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Total Synthesis of (+)-Sundiversifolide

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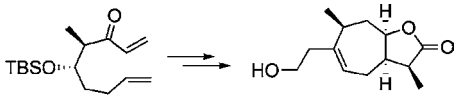
ABSTRACT



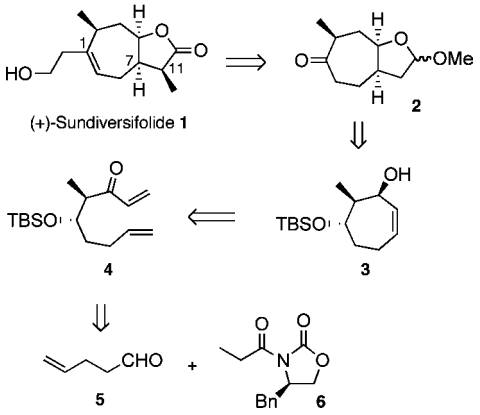
(+)-Sundiversifolide **1**

The first, enantiocontrolled total synthesis of (+)-sundiversifolide has been accomplished using the sequential ring-closing metathesis, [3,3]-sigmatropic rearrangement, and iodolactonization for the key assembly of the cis-fused oxabicyclo[5.3.0]decene framework of the natural product.

Sundiversifolide (**1**) was isolated from the exudates of *Helianthus annuus* L., germinating sunflower seeds, by Tomita-Yokotani and co-workers.[1] This compound inhibited shoot and root growth of cat's-eye by about 50% at a concentration of 30 ppm and also showed species-selective activity in the shoot and root growth of various tested plants, e.g., tomato, crabgrass, and barnyard grass. Although sundiversifolide has been recognized as having an allelopathic function in sunflowers, interestingly, it did not inhibit shoot growth of the sunflower itself. Because of its intriguing structural features, interesting biological profiles, and limited availability, sundiversifolide represents an attractive target for total synthesis.

In this communication, we report the first, enantiocontrolled total synthesis of (+)-sundiversifolide (**1**). Our strategy for sundiversifolide is shown in the retrosynthetic analysis in Scheme 1. We anticipated that the regioselective installation of the olefinic ethanol unit at C1 would be achieved via the Wittig-type olefination−deconjugation−reduction sequence of the ketone **2** or the carbonyl ene reaction[2] of the corresponding *exo*-methylene derivative of **2** with formaldehyde. Introduction of the methyl group at C11 would give sundiversifolide (**1**). The bicyclic ketone **2** with the requisite three stereogenic centers would be assembled via Claisen-type [3,3]-sigmatropic rearrangement followed by iodo lactonization from **3**, which would in turn be constructed by sequential ring-closing metathesis (RCM) of **4** and diastereoselective reduction of the resulting enone. The diene **4** might be prepared from a diastereoselective Evans aldol reaction of **6** with the aldehyde **5** (Scheme 1).

Scheme 1. Retrosynthetic Analysis



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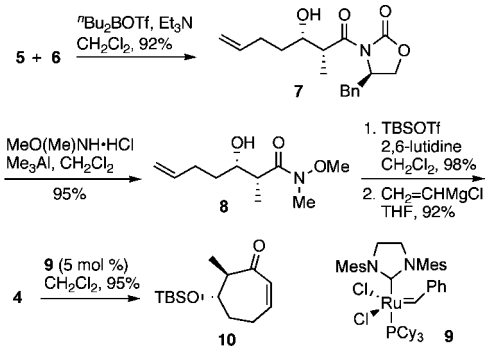
Dibutylboron triflate mediated aldol reaction of **5** with the Evans propionate **6** provided the aldol product **7** in 92% yield as a single diastereomer. The conversion of **7** into the corresponding Weinreb amide **8** was carried out under standard Me_3Al-mediated conditions.[3] Protection of the alcohol moiety as a TBS ether followed by treatment with vinylmagnesium chloride furnished the diene **4** in 90% yield for the two steps. RCM was performed by treatment of **4** with the second-generation Grubbs catalyst **9** (5 mol %) in refluxing CH_2Cl_2 to give the cycloheptenone **10** smoothly in 95% yield (Scheme 2).

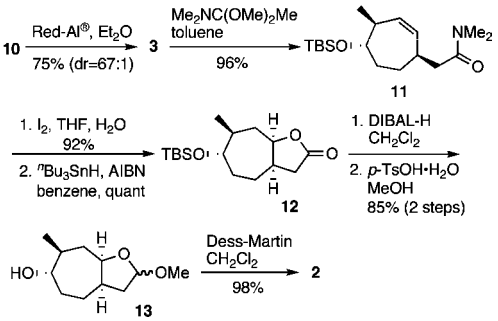
Scheme 2



We examined the diastereoselective reduction of the ketone in **10** under various conditions. The best result was obtained when Red-Al was used as a reducing agent to give the alcohol **3** as a chromatographically separable mixture in a ratio of 67:1 in 75% yield. The absolute configuration of the major diastereomer was confirmed to be the desired *S* by the Kusumi−Mosher method.[4] Attempted [3,3]-sigmatropic rearrangements to construct the γ-lactone moiety provided unsatisfactory results; e.g., the Johnson−Claisen rearrangement of **3** gave a 2.3:1 mixture of the diastereoisomers in 81% yield. Although the Ireland−Claisen protocol produced the corresponding carboxylic acid diastereoselectively, the yield, however, was only 52%. The best result was obtained by employing the Eschenmoser rearrangement.[5] Thus, treatment of **3** with *N*,*N*-dimethylacetamide dimethyl acetal in refluxing toluene produced the amide **11** in 96% yield as a single product. Treatment of **11** with iodine in aqueous THF afforded diastereoselectively the iodolactone in 92% yield, which was exposed to radical deiodination conditions to provide **12** quantitatively. Sequential DIBAL-H reduction and acetalization with *p*-TsOH in MeOH provided the alcohol **13**, which was oxidized with Dess−Martin periodinane to give the bicyclic ketone **2** in good overall yield (Scheme 3).

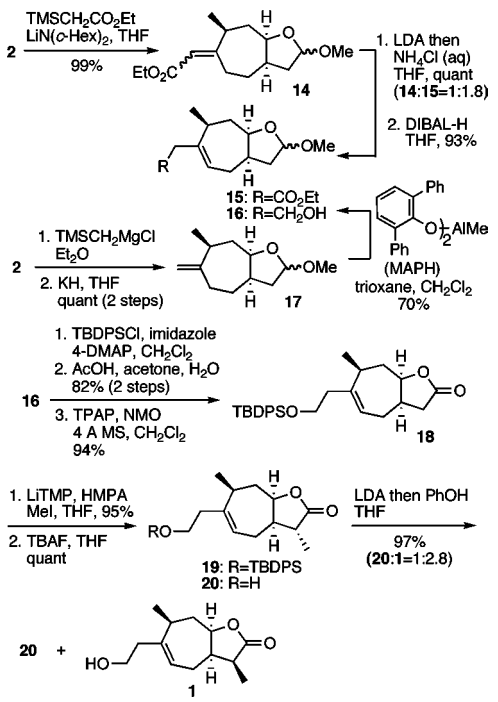
To install the olefinic ethanol appendage at C1, we initially prepared the exocyclic unsaturated ester **14**. Although Wittig

Scheme 3



or Horner−Emmons olefination of **2** did not give **14**, Peterson olefination[6] cleanly produced the compound in excellent yield. It was then exposed to deconjugation conditions[7] to give a separable mixture of the desired deconjugated ester **15** and the starting ester **14** in a ratio of

Scheme 4



1.8:1 quantitatively. The deconjugated ester **15** thus prepared was reduced with DIBAL-H to provide **16**. Although the requisite **16** was obtained, we still hoped to find a more efficient route. Sequential treatment of **2** with trimethylsilylmethylmagnesium chloride and potassium hydride[8] afforded the *exo*-methylene compound **17** which was exposed to the methylaluminum bis(2,6-diphenylphenoxide) (MAPH)-

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mediated carbonyl ene reaction[9] conditions using trioxane to provide **16** in 70% yield from **2**. After protection of the primary hydroxyl function and regeneration of the lactone moiety, the resulting **18** was methylated using lithium tetramethylpiperizide and methyl iodide in HMPA and THF to give **19** diastereoselectively in 95% yield. The stereochemistry at C11 was determined by NOESY experiments and turned out to be the undesired *R*-configuration. After deprotection of the silyl ether, the resulting ketoalcohol **20** was subjected to kinetic protonation conditions using LDA and phenol at −78 °C to produce a chromatographically separable 1:2.8 mixture of **20** and (+)-sundiversifolide **1** {$[\alpha]_D$ +34 (*c* 0.4, $CHCl_3$)} in 97% yield. The spectral properties (^1H and ^{13}C NMR) of the synthetic material were identical with those of the natural product. Because the optical rotation for the natural product has never been reported, the absolute structure could not be determined (Scheme 4).

In summary, we have completed the first, enantiocontrolled total synthesis of (+)-sundiversifolide using sequential RCM, diastereoselective reduction, Eschenmoser rearrangement, and iodolactonization to furnish the cis-fused oxabicyclo-[5.3.0]decene framework of the natural product. A key installation of the olefinic ethanol functionality at C1 was realized regioselectively employing the MAPH-mediated carbonyl ene reaction. The synthetic route developed here is general and efficient and can also be applied to the synthesis of other related natural products, e.g., diversifolide and xanthatin.

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Supporting Information Available: Experimental procedures and spectroscopic and analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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