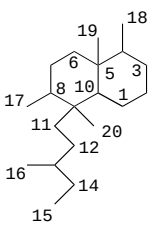
19-Norclerodane Diterpenoids

The Total Synthesis of Racemic Teucvin and 12-*epi*-Teucvin**

Hsing-Jang Liu, Jia-Liang Zhu, I-Chia Chen, Renata Jankowska, Yongxin Han, and Kak-Shan Shia*

During the past three decades, over one thousand clerodane (**1**) diterpenoids, including some 19-nor variants, have been isolated.[1] Owing to their interesting structural features and the wide range of potentially useful biological activities detected for many of the relatively few compounds tested, extensive effort has been directed towards the synthesis of clerodanoids in recent years.[1,2] We report herein the first total synthesis, in racemic form, of teucvin (**2**),[3] an amoebi-



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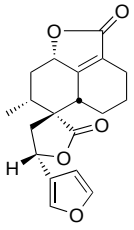

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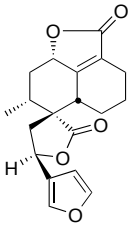

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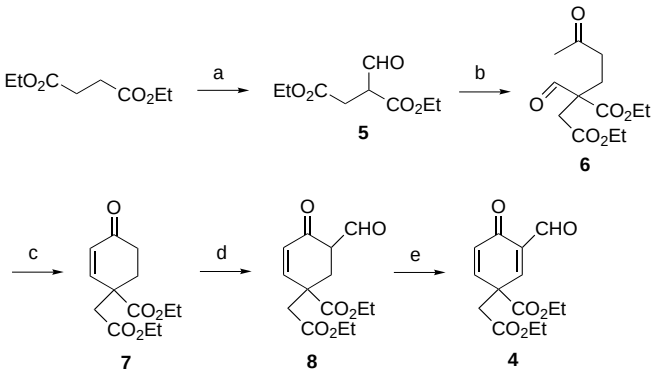
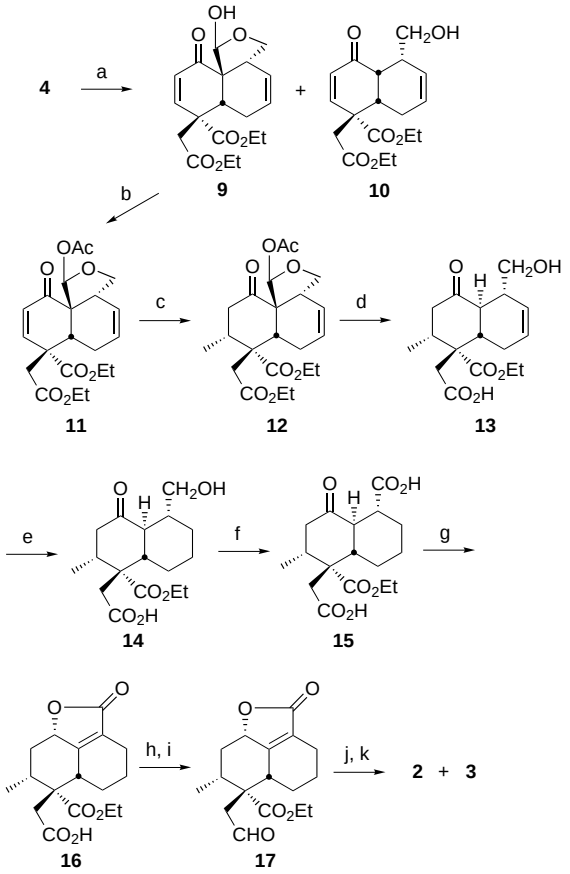
cidal agent and root growth inhibitor[4] that was first isolated in 1973 from *Teucrium viscidum* Blume by Fuijta and coworkers,[3a] and 12-*epi*-teucvin (**3**),[5] a congener of teucvin isolated eleven years later also from a *Teucrium* species by Rodriguez and Savona, et al. These 19-norclerodane diterpenoids are of considerable structural complexity. In addition to the presence of five stereogenic centers, challenging structural features in **2** and **3** comprise a decalin core attached to an α,β-unsaturated-γ-lactone unit and a spiro γ-lactone moiety containing a pendant furyl group.

The present work began with the synthesis of dienophile **4** (Scheme 1). Its Diels–Alder addition to *trans*-2,4-pentadien-1-ol (see Scheme 2), which provided a rapid access to the required decalin core with suitable functionalities at strategic positions, served as a key operation to tackle the synthetic problems associated with the title compounds. Dienophile **4** was prepared from diethyl succinate in five steps in an overall yield of 55% (Scheme 1). Formylation of diethyl succinate with ethyl formate in THF in the presence of sodium hydride and a small amount of ethanol gave the corresponding aldehyde **5**, which was subjected to Michael addition with methyl vinyl ketone using 1,4-diazabicyclo[2.2.2]octane (DABCO) as a base to give the keto aldehyde **6**. The aldol condensation of **6** was subsequently induced under acidic conditions using *p*-toluenesulfonic acid (*p*-TsOH). The resulting enone **7** was formylated with ethyl formate as before to give the formyl enone **8**. Finally, the dienophilic double bond was introduced by dehydrogenation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) to give the desired dienophile **4**.



Scheme 1. Synthesis of dienophile **4**. a) NaH, EtOCHO, EtOH (cat.), THF, RT, 10 h, 90%; b) CH_2=$CHCOCH_3$, DABCO, THF, RT, 10 h, 86%; c) *p*-TsOH, PhH, reflux, $-H_2O$, 8 h, 89%; d) NaH, EtOCHO, EtOH (cat.), THF, RT, 10 h, 89%; e) DDQ, K_2CO_3, THF, 0°C, 20 min, 90%.

Under zinc chloride catalysis, dienophile **4** was found to undergo Diels–Alder reaction rapidly (0°C, 1 h, in CH_2Cl_2) with *trans*-2,4-pentadien-1-ol[6] to give compound **9** in a 83% yield, as a result of concomitant intramolecular hemiacetal formation, together with a small amount (≈7%) of the deformylation by-product **10** (Scheme 2). Before the outset of the current work, we had observed that the placement of an ester group at C4 of various cyclohexenone dienophiles could induce a profound effect on the face-selectivity of the Diels–Alder reaction; the addition of the diene was found to take place specifically from the side containing the ester group.[7] To our delight, this interesting phenomenon of face-control, central to our synthetic design, was also realized experimentally in the Diels–Alder addition of *trans*-2,4-pentadien-1-ol to compound **4**. This reaction occurred in a completely face-selective manner in favor of the face containing the carbethoxy group, thus allowing full control of the two crucial stereogenic centers (C9 and C10 (clerodane numbering)). This key reaction also proceeded with complete stereo- (*cis*-addition and *endo*-addition with respect to the ketone carbonyl group) and regioselectivity (*ortho*-addition); both the observed products originated from the same adduct whose structure was unequivocally established after further transformations (vide infra).



Scheme 2. Synthesis of target compounds **2** and **3**. a) $ZnCl_2$, *trans*-2,4-pentadien-1-ol, CH_2Cl_2, 0°C, 1 h, 90% (**9**:**10** = 11:1); b) Ac_2O, py, DMAP (cat.), RT, 10 h, 90%; c) $(CH_3)_2CuLi$, Et_2O, 0°C, 0.5 h, 82%; d) NaOH, EtOH, H_2O, RT, 10 h, 90%; e) H_2 (60 psi), 10% Pd/C, EtOAc, RT, 6 h, 89%; f) Jones reagent, acetone, 0°C, 1 h, 90%; g) *p*-TsOH, PhH, reflux, 5 h, 85%; h) $(COCl)_2$, PhH, reflux, 10 min; i) LiAl$(t$BuO$)_3$H, THF, −40°C, 1 h, 70% over two steps; j) 3-lithiofuran, Et_2O, −78°C, 20 min; k) LiH, THF, RT, 10 h, 45% over two steps (**2**:**3** = 1:3).

For the incorporation of the required methyl group at C17, the hemiacetal group of **9** was protected as the acetate by using acetic anhydride, pyridine, and a small amount of 4-dimethylaminopyridine (DMAP). The resulting acetate **11** (90% yield) was subsequently treated with lithium dimethyl cuprate. The conjugate addition took place preferentially

from the sterically less hindered side to give ketone **12** as the predominant product (82% yield) along with a minor quantity (13% yield) of the epimeric addition product. The structure of **12** was unambiguously confirmed by an X-ray crystallographic analysis.[8]

The protected acetal group present in compound **12** was removed by treatment with aqueous sodium hydroxide in ethanol. Under these conditions, the more exposed ester group was also selectively hydrolyzed to give acid **13** in 90% yield. A single isomer was obtained and its *trans*-ring junction was induced as a result of thermodynamic control. Catalytic hydrogenation of **13** using 10% Pd/C as a catalyst gave rise to the corresponding saturated compound **14**, which was then oxidized with Jones reagent to give diacid **15** in 80% yield over two steps. The bridged γ-lactone ring was introduced by enol lactone ring formation followed by isomerization of the double bond. This was effected by treatment with *p*-toluenesulfonic acid in refluxing benzene. Under these thermodynamically controlled conditions, the more stable epimer **16** was obtained as the exclusive product in 85% yield. To install the spiro lactone ring, acid **16** was treated with oxalyl chloride to produce the corresponding acid chloride which, without purification, was immediately reduced with lithium aluminum tri-*tert*-butoxy hydride to give aldehyde **17** in 70% yield. This was followed by addition of 3-lithofuran to give a mixture of two epimeric alcohols in a ratio of 3:1 as determined by the ^{1}H NMR analysis. These alcohols, which were found to be rather labile and deteriorated readily upon column chromatography, were immediately subjected to lactonization with lithium hydride in THF, and racemic teucvin (**2**; m.p. 172–174 °C) and 12-*epi*-teucvin (**3**; m.p. 201–203 °C) were produced in a 1:3 ratio and in a total yield of 45% from **17**. The ^{1}H NMR, ^{13}C NMR, and mass spectral data obtained for the synthetic materials are in good agreement with those reported for the naturally occurring compounds.[3,5] Thus, the synthetic challenges presented by the title compounds have been successfully met by employing an intermolecular Diels–Alder approach that is rather efficient in terms of stereo- and regiochemical control, the number of steps involved (sixteen steps), and the overall yield (1.6% for teucvin and 4.8% for 12-*epi*-teucvin).

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Keywords: Diels–Alder reaction · natural products · terpenoids · teucvin · total synthesis

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[8] CCDC-194235 (**12**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

