Structure Characterization and Possible Biogenesis of Three New Families of Nortriterpenoids: Schisanartane, Schiartane, and 18-Norschiartane

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Abstract: Four new, highly oxygenated nortriterpenoids with unique schisanartane skeletons, micrandilactones D–G (**1**–**4**), have been isolated from the leaves and stems of *Schisandra micrantha*, and their structures have been elucidated on the basis of extensive spectral studies. The postulated biogenetic sequences of sixteen highly oxygenated nortriterpenoids and bisnortriterpenoids with new skeletons from three *Schisandra* species are discussed and have been compared from a chemotaxonomic standpoint.

Keywords: biogenesis · natural products · NMR spectroscopy · structure elucidation · terpenoids

Introduction

Triterpenoids are the most ubiquitous, nonsteroidal secondary metabolites in terrestrial and marine flora and fauna. Their presence, even in nonphotosynthetic bacteria, has created interest from both an evolutionary and functional point of view. Although medicinal uses of the compounds from this class are rather limited, considerable recent work in this regard strongly indicates their great potential as drugs.[1] Moreover, despite the great diversity that already exists among the skeletons of triterpenoids, new variants continue to emerge. Some of the new triterpenoid structures possess novel skeletons and represent unique biosynthetic end products. The majority of triterpenoids possess the conventional skeleton arising from the cyclization of squalene-2,3-epoxide to yield fused polycyclic products. More unusual are the incompletely cyclized compounds, or those exhibiting cyclization within the chain, or two consecutive cyclizations rather than the cyclization beginning at one end. While triterpenoids with rearranged carbocyclic skeletons have been isolated quite frequently, there are some whose skeletons are formed through extensive oxidation accompanied by various bond cleavages.[2,3]

With the aim of identifying new natural compounds with interesting biological activities and of investigating the occurrence of natural terpenoids that could be used as natural sources of intermediates for the synthesis of high-added-value compounds, we examined the plants of the genus *Schisandra*,[4–13] which belongs to the economically and medicinally important family Schisandraceae. A series of novel, highly oxygenated triterpenoids with unusual nortriterpenoid or bisnortriterpenoid skeletons, were isolated and reported in our earlier publications: micrandilactone A (**5**),[6] henridilactones A–D (**6**–**9**),[7] lancifodilactones B–E (**10**–**13**),[8] which possess an unprecedented new nortriterpenoid skeleton with a biosynthetically modified eight-membered ring, lancifodilactone A (**14**)[9] and micrandilactones B and C (**15**–**16**).[10,11] In a continuing search for structurally unique and biogenetically interesting precursors, four new compounds, micrandilactones D–G (**1**–**4**), structurally related to micrandilactone A (**5**), were isolated from the leaves and stems of *S. micrantha* A. C. Smith. As sixteen novel, highly oxygenated compounds with three unique skeletons have not previously been encountered in nature, we proposed the names "schisanartane", "schiartane", and "18-norschiartane" for the three skeletons. Orienting these novel compounds in a triterpene perspective reveals the natural context of the schisanartane, schiartane, 18-norschiartane, and the cycloartane skeletons. In this paper, the isolation, structure elucidation, and plausible hypotheses on the biogenesis of the three new triterpenoid skeletons are discussed.

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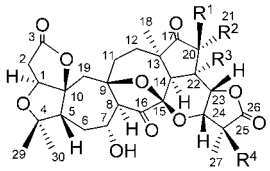
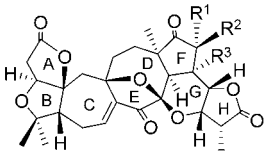
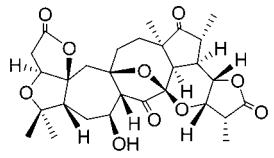


	R^1	R^2	R^3	R^4
1	OH	CH_3	H	H
2	CH_3	OH	H	H
5	OH	CH_3	OH	H
9	CH_3	H	H	H
11	H	CH_3	H	H
13	CH_3	H	H	OH



	R^1	R^2	R^3
3	OH	CH_3	H
6	CH_3	OH	H
7	CH_3	OH	OH
8	H	CH_3	H
12	CH_3	H	H



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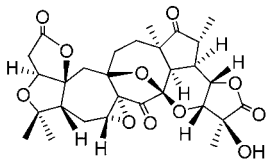

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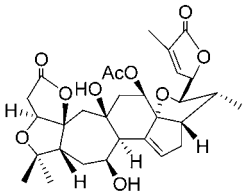

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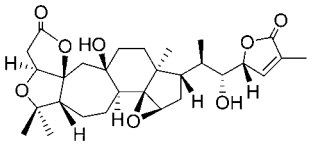

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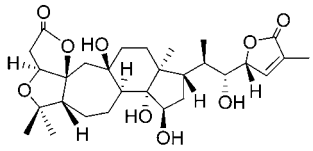

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Results and Discussion

Structure elucidation of micrandilactones D–G (1–4): The molecular composition of micrandilactone D (**1**), $C_{29}H_{36}O_{11}$, was established from HR-EI-MS (*m*/*z* 560.2249) and ^{13}C NMR spectroscopic data. Analysis of the ^1H and ^{13}C NMR (Tables 1 and 2) and HMQC spectra revealed that **1** contains five methyl, five methylene, nine methine, and ten quaternary carbon atoms. The ^1H NMR spectrum exhibited characteristic signals of two proton AB doublets at $\delta_H = 2.19$ and 2.49 ppm with a large coupling constant of $J = 12.7$ Hz attributed to H_2-19. Moreover, a diagnostic oxymethine signal at $\delta_H = 4.50$ ppm (dd, $J = 7.5$, 7.9 Hz) was assigned to the H-7 resonance. Additionally, the signals at $\delta_H = 4.19$ (d, $J = 5.1$ Hz, H-1), 2.87 (dd, $J = 5.1$, 15.0 Hz, H_α-2), and 2.71 ppm (d, $J = 15.0$ Hz, H_β-2) were typical of the ABX-spin-system proton resonances.[6–8] All these signals suggested that compound **1** possessed the same skeleton as micrandilactone A (**5**).

In fact, most of the NMR data for **1** resembled those of **5**. The main differences between the ^{13}C NMR spectra of **1** and **5** were the absence of the signal corresponding to the C-22 oxygenated quaternary carbon atom and the presence of a methine carbon atom ($\delta_C =$ 41.6 ppm). It was therefore suggested that **1** was 22-dehydroxy micrandilactone A. A comparison between the ^1H NMR data of both compounds provided confirmation of the proposed structural assignment. The chemical shift of the H-22 signal ($\delta = 3.16$ ppm), the up-field shift of the H-14 resonance ($\delta = 2.89$, $\Delta\delta_{1,5} =$ 0.42 ppm), the HMBC correlations from Me-21 to C-22, from H-22 to C-15, and from H-14 and H-23 to C-22, as well as the ^1H–^1H COSY spin system H-14/H-22/H-23, confirmed the nature of ring F of **1**. The Me-18 signal ($\delta_H = 0.99$ ppm) resonated at a higher field than the comparable signal in **5** ($\delta_H = 1.58$ ppm) due to the loss of deshielding by the OH-22. Micrandilactone D (**1**) was assigned the same stereochemistry as **5** on the basis of the close relations of all the proton and carbon chemical shifts and proton multiplicities for both compounds.

Micrandilactone E (**2**) was analyzed and its composition found to be $C_{29}H_{36}O_{11}$ by HR-ESI-MS (*m*/*z* 583.2143 $[M+Na]^+$), the same as that of **1**. The ^1H and ^{13}C NMR spectral data of **2** (Tables 1 and 2) were strikingly similar to those of **1**. These similarities, together with the fact that **1** and **2** possess identical molecular formulae, suggested a close relationship between the two compounds. After the assignment of all direct C–H bonds based on HMQC, the large structure of **2** was elucidated as an epimer of **1** at Me-21. In fact, the only significant difference in the ^{13}C NMR spectrum of **2** was the down-field shift of C-20 and C-22 to $\delta_C = 76.4$ and 43.5 ppm (vs $\delta_C = 74.7$, 41.6 ppm in **1**), respectively, and the up-field shift of Me-21 to $\delta_C = 20.6$ ppm (vs $\delta_C = 24.4$ ppm in **1**). These data clearly indicated that **2** and **1** are a pair of epimers at the C-20 position, and that Me-21 has an α-orientation in **1** rather than a β-orientation as in **2**. The β-configuration of Me-21 was also evident from the key ROESY correlations of Me-21/H-23 and Me-21/H-24 (Figure 1).

Abstract in Chinese:

从小花五味子(*Schisandra micrantha*)茎藤部分分离得到了 4 个具有新骨架的高氧化度降三萜：micrandilactones D–G (**1**–**4**)，其化学结构和相对立体化学通过波谱，尤其是 1D 和 2D NMR 解析得到确证。此外，还对从五味子属植物中分离得到的 16 个具有新骨架的高氧化度降三萜和二降三萜的生源途径进行了探讨。

Table 1. ^{1}H NMR spectroscopic data for compounds **1**–**4** in C_5D_5N.[a]

Proton	1	2	3	4
1	4.19 (d, 5.1)	4.32 (d, 6.0)	4.28 (d, 6.3)	4.28 (d, 4.3)
2α	2.87 (dd, 5.1, 15.0)	3.08 (dd, 6.0, 18.6)	3.13 (dd, 6.3, 18.9)	3.19 (dd, 4.3, 14.5)
2β	2.71 (d, 15.0)	2.65 (d, 18.6)	2.77 (d, 18.9)	2.85 (d, 14.5)
5	2.48 (dd, 3.4, 10.3)	2.39 (dd, 6.0, 10.1)	2.18 (overlap)	2.91 (br d, 10.6)
6α	2.08 (m)	2.06 (m)	2.16 (m)	1.64 (m)
6β	2.20 (overlap)			1.79 (m)
7	4.50 (dd, 7.5, 7.9)	4.30 (overlap)	7.06 (dd, 6.8, 7.6)	4.49 (m)
8	2.95 (d, 7.9)	2.72 (d, 9.8)	–	4.05 (d, 7.4)
11α	1.73 (m)	1.77 (m)	1.70 (m)	1.70 (m)
11β	1.98 (m)	1.92 (m)	2.09 (m)	2.00 (m)
12α	1.62 (m)	1.60 (m)	1.46 (m)	1.52 (m)
12β	1.86 (m)	1.92 (overlap)	1.94 (m)	1.82 (m)
14	2.89 (d, 6.5)	2.79 (d, 8.8)	2.87 (d, 9.1)	2.76 (d, 5.5)
18	0.99 (s)	1.23 (s)	1.15 (s)	0.91 (s)
19α	2.49 (AB d, 12.7)	2.52 (AB d, 16.1)	2.34 (d, 2.3)	2.45 (AB d, 13.3)
19β	2.19 (AB d, 12.7)	2.18 (AB d, 16.1)		1.93 (AB d, 13.3)
20	–	–	–	2.55 (m)
21	1.53 (s)	1.68 (s)	1.72 (s)	1.27 (d, 5.5)
22	3.16 (m)	3.33 (d, 8.8)	3.53 (d, 8.8)	2.75 (overlap)
23	4.93 (br s)	5.02 (br s)	5.05 (br s)	4.47 (br s)
24	5.22 (dd, 1.4, 3.2)	5.00 (d, 3.5)	4.74 (dd, 1.8, 2.3)	4.55 (d, 1.6)
25	3.16 (overlap)	3.21 (m)	3.19 (m)	3.01 (m)
27	1.12 (d, 5.8)	1.12 (d, 7.6)	1.61 (d, 7.3)	1.33 (d, 5.9)
29	1.23 (s)	1.32 (s)	1.22 (s)	1.28 (s)
30	1.04 (s)	1.14 (s)	1.03 (s)	1.05 (s)
20-OH	5.40 (s)	4.30 (overlap)	4.42 (s)	–

[a] Data were recorded on a Bruker DRX-500 MHz spectrometer, chemical shift values δ are in ppm, and the coupling constant J is in Hz (in parentheses).

Table 2. ^{13}C NMR spectroscopic data of compounds **1**–**4** in C_5D_5N.[a]

Carbon	1	2	3	4
1	81.4	81.5	80.4	80.3
2	35.0	35.0	35.3	35.9
3	175.1	175.3	175.2	174.8
4	83.9	84.0	83.2	84.3
5	58.1	58.3	57.6	53.5
6	36.4	36.1	23.6	33.8
7	67.7	67.9	135.5	62.9
8	60.1	60.0	137.9	55.3
9	82.2	81.3	82.2	80.5
10	95.7	96.0	94.9	97.1
11	41.3	41.1	39.0	36.4
12	30.7	30.8	31.0	31.5
13	49.3	48.6	49.0	49.9
14	44.8	43.5	44.2	44.6
15	98.1	98.1	98.5	98.9
16	208.2	209.1	198.5	208.7
17	220.0	221.2	221.7	220.3
18	26.6	27.6	28.2	25.7
19	42.4	42.3	42.5	44.5
20	74.7	76.4	76.3	44.0
21	24.4	20.6	20.9	15.1
22	41.6	43.5	43.7	39.9
23	73.6	74.2	74.1	75.2
24	72.4	70.9	70.4	69.1
25	41.7	41.9	42.4	42.0
26	177.6	177.5	177.8	177.9
27	7.7	7.7	8.4	8.2
29	27.7	27.8	27.5	27.9
30	20.9	20.9	20.4	21.0

[a] Data were recorded on a Bruker DRX-500 MHz spectrometer, chemical shifts (δ) are in ppm; assignments were confirmed by ^{1}H–^{1}H COSY, HMQC, and HMBC.

Micrandilactone F (**3**) was isolated as a UV-absorbing substance (λ_{max} = 229 nm), and the molecular formula of $C_{29}H_{34}O_{10}$ was established by HR-ESI-MS and ^{13}C NMR spectra, indicating that it had 18 mass units less than **2**. The ^{13}C NMR spectral data of **3** (Table 2) were very similar to those of **2**, except that two methine signals due to C-7 and C-8 (δ_C = 67.9 and 60.0 ppm) in **2** were replaced by signals for a double bond at δ_C = 135.5 and 137.9 ppm in **3**. These data, and those obtained from HMBC correlations from H-7 to C-6, C-9, and C-16, and from both H_2-6 and H_2-19 to C-8 (Figure 2), fully corroborated the proposed structure of **3** as the 7,8-dehydro derivative of micrandilactone E (**2**).

HR-ESI-MS analysis of micrandilactone G (**4**) demonstrated that it has the molecular formula $C_{29}H_{36}O_{10}$ (*m*/*z* 567.2208 $[M+Na]^+$), which is less than that of **1** by one oxygen atom. The ^{1}H and ^{13}C NMR spectral data (Tables 1 and 2) were analogous to those of **1**. One of the main differences observed in the ^{13}C NMR spectrum was that a signal due to a methine carbon atom (δ_C = 44.0 ppm) at C-20 in **4** was observed in place of the oxygenated quaternary carbon (δ_C = 74.7 ppm) in **1**. Along with the absence of the hydroxyl signal at δ_H = 5.40 ppm, this suggested that the structure of **4** was the 20-deoxy derivative of micrandilactone D (**1**). Moreover, the Me-21 and C-22 signals in the ^{13}C NMR spectrum

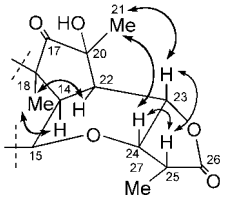


Figure 1. Key ROESY correlations for micrandilactone E (**2**).

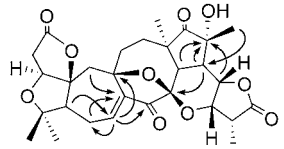


Figure 2. Key HMBC correlations for micrandilactone F (**3**).

were shifted upfield from $\delta = 24.4$ and 41.6 ppm in **1** to $\delta =$ 15.1 and 39.9 ppm in **4**, respectively, in agreement with the above assignment. This assignment was also confirmed by the HMBC correlations observed from H-14 and Me-21 to C-20 and from H-20 to C-22 and C-23 (Figure 3).

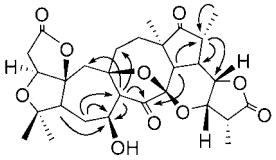


Figure 3. Key HMBC correlations for micrandilactone G (**4**).

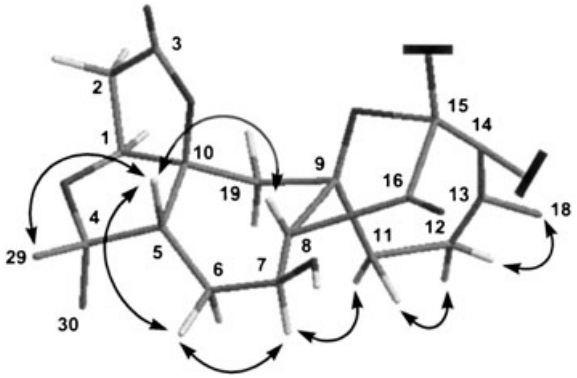


Figure 4. Selected ROESY correlations for **4**. Only key hydrogen atoms have been shown.

Other significant chemical-shift differences observed in **4** with respect to **1** in the NMR spectra were associated with the signals at C-5–C-8 and C-11. HMBC cross peaks observed between H-5 and C-7, between H-6 and C-7 and C-8, and between H-8 and C-7, C-11, C-16, and C-19, fully corroborated the hydroxyl group located at C-7, which was identical to that of **1**. This suggested that the differences between **4** and **1** were to be found in the relative stereochemical orientations of the carbon atoms in the C-5 to C-8 region. The observation of a ROESY correlation (Figure 4) between Me-29 and H-5 established that the stereochemistry at C-5 is the same in both compounds. Meanwhile, the ROESY correlation between H-5 and H-8, and the absence of a correlation between H-5 and H-7 as for those of **1** and **2**, suggested that H-7 is α-oriented and H-8 is β-oriented in **4**, differing from the relative stereochemistry at C-7 and C-8 of **1** and **2**. This proposal was further supported by the downfield chemical shift of H-5 from $\delta = 2.48$ ppm in **1** to $\delta =$ 2.91 ppm in **4** due to the deshielding effect of the 7_β-OH of **4**. Furthermore, a ROESY correlation between H-7 and H_α-11 was consistent with the placement of both protons having an α-configuration. Conformational analysis using a Dreiding molecular model also showed the micrandilactone G structure as depicted in **4**.

Compounds **1**–**4** were inactive when testing for anti-HIV-1 activities and cytotoxicities against human tumor K562 cells.

Possible biogenetic origin of the schisanartane, schiartane, and 18-norschiartane skeletons: Since we reported the first of a new class of triterpenoids, sixteen unique, highly oxidized triterpenoids with unprecedented skeletons have been isolated from three *Schisandra* species: *S. lancifolia*, *S. micrantha*, and *S. henryi* var. *yunnanensis*. Their structures are completely unrelated to any of the compounds isolated from the family Schisandraceae. Interestingly, to date no naturally occurring triterpenoids have been found to have such a highly modified oxidized norcycloartane skeleton. According to the structural features of these compounds, it is likely that three chemotypes exist within the three species, and we proposed the names "schisanartane", "schiartane", and "18-norschiartane" for these new skeletons and a numbering scheme that preserves the numbering of the cycloartane skeletons (Figure 5). Although there is no clear evidence that the complexity of these compounds is necessary rather than fortuitous, the concurrence of highly modified oxidized nortriterpenoid compounds among three *Schisandra* species intrigued us to think rationally about the intrinsic correlations among these three new skeletons and the known cycloartane system. Herein, we are attempting to gain insights into the biosynthetic breadth possible for schisanartane, schiartane, and 18-norschiartane, and propose our own hypotheses for possible biosynthetic mechanisms to trigger further studies and make valuable contributions to our knowledge of triterpenoid chemistry.

The exquisite complexity of the structures of these sixteen novel compounds suggested that specific terpene synthases

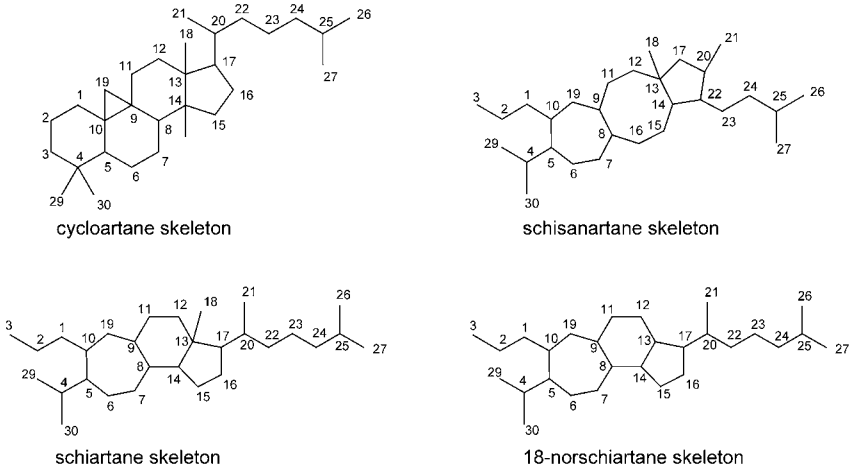


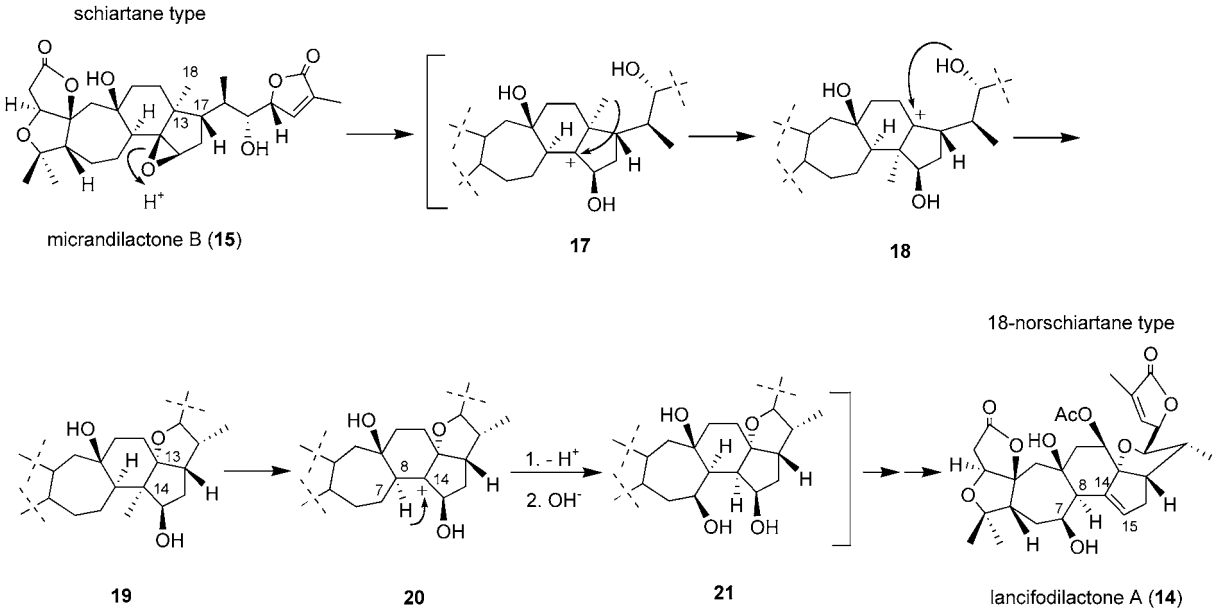
Figure 5. Three new skeletons and the known cycloartane.

and other enzymes strictly control the oxidation, cyclization, rearrangement, and hydride and methyl shifts resulting from different carbocationic intermediates. These enzymes would also display remarkable regio- and stereochemical specificity and could generate compounds with more than 12 stereocenters. The notable stereochemical control and product specificity displayed by these enzymes may arise from their ability to exclude specific reaction pathways, as well as from their ability to promote a discrete single pathway. It was also interesting from the biosynthetic point of view to identify a number of stepwise biogenetic triterpenoid intermediates from three *Schisandra* species. The hypothetical sequence for these sixteen novel compounds (**1**–**16**) shown in Schemes 1, 2, and 3 can be theoretically proposed based on the co-occurrence of the compounds.

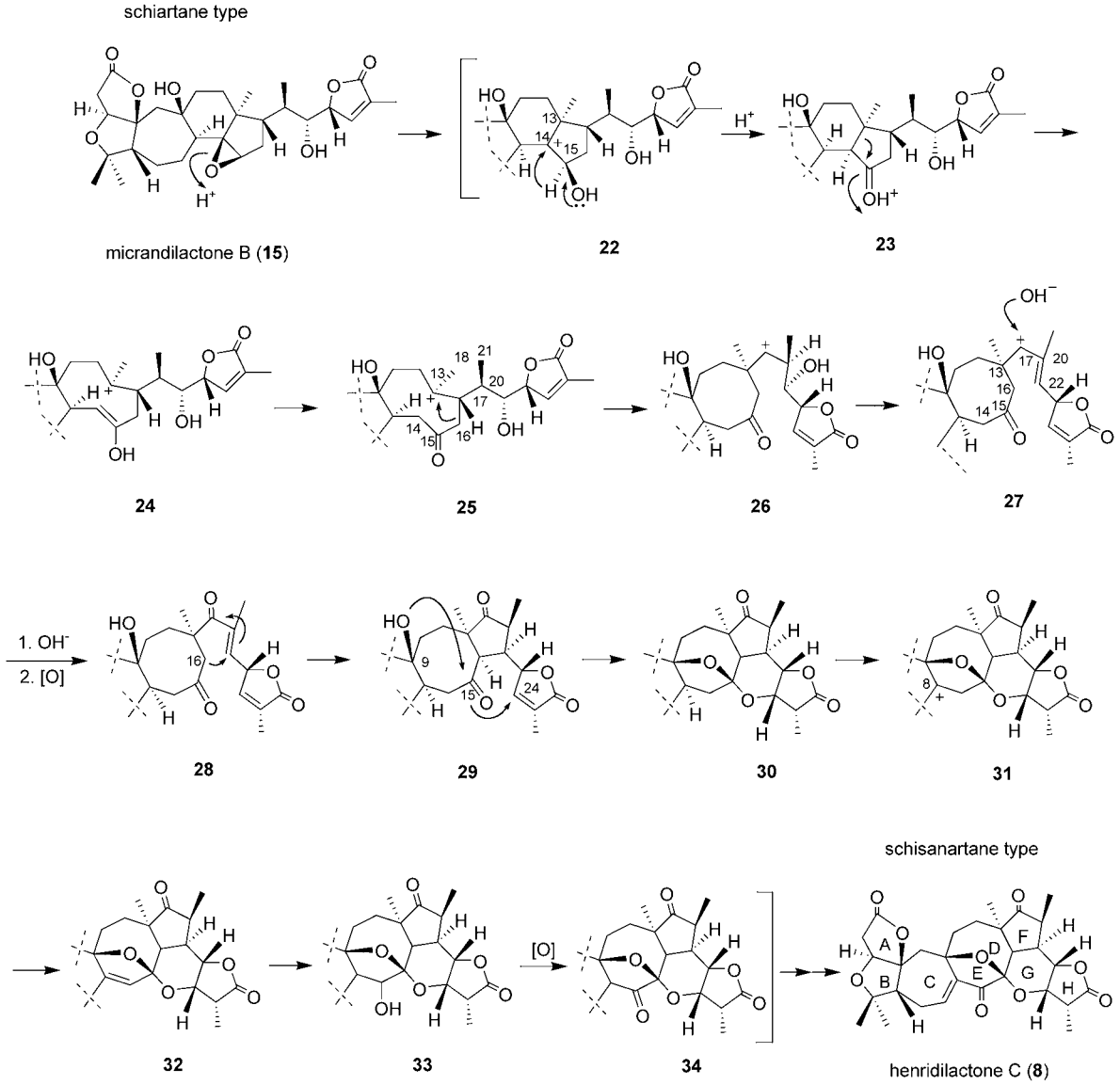
It was considered that the new schiartane skeleton (e.g., **15**)[10,11] should occur early in the scheme at the biogenetic origin of the three novel skeletons because the core skeleton of cycloartane is still preserved. Scheme 1 shows the suggested mechanism, which starts with enzymatic epoxide ring opening of **15**, followed by a 1,2-methyl shift to afford intermediate **18**. Attack of the sidechain OH group on the tertiary cation at C-13 is followed by oxidation of the Me-C-14 group to afford a carboxylic acid, which on decarboxylation gives demethyl derivative **20**. Finally, 1,2-hydride shift, deprotonation, hydration on C-7, dehydration on C-14 and C-15, and acetoxylation on C-12 can yield lancifodilactone A (**14**).

We have noticed that micrandilactones A (**5**) and D–G (**1**–**4**), henridilactones A–D (**6**–**9**), and lancifodilactones B–E (**10**–**13**) are structurally related, so we refer to the entire group of these natural products as schisanartanes. The structures of schisanartanes are most interesting from a biosynthetic point of view because of the unusual arrangement of the eight-membered ring D (Scheme 2). The mechanism proposed for the modification of the schiartane type (i.e., micrandilactone B, **15**) to the schisanartane type of compounds (i.e, henridilactone C, **8**) underscores the fundamental biosynthetic differences from most other cycloartane triterpenoids. The first step would be enzymatic epoxide ring opening similar to the mechanism for lancifodilactone A (**14**) to give the C-14 cation (**22**), which, following a hydride shift, undergoes ring opening to form the nine-membered ring enolic cation **24** and the corresponding ketone structure **25**. The eight-membered ring intermediate **26** might be derived by ring contraction involving migration of the C-16–C-17 bond to the C-13 site. Subsequent dehydration to form the allylic cation **27**, followed by addition of water and oxidation of the resulting alcohol may generate **28**. Subsequent conversion of **28** into **30** may involve three consecutive ring closures between C-16 and C-22, 9-OH and the carbonyl group at C-15, and finally Michael addition on C-24. The intermediate **34** most likely arises from hydride abstraction at C-8 to form cation **31**, followed by deprotonation, hydration, and then oxidation on C-14. Finally, dehydrogenation at C-7,C-8 would provide henridilactone C (**8**).

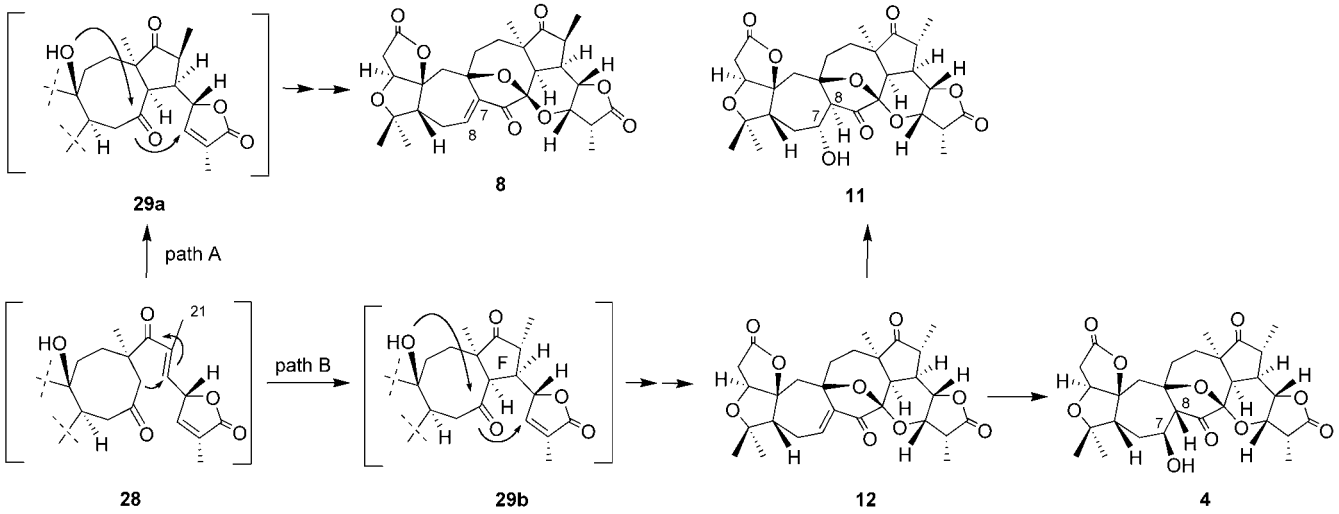
The biogenetic pathway shown in Scheme 3 is an extension of the presentation discussed above for Scheme 2, and suggests some relative configurations of the chiral schisanartanes. We propose that intermediate **28** is a pivotal precursor in the conversion to other structures. Cyclization of **28** to form ring F may proceed through Michael addition of the enolic center at C-16 to the enone center at C-22, affording another enolic intermediate. Subsequent protonation of the enolic center at C-20 yields the epimeric compounds **29a** (path A) or **29b** (path B) with two different orientations of Me-21 at the stereocenter C-20. Compounds **8** and **12** are the first modified eight-membered ring (D) nortriterpenoids



Scheme 1. Plausible biogenetic pathway of the 18-norschiartane type of compounds.



Scheme 2. Hypothetical biogenetic route of schisanartane type of compounds.



Scheme 3. Proposed biogenetic interrelations among the schisanartane compounds.

formed in a biogenetic sequence unique to the family Schisandraceae, and epoxide **10** may be derived from epoxidation of the C-7=C-8 double bond of **12**, and the series **1**–**7**, **9**, **11**, and **13** might be plausibly derived in nature through oxidation and hydration of **8** and **12**. The hydration of the double bond of **12** probably proceeds via a carbocation intermediate, as judged from the two different stereochemistries of C-7 and C-8 (**4** and **11**).

The structures of the *Schisandra* triterpenoids are of interest because the three new schisanartane, schiartane, and 18-norschiartane skeletal types and the known cycloartane skeletal type, co-occur. Lancifodilactones C (**11**) and D (**12**) were produced in all three species (Table 3). Micrandilactone D (**1**) and lancifodilactone E (**13**) were isolated from both *S. lancifolia* and *S. micrantha*, whereas henridilactone A (**6**) was produced by *S. micrantha* and *S. henryi* var. *yunnanensis*. On the other hand, only micrandilactones A–C, E–G (**2**–**5**, **15**, **16**) were obtained from *S. micrantha*, and lancifodilactones A and B (**10** and **14**) were produced exclusively by *S. lancifolia*, whereas only henridilactones B–D (**7**–**9**) were isolated from *S. henryi* var. *yunnanensis*.

Table 3. Comparison of novel triterpenoids from the three *Schisandra* species.

	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**
S. micrantha	+	+	+	+	+	+					+	+	+		+	+
S. lancifolia	+									+	+	+	+	+		
S. henryi						+	+	+	+		+	+				

The results are interesting from a chemotaxonomic and phylogenic point of view. Implicit in the biosynthetic sequences are several "missing" links. This has provided the stimulus for the careful examination of extracts in order to identify the relevant compounds, the structural characteristics of which could be predicted from the biogenetic speculation. Further investigation (including phytochemical and biological studies) of the triterpenoids from this genus is now in progress.

According to The Screening Hypothesis proposed by Jones and Firn,[14] there must have been very significant constraints on the evolution of natural diversity, and the more new chemicals made in a new variant after mutation, the greater the chances are of any one of these chemicals possessing potent, useful biomolecular activity that could enhance the fitness of the producer. So we speculate that the occurrence of three new schisanartane, schiartane, and 18-norschiartane skeletal types of compounds might be produced by the organism to increase its fitness. Further research is needed to shed more light on these hypotheses.

The discovery of three new carbon skeletons adds a new dimension to our understanding of triterpenoid chemistry.

Experimental Section

General: The instrumentation and plant material used in this work were described in our previous paper.[12]

Extraction and isolation: The air-dried and powdered leaves and stems of *S. micrantha* (6.8 kg) were extracted with 70% aqueous Me_2CO (3×20 L, 24 h) at room temperature and the extract was partitioned successively with petroleum ether (2×3 L) and ethyl acetate (EtOAc: 3×5 L). The EtOAc extract (170 g) was subjected to column chromatography (CC) over silica gel (1.5 kg, 100–200 mesh) eluting with a $CHCl_3/Me_2CO$ gradient system (1:0–0:1, 180 L) to give fractions 1–5. Fraction 3 (15 g, $CHCl_3/Me_2CO$ 9:1) was chromatographed on MCI-gel CHP 20P (50–90% MeOH/H_2O, 5 L) to afford three main fractions: 3a–c. Fraction 3b (4 g, 80% MeOH/H_2O) was repeatedly chromatographed over silica gel, using petroleum ether/acetone (9:1), and $CHCl_3$/MeOH (100:1), respectively, to give **1** (54 mg) and **3** (1.5 mg). Compounds **2** (1.4 mg) and **4** (1.1 mg) were further purified by using RP-HPLC with 55% MeOH/H_2O (flow rate 3.0 mL min^{-1}).

Micrandilactone D (1): Colorless prisms; m.p. 183 °C; $[\alpha]_D^{26.3}=+29.15$ ($c=0.22$ in C_5D_5N); ^{1}H and ^{13}C NMR: Tables 1 and 2; MS (70 eV, EI): *m*/*z* (%): 560 (1) $[M]^+$, 542 (23), 532 (33), 514 (80), 499 (23), 472 (25), 454 (65), 426 (30), 314 (36), 187 (59), 155 (55), 91 (57), 69 (92); MS (HR-EI): calcd for $C_{29}H_{36}O_{11}$: 560.2258; found: 560.2249.

Micrandilactone E (2): Colorless prisms; m.p. 156–158 °C; $[\alpha]_D^{25.7}=+42.41$ ($c=0.22$ in MeOH); ^{1}H and ^{13}C NMR: see Tables 1 and 2; IR (KBr): $\tilde{\nu}=$ 3444 (br), 2930, 1774, 1733, 1652, 1239, 1099 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 560 (2) $[M]^+$, 542 (53), 532 (32), 514 (100), 499 (38), 472 (65), 454 (89), 426 (15), 265 (25), 247 (32), 187 (33), 155 (39), 91 (43); MS (HR-ESI): calcd for $C_{29}H_{36}O_{11}Na$: 583.2155; found: 583.2143 $[M+Na]^+$.

Micrandilactone F (3): White solid; $[\alpha]_D^{25.0}=+45.25$ ($c=0.22$ in MeOH); ^{1}H and ^{13}C NMR: see Tables 1 and 2; UV (MeOH): λ_{max} (log ε) = 203.2 (4.32), 229.2 (3.96), 203.2 nm (3.69); MS (70 eV, EI): *m*/*z* (%): 542 (100) $[M]^+$, 527 (11), 514 (25), 499 (15), 471 (15), 454 (44), 275 (28), 215 (18), 189 (30), 151 (43), 91 (43); MS (HR-ESI): calcd for $C_{29}H_{34}O_{10}Na$: 565.2049; found: 565.2041 $[M+Na]^+$.

Micrandilactone G (4): White solid; $[\alpha]_D^{17.4}=+71.43$ ($c=0.11$ in MeOH); ^{1}H and ^{13}C NMR: see Tables 1 and 2; MS (70 eV, EI): *m*/*z* (%): 544 (1) $[M]^+$, 526 (10), 498 (14), 483 (11), 467 (15), 438 (30), 275 (54), 257 (35), 249 (48), 235 (41), 215 (70), 189 (100), 155 (61), 147 (70), 129 (55), 109 (54), 95 (54), 91 (38); MS (HR-ESI): calcd for $C_{29}H_{36}O_{10}Na$: 567.2209; found: 567.2208 $[M+Na]^+$.

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[11] CCDC-236725 (**15**) and -257495 (**16**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
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