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Studies on the Synthesis of *Schisandraceae* Natural Products: Exploring a Cyclopropylcarbinol Ring Expansion Strategy

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Acid mediated cyclopropylcarbinol ring expansion has been shown to be a viable method for the construction of the AB ring framework of lancifodilactone F and related terpenoids of the *Schisandraceae* family of natural products. We found that this rearrangement proceeds with good stereochemical control based on inversion of the C10 cyclopropyl center. Our studies indicate that the *cis*-decalin motif of **31** could be used as a key synthetic precursor of certain *Schisandraceae* metabolites.

Fruits and extracts from the *Schisandraceae* family of plants have been used in traditional Chinese medicine for their immunostimulant and tissue-constricting properties.[1] Efforts to investigate the bioactive constituents of these plants led to the identification of a large family of terpenoids that includes schizandronic acid (**1**),[2] kadsuphilactone B (**2**),[3] nigranoic acid (**3**),[4] lanciphodilactone F (**4**)[5] and micrandilactones A (**5**)[6] and C (**6**)[7] (Figure 1). Most of these natural products possess beneficial antihepatitis, antitumor and antiviral activities. For instance, nigranoic acid (**3**) showed activity on several anti-HIV reverse transcriptase and polymerase assays,[4] while kadsuphilactone B (**2**) was active against hepatitis B virus infection in vitro (IC_{50} = 6 mg/mL).[3] The recently isolated micrandilactone C (**6**) displayed potent activity against HIV-1 replication (EC_{50} = 7.71 mg/mL) with minimal cytotoxicity.[7]

The combination of promising pharmacological profile and novel chemical architecture of *Schisandraceae* natural products has attracted the interest of the synthetic community.[8] From a biosynthetic point of view, these compounds are presumed to arise from a common cycloartane skeleton, integral to the structure of schizandronic acid (**1**), that upon a sequence of plant-specific oxidations, ring expansions and rearrangements could lead to more densely functionalized terpenoids, with exquisite motifs such as the micrandilactones.[9] The opening stages of this biosynthetic proposal could involve conversion of schizandronic acid to natural products **2**, **3** and **4**.[10] Inspired by this concept, we envisioned that oxidation of **7**, reminiscent of the AB motif of schizandronic acid, would form lactone **8** (Scheme 1).

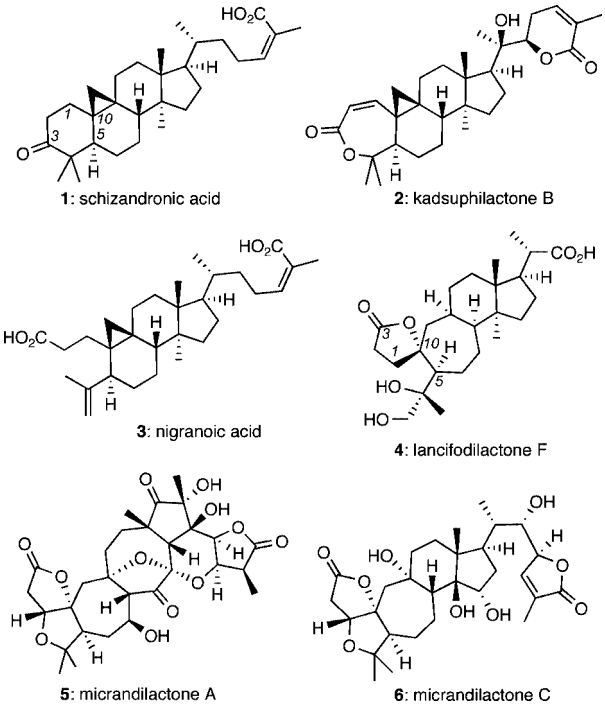

Figure 1. Representative structures of natural products of the *Schisandraceae* family of plants.

Lactone hydrolysis and opening of the cyclopropane ring would then lead to structure **10** which represents the AB ring system of lancifodilactone F. We report here a study on the feasibility of this conversion using simplified scaffolds.

At the onset of this investigation we targeted compound **20**, in which the cyclopropane is embedded in a *trans*-fused decalin motif. The synthesis of **20** is highlighted in Scheme 2, and departed from commercially available 1,4-cyclohexanedione (**11**). Protection of **11** with ethylene glycol produced 90% of the C8 monoketal (schizandronic acid

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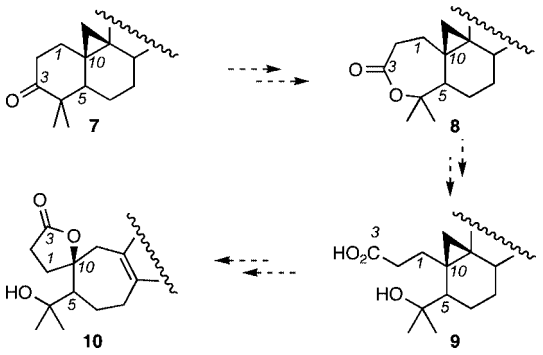
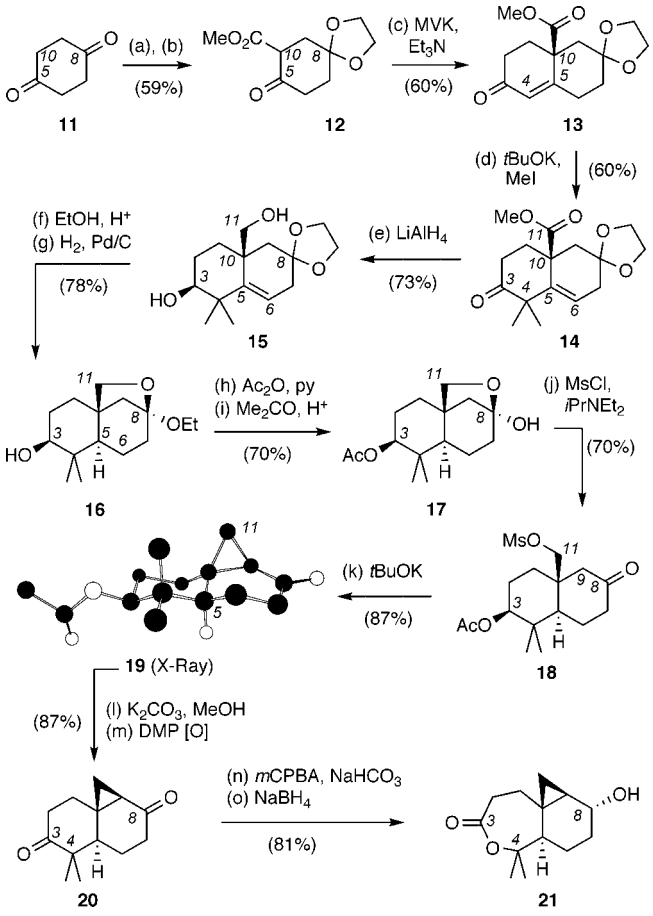


Scheme 1. Proposed biosynthetic pathway for the conversion of schizandronic acid to other related natural products.

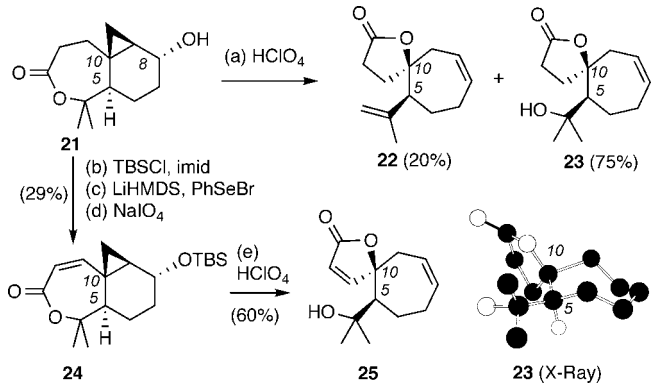
numbering) after recycling the concomitantly formed diketal.[11] Alkylation of the C5 enolate with methyl cyanoformate, followed by Robinson annulation of the resulting β-oxo ester **12** with methyl vinyl ketone, furnished enone **13** (39% combined yield). Treatment of **13** with potassium *tert*-butoxide produced the vinylogous enolate that upon dimethylation at C4 formed **14** (60% yield). Reduction of **14** with lithium aluminium hydride provided diol **15** in good yield. Conversion of **15** to the corresponding C8 ethyl ketal, followed by hydrogenation of the C5–C6 double bond from the more accessible α-face gave rise to **16** (78% combined yield). After acetylation of the C3 hydroxy group, compound **16** was converted to hemiacetal **17** (70% combined yield). Mesylation of **17** produced compound **18** (70% yield after recycling of the secondary mesylate) that, upon treatment with potassium *tert*-butoxide, provided the cyclopropyl ring of **19** (87% yield).[12] The structure of **19** was unambiguously confirmed by a single-crystal X-ray diffraction analysis.[13] Deprotection of the C3 acetoxy group and oxidation of the resulting alcohol gave rise to the desired ketone **20**. Much to our delight, under standard Baeyer–Villiger conditions compound **20** was oxidized selectively across the C3–C4 bond in excellent yield (95%). Reduction of the C8 carbonyl group then produced **21** as a single stereoisomer (85% yield). The stereochemistry of the resulting cyclopropylcarbinol was tentatively assigned by comparison with the ^{1}H NMR spectra of related structures.[14]

With cyclopropylcarbinol **21** in hand, we studied the conditions for the cyclopropane ring expansion reaction (Scheme 3). Treatment of **21** with $BF_3{\cdot}Et_2O$ under anhydrous conditions produced only 20% of **22** in conjuction with several unidentified products.[15] Aqueous acids produced better results favoring the formation of compound **23**. The best results were obtained upon treatment of **21** with 7% aqueous $HClO_4$ in acetonitrile at room temperature, and gave rise to alcohol **23** (75% yield) along with the dehydrated compound **22** (20% yield).[16] The structure of **23** was confirmed through X-ray crystallography.[13] These conditions were also successfully applied to compound **24** that afforded spirolactone **25** in 60% yield. However, it should be noted that similar attempts to open the cyclopropyl ring of the Baeyer–Villiger adduct of **20** were unsuccessful.

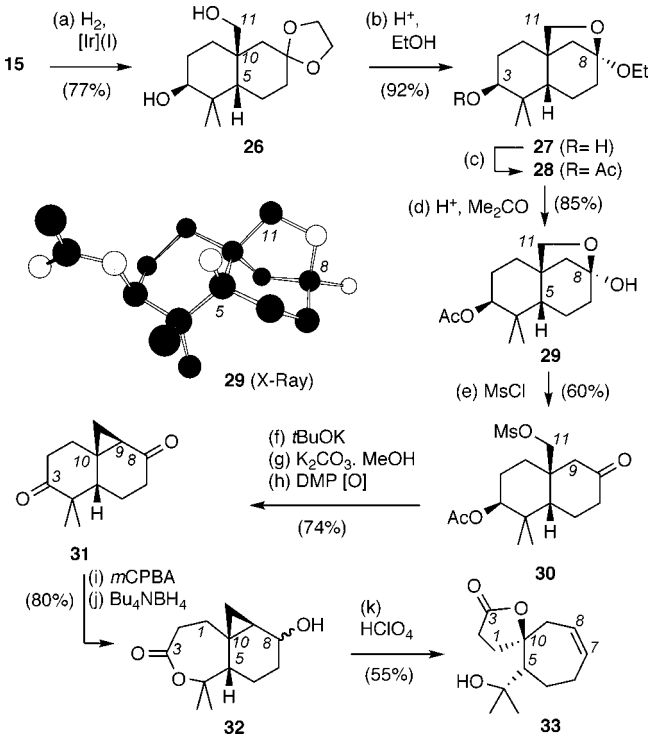


Scheme 2. Reagents and conditions: (a) ethylene glycol (1.3 equiv.), *p*TsOH (0.09 equiv.), benzene, 100 °C, 1.5 h, 35% (90% after recycling); (b) LDA (1.2 equiv.), methyl cyanoformate (1.2 equiv.), HMPA (1.0 equiv.), THF, 0 °C, 1 h, 65%; (c) Et_3N (0.35 equiv.), MVK (1.8 equiv.), MeOH, 25 °C, 40 h, 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) *p*TsOH (0.1 equiv.), EtOH, 100 °C, 20 min, 84%; (g) 10% Pd/C (0.1 equiv.), H_2 (1 atm), EtOH, 25 °C, 12 h, 93%; (h) Ac_2O (3.0 equiv.), pyridine (10 equiv.), CH_2Cl_2, 25 °C, 48 h, 85%; (i) *p*TsOH (0.2 equiv.), wet acetone, 25 °C, 45 min, 82%; (j) *i*Pr_2NEt (1.2 equiv.), MsCl (1.1 equiv.), CH_2Cl_2, 25 °C, 10 h, 40% (70% after recycling); (k) *t*BuOK (1.2 equiv.), benzene, 25 °C, 1.5 h, 87%; (l) K_2CO_3 (1.1 equiv.), wet MeOH, 25 °C, 12 h, 90%; (m) DMP (1.3 equiv.), CH_2Cl_2, 25 °C, 1.5 h, 97%; (n) *m*CPBA (1.5 equiv.), $NaHCO_3$ (2.0 equiv.), CH_2Cl_2, 0 °C, 6 h, 95%; (o) $NaBH_4$ (0.5 equiv.), THF, 0 °C, 4 h, 85%. *p*TsOH: *p*-toluenesulfonic acid monohydrate, LDA: lithium diisopropylamide, HMPA: hexamethylphosphoramide, THF: tetrahydrofuran, MVK: methyl vinyl ketone, LAH: lithium aluminum hydride, MsCl: methanesulfonyl chloride, DMP: Dess–Martin periodinane.

The above studies demonstrate that the lactonization/cyclopropyl ring expansion process occurs with inversion of stereochemistry at the C10 center. These results are in agreement with literature data reporting stereoselective solvolytic cyclopropyl ring expansions in similar substrates.[16,17] It should be noted that the chemical origins of the observed selectivity have not been unambiquously defined, although intimate ion pair,[18] non-classical ions and neighboring group or anchimeric effects have been pro-



Scheme 3. Reagents and conditions: (a) 7% $HClO_4$ (1.0 equiv.), acetonitrile, H_2O, 25 °C, 1.5 h, 75% of **23** and 20% of **22**; (b) TBSCl (2.0 equiv.), imidazole (3.0 equiv.), DMAP (0.2 equiv.), DMF, 25 °C, 14 h, 92%; (c) LiHMDS (2.5 equiv.), PhSeBr (2.0 equiv.), THF, –78 °C, 1.5 h, 48%; (d) $NaIO_4$ (2.0 equiv.), THF/H_2O (1:1), 0 °C, 2 h, 65%; (e) $HClO_4$ (1.0 equiv.), acetone, H_2O, 25 °C, 2.0 h, 60%. LiHMDS: lithium bis(trimethylsilyl)amide, TBSCl: *tert*-butyldimethylsilyl chloride, DMAP: 4-(dimethylamino)-pyridine, DMF *N*,*N*-dimethylformamide.



Scheme 4. Reagents and conditions: (a) $[Ir(Cod)Py(PCy_3)]PF_6$ (0.04 equiv.), H_2 (1 atm), CH_2Cl_2, 25 °C, 5 h, 77%; (b) *p*TsOH (0.05 equiv.), EtOH, 40 °C, 30 m, 92%; (c) AcCl (1.5 equiv.), DMAP (0.07 equiv.), pyridine/CH_2Cl_2 (1:1), 25 °C, 1.5 h, 90%; (d) *p*TsOH (0.15 equiv.), acetone, 40 °C, 2 h, 85%; (e) *i*Pr_2NEt (1.3 equiv.), MsCl (1.3 equiv.), CH_2Cl_2, 0 °C, 5 min, 30% (60% after recycling); (f) *t*BuOK (1.5 equiv.), benzene, 25 °C, 4 h, 95%; (g) K_2CO_3 (1.2 equiv.), NaOMe (0.05 equiv.), MeOH, 25 °C, 24 h, 82%; (h) DMP (1.3 equiv.), CH_2Cl_2, 25 °C, 30 min, 95%; (i) *m*CPBA (1.5 equiv.), $NaHCO_3$ (4.1 equiv.), CH_2Cl_2, 0→25 °C, 8 h, 98%; (j) Bu_4NBH_4 (5.0 equiv.), CH_2Cl_2, 0→25 °C, 8 h, 82%; (k) $HClO_4$ (1.0 equiv.), acetone, H_2O, 25 °C, 1.5 h, 55%.

posed in certain cases.[16,17] Nonetheless, the relative stereochemistry of **22**, **23**, and **25** did not match that found in the structures of lancifodilactone and micrandilactones.

This observation led us to consider inverting the stereochemistry at the C5 center. In principle this would require hydrogenation of **15** from the top face. To this end, diol **15** was treated under a variety of hydrogenation conditions designed to take advantage of the directing effect of the C11 hydroxy group. Best results were obtained with Crabtree's catalyst,[19] which provided **26** in 77% yield (Scheme 4). Compound **26** was then converted to hemiacetal **29** according to the reaction sequence described previously. A single-crystal X-ray diffraction analysis of **29** confirmed the *cis* stereochemistry of the decalin ring.[13] Conversion of **29** to cyclopropyl ketone **31** was accomplished by a sequence of four steps that included: mesylation of the C11 hydroxy group, formation of the C9–C11 bond with *t*BuOK, and deprotection/oxidation of the C3 hydroxy group (45% combined yield). Baeyer–Villiger oxidation of **31**, followed by selective reduction of the C8 carbonyl group, formed cyclopropyl carbinol **32** as a 1:1 mixture of stereoisomers at the C8 center. Treatment of **32** with $HClO_4$ then produced compound **33** along with small amounts of the dehydration product. Compound **33** was found to have the desired (lancifodilactone) stereochemistry at the C5 and C10 centers.

In conclusion, inspired by the proposed biosynthesis of the *Schisandraceae* metabolites, we studied a novel acid-mediated cyclopropylcarbinol ring-expansion reaction as the key rearrangement for the construction of the AB-ring system of lancifodilactone F and related terpenoids. We found that this rearrangement proceeds with good stereochemical control defined by inversion of configuration at the C10 cyclopropyl center. In turn, this illustrates that the desired stereochemistry at the C5 and C10 centers of the lancifodilactone F framework can be installed departing from decalin **31** in which the C5 hydrogen atom and the C10 cyclopropyl ring are *cis* to each other. Our observations enhance the synthetic potential of carbocationic rearrangements in stereocontrolled syntheses. In addition, our studies pave the way for a potentially biomimetic synthesis of selected *Schisandraceae* natural products.

Supporting Information (see footnote on the first page of this article): Experimental procedures and characterization data for compounds **19**–**23**, **25** and **31**–**33** and ^1H and ^{13}C NMR spectra of compounds **15**, **16**, **18**–**25**, **27**, **28**, and **30**–**33**.

Acknowledgments

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