

The First Enantioselective Total Synthesis of (+)-Laurene

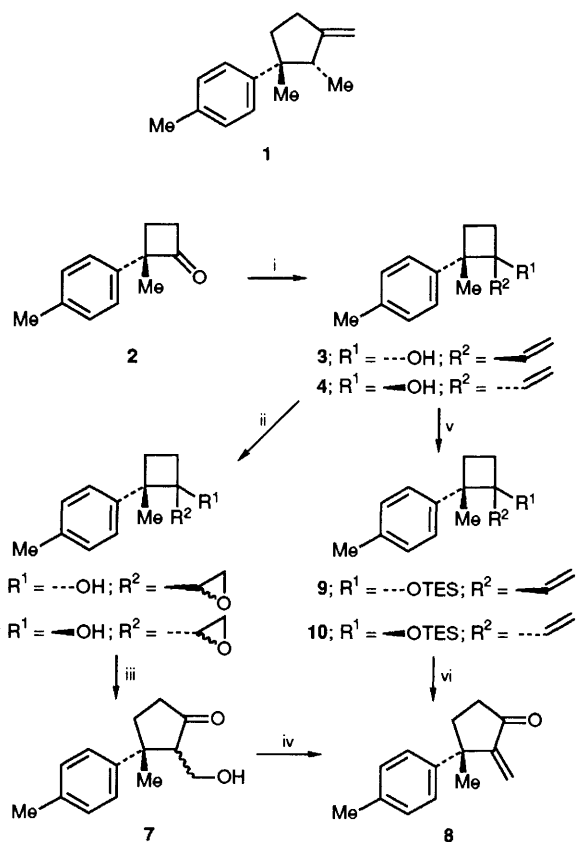
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The cyclopentenone **8**, synthesised by palladium mediated ring expansion of the chiral vinylcyclobutanols **3** and **4**, is converted to the thermodynamically unstable ketone **16** which on methylenation gives (+)-laurene **1**.

(+)-Laurene **1** is a sesquiterpene hydrocarbon which has been isolated from *Laurencia* species and the marine red algae *Laurencia elata*¹ and has a flexible carbon framework for the construction of biologically important similar types of compounds.² Despite the rather simpler substitution pattern on the cyclopentane ring of (+)-laurene **1**, the *cis*-1,2-relation-

ship of the secondary methyl group with the *p*-tolyl group has made both the stereoselective and enantioselective synthesis of this sesquiterpene difficult.³ During our work⁴ directed towards the enantioselective construction of cyclobutanones and its application in the synthesis of biologically desirable compounds, we have developed a novel enantioselective



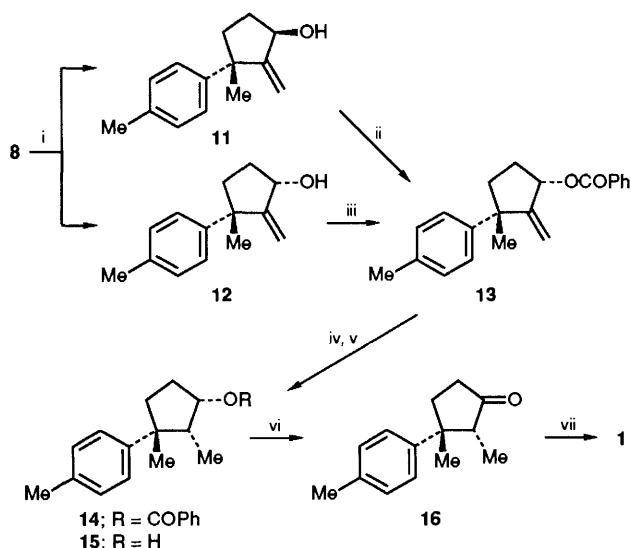
Scheme 1 Reagents and conditions: i, vinylmagnesium bromide, CeCl₃, tetrahydrofuran (THF), -78 °C, 1 h; ii, MCPBA, CH₂Cl₂, 0 °C, 3 h; iii, BF₃·Et₂O, THF, -78 °C, 4 h; iv, MeSO₂Cl, DBU, CH₂Cl₂, room temp., 6 h; v, Et₃SiOTf, 2,6-lutidine, CH₂Cl₂, room temp., 30 min; vi, PdCl₂(MeCN)₂, *p*-benzoquinone, THF, reflux, 2 h

approach to (+)-laurene **1** starting from chiral cyclobutanone **2** and herein we describe the results.†

(*S*)-2-Methyl-2-(*p*-tolyl)cyclobutanone **2** [79% enantiomeric excess (e.e.)], easily prepared^{4†} by tandem asymmetric epoxidation and enantiospecific expansion of 2-cyclopropylidene-2-(*p*-tolyl)-1-ethanol, was subjected to Grignard reaction with vinylmagnesium bromide in the presence of cerium trichloride to give the easily separable allyl alcohols **3** and **4** in 59 and 24% yields respectively. The diastereoisomeric mixture of the epoxides **5** (95%) and **6** (68%) derived by the epoxidation [*m*-chloroperbenzoic acid (MCPBA)] of **3** and **4** respectively, was treated with acid (BF₃·Et₂O) to effect the ring expansion⁵ of the cyclobutane ring giving the same cyclopentanone **7** (95%) as a mixture of diastereoisomers, the dehydration of which was effectively achieved by mesylation followed by base [1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)] treatment to give the enone **8** (80%). Alternatively, the conversion of **3** and **4** into **8** was achieved more effectively by the palladium catalysed ring expansion reaction.⁶ Thus, the triethylsilyl (TES) ethers **9** and **10**, prepared in 90 and 95% yields from **3** and **4** respectively, were subjected to the ring expansion reaction in the presence of a catalytic amount of bis(acetonitrile)palladium chloride and *p*-benzoquinone to give the enone **8** in 86 and 70% yields respectively.

Next, the stereoselective conversion of this enone **8** into the thermodynamically unstable ketone **16** was achieved as

† All new substances exhibited spectroscopic data [IR, ¹H NMR (500 MHz) and mass spectrometry] in accord with the assigned structure and provided acceptable combustion or high resolution mass spectral data.

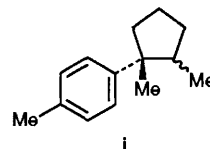


Scheme 2 Reagents and conditions: i, NaBH₄, CeCl₃, MeOH, 0 °C, 5 min; ii, EtO₂CN=NC(=O)Et, Ph₃P, PhCO₂H, benzene, room temp., 3 h; iii, PhCOCl, pyridine, room temp., 1.5 h; iv, H₂, Rh-Al₂O₃, EtOH, room temp., 6 h; v, LiOH, MeOH-H₂O, reflux, 2.5 h; vi, Prⁿ₄NRuO₄, *N*-methylmorpholine *N*-oxide, 4 Å, molecular sieves, CH₂Cl₂, room temp., 12 h; vii, Zn, TiCl₄, CH₂Br₂, CH₂Cl₂-THF, room temp., 12 h

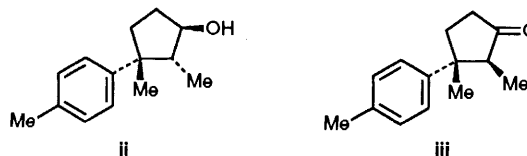
follows.‡ The reduction (NaBH₄, CeCl₃) of the enone **8** gave allyl alcohols **11** (72%) and **12** (19%). The major alcohol **11** was then converted into the benzoate **13** (98%) with inversion of chirality at the hydroxy group under Mitsunobu conditions (diethyl azodicarboxylate, Ph₃P, PhCO₂H). The benzoate thus obtained was identical with the sample prepared (99%) by esterification (PhCOCl, pyridine) of the minor alcohol **12**. The catalytic hydrogenation§ (H₂, Rh-alumina) of this benzoate **13** afforded **14** (92%) stereoselectively which on hydrolysis (LiOH) gave the alcohol **15** (100%). The conditions for the oxidation of **15** were carefully examined¶ and tetra-*n*-propylammonium perruthenate (Prⁿ₄NRuO₄) catalysed oxidation⁷ was found to be the best for this purpose affording the desired ketone **16** (92%) as a sole product without detectable amount of epimerised product. Finally, the methylenation¶¶ of the ketone **16** was effectively achieved by Nozaki-Lombardo⁸ procedure (Zn, TiCl₄, CH₂Br₂) to give (+)-laurene **1** (40%) { [α]_D²⁵ 34.7 (EtOH); lit.^{1a} [α]_D²³ +48.7 (EtOH)}.

‡ The direct hydrogenation of the enone **8** showed poor selectivity affording the desired ketone **16** and its diastereoisomer in the ratio of 3:2.

§ The direct catalytic hydrogenation of the allyl alcohol **11** or **12** under various conditions gave only the hydrogenolysis products **i** as a diastereoisomeric mixture.



¶ It has been pointed out^{3a} that the ketone **16** was easily epimerised into the thermodynamically more stable isomer **iii** on the oxidation of the alcohol **ii** and the methylenation of **16** under Wittig conditions.



Thus, we have completed the first enantioselective total synthesis of (+)-laurene and this methodology could be applied to the enantioselective synthesis of this type of biologically important compounds.

Received, 1st September 1992; Com. 2/04663F

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