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SYNTHESIS OF (–)-HELIANNUOL E *VIA* MERCURIC TRIFLATE CATALYZED ARYLENE CYCLIZATION

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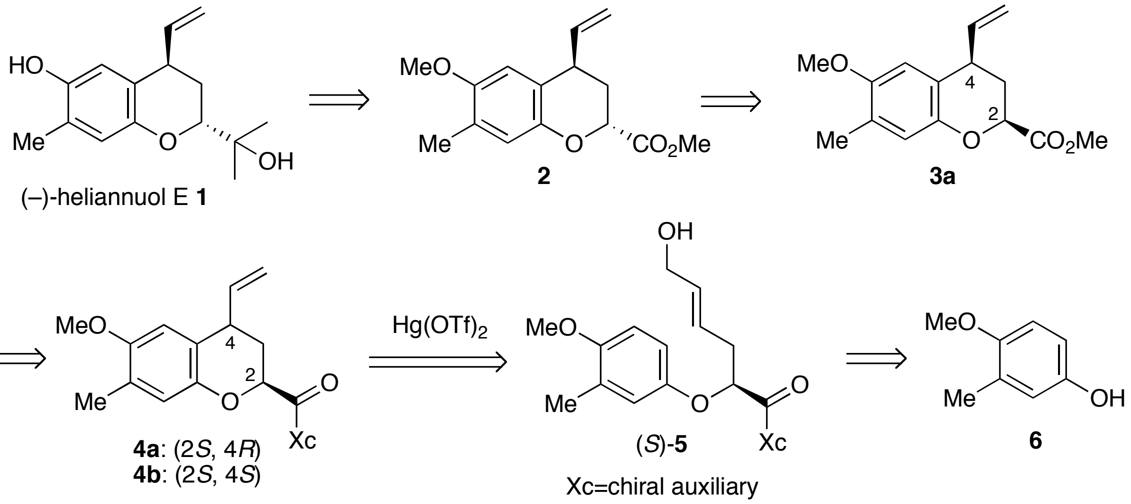
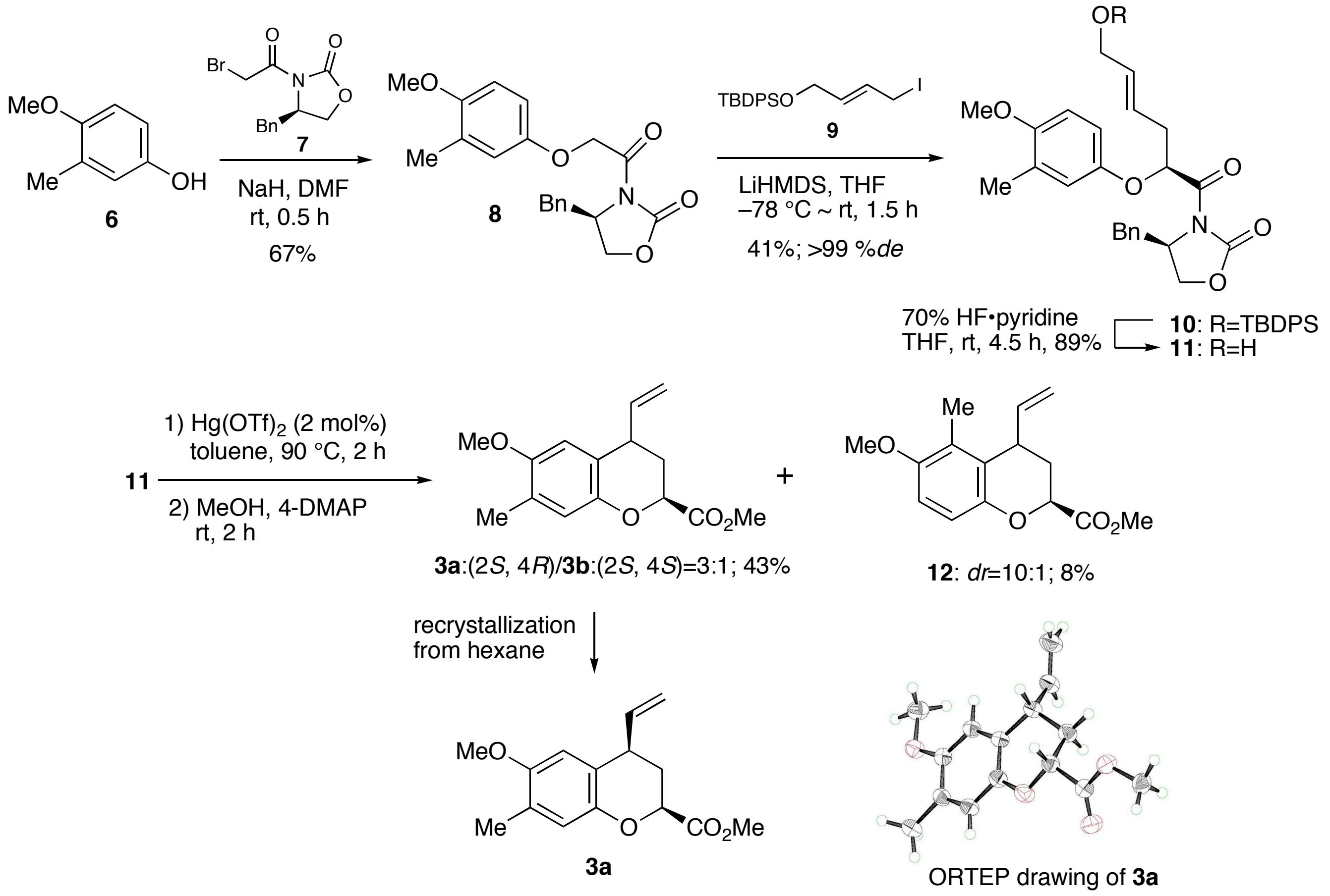
Abstract – The third-generation synthesis of (–)-heliannuol E has been accomplished employing mercuric triflate catalyzed arylene cyclization as the key step.

Heliannuol E (**1**),[1] an irregular sesquiterpenoid exhibiting allelopathic activity, was isolated from the extracts of *Helianthus annuus* L. cv. SAH-222® by Macías and co-workers. This natural product possesses a characteristic 4-vinylchroman skeleton with two tertiary stereogenic centers at the C2 and C4 positions. The absolute configurations were established to be 2*R* and 4*R* by the synthesis of Nishiyama and co-workers.[2b] Because of its fascinating structural features and allelopathic activity, three enantioselective[2] and two racemic syntheses[3] have been reported. One of the drawbacks in the previous enantioselective syntheses[2] is the introduction of the vinyl moiety at the benzylic position; that is, the use of a stoichiometric amount of *o*-nitrophenylselenocyanate for the dehydration of the primary alcohol.[4] In a recent publication, Nishizawa and co-workers demonstrated that the mercury(II) trifluoromethanesulfonate [$Hg(OTf)_2$][5] catalyzed arylene cyclization[6] proceeded cleanly to give the six-membered carbocycle fused to aryl and indole rings with a vinyl moiety at the benzylic position. We thought that this transformation could be used to construct the vinylchroman backbone of heliannuol E. Herein we report the synthesis of (–)-heliannuol E (**1**) using a $Hg(OTf)_2$ catalyzed arylene cyclization as the key step. Approaching the synthesis from a retrosynthetic perspective, we envisioned the following scheme: (–)-**1** would be derived from the bicyclic ester (2*R*, 4*R*)-**2** by a sequential Grignard reaction and demethylation. The ester **2** would be obtained by the C2-epimerization of (2*S*, 4*R*)-**3a**, which would be prepared from the optically active allyl alcohol (*S*)-**5** with an acyl moiety containing a chiral auxiliary (Xc) by the $Hg(OTf)_2$ catalyzed cyclization followed by methanolysis of the resulting **4a,b**. We chose (*S*)-**5** as a substrate based upon mechanistic consideration of the possible transition states in the key cyclization (shown in Scheme 3), in which the product with a *cis* relationship between the two substituents at the C2 and C4 positions would predominate. Since the C2 stereogenic center can be epimerized, the major diastereoisomer would be converted to (–)-**1**. The allyl alcohol **5** could be derived from 4-methoxy-3-methylphenol (**6**). (Scheme 1)



Scheme 1. Retrosynthetic Analysis

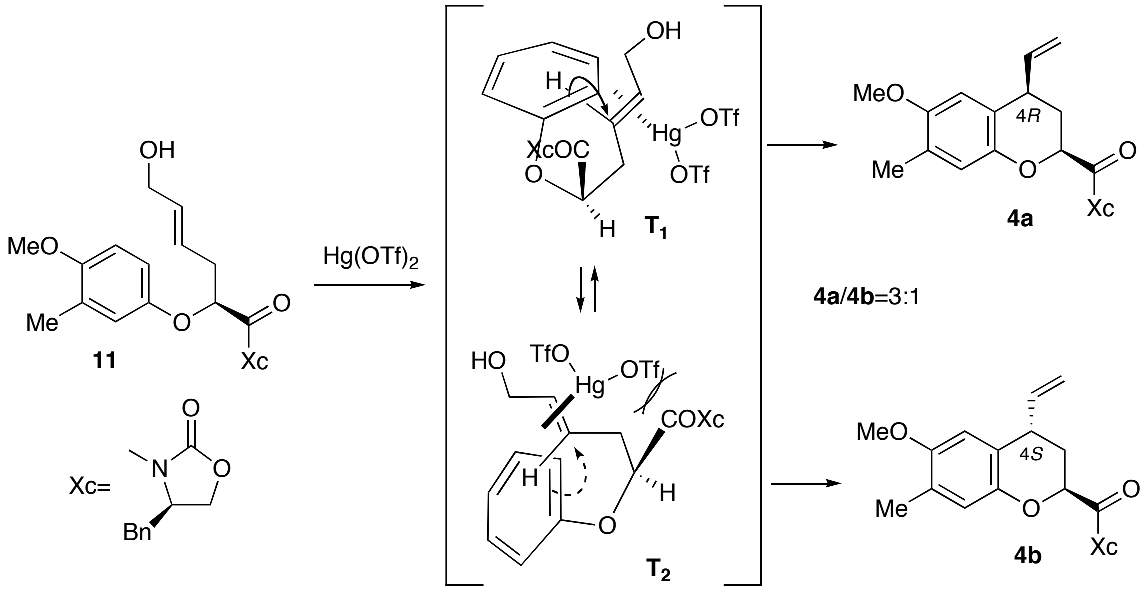
As the chiral auxiliary for the creation of the tertiary stereogenic center at the future C2 (chroman numbering), we chose the Evans' bromoacetyloxazolidinone **7**.[7] The phenol **6**[8] was reacted with **7** in the presence of NaH to produce the ether **8** which was treated with the allylic iodide **9**[9] and LiHMDS as a base[10,11] to give **10** with high diastereoselectivity (>99 %de). After desilylation, the allyl alcohol **11**, the substrate for the key conversion, was treated with 2 mol% of $Hg(OTf)_2$ in toluene (0.05 M solution) at 90 °C for 2 h. The resulting mixture of cyclized products, which was immediately exposed to a methanol solution containing 4-DMAP at rt for 2 h,[11] provided the expected **3** (*cis*:*trans*=3:1) and the regioisomer **12** (*dr*=10:1) in 43% and 8% yield, respectively. Both could be separated by silica gel column chromatography and were obtained as an inseparable mixture of diastereoisomers. Fortunately, **3** was obtained as a crystalline solid and recrystallization from hexane produced **3a** in 31% yield (from **11**), the X-ray crystallographic analysis[12] of which showed that the structure of the major diastereoisomer was (2*S*, 4*R*)-**3a**, as we had predicted. (Scheme 2)



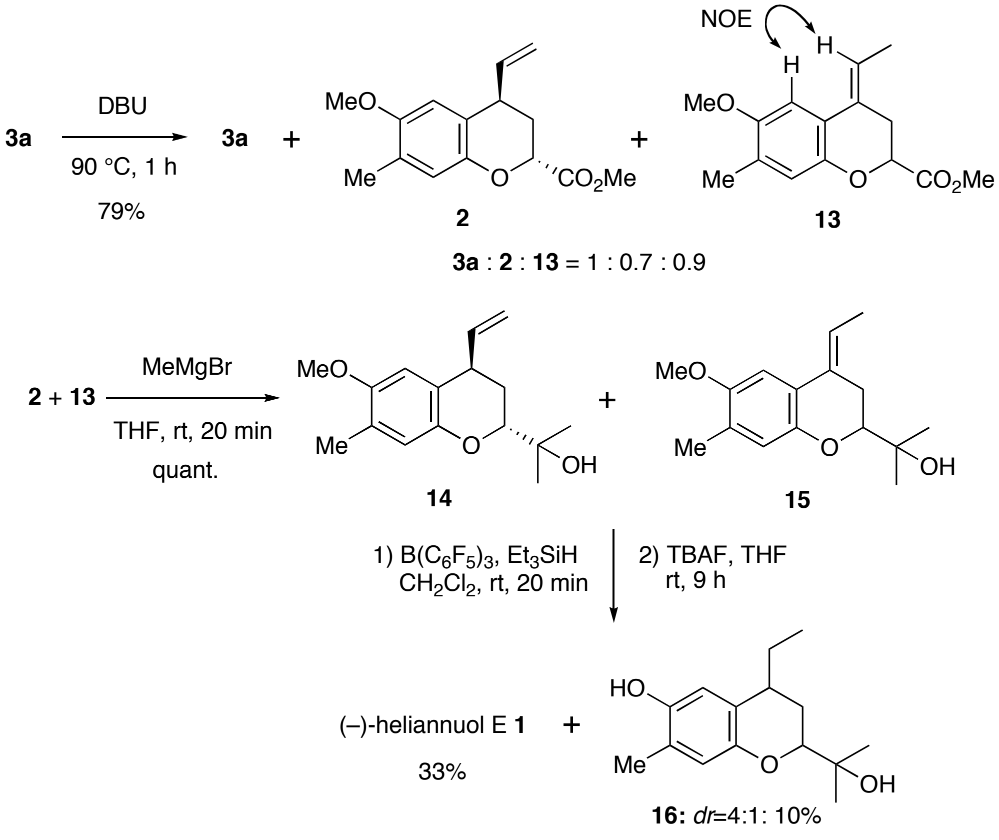
Scheme 2. Preparation of (2*S*, 4*R*)-Methyl 6-methoxy-7-methyl-4-vinylchroman-2-carboxylate (**3a**).

The diastereoselectivity can be explained by comparing the possible π-complex[6] transition states T_1 and T_2. In transition state T_2, the steric repulsion between the acyl moiety (COXc) and the complexed mercury can be observed, and the sterically less demanding transition state T_1 should predominate with *cis*-**4a** being generated as the major product. (Scheme 3)

Next we examined the epimerization at C2 of **3a**. Treatment of **3a** with DBU at 90 °C for 1h[13] provided the recovered **3a** and two new products, the epimerized **2** and the exocyclic alkene **13**,[14] in a ratio of 1:0.7:0.9 in 79% yield. *Cis*-**3a** was separated by preparative HPLC;[15a] however, **2** and **13** were inseparable. A mixture of **2** and **13** was reacted with MeMgBr in THF and still gave an inseparable mixture of the tertiary alcohols **14** and **15** (ca. 1:1) quantitatively. Final demethylation[3b,16] was realized by sequential treatment with tris(pentafluorophenyl)borane/triethylsilane and TBAF to give a separable[15b] mixture of (–)-heliannuol E **1** and the reduced product **16** (*dr*=4:1, inseparable)[17,18] in 33% and 10% yield, respectively, along with unidentified products which would be generated from **15**. The spectral properties and the optical rotation {$[\alpha]_D$ –88.5 (*c* 0.45, $CHCl_3$); lit.[2b] $[\alpha]_D$ –77.1 (*c* 0.10, $CHCl_3$), lit.[2c] $[\alpha]_D$ –76.5 (*c* 0.08, $CHCl_3$)} of the synthetic **1** were identical with those of the natural product. (Scheme 4)



Scheme 3. Transition States for the Arylene Cyclization.



Scheme 4. Synthesis of (–)-Heliannuol E (1).

In summary, we have completed the enantioselective total synthesis of (–)-heliannuol E (**1**), which is the third-generation synthesis from our group, using a $Hg(OTf)_2$ catalyzed arylene cyclization as the key step.

This is the first example of a diastereoselective Nishizawa cyclization for the synthesis of a chroman derivative. The synthetic route developed here can be applied to the synthesis of other heliannane sesquiterpenoids.

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12. Crystal data of **3a**: $C_{15}H_{18}O_4$, formula weight 262.30, mp 96-96.5 °C, orthorhombic, space group $P2_12_12_1$, a = 7.6220(6) Å, b = 7.9760(6) Å, c = 22.853(2) Å, V = 1389.3(2) $Å^3$, Z = 4, Dcalc = 1.254 g/cm^3, F(000) = 560.00, crystal dimensions = 0.80x0.70x0.50 mm, number of observations (all reflections) = 12440, number of variables = 190, reflection/parameter ratio = 65.47, R (all reflections) = 0.075, R ($I>2.00\sigma(I)$) = 0.073, Rw (all reflections) =0.148. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 714678. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ,

UK [fax: +44(0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

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14. From the ^{1}HNMR of a mixture of **2** and **13**, it was revealed that **13** was obtained as a single product. The stereochemistry was determined to be *E* from NOE spectral correlations (between the olefin proton and the C5-aromatic proton) as shown in Scheme 4.
15. Conditions of HPLC separation: (a) Column, Mightysil 60 250-20; eluent, hexane/AcOEt=9:1; flow rate, 5 ml/min. (b) Column, Mightysil 60 250-20; eluent, hexane/AcOEt=7:3; flow rate, 5 ml/min.
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17. Compound **16** would be generated from **15** by treatment with $B(C_6F_5)_3$ and Et_3SiH. An example of the similar transformation has been reported by Wanner, *et al.*, see: C. E. Hoesl, G. Höfner, and T. T. Wanner, *Tetrahedron*, 2004, **60**, 307.
18. Hydrogenation of **1** (H_2, 5% Pd-C, EtOH, rt, 0.5 h) provided the reduced product (51%), dihydroheliannuol E, which was identical with the minor diastereomer of **16**. It was clarified that the stereochemistry of the major diasteromer was *cis*, however, the absolute structure is unknown.