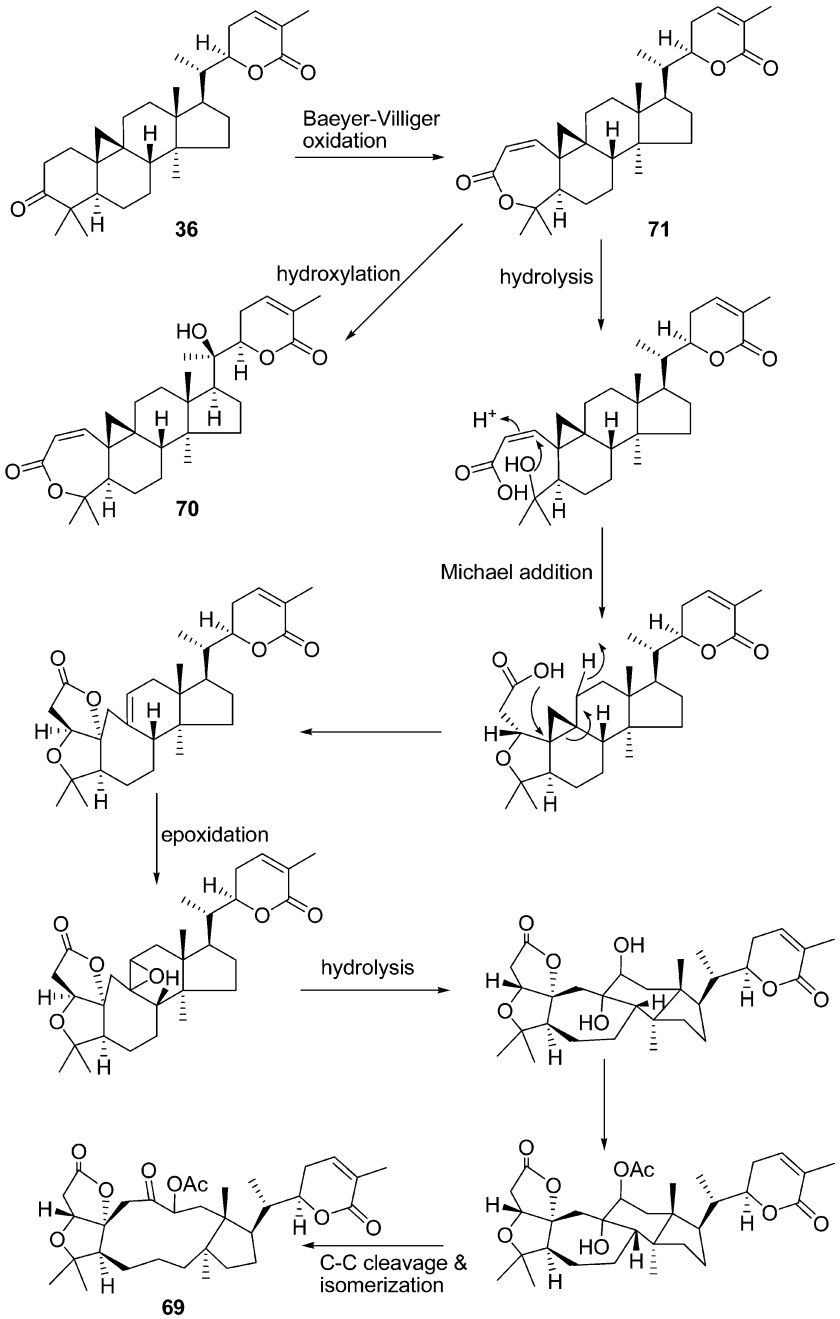
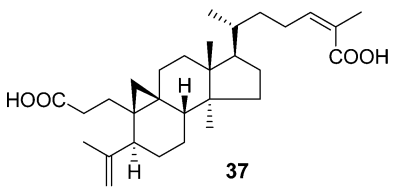
techniques with the aid of computer modeling in 1996, and at this time was found to be active in several reverse transcriptase and polymerase assays.[9] From the leaves and stems of *S. chinensis*, wuweizilactone acid (**38**) was isolated,[64] which featured a novel eight-membered lactone ring and showed weak anti-HIV-1 activity *in vitro*. Coccinetanes A–H (**39–46**)[65] have been isolated from the medicinal plant *K. coccinea*. Among them, coccinetane C (**41**) and coccinetane F (**44**) were isolated as diastereoisomeric mixtures of allylic secondary hydroperoxides and an allylic secondary alcohol group at C-24, repestively. Coccinetane D (**42**) was obtained as an inseparable diastereoisomeric mixture of C-24,C-25 epoxides. Changnanic acid (**47**) and kadsulactone acid (**48**) were isolated from the roots of *K. longipedunculata*.[66] The 12-acetoxy derivative of **48**, polysperlactone B (**49**), was isolated from the stems of *K. polysperma*.[67] Extensive phytochemical studies on the roots and stems of *K. heteroclita* collected from different places resulted in the isolation of the 3,4-secocycloarta-4(28),17(20), 24*Z*-triene-3,26-dioic acid (**50**),[68] ethyl 3,4-secolanosta-4(28), 24*Z*-dien-26,22-olid-3-oate (**51**) and the corresponding Δ^4-isomer (**52**) and 6,7-didehydro derivative (**53**),[69] schisanlactone E (**54**),[60] heteroclitalactones A–M (**55–67**),[60,70] and kadsulactone A (**68**).[71] Compound **50** was bioactive for preventing and treating AIDS, and might be a promising lead compound for the preparation of AIDS drugs.[68] Compounds **51–53** are likely to be artificial products formed during the extraction process.[69] Kadsuphilactones A (**69**) and B (**70**)[72] were isolated from the Taiwanese medicinal plant *K. philippinensis*. Their structures were elucidated on the basis of extensive spectroscopic methods, including two-dimensional NMR techniques. The structure of kadsuphilactone A (**69**), which features an eleven-membered ring, was confirmed by X-ray crystallographic analysis. Kadsuphilactone B (**70**) exhibited anti-HBV (hepatitis B virus) activity with an IC_{50} value of 6 μg mL^{-1} by the HBsAg enzyme immunoassay *in vitro*. Since kadsuphilactone A (**69**) has an unusual ring system and compounds **36**, **69**, **70** and **71** all occur in the same plant, Dr Y. C. Shen and co-workers proposed a biosynthetic pathway for **69** and the relationships between these four triterpenoids. This pathway involves Baeyer–Villiger oxidation, hydrolysis, Michael addition, epoxidation, hydroxylation, and finally oxidation with ring expansion, starting from kadsulactone (**36**) or schisanlactone B (**71**) as the precursor (Scheme 1).[72,73]



Scheme 1 Proposed biosynthesis of **69** and **71**.[72]

Schiprolactone A (**72**),[74] with a 23,27-cyclised side chain, was isolated from the stems of *S. propinqua*. Schisanterpene A (**73**)[75] was isolated from the stems of *S. propinqua*. Other 3,4-seco-cycloartane triterpenoids were also identified from various species, such as kadsudilactone (**74**) (from the stems of *K. coccinea*),[76] schisanlactone C (**75**) (from the fruits of a unidentified *Schisandra* species),[48] polysperlactone A (**76**) (from the stems of *K. polysperma*),[67] lancilactones A–C (**77–79**) (from the stems and roots of *K. lancilimba*),[8] lancifoic acid (**80**) (from the leaves and stems of *S. lancifolia*),[77] and two triterpenoid glucosides (**81–82**) (from *K. japonica*),[78] Among them, lancilactone C (**79**) inhibited HIV replication with an EC_{50} value of 1.4 μg mL^{-1} and a therapeutic index of greater than 71.4.[8] Compound **81** is useful as an anti-androgenic agent for the prevention and treatment of hair diseases (such as male hair loss), prostate hypertrophy, prostate cancer and related diseases, and compound **82** showed an IC_{50} of 4.3×10^{-8} M against androgen receptor binding activity.[78]

2.2.3 14(13→12)-*abeo*-Cycloartanes. From the leaves and stems of *K. longipedunculata*, longipedlactones A–I (**83–91**) were isolated,[79] which were found to have an unprecedented rearranged pentacyclic system. Their structures were determined on the basis of comprehensive spectroscopic analysis, with the structures of longipedlactones A (**83**) and F (**88**) being confirmed by single-crystal X-ray analysis. In the original paper, the



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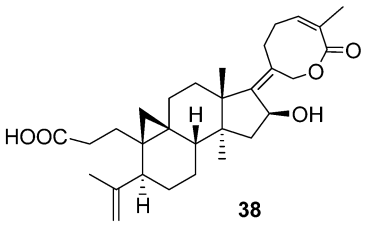

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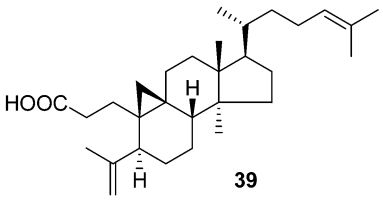

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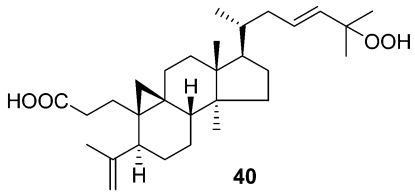

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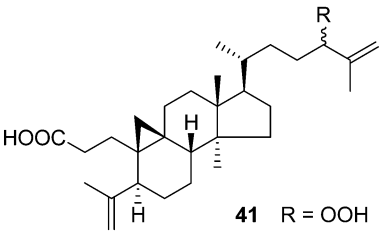
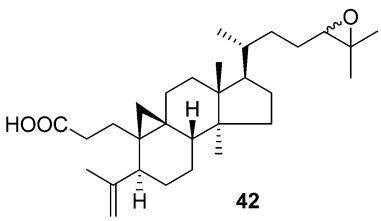


41 R = OOH
44 R = OH



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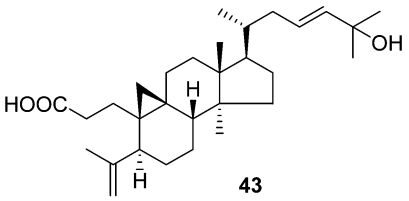

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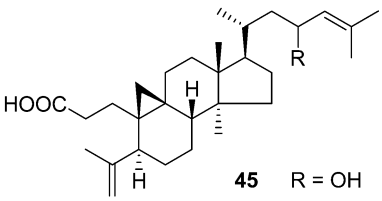
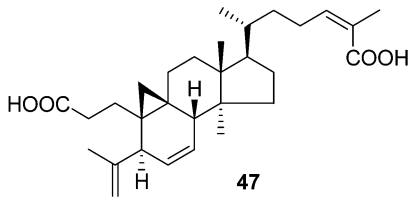
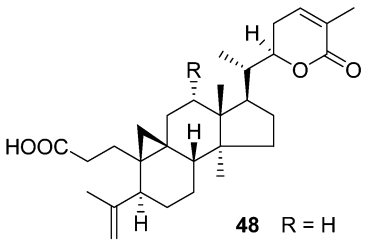


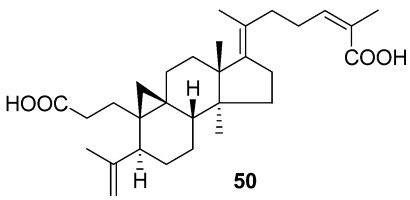
45 R = OH
46 R = OAc



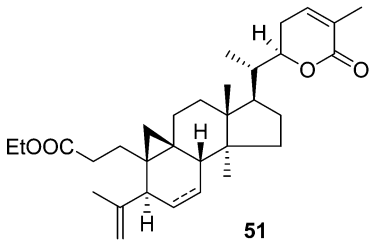
47
49 R = OAc



48 R = H



50
53 $\Delta^{6,7}$



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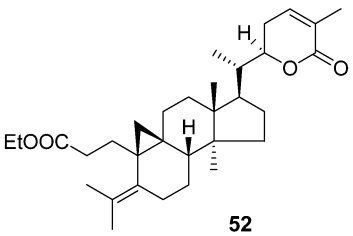

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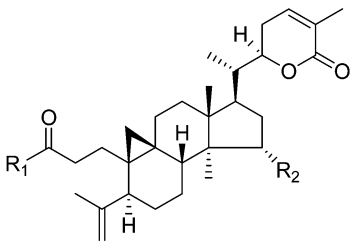
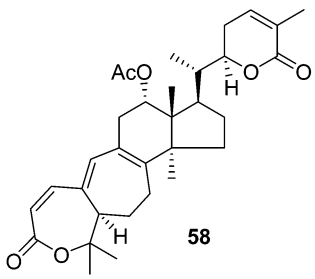


54 R_1 = OH, R_2 = H
55 R_1 = OH, R_2 = OAc
56 R_1 = OMe, R_2 = OAc
57 R_1 = OEt, R_2 = OAc
60 R_1 = OMe, R_2 = H



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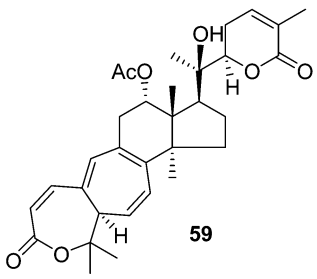

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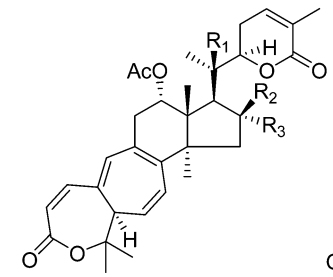
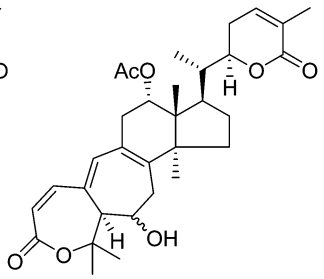


61 R_1 = H, R_2 = H, R_3 = H
62 R_1 = OH, R_2 = H, R_3 = H
63 R_1 = OH, R_2 = OH, R_3 = H
64 R_1 = OH, R_2 = H, R_3 = OAc
65 R_1 = OH, R_2 = R_3 = O



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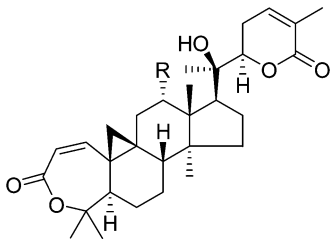
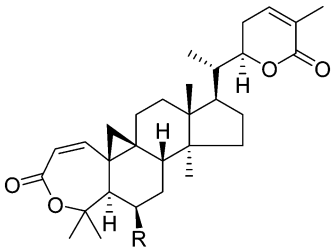
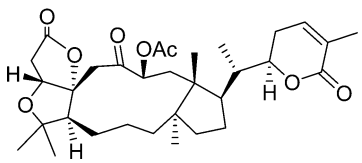


67 R = OAc
70 R = H



68 R = OH
71 R = H



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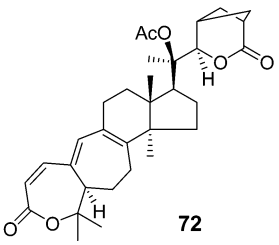

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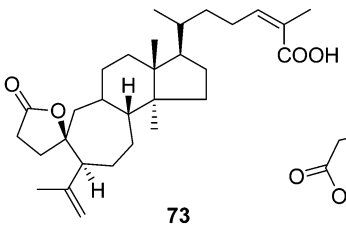

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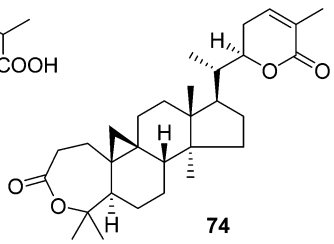

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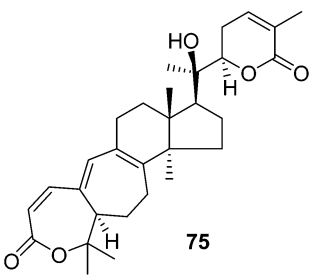

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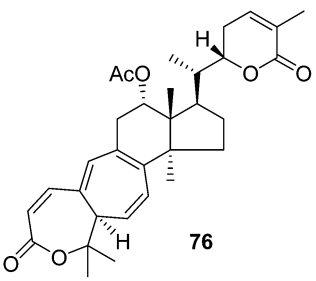

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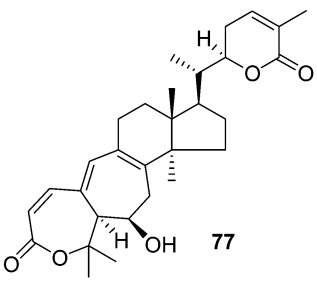

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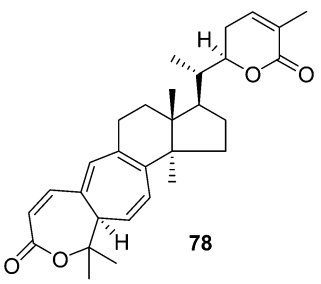

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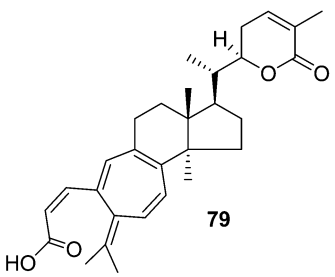

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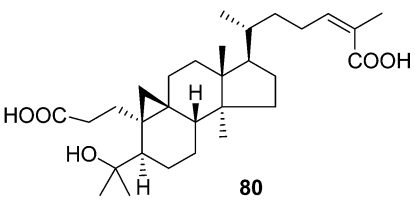

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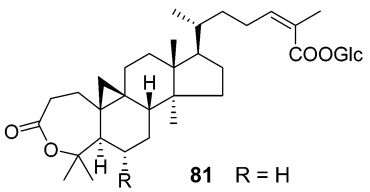
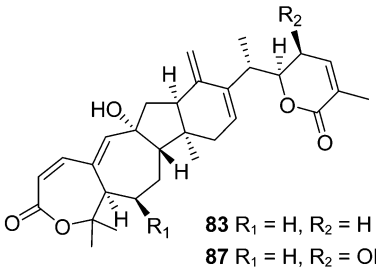


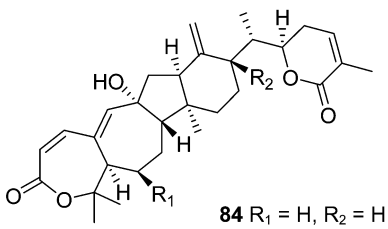
81 R = H
82 R = OH

structures for longipedlactones A (**83**) and F (**88**) from the X-ray analyses were not transcribed correctly: the incorrect stereochemistry at C-20 was given, and this should be corrected to the α-configuration in all the longipedlactones, as shown here. Of these compounds, longipedlactones A–C (**83–85**), F (**88**) and H (**90**) showed significant cytotoxicity against A549, HT-29 and K562 cell lines *in vitro*, with IC_{50} values of 0.84–11.38 μM. However, no cytotoxicities were observed for longipedlactones D (**86**) and G (**89**). Studies of the structure–activity relationship suggested that the formation of a double bond between C-10 and C-19 conjugated with an α,β-unsaturated lactone in **83–85**, **88** and **90** gave them significant cytotoxicity. In contrast, for **86** and **89**, the double bond is replaced by an epoxy ring. This destroys the conjugated system, resulting in loss of cytotoxicity. Thus, it is reasonable to assume that the extended conjugated system (the α,β,γ,δ-unsaturated lactone) is probably crucial to the antitumor activity.[79] Finally, another member, named longipedlactone J (**92**), was isolated from the stems of *K. heteroclita*.[80]

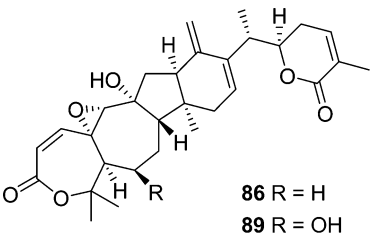
2.2.4 Norcycloartanes. There are four norcycloartane triterpenoids found from the Schisandraceae family. Micranoic acid B (**93**), an octanortriterpenoid due to the loss of the entire C-17 side chain, was isolated from the leaves and stems of *Schisandra micrantha*.[56] Lancifodilactone F (**94**),[81] possessing an unprecedented rearranged pentanortriterpenoid backbone, was isolated from the leaves and stems of *S. lancifolia*. Its structure



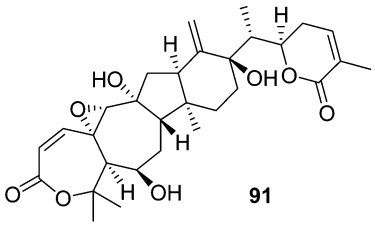
83 R_1 = H, R_2 = H
87 R_1 = H, R_2 = OH
88 R_1 = OH, R_2 = H
92 R_1 = OAc, R_2 = H



84 R_1 = H, R_2 = H
85 R_1 = H, R_2 = OH
90 R_1 = OH, R_2 = OH



86 R = H
89 R = OH



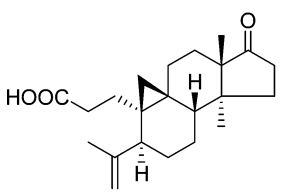
91

was established by comprehensive NMR and MS spectroscopic analysis, coupled with a single-crystal X-ray experiment. This compound featured an unprecedented rearranged pentanor-triterpenoid backbone and showed anti-HIV activity with an EC_{50} of 20.69 ± 3.31 μg mL^{-1} with a selectivity index of more than 6.62. In the original paper, the structure for lancifodilactone F (**94**) from the X-ray analysis was not transcribed correctly: the incorrect stereochemistry at C-8 was given, and this should be corrected to the β-configuration, as shown here. Meanwhile, a new trinorcycloartane triterpenoid with weak anti-HIV-1 activity *in vitro*, lancifodilactone H (**95**), was found from the same plant.[77] This compound features a seven-membered lactone ring, which was confirmed by single-crystal X-ray diffraction. Another trinortriterpenoid, named schisanterpene B (**96**), was isolated from the stems of *S. propinqua*, which also lacks C-25, C-26 and C-27 in the side chain, similar to **95**.[82]

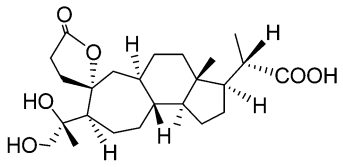
2.2.5 Kadlongilactone-type triterpenoids. Two novel triterpene dilactones, kadlongilactones A (**97**) and B (**98**), have been isolated from the leaves and stems of *K. longipedunculata*.[27] Their structures were established by single-crystal X-ray crystallography. Both compounds exerted significant inhibitory effects against human tumor K562 cells, with IC_{50} values of 1.40 and 1.71 μg mL^{-1}, respectively.[27] Since the two compounds featured an unprecedented rearranged hexacyclic system, these triterpenoids were assigned to a new group, the kadlongilactone-type triterpenoids.

Subsequent studies on the same plant led to the isolation of another four members, kadlongilactones C–F (**99–102**).[83] Their structures were established on the basis of their detailed spectroscopic analysis, and DFT computational methods were applied in the structural validation of compounds **100** and **102**. It was interesting that the ring D inverted from the chair-form in **99** to the boat-form in both kadlongilactones D (**100**) and E (**101**) when the C-16 position was substituted with a β-oriented group. In **102**, the C-16,C-17 epoxide with an adjacent hydroxyl was confirmed on the basis of carbon chemical shift calculations by a DFT computational method.[83]

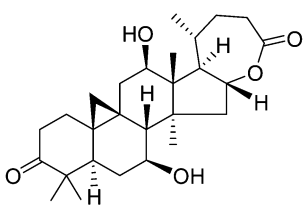
From a biosynthetic point of view, the kadlongilactone-type triterpenoids are related to the 14(13→12)-*abeo*-cycloartane type triterpenoids. A plausible biosynthetic pathway for the two types can be proposed starting from kadsudilactone (**74**) as a precursor (Scheme 2).[79] Ring expansion, oxidation and dehydrogenation of kadsudilactone results in intermediate **A**, which is followed by hydroxylation at C-13 to afford intermediate **B**, which then undergoes a Wagner–Meerwein rearrangement to give the 14(13→12)-*abeo*-cycloartane skeleton. Subsequent hydroxylation at C-9 and C-17 and dehydration at C-16 and C-17 yields longilactone A (**83**). Further oxidation, dehydration, cyclization and hydroxylation reactions can then lead to kadlongilactone



93



94



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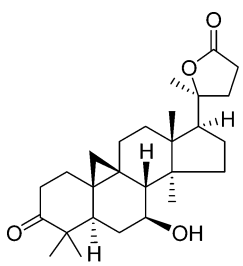

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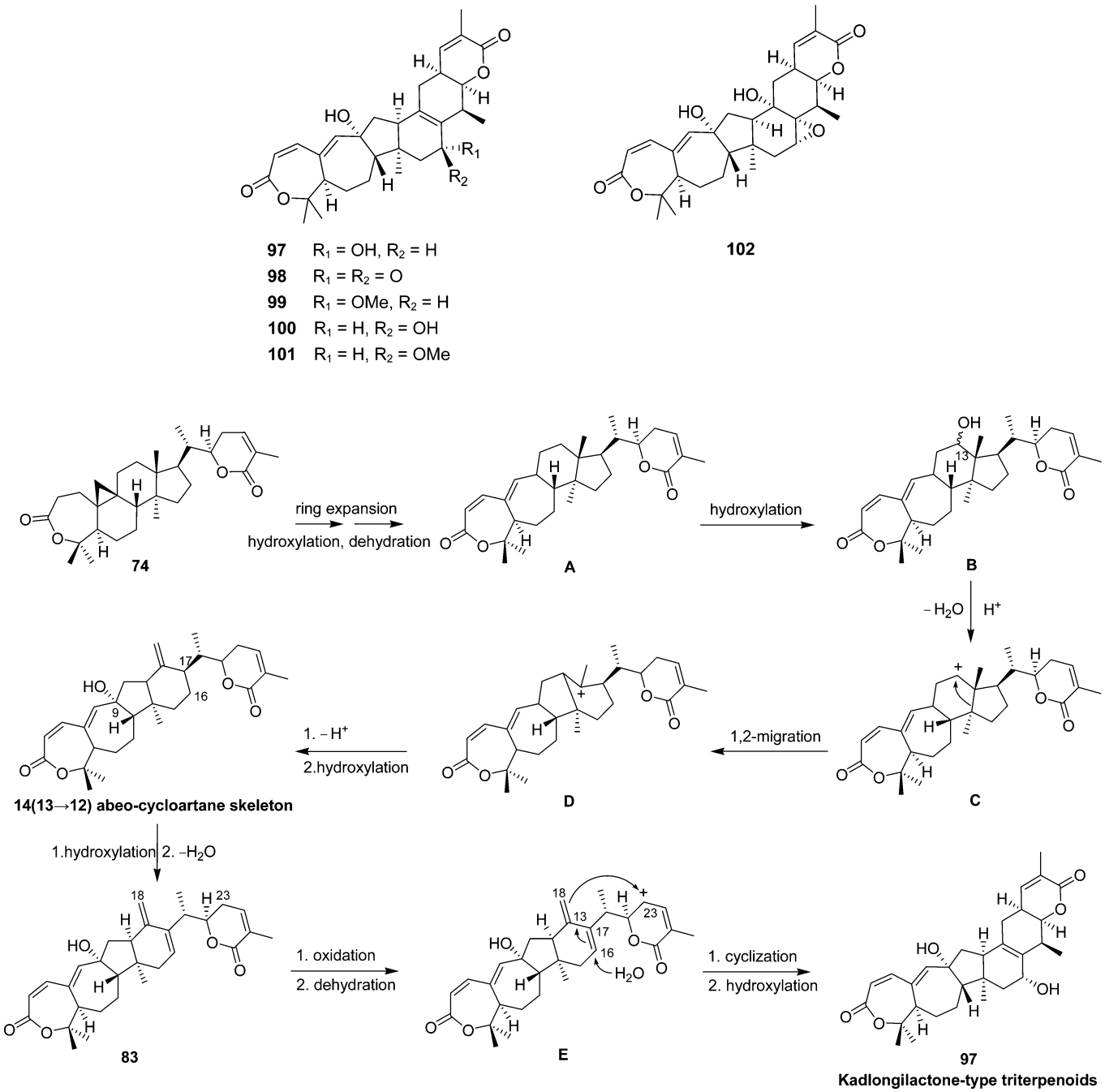


Scheme 2 Proposed biosynthetic relationships between the 14(13→12)-*abeo*-cycloartanes and the kadlongilactone-type triterpenoids.[79]

A (**97**), one of the representatives of the kadlongilactone-type triterpenoids.

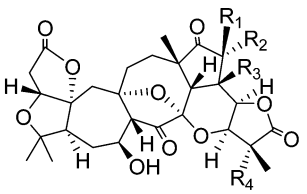
2.3 *Schisandra* nortriterpenoids

In the last five years, more than 60 biosynthetically related, highly oxygenated, polycyclic nortriterpenoids have been found from the plants of the Schisandraceae family by our group. Interestingly, all of them were isolated from plants of genus *Schisandra*, so we assigned this series of unique nortriterpenoids as *Schisandra* nortriterpenoids. These were further classified into six groups according to the different carbon connections and rearrangement patterns: the schisanartane (**C1**), schiartane (**C2**), 18-norschiartane (**C3**), 18(13→14)-*abeo*-schiartane (**C4**), pre-schisanartane (**C5**), and wuweiziartane (**C6**) groups.

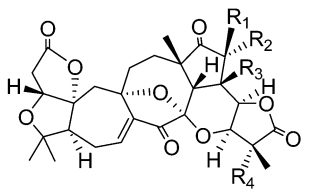
2.3.1 Schisanartane-type. Micrandilactone A (**103**) was first reported from the stems and leaves of *S. micrantha* in 2003.[24] This compound was the first example to feature an unusual, highly oxidized C_{29} skeleton with a biosynthetically modified eight-membered ring D. Its structure was finally determined by single-crystal X-ray analysis.

The discovery of **103** can be considered to be a milestone in the discovery of *Schisandra* nortriterpenoids from the

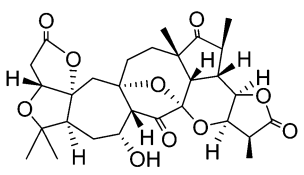
Schisandraceae family, because many structurally related members have since been found from *S. micrantha* or other species in this family. Continued studies on *S. micrantha* led to four other members, micrandilactones D–G (**104–107**).[84] From the leaves and stems of *S. lancifolia*, lancifodilactones B–E (**108–111**),[85] G (**112**),[86] and I–N (**113–118**),[87] were isolated. Among them, lancifodilactone G (**112**) was a novel, highly oxygenated nortriterpenoid featuring a partial enol structure and a spirocyclic moiety. Its structure was determined by single-crystal X-ray analysis. This compound exerted minimal cytotoxicity against C8166 cells (CC_{50} >200 μg mL^{-1}) and showed weak anti-HIV activity with an EC_{50} value of 95.5 ± 14.2 μg mL^{-1}. The phenomenon of why this compound exists as an enol isomer not as ketone isomer are also discussed based on the theoretical evidence.[86] The structures of lancifodilactones I (**113**) and L (**116**) were both determined by single-crystal X-ray



	R_1	R_2	R_3	R_4
103	CH_3	OH	OH	H
104	CH_3	OH	H	H
105	OH	CH_3	H	H
109	CH_3	H	H	H
111	H	CH_3	H	OH
116	CH_3	H	H	OH
122	H	CH_3	H	H



	R_1	R_2	R_3	R_4
106	OH	CH_3	H	H
110	CH_3	H	H	H
118	CH_3	H	H	OH
119	CH_3	OH	H	H
120	CH_3	OH	OH	H
121	CH_3	H	H	H



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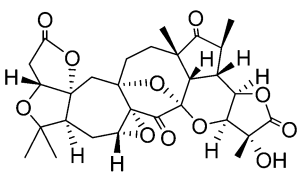

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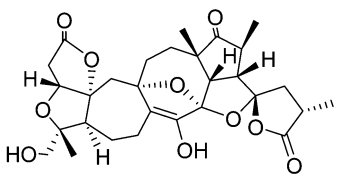

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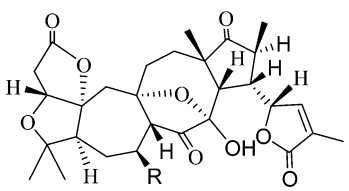
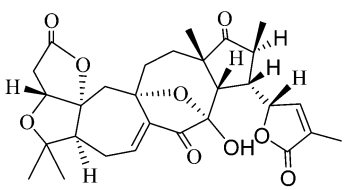


113 R = OH
114 R = OAc



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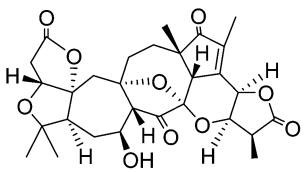

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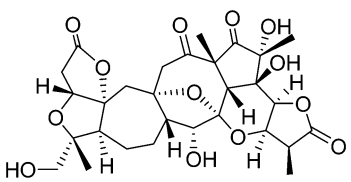

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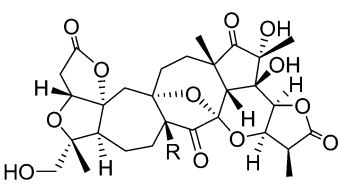
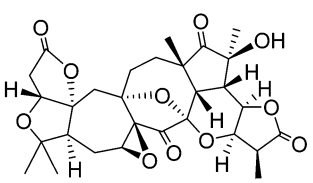


124 R = OH
125 R = H



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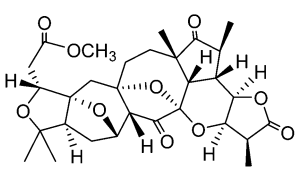

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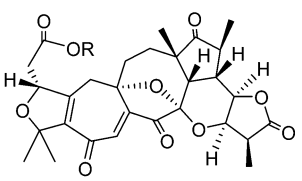
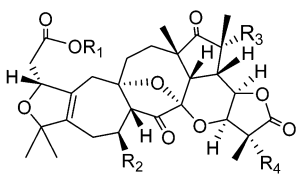


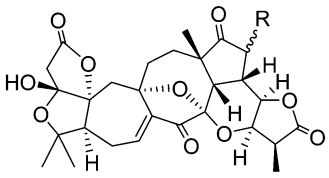
128 R = CH_3
129 R = C_2H_5

crystallography.[87] Henridilactones A–D (**119–122**) were isolated from the leaves and stems of *S. henryi* var. *yunnanensis*.[88] From the aerial parts of *S. propinqua* var. *propinqua*, propindilactones A–D (**123–126**), were isolated.[89] Ten ring-A-opened compounds, rubriflorins A–J (**127–136**), were isolated from the leaves and stems *S. rubriflora*, and all these compounds showed weak activity against HIV-1.[90,91] Rubrifolins A (**127**) and B (**128**), which were given duplicate names with two lignans, have also been reported from *S. rubriflora*. Schindilactones A–G (**137–143**), the first examples of C-1 hydroxyl-substituted schisanartane-type triterpenoids, were isolated from leaves and stems of *S. chinensis*.[25,64] Sphenadilactones A–B (**144–145**)[92] and sphenalactones A–D (**146–149**),[93] were recently isolated from the leaves and stems of *S. sphenanthera*. Their structural elucidations were accomplished by extensive NMR analysis, and the relative stereochemistry of sphenadilactone A (**144**) was established by single-crystal X-ray crystallography. Somewhat special were sphenadilactone A (**144**), which possessed a more complex ring system, and sphenalactones A–D (**146–149**), which were further oxidized and had lost the C-1, C-2 and C-3. In addition, compounds **144** and **146–149** showed anti-HIV-1 activity with EC_{50} values in the range 35.5–137.0 μg mL^{-1} and low cytotoxicity against C8166 cells (CC50 >200 μg mL^{-1}).[92,93] In the original papers, compounds **103–122** had the wrong absolute configuration.[24,84]

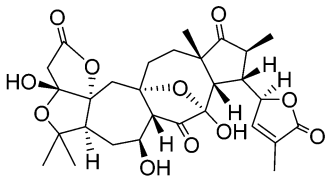
2.3.2 Schiartane-type. The schiartane-type triterpenoids are rare. So far only two members, micrandilactones B and C (**150–151**),[20] have been reported, from the leaves and stems of *S. micrantha*. Their relative stereochemistries were both established by single-crystal X-ray analysis,[20] and the absolute stereochemistry of micrandilactone B (**150**) was determined by a modified Mosher method.[25] Since the two compounds featured the loss of C-28 in their structures and represent another new class of nortriterpenoids from Schisandraceae family, we have assigned this type of triterpenoid as the schiartane-type.[84] Interestingly, micrandilactone C (**151**) possessed anti-HIV activity with an EC_{50} value of 7.71 μg mL^{-1}, and exerted its potent activity in protecting $HIV\text{-}1_{IIIB}$ infected MT-4 host cells from dying with a selectivity index of more than 425.5 at a concentration of 0.47 μg mL^{-1}. However, micrandilactone B (**150**) only showed weak anti-HIV-1 activity.[20]



	R_1	R_2	R_3	R_4
130	H	OH	H	H
131	H	OAc	H	H
132	H	OAc	H	OH
133	C_2H_5	OH	H	H
134	C_2H_5	OH	H	OH
135	C_2H_5	OH	OH	OH
136	CH_3	OH	H	H



137 R = β-CH_3
138 R = α-CH_3



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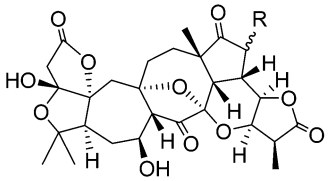
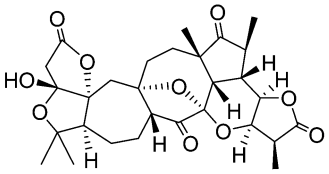


140 R = β-CH_3
141 R = α-CH_3



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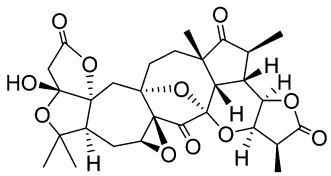

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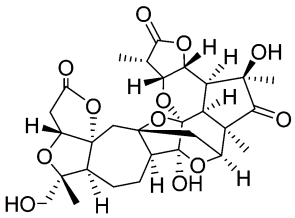

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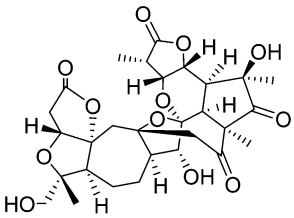

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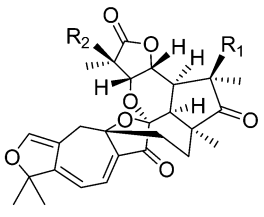
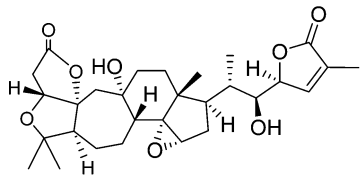


146 R_1 = OH, R_2 = H
147 R_1 = H, R_2 = OH
148 R_1 = OH, R_2 = OH
149 R_1 = H, R_2 = H



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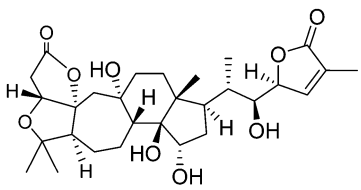

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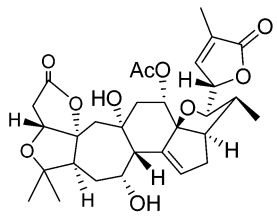

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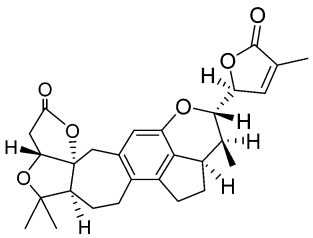

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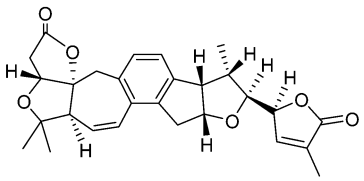

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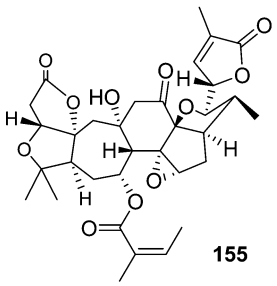

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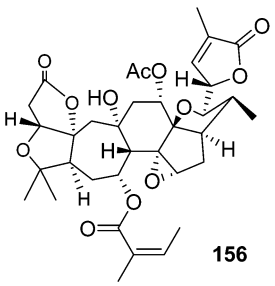

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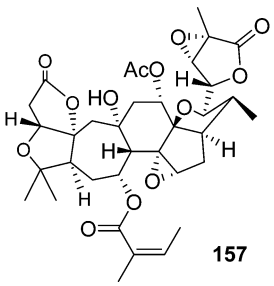

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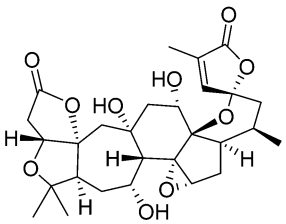
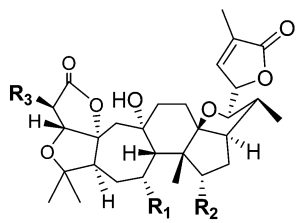


158

2.3.3 18-Norschiartane-type. This is a group of bisnor-triterpenoids with C-18 and C-28 missing. Lancifodilactone A (**152**) was the first to be reported, and was isolated from the stems and leaves of *S. lancifolia*.[21] Subsequently, other six members were found. Rubriflordilactones A (**153**) and B (**154**), possessing a modified aromatic D-ring, were isolated from the leaves and stems of *S. rubriflora*.[22] Rubriflordilactone A (**153**) showed weak anti-HIV-1 activity, and rubriflordilactone B (**154**) exhibited an EC_{50} value of 9.75 μg mL^{-1} against HIV-1 replication. Wuweizidilactones A–B (**155–156**)[23] and G–H (**157–158**)[64] were isolated from the leaves and stems of *S. chinensis*, and all showed weak anti-HIV activity. The structures of compounds **152–155** were all established on the basis of extensive spectroscopic methods, including two-dimensional NMR techniques, and confirmed by X-ray crystallographic analysis.[21–23]

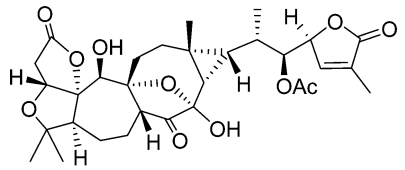
2.3.4 18(13→14)-*abeo*-Schiartane-type. This type of triterpenoid is very unusual, in that the C-14 methyl group is β-oriented rather than α-oriented. The most reasonable explanation is that this methyl group derives from the biosynthetic shifting of the 18-methyl on C-13. So far, only four members, named wuweizidilactones C–F (**159–162**), have been isolated, all from the aerial parts of *S. chinensis*. These were deduced to be the key intermediates in the biosynthesis of the 18-norschiartane-type triterpenoids.[23] In addition, all four compounds showed weak anti-HIV activities.[23]

2.3.5 Pre-schisanartane-type. The pre-schisanartane-type triterpenoids have a 7/8/3 fused carbocycle. Most importantly, the occurrence of this type of compound has provided new insight into the biosynthesis of schisanartane-type triterpenoids. Up to now, only two examples, pre-schisanartanins A (**163**)[25] and B (**164**),[64] have been isolated, both from the leaves and stems of *S. chinensis*. Both compounds showed weak anti-HIV activity. Besides the extensive 2D NMR spectra, single-crystal X-ray diffraction was applied in the elucidation of **163**. In order to embody the importance of this kind of triterpenoids in the biosynthetic pathway of schisanartane-type triterpenoids, we gave the trivial names of compounds **163** and **164** the prefix "pre-". Accordingly, this type of triterpenoid was assigned as the pre-schisanartane-type.



159 R_1 = OAc, R_2 = OH, R_3 = H
160 R_1 = H, R_2 = OH, R_3 = H
161 R_1 = H, R_2 = OAc, R_3 = H
162 R_1 = H, R_2 =OAc, R_3 = OH

2.3.6 Wuweiziartane-type. Schintrilactones A (**165**) and B (**166**), isolated from *S. chinensis*,[26] are the only representatives of this class of triterpenoids, bearing a modified five-membered D



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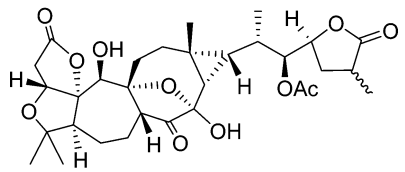
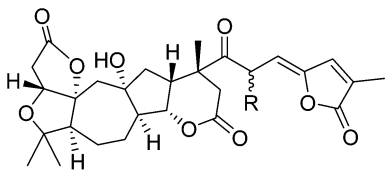


164

ring, a δ-lactone E ring, and a stereogenic center at C-20. Interestingly, the two compounds occurred as a pair of configurationally unstable isomers, and thus slowly interconvert. Their absolute structures were determined by means of spectroscopic evidence and comparison of their experimental CD curves with those derived from quantum chemical CD calculations. Both compounds showed weak anti-HIV activity.



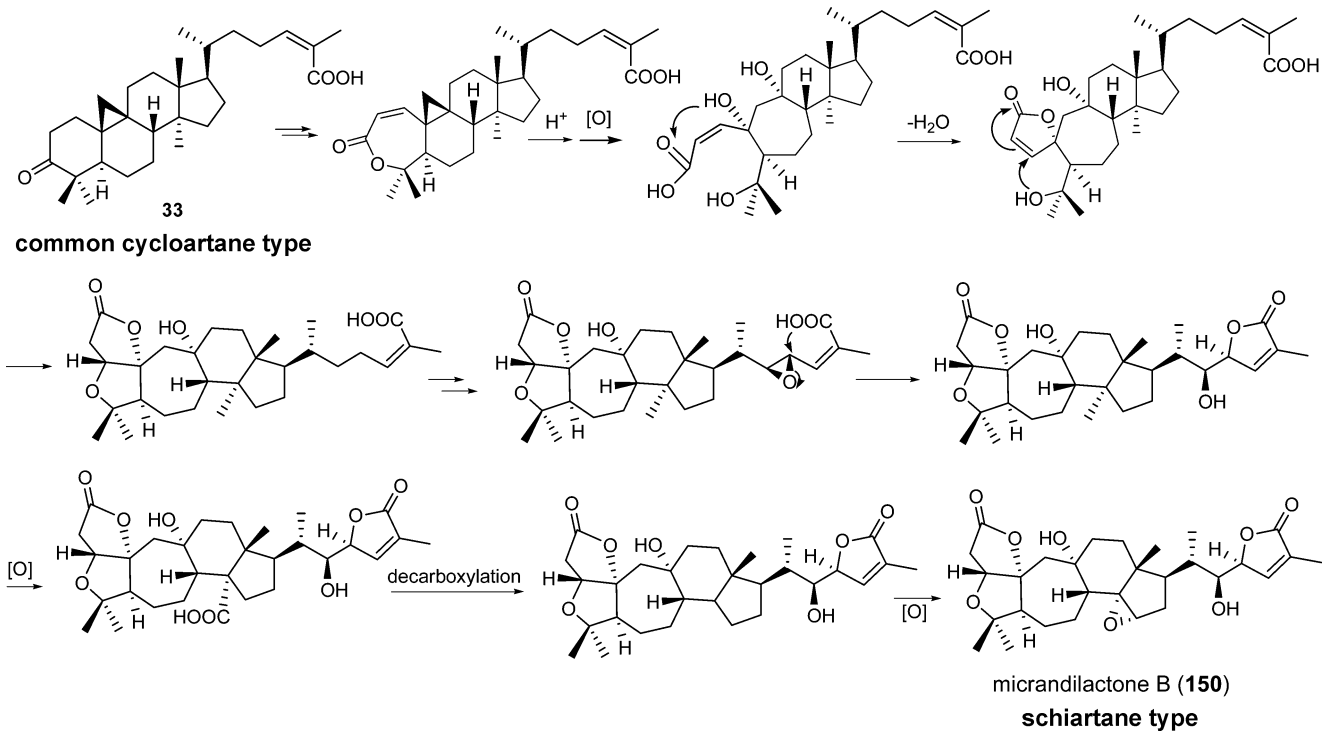
165 R = β-Me
166 R = α-Me

3 Proposed biosynthetic pathways

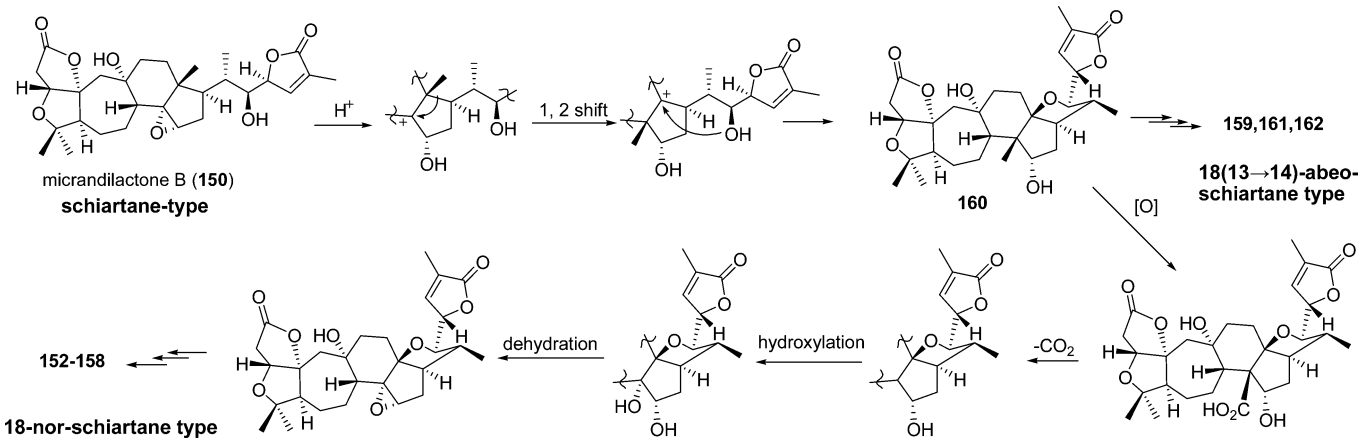
Of the six skeletons of the *Schisandra* nortriterpenoids, the schiartane skeleton is considered to be the first on the biosynthetic pathway from the cycloartane triterpenoids because the core cycloartane skeleton is preserved. A possible biosynthetic pathway, starting from schizandronic acid (**33**), is shown in Scheme 3.[64] In this route, ring expansion, 3,4-oxidative cleavage, oxidation and decarboxylation at C-28 and epoxidation finally lead to the formation of micrandilactone B (**150**).

18-Norschiartane and 18(13→14)-*abeo*-schiartane triterpenoids may be both derived from micrandilactone B (**150**). Our group have proposed a biosynthetic route to the 18-norschiartane triterpenoids as shown in Scheme 4.[23,84] This route starts with enzymatic epoxide ring opening of **150**, followed by a 1,2-methyl shift and attack of the side chain OH group on the tertiary cation at C-13 to afford wuweizidilactone D (**160**) as an intermediate. Subsequent oxidation of the 14-Me group of **160** affords a carboxylic acid, which undergoes decarboxylation to give a demethyl derivative. Then, a series of hydroxylation, dehydration and acetoxylation steps yields the 18-norschiartane nortriterpenoids **152–158**. This biosynthetic pathway was corroborated by the isolation of the key intermediate, the 18(13→14)-*abeo*-schiartane triterpenoid wuweizidilactone D (**160**), and its analogues (**159**, **161** and **162**).[23]

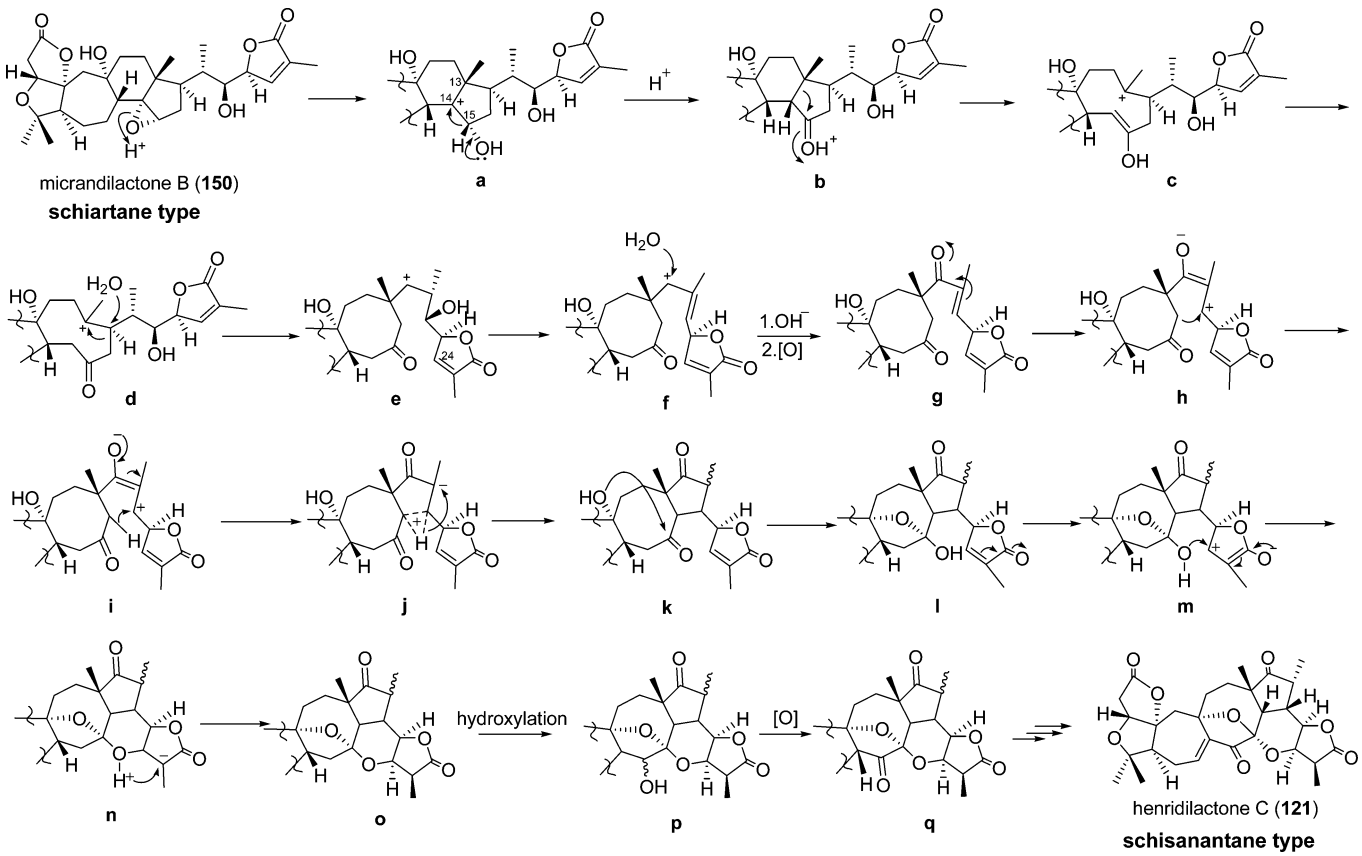
The structures of schisanartane nortriterpenoids were the most interesting from a biosynthetic point of view because of the unusual arrangement of the eight-membered ring D. A possible biosynthetic route to the schisanartane type nortriterpenoids was first proposed by our group, and is shown in Scheme 5.[84] The first step would be enzymatic epoxide ring opening, similar to the mechanism for the 18-norschiartane and



Scheme 3 Proposed mechanism for the formation of the schiartane skeleton.[64]



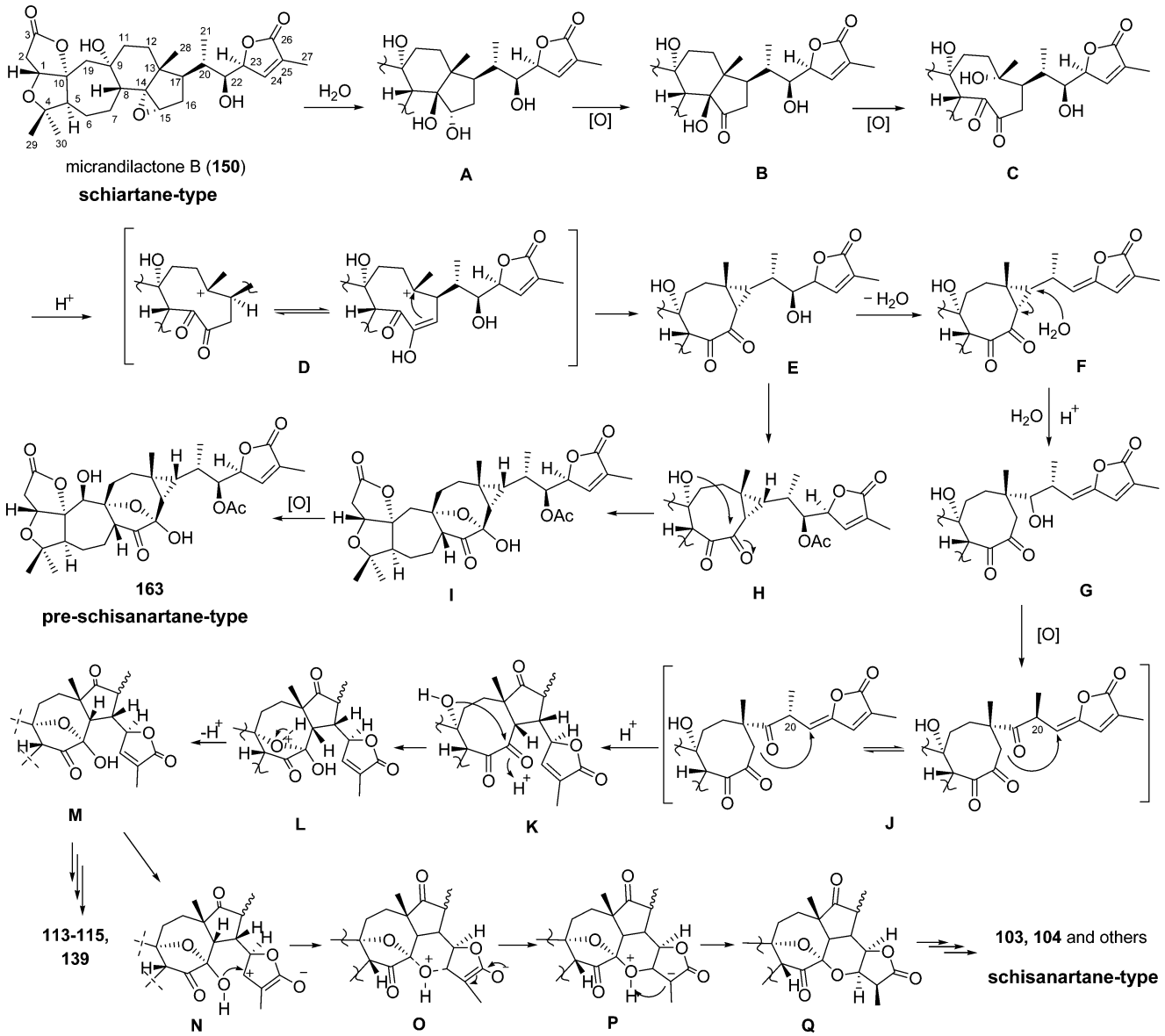
Scheme 4 Hypothetical biosynthetic routes to the 18-norschiartane and 18(13→14)-*abeo*-schiartane nortriterpenoids from schiartane.[23,84]



Scheme 5 The original hypothetical biosynthetic route to the schisanartane nortriterpenoids from schiartane.[84]

18(13→14)-*abeo*-schiartane nortriterpenoids (Scheme 4) to give a C-14 cation (**a**). Subsequent hydride shift, ring opening and 1,2-migration forms a nine-membered-ring intermediate (**e**). Then, dehydration, addition of water, oxidation, and Michael addition generate compound **o**. Subsequent hydroxylation and oxidation at C-14 and dehydrogenation at C-7,C-8 provides henridilactone C (**121**).

However, the recent discovery of pre-schisanartane nortriterpenoids provided us with a new insight into the biosynthesis of the schisanartane nortriterpenoids. Accordingly, we proposed a new possible biosynthetic route to the schisanartanes and the pre-schisanartanes (Scheme 6).[25] In this route, micrandilactone B (**150**) was again considered to be the precursor. The epoxy ring in **150** undergoes hydrolysis, resulting in a 14,15-dihydroxy intermediate (**A**). This undergoes oxidative cleavage of the C-13–C-14 bond and oxidation of 15-OH to generate a 14,15-diketone intermediate (**C**). This intermediate can easily convert to the nine-membered-ring enolic cation intermediate **D** under acidic conditions. This C-13 cation reacts with the electrophilic center (C-16), thus giving **E**, which can then be converted to **163** in a few



Scheme 6 A new hypothetical biosynthetic route to the schisanartanes, showing the close relationship between the pre-schisanartanes and the schiartanes.[25]

straightforward steps. In addition, **E** can also be converted to **K** by a sequence of oxidation and Michael addition reactions. Subsequent oxidation, acetoxylaction and dehydration can then form compounds **113–115** and **139**. Furthermore, **K** can be further transformed to **103–109** and other schisanartane norterpenoids by a sequence of Michael addition and other straightforward reactions.

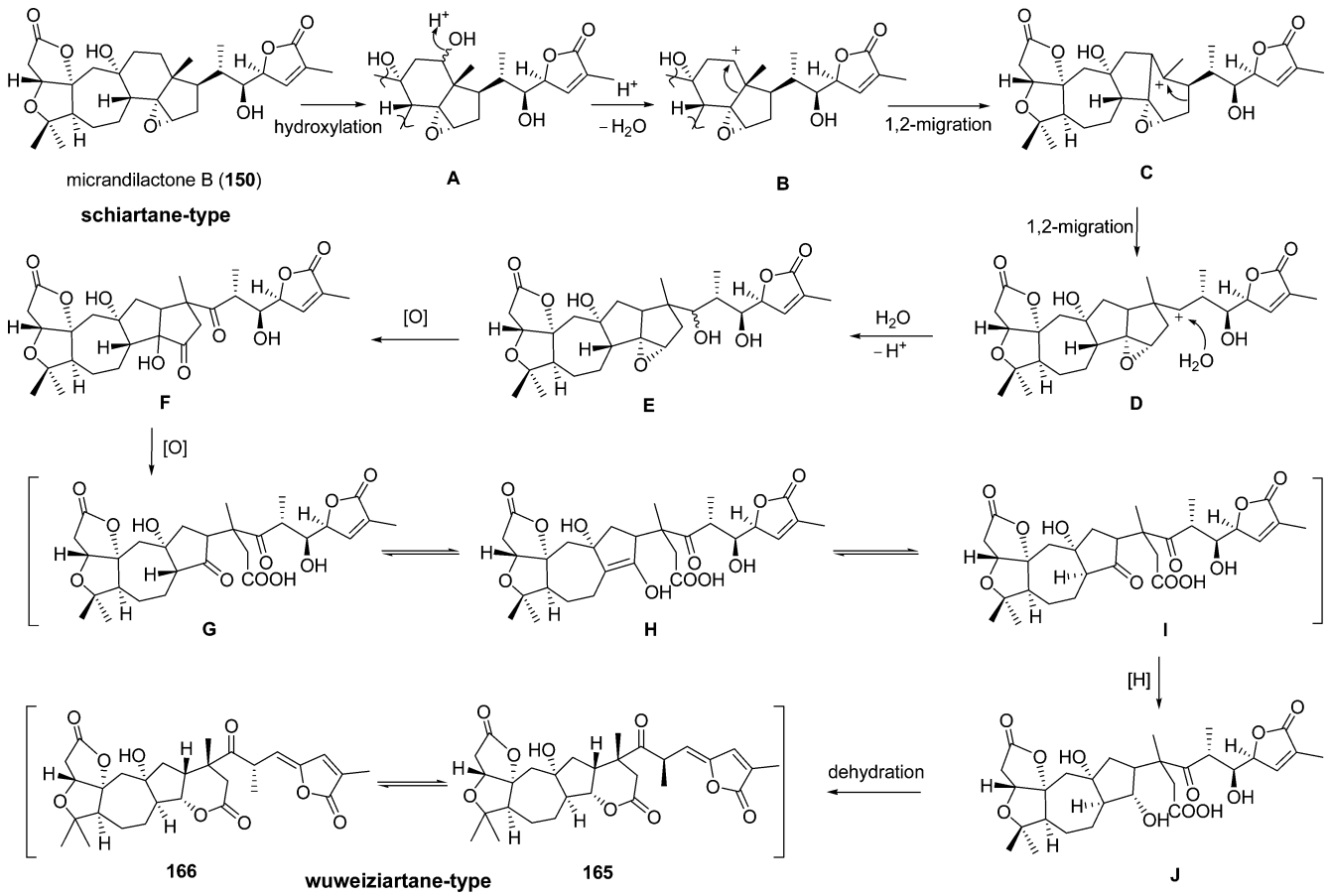
In addition, wuweiziartane nortriterpenoids **165** and **166** can also be formed from micrandilactone B (**150**) (Scheme 7). It is proposed that hydroxylation and two Wagner–Meerwein reactions take place, resulting in the formation of key intermediate **D**. Subsequent hydration, oxidation, isomerisation and dehydration finally lead to the formation of **165** and **166**.

In conclusion, the six novel nortriterpenoid skeletons discussed are proposed to be biosynthetically related, and they might be all be derived from the cycloartane triterpenoids.

4 Synthesis and biotransformation

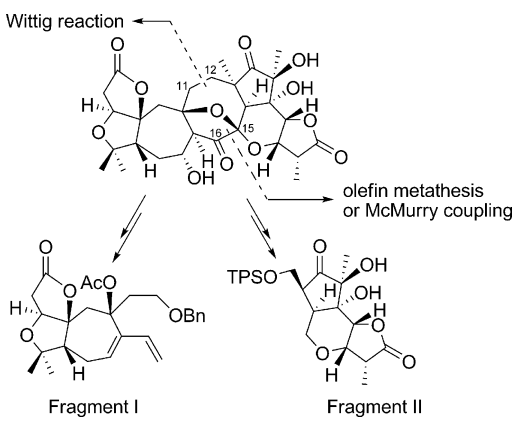
Synthetic studies into the Schisandraceae triterpenoids began only recently, with the discovery of the complex structures and the promising pharmacological profiles of the novel *Schisandra* nortriterpenoids.[94–97] In particular, the schisanartane nortriterpenoids are distinguished by their novel triterpene framework, and their dense pattern of oxygenation. The biosynthetically modified eight-membered D ring linked by a ketal presents a challenge to synthetic chemists with regard to its unfavorable entropy, bond angle deformations, and destabilizing transannular interactions.[98,99] Therefore, the schisanartane nortriterpenoids are a particularly challenging and attractive target for the synthetic community.

As mentioned previously, the first report of a schisanartane nortriterpenoid was micrandilactone A (**103**) (initially, the



Scheme 7 A hypothetical biosynthetic route to the wuweiziartanes from the schiartanes.

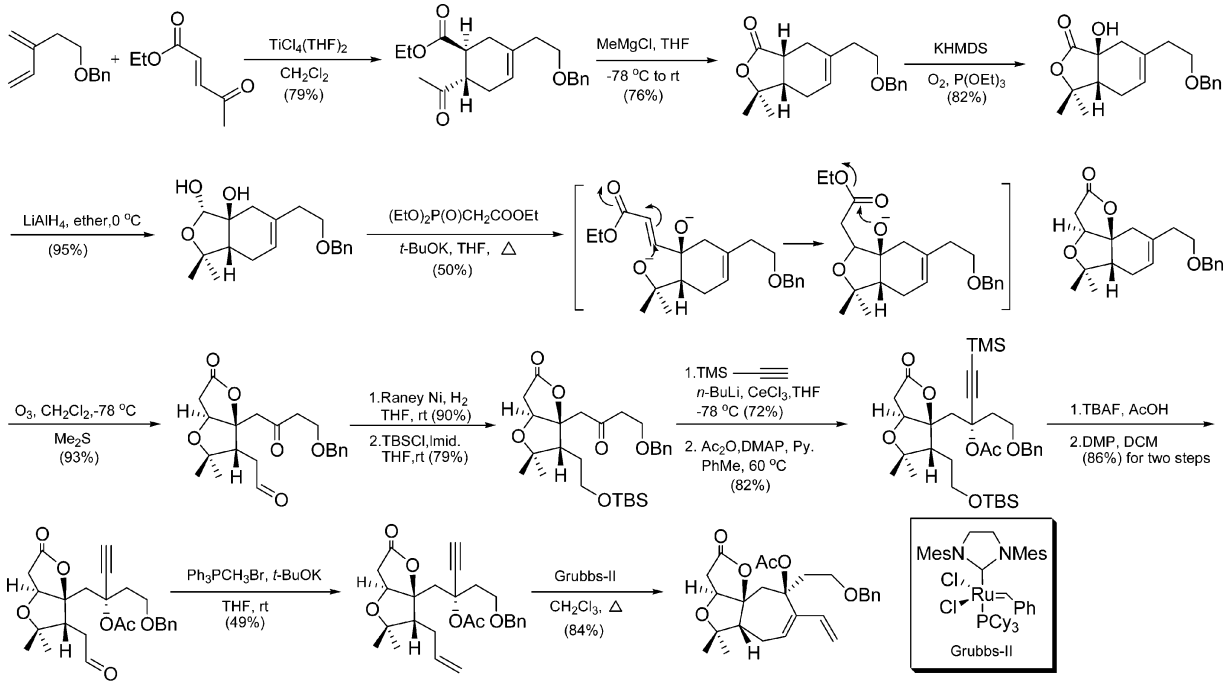
misinterpretation of X-ray data led to it being incorrectly reported as the enantiomer). Following this, Prof. Z. Yang and co-workers carried out total synthesis studies.[94,95] Fragments I and II, derived by retrosynthetic analysis (Scheme 8), which have the necessary functionalities to allow their union by a Wittig reaction (C-11–C-12) and olefin metathesis or McMurry coupling (C-15–C-16), were synthesized in a stereocontrolled manner. The synthesis of Fragment I (Scheme 9), was accomplished using an intermolecular Diels–Alder reaction and an enyne RCM reaction as the key steps.[94] The efficient stereoselective construction of Fragment II was accomplished in 15 steps (Scheme 10). This approach featured a Co-thiourea-catalyzed intramolecular Pauson–Khand reaction and a Pd-thiourea-catalyzed tandem alkoxycarbonylation.[95] Other approaches to the two fragments were also attempted, but were not so successful.[94,95]



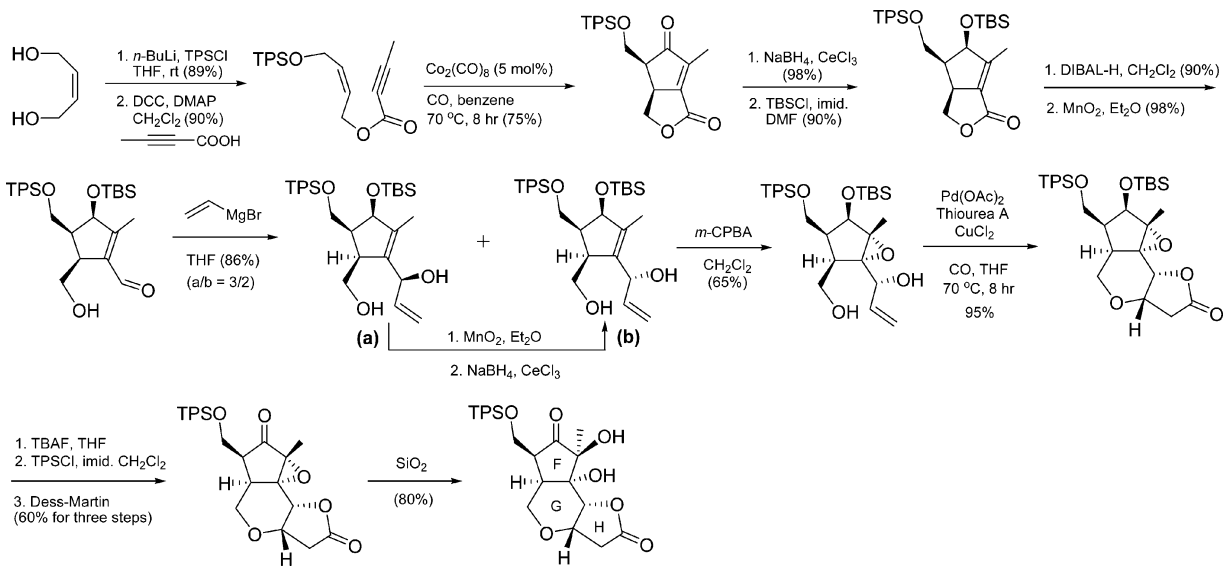
Scheme 8 Retrosynthetic analysis of Fragments I and II of micrandilactone A (**103**).[94]

The biosynthesis of the AB-ring system of lancifodilactone F (**94**) (initially, the misinterpretation of X-ray data led to it being incorrectly reported as the enantiomer) could be considered to arise from a common cycloartane skeleton, integral to the structure of schizandronic acid (**33**) as shown in Scheme 3. Its chemical synthesis was reported by Prof. E. A. Theodorakis and coworkers recently (Scheme 11).[96] This approach uses a novel acid-mediated cyclopropylcarbinol ring-expansion reaction as the key rearrangement for the construction of the AB-ring system.

The biotransformation of nigranoic acid (**37**) was reported by K. Q. Zhang and coworkers in 2007 (Scheme 12).[100] Three new products from the co-cultures of nigranoic acid and *Gliocladium roseum* YMF1.00133 were obtained. The major metabolite was identified as 15β-hydroxynigranoic acid, and the minor metabolites as 6α,15β-dihydroxynigranoic acid and 7β,15α-dihydroxynigranoic acid by mass spectrometry and NMR spectroscopy.



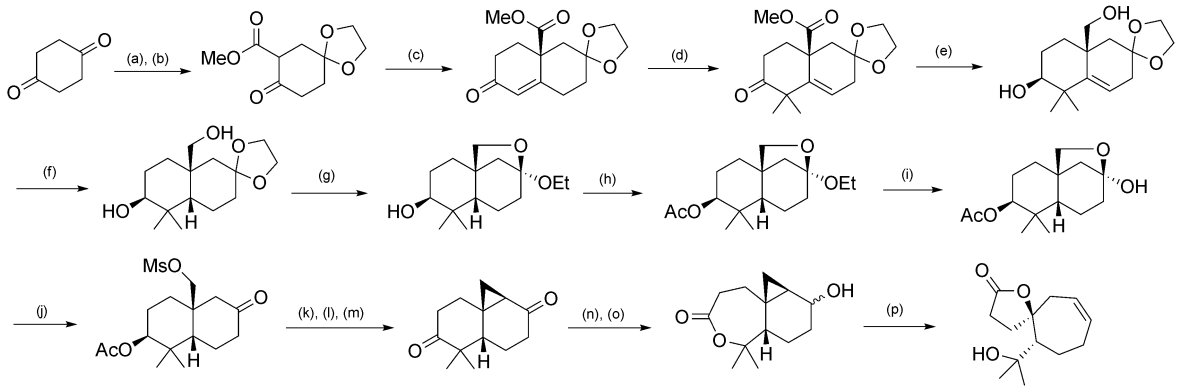
Scheme 9 Synthesis of Fragment I of micrandilactone A (**103**).[95]



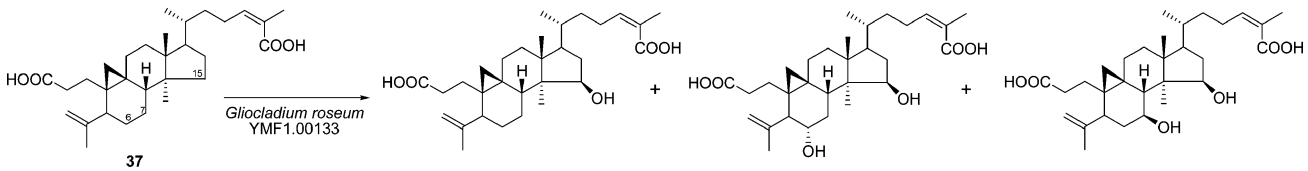
Scheme 10 Synthesis of Fragment II of micrandilactone A (**103**).[94]

5 Conclusions and future prospects

The family Schisandraceae are economically and medicinally important and include many species with a variety of uses.[1–19] From this family, 166 triterpenoids with different structural skeletons have been isolated and characterized, some of which have exhibited promising bioactivities. In particular, the recently discovered *Schisandra* nortriterpenoids are attractive to the pharmacological and synthetic communities for their complex structures with unusual motifs. Although medicinal uses of these compounds are currently limited, their structures are biosynthetically unique, and they may therefore possess potentially significant bioactivities. Continuing study into the plants of the family Schisandraceae might lead to the discovery of more related compounds with interesting biological activities, and we anticipate further progress in the search for medicinal applications with the development of pharmacological models. In addition, the proposed biosynthetic pathway for these compounds may trigger further studies and make valuable contributions to biomimetic semisynthesis or total chemical synthesis. Therefore, further studies of the synthesis,



Scheme 11 Synthesis of AB-ring system of lancifodilactone F (**94**).[96] *Reagents and conditions*: (a) ethylene glycol (1.3 equiv.), *p*-TsOH (0.09 equiv.), benzene, 100 °C, 1.5 h, 35% (90% after recycling); (b) LDA (1.2 equiv.), methyl cyanoformate (1.2 equiv.), HMPA (1.0 equiv.), THF, 0 °C, 1 h, 65%; (c) Et_3N (0.35 equiv.), MVK (1.8 equiv.), MeOH, 25 °C, 40 h, then pyrrolidine (0.2 equiv.), AcOH (0.2 equiv.), benzene, 100 °C, 2 h, 60%; (d) *t*-BuOK (2.1 equiv.), MeI (6.0 equiv.), *t*-BuOH, 40 °C, 3 h, 60%; (e) LAH (1.4 equiv.), THF, 0 to 25 °C, 12 h, 73%; (f) $[Ir(cod)Py(PCy_3)]PF_6$ (0.04 equiv.), H_2 (1 atm), CH_2Cl_2, 25 °C, 5 h, 77%; (g) *p*-TsOH (0.05 equiv.), EtOH, 40 °C, 30 min, 92%; (h) AcCl (1.5 equiv.), DMAP (0.07 equiv.), pyridine–CH_2Cl_2 (1 : 1), 25 °C, 1.5 h, 90%; (i) *p*-TsOH (0.15 equiv.), acetone, 40 °C, 2 h, 85%; (j) iPr_2NEt (1.3 equiv.), MsCl (1.3 equiv.), CH_2Cl_2, 0 °C, 5 min, 30% (60% after recycling); (k) *t*-BuOK (1.5 equiv.), benzene, 25 °C, 4 h, 95%; (l) K_2CO_3 (1.2 equiv.), NaOMe (0.05 equiv.), MeOH, 25 °C, 24 h, 82%; (m) DMP (1.3 equiv.), CH_2Cl_2, 25 °C, 30 min, 95%; (n) *m*-CPBA (1.5 equiv.), $NaHCO_3$ (4.1 equiv.), CH_2Cl_2, 0→25 °C, 8 h, 98%; (o) $Bu_4N\,BH_4$ (5.0 equiv.), CH_2Cl_2, 0→25 °C, 8 h, 82%; (p) $HClO_4$ (1.0 equiv.), acetone, H_2O, 25 °C, 1.5 h, 55%.



Scheme 12 Biotransformation of nigranoic acid (**37**) by *Gliocladium roseum* YMF1.00133.[100]

biotransformation and pharmacological activity of the *Schisandra* nortriterpenoids should continue to be interesting and rewarding.

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