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First Asymmetric Total Syntheses and Determination of Absolute Configurations of (+)-Eudesmadiene-12,6-olide and (+)-Frullanolide

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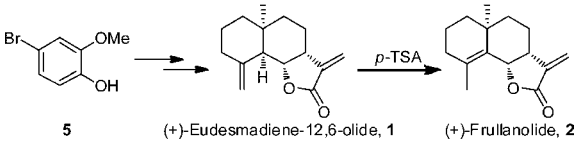
ABSTRACT



The first asymmetric total syntheses of sesquiterpene lactones (+)-eudesmadiene-12,6-olide (1) and (+)-frullanolide (2) have been accomplished from 4-bromo-2-methoxyphenol (5) in 12 and 13 synthetic steps, respectively, and the absolute configurations of these two natural products were determined.

(+)-Eudesmadiene-12,6-olide (**1**) was isolated from the plant of the *Frullania muscicol* in 1994 by Sim-Sim and co-workers.[1a] Recently, it has been found to have *in vivo* antitrypanosomal activity against *Trypanosoma brucei brucei* GUTat 3.1, with an EC_{50} value of 0.18 g/mL, and cytotoxicity against the MRC-5 cell in a concentration of 6.5 g/mL (EC_{50}).[1b] (+)-Frullanolide (**2**) is an allergy-producing substance that occurs in certain plant material of the *Frullania tamarisci* (L.).[2] Compounds **1** and **2** are densely oxygenated members of the eudesmanolide family of sesquiterpene lactones, which also include their stereoisomers arbusculin B (**3**) and critonilide (**4**, Figure 1).[3] α-Methylene-γ-butyrolactones, which are a very often encountered skeleton, have biological activity such as allergenic activity,[2a,c] exhibiting growth-inhibitory activity *in vivo* against animal tumor systems and *in vivo* against cells derived from human carcinoma of the nasopharynx (KB),[4] or effecting regulation of plant growth and anti-mitotic activity.[5]

Several methods have been reported for the synthesis of (±)-frullanolide (**2**).[6] A convergent route to α-substituted acrylic esters and application to the total synthesis of (±)-frullanolide was developed by Still and co-workers in 1977.[6a] Later, Petragnani et al. reported a synthesis of (±)-frullanolide from 2-phenylselenopropanoic acid.[6d,e] Subsequently, Clive and co-worker developed an elegant synthesis of (±)-frullanolide from hydronapthalene derivatives.[6g] However, syntheses of eudesmadiene-12,6-olide and chiral (+)-frullanolide are still lacking. We are

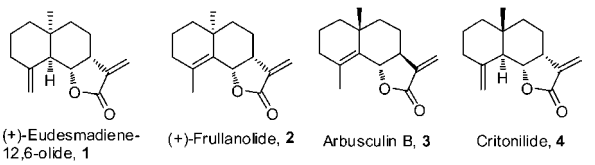


Figure 1. Various types of eudesmanolide family of sesquiterpene lactones.

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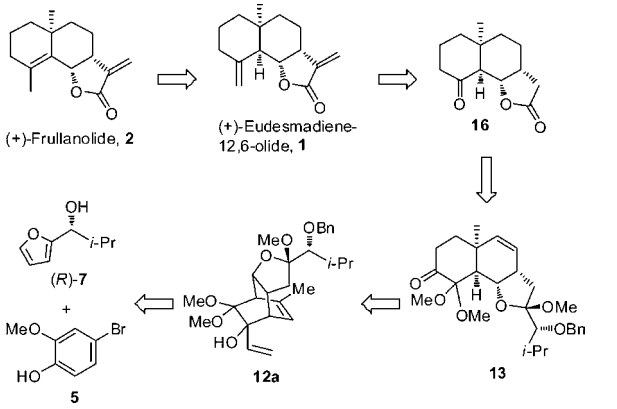
interested in the molecules (+)-eudesmadiene-12,6-olide (**1**) and (+)-frullanolide (**2**) because of their significant biological activities and structural characteristics, their substituents possessing all *cis*-configurations, and their absolute configurations which, to our knowledge, are not yet known, and we wish to develop a more general and highly stereocontrolled total synthetic method.

Masked *o*-benzoquinones (MOBs),[7] a highly reactive class of cyclohexa-2,4-dienones with extensive utility, can be easily generated in situ by oxidation of the corresponding 2-methoxyphenols with hypervalent iodine reagents[8] such as diacetoxyiodobenzene (DAIB) in the presence of an appropriate alcohol. In the course of our investigations on the Diels–Alder reactions of MOBs, we developed a flurry of synthetic strategies to synthesize natural and unnatural products.[9] Recently, we published intriguing results from a highly diastereoselective and asymmetric Diels–Alder protocol of MOBs leading to highly functionalized and novel tricyclic ring systems with multiple stereogenic centers[10] and disclosed the results of photooxygenation reactions of

Scheme 1. Retrosynthetic Analysis of **1** and **2**



MOBs affording a variety of functionalized cyclopentenones.[11] We have also developed a three-step synthesis of optically pure bicyclo[2.2.2]oct-5-en-2-ones via carbohydrate-templated asymmetric intramolecular Diels–Alder reactions of MOBs[12] and reported the syntheses of optically pure conduramines via a hetero-Diels–Alder reaction of MOBs with homochiral nitroso dienophiles.[13] We herein report the first asymmetric total synthesis of sesquiterpene lactones (+)-eudesmadiene-12,6-olide (**1**) and (+)-frullanolide (**2**) using an MOB strategy and the determination of their absolute configurations.

Retrosynthetically, the tricyclic compound **13** constitutes the key building block for the syntheses of **1** and **2**. Logically, the intermediate **13** could be conceived by a protocol involving the anionic oxy-Cope rearrangement from bicyclo[2.2.2]octenone **12a** which could be formally envisioned by the asymmetric intermolecular Diels–Alder reaction of the corresponding MOB derived from 4-substituted 2-methoxyphenol (**5**) with homochiral furan (*R*)-**7**. Here the furan behaves as a dienophile rather than a diene, as well as a precursor of the γ-butyrolactone moieties in **1** and **2**, followed by coupling and Grignard reactions (Scheme 1). The chemoselective addition of the homodiene of the MOB onto the less substituted double bond of furan (*R*)-**7** will control the proper regiochemistry of the γ-butyrolactone ring; the endoaddition will dictate all *cis*-configurations of substituents in **1** and **2** after the anionic oxy-Cope rearrangement. The facially selective addition from the less hindered side of furan (*R*)-**7** will ensure the high diastereoselectivity in **13** and eventually result in the high enantioselective formation of **1** and **2**. Thus the design will be a short and efficient entry to **1** and **2** with anticipated high chemo-, regio-, stereo-, and diastereoselectivities.[14]

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Scheme 2. Synthesis of Key Intermediate **13**

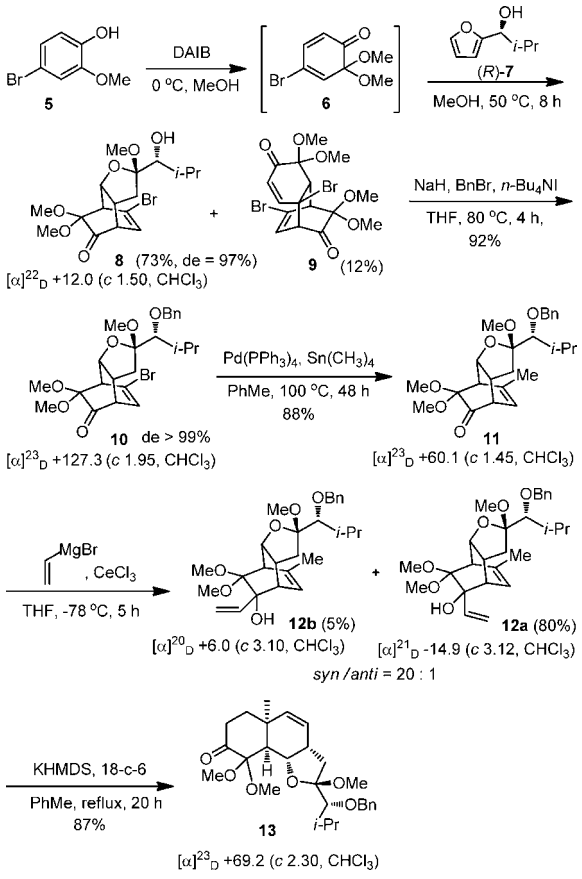
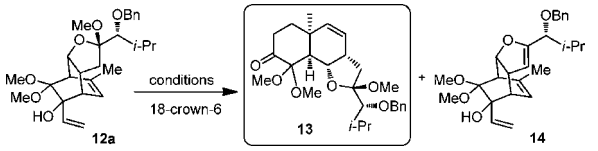


Table 1. Optimization of Reaction Conditions for the Anionic Oxy-Cope Rearrangement of **12**



entry	base/ equiv	solvent	t (h)	T (°C)[a]	products/ yields (%)[b]
1	KH/5	THF	24	rt	–[c]
2	KH/5	THF	24	80	–[c]
3	KHMDS/5	THF	24	80	**12a** /70 + **14** /15
4	KHMDS/5	PhMe	24	100	**12a** /30 + **13** /50
5	KHMDS/5	PhMe	20	130	**13** /87

[a] Oil bath temperature. [b] Isolated yields after silica gel column chromatography. [c] Recovered starting material.

Initially we planned to use 4-methyl-2-methoxyphenol as a starting material to address the possibility of an efficient construction of functionalized bicyclic compound **12a**; however, the corresponding MOB did not add to homochiral furan (*R*)-**7**[15] but proceeded mainly with dimerization.[16] Thus we tried a detour strategy[17] and started with the intermolecular Diels–Alder reactions of MOB **6** prepared in situ from commercially accessible 4-bromo-2-methoxyphenol (**5**) in the presence of DAIB and homochiral furan (*R*)-**7** to obtain Diels–Alder adduct **8** in 73% yield with 97% de; the chemical yield of **8** is due to the formation of dimer **9** (Scheme 2).[10] Compound **8** was treated with benzyl bromide, in the presence of tetrabutylammonium iodide, and sodium hydride at 80 °C for 4 h to give the benzylated product **10** in 92% yield which, upon simple recrystallization, was obtained in high de (> 99%). The homochiral **10** is a viable substrate for the cross-coupling reaction to afford **11**, in excellent yield, which was treated with a vinylmagnesium bromide–cerium(III) chloride reagent system to generate *syn*-**12a** and *anti*-**12b** (20:1) in 80% and 5% isolated yields, respectively.[18]

With compound **12a** in hand, we screened with KH and KHMDS under various conditions; the best results were obtained when **12a** was treated with KHMDS and 18-crown-6 in refluxing toluene to give *cis*-decalin **13** in 87% yield via anionic oxy-Cope rearrangement (Table 1, Scheme 2).[19] The relative configuration was confirmed with nuclear Overhauser enhancement experiments (NOE, Figure 2) and X-ray diffraction studies (Figure 3 for ORTEP diagram and CCDC 900657). The absolute stereochemistry with four stereogenic centers (5*S*,6*S*,7*R*, 10*R*) of **13** was thus determined accordingly as the chiral center C-13 derived from the corresponding part of homochiral furan (*R*)-**7** maintaining the same configurations. All the products were well characterized with their spectral data (see Supporting Information).

The key intermediate **13** under the Huang-Minlon reduction conditions[20] provided enol ether **15**, which was further transformed into **16** in 75% yield via tandem reactions including hydrolysis of the enol ether, hydrogenation of the double bond and the hydrogenolysis of the benzyl group, and sodium periodate mediated oxidative–elimination reactions. After having compound **16** in hand, we tried with several reagents to convert its carbonyl group into the methylene group of **17**; the best results were obtained when compound **16** was treated with the Takai reagent[21] in THF/CH_2Cl_2 at 0 °C (Table 2, Scheme 3).

To achieve the synthesis of our target molecule (+)-eudesmadiene-12,6-olide **1**, compound **17** was treated with paraformaldehyde[3b,22] in the presence of sodium hydride

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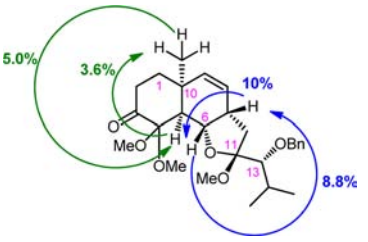


Figure 2. ^{1}H NMR studies of NOE (%) for **13**.

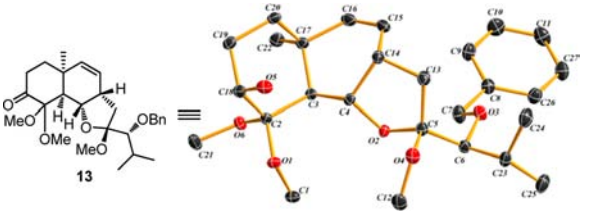
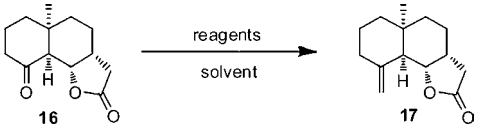


Figure 3. ORTEP diagram of key intermediate **13**.

Table 2. Survey of Reaction Conditions to Transform **16** into **1**



entry	reagents	solvent	T (°C)[a]	t (h)	yield (%)[b]
1	CH_3PPh_3Br, NaH	THF	0 °C to rt	5	40
2	CH_3PPh_3Br, KO*t*Bu	THF	0 °C to rt	7	35
3	CH_3PPh_3Br, *n*BuLi	THF	0 °C to rt	8	42
4	CH_3PPh_3Br, *n*BuLi	THF	−78 °C to rt	8	44
5	Zn, CH_2I_2, $TiCl_4$	THF/CH_2Cl_2	rt	15	53
6	Zn, $PbCl_4$, CH_2I_2, $TiCl_4$	THF/CH_2Cl_2	−78 °C to rt	20	71
7	Zn, $PbCl_4$, CH_2I_2, $TiCl_4$	THF/CH_2Cl_2	0 °C to rt	24	78

[a] Oil bath temperature. [b] Isolated yields after silica gel column chromatography.

to produce the desired compound **1** in 68% yield. Finally, **1** was converted into another important sesquiterpene lactone (+)-frullanolide **2** in the presence of *p*-toluenesulfonic acid (Scheme 3).[23] The spectral data and the specific rotations of the presently synthesized compounds **1** and **2** are in good agreement with those reported.[1a]

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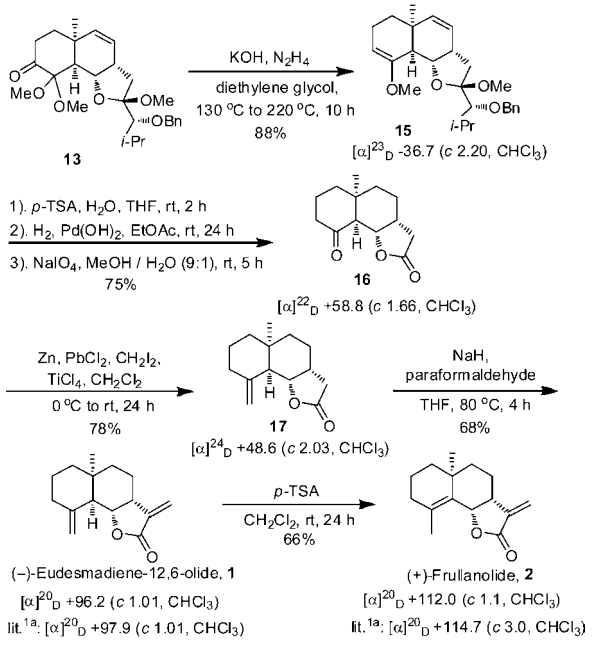
Scheme 3. Syntheses of (+)-Eudesmadiene-12,6-olide (**1**) and (+)-Frullanolide (**2**)



In conclusion, we have successfully accomplished the first asymmetric total syntheses of (+)-eudesmadiene-12,6-olide **1** and (+)-frullanolide **2** in 14.4% and 9.5% overall yields and 12 and 13 synthetic steps, respectively; an asymmetric intermolecular Diels–Alder reaction of MOB **6** with homochiral furan (*R*)-**7**, in high chemo-, regio-, stereo-, and diastereoselectivities, and an anionic oxy-Cope rearrangement with **12a** are the key steps. The absolute stereochemistry with four stereogenic centers (5*S*,6*S*,7*R*,10*R*) of **13**, and accordingly those of **1** and **2**, was determined from the X-ray diffraction studies of **13** and its chiral center C-13 derived from the chiral carbon atom of homochiral furan (*R*)-**7**.

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Supporting Information Available. Experimental details; ^{1}H, ^{13}C NMR and DEPT spectra for compounds **1**, **2**, **10**–**17**; ^{1}H–^{1}H COSY spectrum for compound **13**; and HPLC chromatogram for compound **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.