Total syntheses of (±)-montanin A and (±)-teuscorolide†

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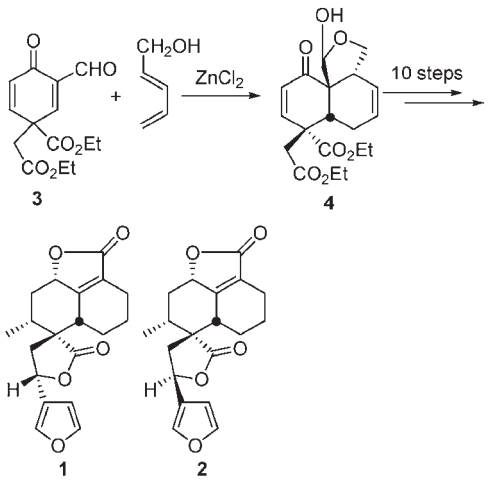
The first total syntheses of (±)-montanin A and (±)-teuscorolide have been achieved from an advanced precursor previously developed *via* a Diels–Alder strategy; in the synthetic sequence, the synthesis of montanin A was first accomplished in 8 steps, from which teuscorolide was readily achieved in 2 steps by using a novel furan oxidative cyclization–retro-cyclization process as a key operation.

In the past years, hundreds of clerodane diterpenoids including some 19-nor variants have been isolated from plants of the genus *Teucrium*.[1] This group of compounds has attracted considerable interest from the natural products community as many of them exhibit interesting antifeedant,[2] antifungal, antimicrobial[3] and antitumor[4] activities. In addition, the complex molecular architectures have also stimulated interest in their total syntheses.[5] Since more than half of the *Teucrium* clerodanes commonly possess a decalin framework containing a spiro γ-lactone ring with a pendant furyl group,[1] and are only set apart from each other by different oxygenated functionalities at C-3 to C-7 positions (clerodane numbering), it will be desirable to devise a common synthetic approach to allow access to a number of individuals with minor adjustment of synthetic steps within a general scheme. Recently, our laboratory reported the first total synthesis of teucvin (**1**), a teucrium clerodane diterpenoid possessing amoebicidal and root growth inhibiting activities, and its naturally occurring 12-epimer (**2**).[6] In our synthetic sequence, a highly facial- and regioselective intermolecular Diels–Alder reaction between dienophile **3** and *trans*-2,4-pentadien-1-ol was utilized as the key operation for the construction of the decalin core in a single step, possessing the functional groups at the strategic positions with the correct steric sense. From the Diels–Alder adduct **4**, the syntheses of **1** and **2** were achieved in 10 steps (Scheme 1). After this accomplishment, our efforts have been continuously directed to applying this strategy to the syntheses of other *Teucrium* diterpenoids, and these have cumulated in the first total synthesis, in racemic form, of montanin A (**5**) and teuscorolide (**6**) (Fig. 1).

Characterised by a furanyl moiety fused with the decalin core at C4–C6, montanin A (**5**) was first isolated from the aerial part of *Teucrium montanum* L.[7] It has been regarded as a biogenetic congener of several other *Teucrium* clerodanes,[8] and their chemical correlations have also been documented.[7,9] The



Scheme 1

structure of teuscorolide (**6**) is similar to that of **1** except for the C6–C7 double bond. It was first isolated from the aerial part of *Teucrium scorodonia* L. (Labiatae),[10] a widespread plant known as wood sage and often used in domestic herbal practice in the treatment of skin afflictions, diseases of the blood, fevers and colds.[11] Although the biological activities of **5** and **6** are undetermined, the unique structural features including the furan moiety of **5** and the γ,δ-unsaturated lactone functionality of **6**, both fused with a compact decalin framework, have presented some challenges for their total synthesis. In this paper, we wish to report a convergent synthesis of **5** starting from an intermediate previously developed in our Diels–Alder approach, and the easy conversion of **5** into **6** *via* a novel furan oxidative cyclization–retro-cyclization sequence.

The synthesis of **5** was designed in such a way that the fused furan ring was to be installed prior to the C-9 spiro lactone ring. We envisaged that the furanyl moiety could be incorporated from an α,β-unsaturated lactone ring *via* a process involving the reduction of a lactone into a lactol, followed by dehydration of the resulting lactol. Our synthesis toward **5**

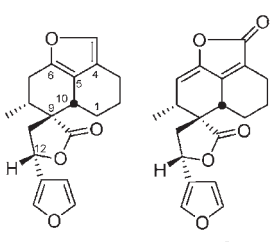


Fig. 1 Structures of montanin A (**5**) and teuscorolide (**6**).

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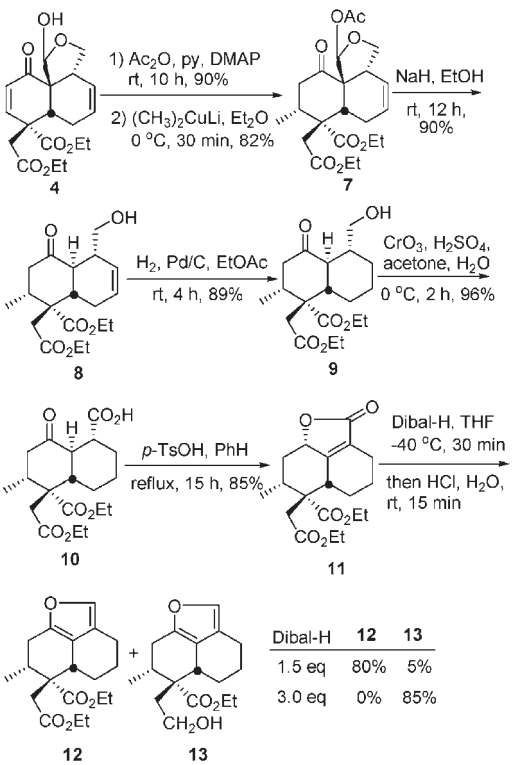
then commenced by converting **7**, a compound that was derived from **4** by acetylation and subsequent conjugate addition,[6] into lactone **11** (Scheme 2). In the sequence, compound **7** was first treated with sodium ethoxide in ethanol to give alcohol **8** in 90% yield *via* successive deacetylation and deformylation. The C=C double bond in **8** was then removed by hydrogenation to afford saturated keto alcohol **9** in 89% yield. The oxidation of **9** by Jones reagent provided keto acid **10** in 96% yield. Treatment of **10** with *p*-toluenesulfonic acid in refluxing benzene resulted in the formation of lactone **11** as a result of enol lactone ring formation followed by migration of the ensuing double bond.

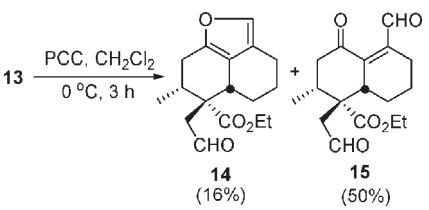
After obtaining **11**, we then prepared to install the fused furan ring that is seen in montanin A (**5**). To reduce the lactone to the corresponding lactol, several reducing reagents including Red-Al, $NaBH_4$, Dibal-H and $LiAlH_4$ were tested. Among these, Dibal-H was found to be superior to the others in offering less side products. The initial attempt of using 1.5 equivalents of Dibal-H to reduce **11** followed by treating the resulting lactol intermediate with 15% HCl aqueous solution gave the formation of **12** and **13** in 80% and 5%, respectively. Compared with **12**, **13** was considered to be a more suitable intermediate for the subsequent assembly of the spiro γ-lactone ring due to the predictable ease of transforming the primary hydroxyl group into an aldehyde group. After examining several reaction conditions, we found that the use of at least 3 equivalents of Dibal-H could result in the exclusive generation of **13** in 85% yield.

With **13** in hand, the stage was then set to construct the spiro γ-lactone ring of montanin A (**5**). Based on previous experiences,[6] we postulated that if we could convert the hydroxyl group of **13** into an aldehyde group, the subsequent reaction of the aldehyde with 3-lithiofuran followed by lactonization of the resulting alcohol would complete the total synthesis of **5**. At the beginning, we tried to oxidize **13** with PCC in dichloromethane. However, under these conditions, the pivotal intermediate **14** was only formed in 16% yield, plus keto aldehyde **15** in 50% yield (Scheme 3). We rationalized that the formation of **15** could be due to a 4 + 2 cylization of the furan ring with Cr(VI)=O and a subsequent retro-cyclization reaction. Moreover, the employment of PDC/CH_2Cl_2, Dess–Martin periodinane/CH_2Cl_2 and Swern oxidative conditions [$DMSO/(CO)_2Cl_2/Et_3N/CH_2Cl_2$] also turned out to be unsuccessful in providing satisfying yields of **14**. After considerable experimentation, it was discovered that the desired product **14** could be obtained in 88% yield by using silver carbonate combined with Celite in benzene.[12] Compound **14** thus obtained was then submitted to the addition reaction with 3-furyllithium, generated *in situ* from *n*-butyllithium and 3-bromofuran, to provide alcohol **16** in 40% yield, along with an equal amount of the epimeric product **17**. After chromatographic separation, alcohol **16** was further subjected to intramolecular transesterification mediated by lithium hydride in refluxing THF to furnish montanin A (**5**) in 95% yield (Scheme 4). The spectral data (IR, ^1H NMR, mass spectra) of the synthetic material[13] were found to be in good agreement with those of the natural product reported in the literatures.[7,14]

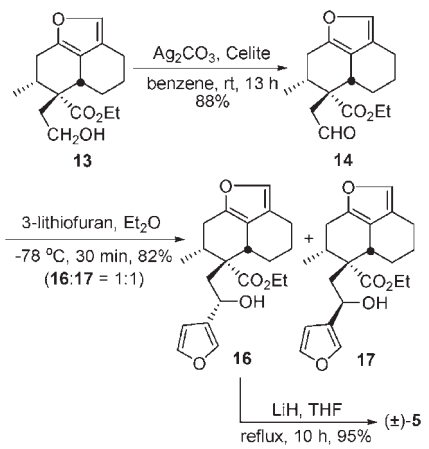
With the completion of **5**, we then turned our attention to the second target molecule, teuscorolide (**6**). Borrowing the experiences from the synthesis of **5**, we predicted that the γ,δ-unsaturated lactone functionality of **6** could be derived from the fused furan moiety of **5**. To meet this end, we first treated **5** with PDC in DMF. This operation allowed the conversion of the fused



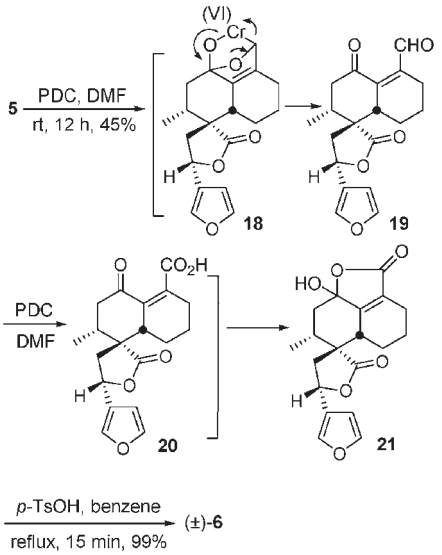
Scheme 2



Scheme 3



Scheme 4



Scheme 5

furan ring into a unique, α,β-unsaturated-γ-hydroxyl-γ-lactone unit, while keeping the C12 furyl appendage intact. Compared with furyl pendant at C12, the relatively higher reactivity of the fused furan moiety with PDC might be attributed to the ring strain. A plausible mechanism for this conversion is illustrated in Scheme 5. When **5** was exposed to four equivalents of PDC, a cycloaddition reaction between the furan diene moiety and the chromium–oxygen double bond is presumed to take place to generate intermediate **18**. Once formed, **18** might quickly participate in a retro ring opening reaction, resulting in the formation of a keto aldehyde intermediate **19**, which, in the presence of an excess amount of PDC, could be further oxidized to a keto carboxylic acid intermediate **20**. The spontaneous intramolecular cyclization of **20** would eventually produce compound **21** as a single diasteroisomer.[15] At the end, acid-promoted dehydration of compound **21** proceeded smoothly to furnish **6** in a quantitative yield.[16] The spectral data (IR, ^{1}H NMR, ^{13}C NMR, mass spectra) of **6** were also found to agree with those reported for the natural product.[17]

In conclusion, we have described the concise syntheses of (±)-montanin A (**5**) in 8 steps from the intermediate which we previously developed *via* a Diels–Alder approach. Additionally, the conversion of **5** into another clerodane diterpenoid, teuscorolide (**6**), has been achieved in a short synthetic sequence. Once again, these studies have demonstrated the utility of the Diels–Alder strategy in the synthesis of *Teucrium* clerodanes.

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13 The spectral data of **5** are as follows: IR (neat): 3055, 1762, 1423, 1265, 896, 741 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45 (s, 1H), 7.42 (m, 2H), 7.04 (bs, 1H), 6.39 (m, 1H), 5.42 (t, J = 8.5 Hz, 1H), 2.78 (m, 2H), 1.13 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 175.5 (C), 147.9 (C), 144.1 (CH), 139.6 (CH), 136.2 (CH), 125.3 (C), 119.7 (C), 117.0 (C), 108.1 (CH), 71.6 (CH), 50.7 (C), 43.3 (CH), 39.7 (CH_2), 36.1 (CH), 30.0 (CH_2), 29.7 (CH_2), 25.6 (CH_2), 19.1 (CH_2), 17.7 (CH_3); HRMS (FAB): calcd for $C_{19}H_{20}O_4$ [M + 1]$^+$: 312.1362; found: 312.1362.
14 The structure of **5** was further proved by converting **5** into teucvin (**1**) *via* an autooxidation reaction in $CHCl_3$ at room temperature for 2 days. The spectral data of the resulting compound are shown to be identical with those reported previously[6].
15 The stereochemistry of **19** at C6 (clerodane numbering) was not identified.
16 The spectral data of **6** are as follows: IR (film): 3055, 1762, 1710 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46 (t, J = 0.7 Hz, 1H), 7.44 (d, J = 1.7 Hz, 1H), 6.38 (t, J = 0.9 Hz, 1H), 5.39 (t, J = 8.5 Hz, 1H), 5.31 (d, J = 2.1 Hz, 1H), 2.70–2.90 (m, 2H), 2.68 (dd, J = 14.0, 8.3 Hz, 1H), 2.44 (dd, J = 14.0, 8.32 Hz, 1H), 2.22–2.40 (m, 7H), 1.21 (d, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 175.4 (C), 169.5 (C), 150.1 (C), 147.3 (C), 144.3 (CH), 139.6 (CH), 124.7 (C), 124.2 (C), 108.0 (CH), 107.9 (CH), 71.5 (CH), 53.5 (C), 41.0 (CH), 39.8 (CH_2), 37.4 (CH), 29.6 (CH_2), 22.4 (CH_2), 19.4 (CH_2), 16.8 (CH_3); HRMS (FAB): calcd for $C_{19}H_{19}O_5$; [M + 1]$^+$: 327.1232; found: 327.1229.
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