Preparation of (+)-Tricyclo[6.2.1.0²,⁷]undec-2(7)-en-3-one and
Its Conversion into (+)-epi-β–Santalene

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Optically pure (+)-tricyclo[6.2.1.0²,⁷]undec-2(7)-en-3-one was first prepared from (+)-tricyclo[6.2.1.0²,⁷]undeca-4,9-dien-3-one in four steps. Conjugated addition occurred selectively from the methano-bridge side to give the 1,4-adduct which was converted into natural (+)-epi-β-santalene.

Recently, we developed[1] an efficient enantiocontrolled route to both enantiomeric forms of tricyclo[6.2.1.0²,⁷]undeca-4,9-dien-3-one (1) from a single *meso* symmetric diol precursor by employing lipase-mediated asymmetrization. This tricyclic dienone (1) could serve as a chiral equivalent of cyclohexa-2,5-dienone to produce a variety of optically pure natural products[2] in an enantiocontrolled manners owing to its biased structure and facile extrusion of cyclopentadiene. To extend its utility, we examined the conversion of the tricyclic 4-en-3-one (1) into the unknown tricyclic 2(7)-en-3-one system (5) using the (+)-enantiomer as the substrate. We now wish to report the first acquisition of the optically active tricyclic 2(7)-en-3-one compound [(–)-5] and its utilization as a building block for an enantioselective synthesis of (+)-epi-β-santalene[3] (15), a fragrance component of East Indian Sandalwood.

The (+)-dienone[1] [(+)-1] was first hydrogenated on Adams catalyst to give the tricyclic ketone[4] (2), [α]$_D$²⁹ +231.7° (c 1.55, CHCl₃), in an excellent yield. Exposure of 2 to trimethylsilyl triflate in the presence of triethylamine[5] yielded the enol ether (3) regioselectively which was immediately treated with phenylselenyl chloride[6] to give the 2-phenylselenide (4), mp 84-84.5 °C, [α]$_D$²⁸ –114.6° (c 0.61, CHCl₃), accompanied by the readily separable isomeric 4-phenylselenide (~3%). On oxidation with 30% aqueous hydrogen peroxide, the former furnished the (+)-enone [(+)-5], [α]$_D$²⁹ +122.4° (c 1.26, CHCl₃), having 2,7-olefin bond in 73% overall yield from the saturated ketone [(+)-2]. The same (+)-enone (5) could be also obtained in 86% overall yield from (+)-2 in more facile way by treating the enol ether (3) with palladium(II) acetate,[7] though the product was accompanied by about 6% of the inseparable 4,5-olefinic isomer.

To know whether the *exo*-face selectivity still holds in the conjugated addition on the 2,7-olefin system as the 4,5-olefin counterparts,[8,9] 5 was treated with methylmagnesium bromide in the presence of copper(I) iodide and trimethylsilyl chloride[10]

to obtain the silyl enol ether of the 1,4-adduct from which we expected to obtain either β-santalene or epi-β-santalene depending on the stereochemistry of the product. The 1,4-addition did occur diastereoselectively to give a single silyl ether which was found to be the *exo*-adduct (6) by the transformation shown below.

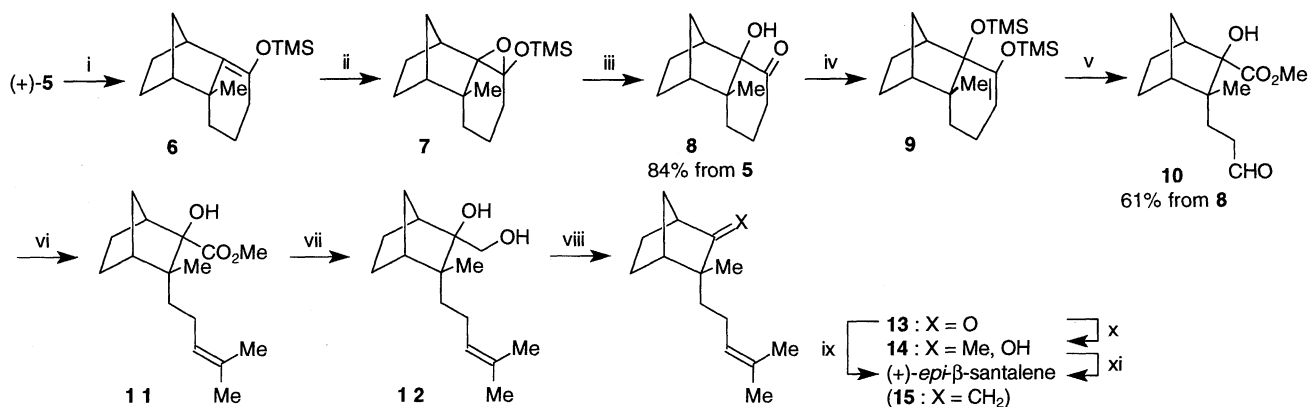Thus, the ether (6) was treated immediately with *m*-chloroperbenzoic acid[11] to give the epoxide (7) which afforded the α-hydroxyketone (8), mp 107-108 °C, [α]$_D$²⁹ +135.7° (c 1.09, CHCl₃), on acid hydrolysis. Overall yield of 8 from 5 was 84%. To transform 8 into natural (+)-epi-β-santalene (15), 8 was first treated with trimethylsilyl triflate[5] to yield the disilyl ether (9) which was cleaved by ozonolysis to give rise to the formyl-ester (10), [α]$_D$³⁰ +5.5° (c 1.13, CHCl₃), after reductive work up followed by esterification. Overall yield of 10 from 8 was 61%. Isopropylidene group was introduced by Wittig reaction to give 11, [α]$_D$²⁶ –2.2° (c 0.96, CHCl₃), in 63% yield, which was reduced to the glycol (12), mp 79-79.5 °C, [α]$_D$³¹ –25.3° (c 1.39, CHCl₃), in 88% yield by sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al).

Since the requisite olefination could not be carried out by double dehydroxylation[12] of the 1,2-glycol moiety, 12 was first cleaved to give the ketone (13), [α]$_D$²⁸ –2.5° (c 1.09, hexane). This was then subjected to the Nozaki reaction[13] using dibromomethane, zinc, and titanium(IV) chloride to install the methylene group to afford natural (+)-epi-β-santalene (15), [α]$_D$³⁰ +27.4° (c 1.95, CHCl₃) [lit. [α]$_D$²⁹ +26.9° (c 0.40, CHCl₃)³ᵇ; [α]$_D$²⁵ +25.9° (c 0.39, CHCl₃)³ᶜ; [α]$_D$²⁷ +26.4° (c 0.39, CHCl₃)³ᵈ] in 71% overall yield from 12. This has unambiguously confirmed the stereochemistry of the 1,4-adduct (6) to have the methyl group on β-face of the molecule. The ketone (13) could also be transformed into the same natural product (15) in 89% overall yield in two steps. Thus, 13 was first transformed selectively into the single tertiary alcohol (14), [α]$_D$³² +9.5° (c 1.19, CHCl₃), which was then refluxed in HMPA[14] to give 15 very facilely.

In conclusion, we have developed a procedure for the preparation of optically pure tricyclo[6.2.1.0²,⁷]undec-2(7)-en-3-on (5) starting from a readily accessible chiral building block
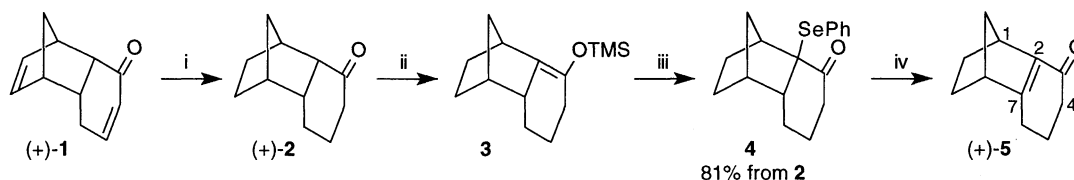
Scheme 1. *Reagents and conditions*: i. H₂, PtO₂, AcOEt, r.t., 97%; ii. TMSOTf, Et₃N, CH₂Cl₂, 0 °C, 30 min; iii. PhSeCl, CH₂Cl₂, –78 °C; iv. 30% H₂O₂, THF, 0 °C, 10 min, 90%.

(+)-5

OTMS
6

OOTMS
7

OH
O
8
84% from 5

OTMS
OTMS
9

OH
CO₂Me
10   CHO
61% from 8

OH
CO₂Me
11   Me

OH
OH
Me
12   Me

X
Me

13 : X = O
14 : X = Me, OH
(+)-epi-β-santalene
(15 : X = CH₂)

Scheme 2. *Reagents and conditions*: i. MeMgBr, CuBr·SMe₂, TMSCl, HMPA, THF, –78 °C ~ –20 °C, 2 h; ii. *m*-CPBA, NaHCO₃, CH₂Cl₂, –78 °C, 5 h; iii. 5% HCl, THF, r.t., 10 min, 84% from 5; iv. TMSOTf, Et₃N, CH₂Cl₂, 0 °C, 30 min; v. O₃, NaHCO₃, CH₂Cl₂, –78 °C, 5 min then Me₂S, then CH₂N₂, 61% from 8; vi. (Ph₃PPrⁱ)⁺I⁻, *n*-BnLi, THF, –78 ~ 0 °C, 2 h, 63%; vii. Red-Al, Et₂O, 0 °C, 30 min, 88%; viii. NaIO₄, THF, aq. NaIO₄, r.t., 96%; ix. Zn, CH₂Br₂, TiCl₄, THF, r.t., 74%; x. MeLi, –78 °C ~ 0 °C, THF, 96%; xi. HMPA, reflux, 20 min, 93%.

(1) and confirmed the stereochemistry of the nucleophilic 1,4-addition being introduced from the methano-bridge face (*exo*-addition) of the molecule.

References and Notes

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