

Enantioselective total synthesis of (–)-heliannuol A

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An efficient and enantiocontrolled total synthesis of (–)-heliannuol A has been accomplished by employing ring closing metathesis and sequential diastereoselective epoxidation and regioselective reductive cleavage of the epoxide ring.

(–)-Heliannuol A (**1**)¹ is a naturally occurring sesquiterpenoid exhibiting strong allelopathic activity. Isolated by Macías and coworkers from aqueous extracts of fresh sunflower leaves (*Helianthus annuus* L. var. SH-222) (Fig. 1), this intriguing natural product has a unique carbon skeleton made up of an oxygen containing eight-membered heterocycle fused to the aryl ring and two tertiary stereogenic centres (C-7 and 10) whose absolute configurations were determined to be *R* and *S*, respectively, by our enantioselective total synthesis of (+)-heliannuols D and A,² the unnatural enantiomers. Here we report an efficient enantiocontrolled total synthesis of the natural enantiomer (–)-heliannuol A (**1**).

Our basic strategy is shown in Scheme 1. We envisaged a pivotal construction of the eight-membered heterocycle in **1** employing the ring closing metathesis (RCM)^{3,4} of the diene (**3**), in which the benzylic tertiary stereogenic centre (C-7) would be generated *via* a lipase mediated asymmetric acetylation of the prochiral diol (**5**).² The second stereogenic centre at C-10 would be created by diastereoselective epoxidation of the double bond in **2** followed by regioselective hydride reduction.

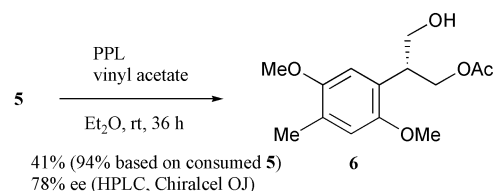
Porcin pancreatic lipase (PPL) mediated transesterification of the prochiral diol (**5**) in diethyl ether using vinyl acetate as an acetyl donor provided the (*R*)-monoacetate (**6**) in 41% yield (94% yield based on the consumed **5**) with 78% ee (HPLC on a Chiralcel OJ column).

Removal of the hydroxy moiety in **6** by tosylation and subsequent reduction with sodium borohydride in DMSO followed by alkaline hydrolysis furnished the alcohol (**7**),

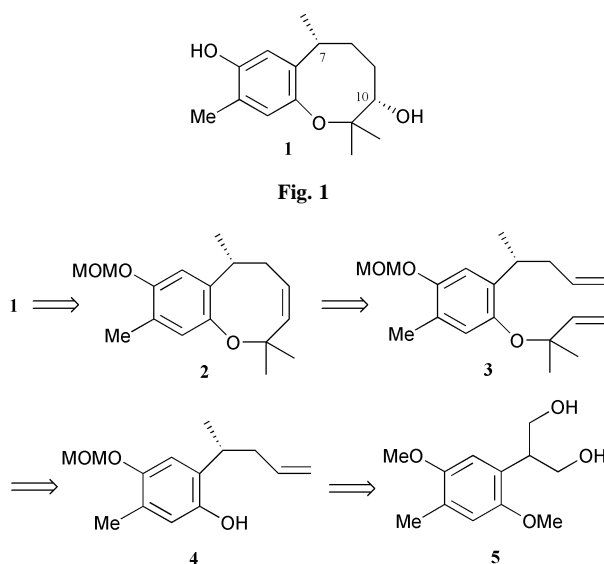
which, fortunately, was obtained as a crystalline solid. Recrystallization from hexane gave the optically pure **7** in 67% yield from **6**.

Mesylation followed by cyanation produced the cyanide (**8**) which was hydrolyzed to provide the carboxylic acid (**9**). To differentiate between the two methoxy moieties on the aryl ring, compound **9** was then treated with boron tribromide in methylene chloride (CH₂Cl₂) to give the lactone (**10**), whose phenolic hydroxy group was protected as the methoxymethyl (MOM) ether to furnish **11**. Sequential reduction with diisobutylaluminium hydride (DIBAL-H) and Wittig reaction produced the phenolic alkene (**4**) in good overall yield.

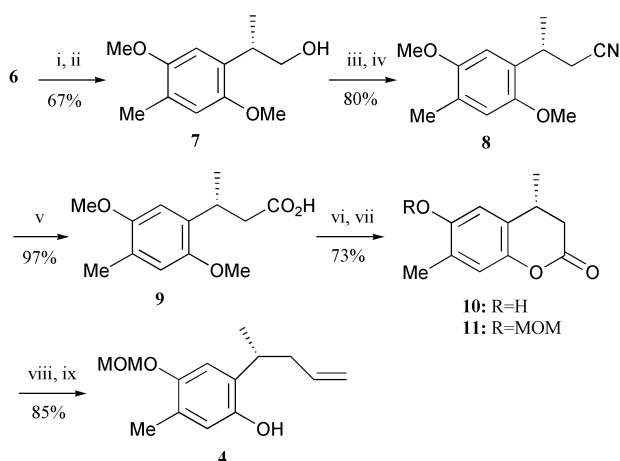
Although the conversion^{4,5} of **4** into the diene (**3**) proved very difficult, we were finally able to obtain the substrate for the key RCM reaction cleanly by employing the π -allyl palladium species generated from the mixed carbonate.⁶ Thus, reaction of **4** with *i*-butyl-2-methyl-3-buten-2-yl carbonate in the presence of tetrakis(triphenylphosphine)palladium in THF gave the diene (**3**) in 82% yield as a single product. We were then able to begin construction of the eight-membered heterocycle *via* the RCM reaction. Treatment of **3** with 10 mol% of (tricyclohexyl)phosphine[1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene]ruthenium(IV) dichloride in CH₂Cl₂ at room temperature furnished the desired cyclized product (**2**) in 88% yield. To evaluate the substrate-controlled diastere-



Scheme 2



Scheme 1



Scheme 3 Reagents and conditions: i, TsCl, Et₃N, 4-DMAP, CH₂Cl₂, rt; ii, NaBH₄, DMSO, 60 °C then K₂CO₃, MeOH (aq.), rt; iii, MsCl, Et₃N, CH₂Cl₂, rt; iv, KCN, KI, 18-crown-6, DMSO, 60 °C; v, NaOH, MeOH (aq.), reflux; vi, BBr₃, CH₂Cl₂, rt; vii, MOMCl, *i*-Pr₂NEt, CH₂Cl₂, reflux; viii, *i*-Bu₂AlH, CH₂Cl₂, –78 °C; ix, Ph₃P⁺CH₃Br[–], *t*-BuOK, toluene, rt.

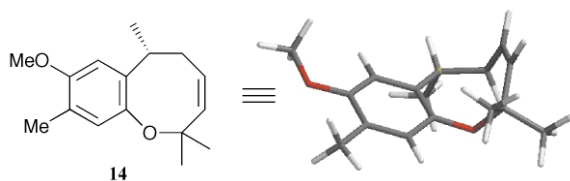
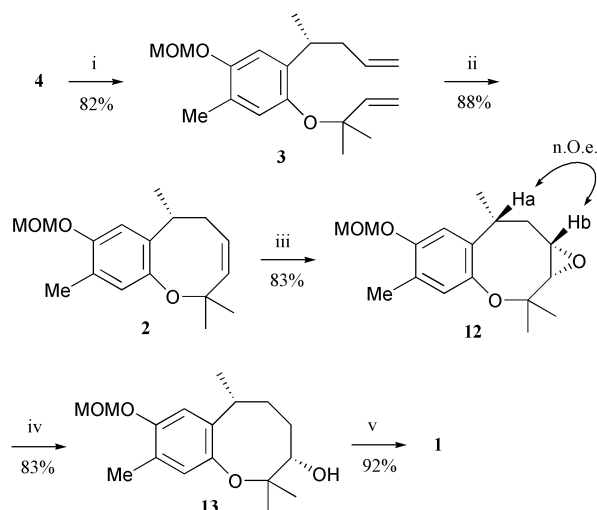


Fig. 2 The most stable conformation calculated for **14**.



Scheme 4 Reagents and conditions: i, *i*-BuOCOOC(Me)₂CH=CH₂, Pd(PH₃)₆, THF, rt; ii, tricyclohexylphosphine[1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene][benzylidene]ruthenium(IV) dichloride, CH₂Cl₂, rt; iii, CF₃COCH₃, Oxone®, Na₂·EDTA·2H₂O, NaHCO₃, CH₃CN, 0 °C; iv, LiAlH₄, THF, rt; v, 6N HCl, THF, rt.

oselective epoxidation of **2**, we examined a 3D model of the energy minimum conformation[†] of **14**, which is the methoxy analog of **2**. As shown in Fig. 2, epoxidation would proceed from the bottom face of the double bond to afford the desired α -epoxide.

Oxidation of **2** with methyl(trifluoromethyl)dioxirane⁷ generated *in situ* from methyl trifluoromethyl ketone and Oxone® in the presence of Na₂·EDTA·2H₂O and sodium hydrogen carbonate in acetonitrile provided only the epoxide (**12**)[‡] in 83% yield. The stereochemistry was confirmed by the observation of a distinct NOE correlation between the Ha (δ 3.11) and Hb (δ 2.55) protons. Hydride reduction of the epoxide occurred

on the sterically less congested carbon (C-9) regioselectively by treatment with lithium aluminium hydride to give the alcohol (**13**) in 83% yield as a single product. Finally, acidic hydrolysis of the MOM ether produced heliannuol A (**1**), whose ¹H NMR and ¹³C NMR,[‡] as well as optical rotation, [α]_D –78 (*c* 2.4, MeOH) {[α]_D –55 (*c* 0.3, MeOH)}, were identical with those of the natural product.

In summary, we have completed the first enantioselective total synthesis of the natural enantiomer (–)-heliannuol A. The synthetic route developed here is general and efficient and can also be applied to the synthesis of related heliannuols.

We thank Professor Macías (University of Cádiz) for providing us with spectral data of the natural heliannuol A.

Notes and references

[†] Molecular mechanic calculations were carried out using Titan 1.0.5 molecular modeling software (Wavefunction, Inc.), with MMFF as the force field. The Monte Carlo conformational search was carried out without imposing any constraints.

[‡] Selected spectroscopic data for **12**; colorless oil; [α]_D –80 (*c* 0.43, CHCl₃); δ _H (400 MHz, CDCl₃) 1.21 (3H, d, *J* 6.8 Hz), 1.46 (3H, s), 1.56 (3H, s), 2.18 (3H, s), 2.33–2.20 (2H, m), 2.55 (1H, d, *J* 4.0 Hz), 2.96 (1H, dq, *J* 6.4 and 6.5 Hz), 3.11 (1H, ddd, *J* 3.6, 4.0, 11.2 Hz), 3.51 (3H, s), 5.15 (2H, dd, *J* 6.4, 10.2 Hz), 6.75 (1H, s), 6.77 (1H, s); δ _C (100 MHz, CDCl₃) 15.9 (CH₃), 25.0 (CH₃), 27.4 (CH₃), 29.4 (CH₃), 34.1 (CH₂), 37.2 (CH), 56.1 (CH), 57.7 (CH), 59.3 (CH), 79.7 (C), 95.0 (CH₂), 116.2 (CH), 125.4 (C), 128.6 (CH), 137.7 (C), 146.3 (C), 152.2 (C); *m/z* (EI) 292 (M⁺); HRMS (EI) calc. for C₁₇H₂₄O₄: C, 292.1675. Found: 292.1658.

For **1**; δ _H (400 MHz, CD₃OD, –30 °C) 1.15, 1.31 (3H, s), 1.31, 1.44 (3H, s), 1.36 (2H, m), 1.22, 1.27 (3H, d, *J* 6.8), 1.65, 1.88 (2H, m), 2.08, 2.10 (3H, s), 3.23 (1H, m), 3.47, 3.56 (1H, m), 6.46, 6.51 (1H, s), 6.60, 6.65 (1H, s); δ _C (100 MHz, CD₃OD, –30 °C) 16.1 (CH₃), 16.3 (CH₃), 18.2 (CH₃), 29.7 (CH₃), 30.1 (CH), 31.5 (CH₂), 38.5 (CH₂), 78.9 (CH), 82.9 (C), 114.7 (CH), 122.3 (C), 127.5 (CH), 138.2 (C), 146.3 (C), 153.1 (C); *m/z* (EI) 250 (M⁺); HRMS (EI) calc. for C₁₅H₂₂O₃: C, 250.1569. Found: 250.1587.

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