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A Concise Enantiocontrolled Total Synthesis of (-)-α-Bisabolol and (+)-4-Epi-α-bisabolol

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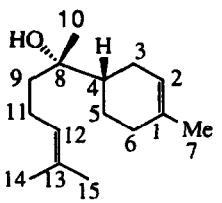
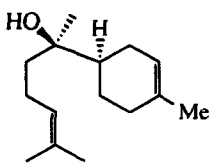
Abstract: The regiocontrolled hydrogenation of the cyclohexadiene **6**, synthesised from the chiral cyclobutanone **3** was effectively achieved with [1,4-bis(diphenylphosphino)butane](1,5-cyclooctadiene)rhodium (I) tetrafluoroborate as catalyst to give the olefins **7** and **8** which were converted into (-)-α-bisabolol **1a** and (+)-4-epi-α-bisabolol **15** *via* **9** and **10**, **11** and **12**, and **13** and **14**.

The sesquiterpene α-bisabolol **1** is an important fragrant constituent which has been isolated from the essential oils of a wide variety of plants, shrubs, and trees[1] and has been shown to occur in nature in both(-)-[1c-k] and (+)-enantiomeric forms[1l,m] **1a** and **1b**, although the (-)-enantiomer **1a** is the most wide spread and possesses physiological activities.[1g,2] The absolute configuration of two chiral centers in **1a** has been determined to be 4S, 8S.[3] Although the many efforts[4] have been devoted to the synthesis of **1**, the most of them have resulted in a synthesis of the diastereoisomeric mixture of the racemate, and the enantiocontrolled approach to this sesquiterpene has been limitted.[5]



1a



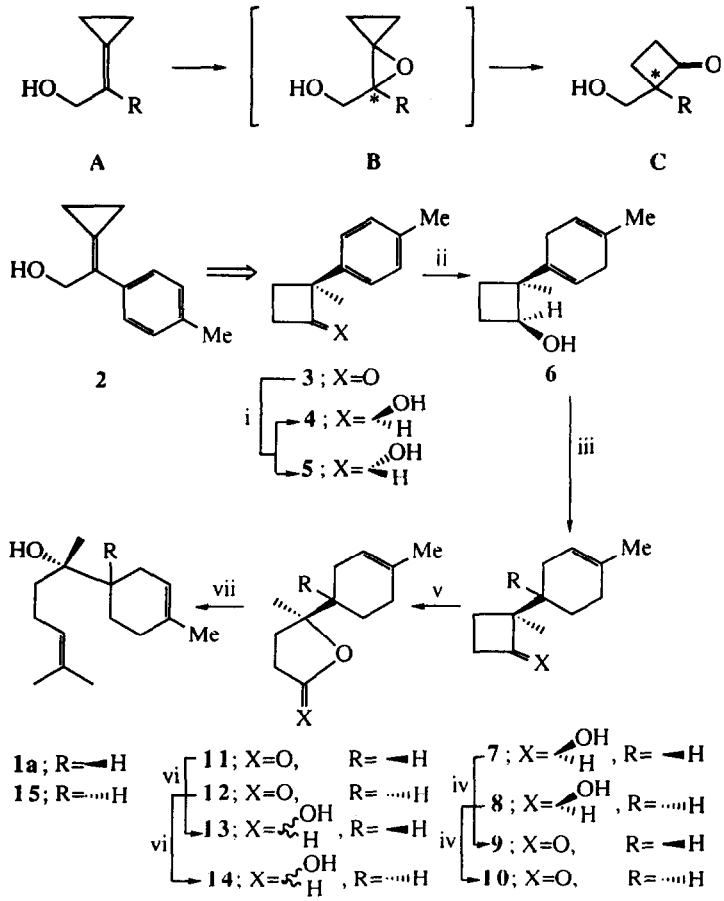
1b

Scheme 1

In the course of our studies[6] directed towards the enantioselective synthesis of cyclobutanones and its application in the synthesis of biologically desirable compounds, we have developed a novel enantioselective

approach to (-)-α-bisabolol **1a** and (+)-4-epi-α-bisabolol **15** starting from the chiral cyclobutanone **3** and herein we describe the results.[7]

Recently we have disclosed that chiral bicyclooxapentane **B**, generated in *situ* by the asymmetric epoxidation of 2-cyclopropylidene-1-ethanol **A**, rearranged directly in an enantiospecific manner under the same reaction conditions to afford the chiral cyclobutanone **C** in moderate to high enantiomeric excess (e.e.).[6a]



Scheme 2

Scheme 2 *Reagents and conditions* : i, $NaBH_4$, MeOH, 0 °C, 15 min; ii, Li, EtOH, THF, -78 °C, 4 h; iii, H_2, [Rh(COD)DIPHOS-4] BF_4 , CH_2Cl_2, room temp., 6 h; iv, DMSO, $(COCl)_2$, THF, -78 °C, 10 min then Et_3N, -78 °C, 5 min; v, 70 % *t*-BuOOH, 10 % NaOH, THF, room temp., 2.5 h; vi, DIBAL, CH_2Cl_2, -78°C, 4 h; vii, isopropylidenetriphenylphosphorane, THF, reflux, 4 h.

Thus, (S)-2-methyl-2-*p*-tolylcyclobutanone **3**[6a] (78% e.e.) prepared in this manner starting from 2-cyclopropylidene-2-(*p*-tolyl)-1-ethanol **2**, was subjected to the reduction with sodium borohydride ($NaBH_4$) to give the easily separable alcohols **4** and **5** in 90 and 10 % yields respectively. The key step in this synthesis,

the regiocontrolled hydrogenation of one of the two trisubstituted olefins of **6** which was prepared by Birch reduction of the major product **4** in 98 % yields, was effected through the intramolecular participation of the hydroxy group at homoallylic position with the catalyst, [1,4-bis(diphenylphosphino)butane](1,5-cyclooctadiene) rhodium(1) tetrafluoroborate{[Rh-(COD)DIPHOS-4] BF_4}[8] to afford the alcohols **7** and **8**. The mixture of these alcohols was successively converted by Swern oxidation [DMSO, $(COCl)_2$, Et_3N] into the easily separable butanones **9** and **10** in 25 and 28 % overall yields respectively. These butanones **9** and **10** were subjected independently to Baeyer-Villiger oxidation (*t*-BuOOH, NaOH) giving the lactones **11** and **12** in 74 and 74 % yields. Finally, Wittig reaction (isopropylidenetriphenylphosphorane) of the lactols **13** and **14** prepared in 100 and 86 % yields by the reduction [diisobutylaluminium hydride (DIBAL)] of the lactones **11** and **12** furnished our aimed products (-)-α-bisabolol **1a** {$[\alpha]_D^{25}$-39.8° (*c* 0.53, $CHCl_3$); lit.,[1k] $[\alpha]_D$-38.8° (*c* 2.45, $CHCl_3$)} and (+)-4-epi-α-bisabolol **15** {$[\alpha]_D^{25}$+48.3° (*c* 0.67, $CHCl_3$); lit.,[5b] $[\alpha]_D$+45.3° (c 2.8, $CHCl_3$)} in 81 and 66 % yields, respectively.

Thus, we could provide a concise procedure for the enantiocontrolled synthesis of (-)-α-bisabolol **1a** and (+)-4-epi-α-bisabolol **15**, hence (+)-α-bisabolol **1b** and (-)-4-epi-α-bisabolol starting from (s)-2-methyl-(2-*p*-tolyl)cyclobutanone[6a] and this methodology could be applied to an enantioselective synthesis of this type of biologically important compounds.

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7 All new substances exhibited spectroscopic data [IR, ^{1}HNMR (500 MHz) and mass spectrometry] in accord with the assigned structure and provided acceptable combustion or high resolution mass spectral data. The numbering cited here based on sesquimenthane.[3b,4a,5b]

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