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First asymmetric synthesis of both enantiomers of andirolactone

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Abstract—We have achieved the first asymmetric synthesis of (+)- and (−)-andirolactone. The key steps were separation of limonene oxide diastereomers, asymmetric oxidation induced by the chiral intermediate and ring-closing metathesis in the presence of catalytic amounts of Lewis acid to form the spirocyclic butenolides.

The spirocyclic butenolide core is found in a number of pharmacologically relevant natural products. Many examples such as chlorotricolide[1a,b] and hydnuferruginine[1c] (Fig. 1) possess a spirocyclic butenelide core, and show excellent biological properties. Considerable efforts have been devoted to the chemical synthesis of these compounds in the past decades due to their interesting antibiotic activity and attractive molecular structure.

Andirolactone (**1**), a spirocyclic butenolide natural terpenoid with potential biological and medicinal properties, was isolated from wood of the libanese cedar (*Cedrus libanotica*).[2] The interesting structure and biological activity of the andirolactone have drawn much attention to the synthetic community, and several groups have developed different approaches to construct the attractive natural products.[3] To date, several total syntheses of andirolactone have been reported; however, all of them are racemic synthesis. Srikrishna and Sharma reported the first synthesis of andirolactone,[3a] which was carried out following a radical cyclization approach to form the spirolactone ring. The method was later improved by Krause[3b] by using the propynoate/cuprate method. Larock and co-workers[3c] prepared the target molecule using the palladium promoted cyclization of acyclic allylic esters of chloromercurio-acetic acid. Recently, Tamariz and co-workers,[3d] Quayle and Ward,[3e] and Ortuno[3f] have also published their elegant approaches to this natural product. We report herein the first asymmetric synthesis of **1** through ring-closing metathesis (RCM) reaction[4] from cheap, commercially available starting materials. In particular, we wish to develop a method for the introduction of spirocyclic butenolide as a chiral building block.

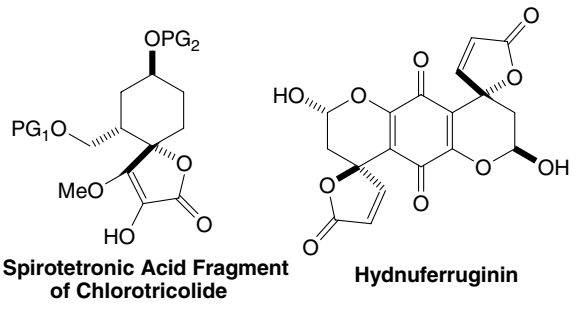

Figure 1. Some bioactive natural products containing spirocyclic butenolide units.

The retrosynthesis, outlined in Scheme 1, was based on the application of RCM as the key cyclization step that favored the formation of the spirocyclic butenolide. Preparation of diene (+)-**6**, the cyclization precursor, involved stereospecific oxidation of epoxide (−)-**3** with selenium dioxide, which in turn would be obtained by separation of the commercially available (1:1) diastereomeric mixture of limonene oxides.

Our general approach to (+)-andirolactone **1** is outlined in Scheme 2. The mixed *cis* and *trans* epoxides (−)-**2**[5] were converted to (−)-**3** (dr > 20:1, by ^{1}H NMR

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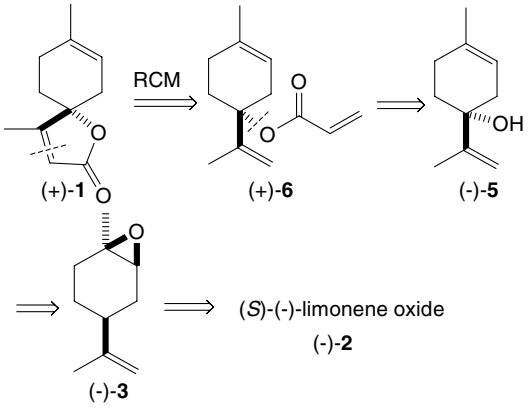
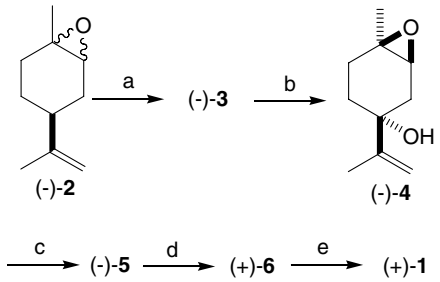


Scheme 1. Retrosynthetic analysis.

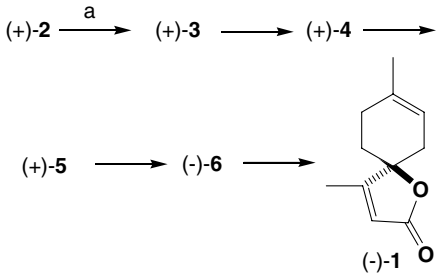


Scheme 2. Reagents and conditions: (a) Ref. 5; (b) Ref. 7; (c) Ref. 8; (d) CH_2=CHCOCl, *i*-Pr_2NEt, CH_2Cl_2, rt, 24 h, 56%; (e) $RuCl_2$(=CHPh)(PCy_3)$_2$, CH_2Cl_2, 35 °C, 48 h, 63%.

analysis) and in 54% theoretical overall yield through five steps following the procedure of Newhall.[6] The hydroxy group with retention of configuration at C-4 was introduced by the reaction of (−)-**3** with *t*-BuOOH in the presence of SeO_2.[7] The oxirane ring of the epoxy alcohol (−)-**4** was then removed to yield (−)-**5** by a modified procedure of Cornforth et al.[8] It needs to be pointed out that the oxirane ring was critical for the stereoselectivity. For example, direct treatment of optically active limonene with SeO_2 leads to the racemic alcohol **5**.[9] Esterification of (−)-**5** was carried out using acryloyl chloride and *i*-Pr_2NEt in CH_2Cl_2 to accomplish the synthesis of precursor (+)-**6** for RCM reaction. When triethylamine was used in this esterification reaction, it did not proceed smoothly even under reflux conditions.

Having secured good access to this key intermediate (+)-**6**, we attempted the cyclization of the spirocyclic butenolide entity by RCM reaction. Although electron deficient alkenes in general and acrylates in particular are known to be problematic substrates for this kind of transformation.[10] We were pleased to find that the cyclization proceeds smoothly with catalytic amounts of first generation Grubbs' catalyst in the presence of catalytic amounts of Ti(O*i*-Pr)$_4$.[10b]

The spectroscopic data of synthetic (+)-**1**[11] were in good agreement with those recorded for both natural[2] and synthetic racemic andirolactone[3] except for their specific optical rotations. Whereas synthetic (+)-**1** showed $[\alpha]_D^{20}$ +100 (*c* 2.6, $CHCl_3$), the $[\alpha]_D^{25}$ value of natural **1** was reported to be +3.2 (*c* 2.1, $CHCl_3$). The strong discrepancy between the natural product and compound (+)-**1** suggested that natural **1** might be a mixture of two enantiomers or a contaminant with impurities. The result suggested a difference in the optical property and promoted us to prepare the corresponding enantiomer (−)-**1** to clarify this situation.



Scheme 3. Reagents and conditions: (a) Ref. 12.

The synthesis of (−)-**1**, summarized in Scheme 3, required the use of (*R*)-(+)-limonene oxide as the starting material. This enantiomer was synthesized following the similar sequence shown in Scheme 2. Kinetic resolution of a mixture of the (*R*)-(+)-limonene oxide (+)-**2** with 0.15 equiv of pyrazole and 30 equiv of water afforded *trans*-limonene oxide (+)-**3** (dr > 20:1)[12] in 77% of the theoretical yield. Following the procedure for the preparation of (+)-**6**, the *trans*-limonene oxide (+)-**3** was transformed into diene (−)-**6** in 28% overall yield (3 steps). Ring-closing olefin metathesis of (−)-**6** provided (−)-**1**[13] {$[\alpha]_D^{20}$ −99 (*c* 1.3, $CHCl_3$)} in 66% yield.

Now, we have both enantiomers in hand, which specific rotations showed opposite. To determine the absolute stereochemistry of natural andirolactone, the ee of synthesized (+)-**1** and (−)-**1** were measured by chiral HPLC, which showed 86% ee for (+)-**1** and 89% ee for (−)-**1**.[14] On the basis of the present data, we suggested strongly that natural **1** was reported as a racemate based on the specific optical rotation. Although there was a strong discrepancy in the optical rotation, this discrepancy is similar to what has been found for other compounds.[15]

In summary, we have achieved the first asymmetric synthesis of both enantiomers of andirolactone and provided (+)-**1** in 5.5% overall yield and (−)-**1** in 7.0% overall yield from (*S*)-limonene oxide and (*R*)-limonene oxide, respectively. Stereoselective introduction of the tertiary hydroxyl group by substrate controlled allylic oxidation and ring-closing metathesis afforded spirocyclic butenolide in an asymmetric fashion. This approach may provide an alternative access to the spirocyclic butenolide analogs.

Acknowledgments

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11. *The spectroscopic data of the (+)-andirolactone*: $[\alpha]_D^{20}$ +100 (*c* 2.6, $CHCl_3$); IR (film): $\nu_{max} = 2918$, 1750, 1644, 1438, 1383, 1318, 1273, 1245, 1215, 1195, 1092, 1065, 1026, 960, 943, 877, 847, 798, 774 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.63–1.68 (1H, m, CH_2), 1.73 (3H, s, CH_3), 1.87–2.10 (3H, m, $2CH_2$), 2.04 (3H, s, CH_3), 2.34–2.53 (2H, m, CH_2), 5.38 (1H, s, CH=), 5.76 (1H, s, CH=); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.2, 23.3, 26.8, 29.7, 33.0, 87.1, 116.2, 116.4, 133.8, 172.2, 172.6 ppm; LRMS (EI) *m/z*: 178 (15.7%, M^+), 163 (7.0), 145 (5.6), 111 (32), 91 (4.2), 82 (7.1), 68 (100), 67 (42), 39 (22); HRMS (ESI) calcd for $C_{11}H_{15}O_2$: 179.1067, found for $[M+H]^+$: 179.1061.
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14. The ee of both enantiomers were determined by chiral HPLC using the following conditions: Chiralpak AD-H column, 10% 2-propanol in hexane, flow rate: 0.5 mL/min retention time of (+)-**1** is 14.3 min and (−)-**1** is 15.6 min.
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