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The enantioselective syntheses of bisabolane sesquiterpenes Lepistirone and Cheimonophyllon E

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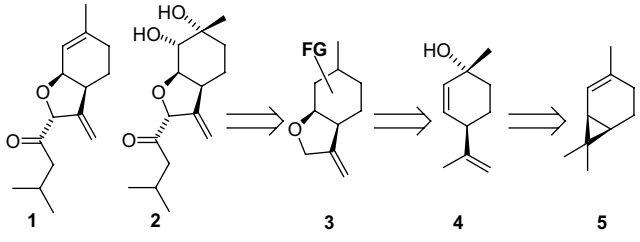
Abstract—The synthetic approach to the bisabolane sesquiterpenes Lepistirone **1** and Cheimonophyllon E **2** involves the transformation of (+)-2-carene (**5**) into the *p*-menthane furans **8** and **11**. Regio- and stereoselective alkylation, and standard reactions complete the enantioselective syntheses.

The bisabolane sesquiterpene Lepistirone (**1**) is the major volatile metabolite isolated from liquid cultures of *Lepista irina* (Basidiomycotina), an edible fungal species with an odor reminiscent of orange blossoms.[1] The closely related Cheimonophyllon E (**2**) is an antimicrobial and nematicidal bisabolane isolated from cultures of the basidiomycete *Cheimonophyllum candidissimum*.[2,3]

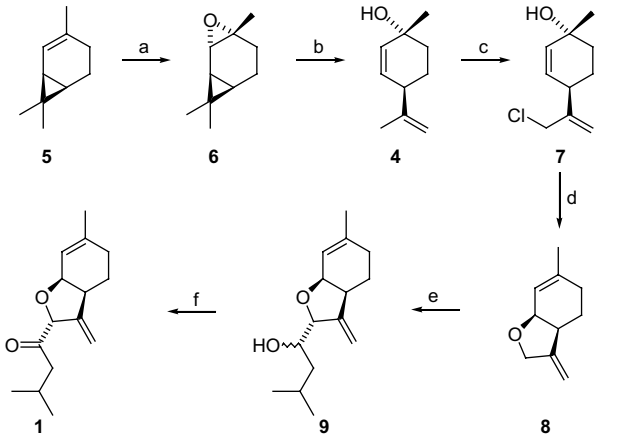
The structures and relative stereochemistries of **1** and **2** were determined by conventional spectroscopic analyses, and NOESY experiments. The structure of Lepistirone (**1**) is proposed with its absolute configuration as depicted, by application of the octant rule, whereas the structure of Cheimonophyllon E (**2**) is proposed as the relative configuration.

We report herein enantioselective syntheses of sesquiterpenes **1** and **2**, based upon disconnection of the α-ketoprenyl side chain, and functional group modifications via **3** (FG = functional groups) and **4** leading to commercially available (+)-2-carene (**5**) (Scheme 1).



Scheme 1.

2-Carene epoxide (**6**),[4,5] obtained from (+)-2-carene (**5**),[6] underwent an isomerization reaction catalyzed by ZrO_2–TiO_2[7] generating 2,8-*para*-menthadienol-1 (**4**)[5,7,8] (Scheme 2, 50% yield for two steps). Allylic chlorination[9] with $Ca(OCl)_2$ furnished the chloride **7**[10] in 40–55% yield. Simultaneous hydrolysis[11] and cyclization



Scheme 2. Reagents and conditions: (a) MCPBA, $NaHCO_3$, CH_2Cl_2, rt, 4 h; (b) ZrO_2–TiO_2, dry toluene, 80 °C, 10 min (50% for two steps); (c) $Ca(OCl)_2$ 70%, H_2O, dry ice, CH_2Cl_2, 15 min, 40–55%; (d) HMPA/H_2O, 60 °C, 18 h, 70%; (e) −65 °C, (2 equiv) *t*-BuLi (0.78 M), (2 equiv) $ZnCl_2$, 10 min, $(CH_3)_2CHCH_2CHO$, 10 min, 52%; (f) PDC, CH_2Cl_2, rt, 24 h, 67%.

Keywords: Lepistirone; Cheimonophyllon; Bisabolane; 2-Carene.
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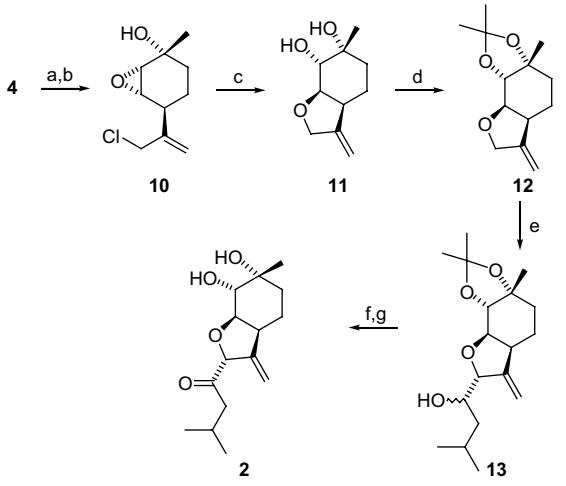

Scheme 3. Reagents and conditions: (a) *t*-BuOOH (90%), $VO(acac)_2$, benzene, rt, 20 h, 60%; (b) $Ca(OCl)_2$ 70%, H_2O, dry ice, CH_2Cl_2, 1 h, 57%; (c) HMPA/H_2O, 60 °C, 22 h, 75%; (d) $Me_2C(OMe)_2$, PTSA (cat), acetone, rt, 3 h, 85%; (e) −65 °C (1 equiv) *sec*-BuLi (0.52 M), (1 equiv) $ZnCl_2$, 10 min, $(CH_3)_2CHCH_2CHO$, 10 min, 72%; (f) PDC, CH_2Cl_2, rt, 24 h, 70%; (g) PPTS, MeOH, 50 °C, 48 h, 78%.

using water/HMPA produced the *cis*-fused tetrahydrofuran **8** in 70% yield.

The proposed stereochemistry for **8** is based upon analysis of the ring junction carbinolic hydrogen being a broad singlet at δ 4.24 ppm (slightly hidden beneath the AB quartet of the tetrahydrofuran methylene hydrogens), and also is expected for mechanistic and stereoelectronic reasons.

The crucial alkylation of **8** with isovaleraldehyde was then tested using a modification of Evans' procedure[12] by exchange of the first formed lithium carbanion to the organo-zinc species. Thus, reaction of **8** at −65 °C with 2 equiv of *t*-butyllithium, 10 min reaction then addition of 2 equiv of zinc chloride, a further 10 min reaction time, and then addition of isovaleraldehyde led to the desired product **9** in 52% yield. The stereochemistry proposed is based upon the expected convex face approach of the aldehyde to the *cis*-fused bicyclic carbanion of **8**. Oxidation of the alcohol **9** with PDC (67% yield) completed the synthesis of Lepistirone (**1**) (Scheme 2).

In the synthesis of Cheimonophyllon E (Scheme 3), stereoselective *syn*-epoxidation[13] of **4** gave an epoxide in 60% yield, which was subjected to allylic chlorination[9] with $Ca(OCl)_2$ leading to compound **10** in 57% yield. The simultaneous hydrolysis[11] and cyclization of **10** using water/HMPA furnished tetrahydrofuran **11** in 75% yield, and subsequent protection of the diol function with 2,2-dimethoxypropane (85% yield) provided **12**. Metallation at −65 °C with 1 equiv of *sec*-butyllithium, exchange to the organozinc species,[12] and reaction with isovaleraldehyde led to **13** in 72% yield. Finally, PDC oxidation (70% yield) of **13** followed by deprotection (78% yield) of the acetonide group completed the synthesis of Cheimonophyllon E (**2**).

The *syn* epoxidation of **4** is completely stereoselective as expected by the reaction conditions, and confirmed by the subsequent reactions of cyclization and specially of the *cis*-diol protection. Once again we predict the stereoselectivity of the alkylation as being from the convex face of **12** leading to **13**, and thus this synthetic sequence leads with complete stereoselectivity to the creation of the four new stereogenic centres of **2**.

The relative stereochemistries depicted for synthetic **1** and **2** were confirmed by ^1H NMR, ^{13}C NMR, IR, MS and differential NOE spectroscopy, and the spectral data are identical with those reported in the literature[1–3] for the two natural products Lepistirone and Cheimonophyllon E.

In conclusion, we have developed short, efficient and enantioselective syntheses of bioactive sesquiterpenes Lepistirone (**1**) (six steps; overall yield 6.7%) and Cheimonophyllon E (**2**) (nine steps; overall yield 4.3%) starting from readily available (+)-2-carene.

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