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An efficient synthetic approach to the aromatic sesquiterpenoids via a SmI_2-promoted construction of quaternary centre

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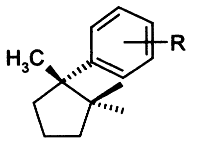
The total synthesis of the natural (±)-cuparene (**1**) and (±)-herbertene (**2**) has been carried out in eight steps from 2-cyclohexen-1-one (**3**) via a key quaternary carbon centre construction using a SmI_2-promoted rearrangement of 2,3-epoxy alcohol.

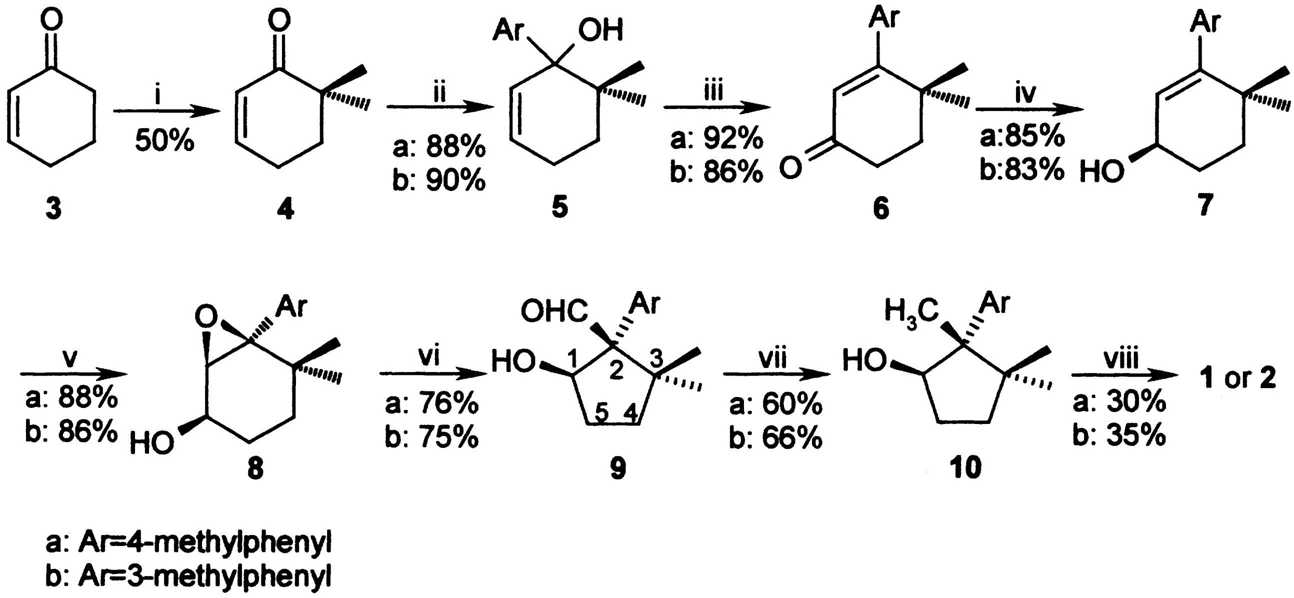
Keywords: quaternary carbon centre, 2,3-epoxy alcohol

The quaternary carbon-containing aromatic sesquiterpenoids (*e.g.* **1**–**2**, Fig. 1) belong to a large group of naturally occurring compounds, some of which exhibit important biological properties, such as antifungal, neurotrophic and anti-lipid peroxidation activities.[1] A particulary interesting structural feature is that they possess two quaternary carbon centres, one bearing the aromatic group, on adjacent carbons of a five-membered ring. Because of this crowded molecular structure and their important biological activities, syntheses of these compounds have attracted the interest of organic chemists. Several synthetic approaches have been reported, some which involve the Heck reaction, Fisher indolisation, a Diels–Alder reaction or a Reetz alkylation.[2] In connection with our recent efforts towards the quaternary carbon construction, we have found that a 2,3-epoxy alcohol such as **8**, when treated with the Lewis acid, SmI_2 in THF at reflux temperature, will undergo a C–C rearrangement to form a 2-quaternary-1-hydroxy aldehyde **9** in 76% yield. The stereochemistry of both C-1 and C-2 was constructed during this reaction. Though Yamamoto has reported a similar rearrangement, it seems to be effective only with the hydroxy-protected substrate and required a complicated reagent MABR [methylaluminium bis(4-bromo-2,6-di-*t*-butylphenoxide)].[3] C. W. Bird also reported a similar $BF_3{\cdot}Et_2O$-promoted rearrangement of an epoxide without an α-hydroxy group, but the reaction gave the very low yield 22% of the product.[4] The use of the α-hydroxy–epoxide is of significant advantage in that there is the possibility of chiral syntheses of this kind of natural products. For example, a preliminary reaction demonstrated that a chiral key intermediate **10a** could be obtained with 66% ee if **6a** was reduced with Corey reagent CBS-Me.[5] These valuable facts encouraged us to develop alternatively a short synthetic approach as shown in Scheme 1. As examples of this method, we present the total synthesis of (±)-cuparene (**1**) and (±)-herbertene (**2**), isolated from *Cupressaceae*[6] and *Herberta adunca*,[7] respectively.



1. R = 4'-Me Cuparene
2. R = 3'-Me Herbertene

Figure 1



Scheme 1 *Reagent and conditions:* (i) MeI, KO^tBu, HMPA, THF, –35°C; (ii) ArLi, Et_2O, 0°C; (iii) PCC, CH_2Cl_2, r.t.; (iv) $NaBH_4$, MeOH, 0°C; (v) *m*-CPBA, CH_2Cl_2, 0°C; (vi) SmI_2, $(CH_2Cl)_2$, reflux; (vii) *p*-$TsNHNH_2$, MeOH, reflux, then, LAH, THF, reflux; (viii) NaH, CS_2, MeI, THF, 0°C, then, *n*-Bu_3SnH, AIBN, toluene, reflux.

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Our synthesis started from the commercially available 2-cyclohexen-1-one (**3**), as shown in Scheme 1. The first step involved the construction the quaternary carbon with two methyl group. Dimethylation of **3** with MeI using a one-pot reaction readily afforded the required intermediate **4**. Arylation of the unsaturated ketone **4** with 4-methylphenyl lithium (prepared with lithium and 4-bromotoluene) afforded the tertiary alcohol **5a**. The PCC oxidative rearrangement of the allylic alcohol **5a** furnished the α,β-unsaturated ketone **6a**, which was subsequently converted into the allylic alcohol **7a** by reduction with $NaBH_4$. Epoxidation of **7a** with *m*-CPBA afforded the α-hydroxy epoxide **8a** as a single product. After rearrangement of 2,3-epoxy alcohol **8a** with SmI_2 in THF, the compound **9a** was obtained, whose stereochemistry was determined by 1D and 2D NMR.[8] Thus, we have succeeded in the stereoselective construction of the secondary quaternary carbon. The remaining steps involved the removal of the hydroxy and aldehyde carbonyl groups. Compound **9a** was converted to a tosylhydrazone, which was not purified but subjected to a direct reduction with $LiAlH_4$ to give the alcohol **10a** in an acceptable yield 60%. Treatment of **10a** with NaH and CS_2 afforded the xanthate ester, which was reduced, without purification, with *n*-Bu_3SnH to give (±)-cuparene (**1**).

When the α,β-unsaturated ketone **4** was reacted with 3-methylphenyl lithium (prepared with lithium and 3-bromotoluene) the tertiary alcohol **5b** was obtained. Following the similar route above resulted in the total synthesis of (±)-herbertene (**2**). An efficient method has been developed for the stereoselective construction of a quaternary carbon using the SmI_2-promoted rearrangement reaction. A further high enatioselective synthesis utilising this key reaction is ongoing.

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Techniques used: TLC, ^{1}H and ^{13}CNMR, EIMS, HRMS

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8 The NOESY spectrum for compound **9a** shows the strong correlations between H-1 and Ar-H, and between H-1 and $ArCH_2$-H.