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Photomediated asymmetric synthesis of (−)-cuparene†

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Generation of a benzylic quaternary stereocentre *via* the photomediated cyclisation of a chiral α-(aminobutyl)styrene followed by a microwave-assisted Cope elimination has led to a total synthesis of the sesquiterpene (−)-cuparene.

The presence of a quaternary stereocentre adjacent to an aromatic ring is a common structural feature in a number of naturally occurring compounds. Prominent amongst these are the cuparene and herbertane class of sesquiterpenoids, characterised by the presence of adjacent quaternary carbon atoms on a cyclopentane ring, but differing in the position of methyl substitution on the aromatic ring (Fig. 1). Some of these compounds, particularly those with oxygen functionalities, show a wide range of biological activity, including potent antifungal, neurotrophic and inhibition of lipid peroxidation.[1]

The challenge of establishing a hindered, quaternary stereocentre on a five-membered ring has made the cuparene and herbertane sesquiterpenoids popular synthetic targets.[2] However, the additional challenge of controlling the absolute stereochemistry at a sterically congested quaternary stereocentre has meant that far fewer of these approaches can be or have been rendered asymmetric.[3] Our approach to cuparene is based on the photomediated ring closure of α-(dimethylaminobutyl)styrene **1** to cyclopentane **2** reported by Lewis *et al.* (Scheme 1).[4] This reaction is proposed to proceed via electron transfer from the ground state amine to the singlet excited state of the styrene, followed by a 1,6-hydrogen transfer and subsequent cyclisation of the resulting diradical. It occurred to us that the Lewis cyclisation could be applied to a synthesis of the cuparene skeleton if such a reaction can tolerate substitution in both the aromatic ring and connecting chain (**3**, Scheme 1). Deamination of the resulting cycloadduct **4** should then furnish the natural product. Furthermore, the possibility of employing chiral amines in place of dimethylamine could offer a means to control the absolute configuration at the new stereocentre, and hence lead to an asymmetric synthesis of the natural product.

In order to test this hypothesis, pyrrolidine **8** was chosen as an initial target. We have developed two routes for the preparation of this photochemical precursor (Scheme 2). In the first, alkylation of pyrrolidine with the known bromide **6**[5] gave a slow but clean transformation to aminostyrene **8** (Scheme 2).

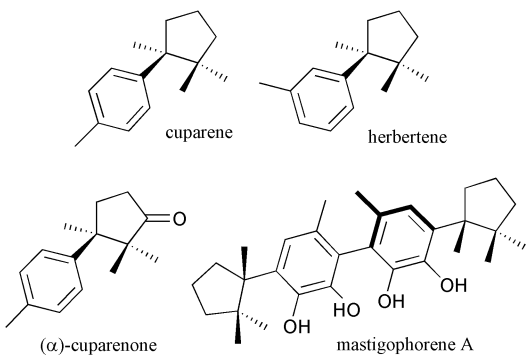
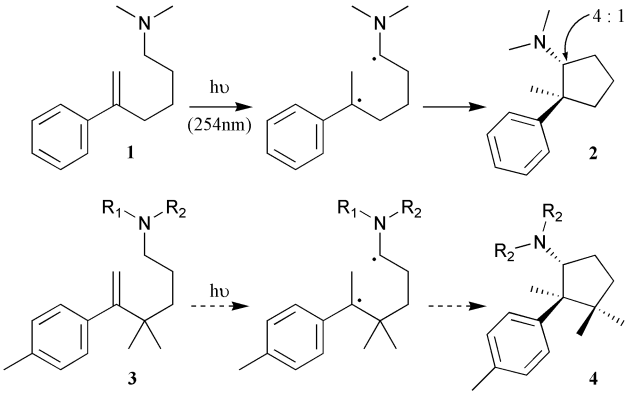
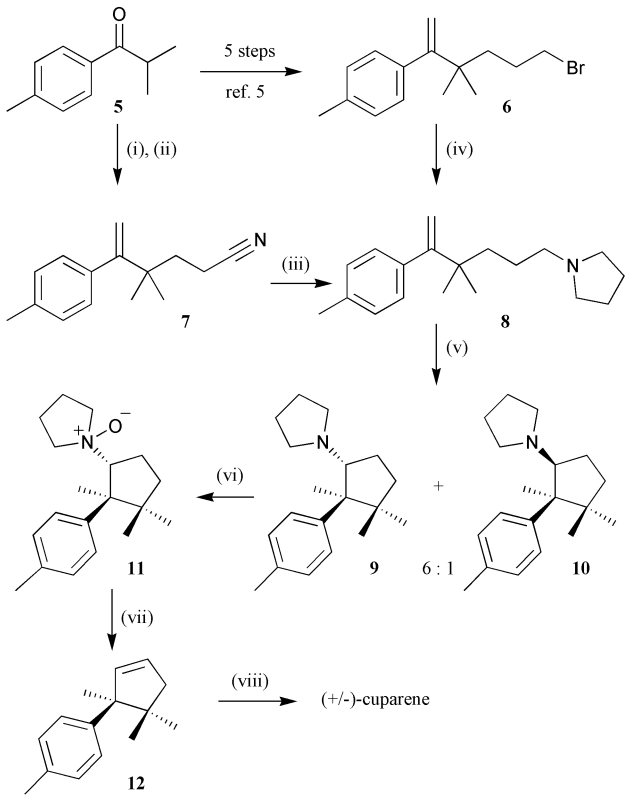


Fig. 1 Cuparene and herbertane sesquiterpenoids.



Scheme 1 Photomediated cyclisation of α-(aminobutyl)styrenes.



Scheme 2 *Reagents and conditions*: (i) acrylonitrile, triton B (40% w/w), 1,4-dioxane, 35 °C, 50 h, 68%; (ii) Ph_3PMeBr, KO^tBu, toluene, 6 h, 62%; (iii) CuCl, pyrrolidine, EtOH, reflux then $NaBH_4$, EtOH, 84%; (iv) pyrrolidine, Na_2CO_3, EtOH, reflux, 4 d, 95%; (v) *hν* (265 nm), hexane, rt, 0.005 M, 20 min, 62% of **9**; (vi) *m*-CPBA, CH_2Cl_2, 83%; (vii) μw (100 W), DMSO, 200 °C, 1 min, 72% or THF, 60 °C, 8 h, 40%; (viii) H_2, 5% Pd/C, EtOAc, rt, 82%.

† Electronic supplementary information (ESI) available: experimental procedures and data including copies of ^{1}H-NMR and ^{13}C-NMR spectra for all new compounds, and NOESY spectra for compounds **9**, **10**, **11**, **15** and **16**. See http://www.rsc.org/suppdata/cc/b3/b300815k/

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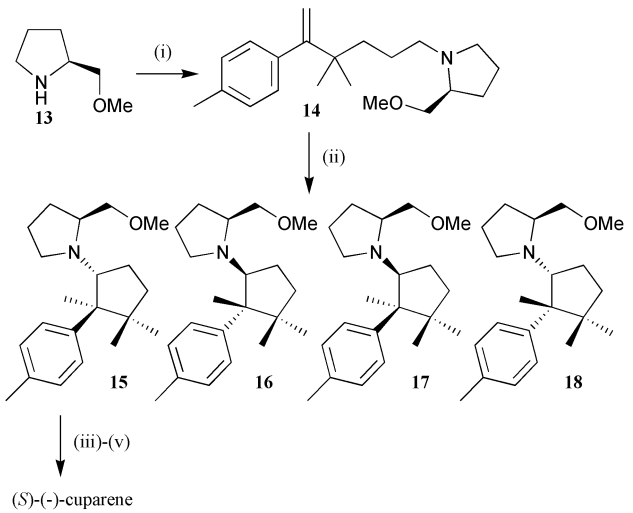
Alternatively, **8** could be prepared from 4-methylisobutyrophenone **5** *via* a three step sequence involving conjugate addition to acrylonitrile, Wittig reaction, and a one-pot reductive amination of nitrile **7** *via* an amidine intermediate.[6]

Irradiation of **8** with a 400 W medium pressure mercury arc lamp in an immersion well reactor under high dilution conditions (0.005 M) cleanly gave a mixture of two cycloadducts in a 6 : 1 ratio as determined by integration of the ^{1}H-NMR spectrum of the crude reaction mixture. The combined yield of the two cycloadducts was 100%, and we were able to separate the major diastereomer **9** in 62% isolated yield by careful column chromatography. NOESY measurements on both **9** and **10** proved that the major isomer **9** had the pyrrolidine and aromatic rings *trans* to one another.‡ Hence we observe the same sense and slighly higher levels of diastereoselectivity as compared with the Lewis system (Scheme 1).

Conversion of cycloadduct **9** to cuparene requires a method for removal of the amine auxiliary. We have developed a three step sequence to achieve this. Oxidation to the *N*-oxide **11** was readily achieved using *m*-CPBA in dichloromethane.[7] The thermally induced Cope elimination of **11** to produce alkene **12** proved more troublesome, with yields at best 40% (THF, 60 °C, 8 h), coupled with formation of significant amounts of other unidentifiable byproducts. Control experiments with independently synthesised *N*-hydroxypyrrolidine (the byproduct in the Cope elimination) proved the alkene **12** to be stable under the reaction conditions and to temperatures up to at least 150 °C in deuterated DMSO. Eventually we found that performing the reaction in a microwave reactor greatly improved the yield of alkene **12**. In practice, a solution of the *N*-oxide in DMSO is allowed to warm up from 25 °C to 200 °C over a period of one minute in the chamber of a 100 W focussed microwave reactor and then allowed to cool to room temperature. Standard work-up and chromatography gave the alkene **12** in 72% yield. Finally, hydrogenation of the double bond completed a racemic synthesis of cuparene.§

In order to render the synthesis asymmetric, we have incorporated a chiral amine into the cyclisation precursor. Alkylation of (*S*)-(+)-2-(methoxymethyl)pyrrolidine **13**[8] with alkyl bromide **6** provided cyclisation precursor **14** in 77% yield (Scheme 3). Gratifyingly, irradiation of **14** also resulted in clean cyclisation (100% by crude ^{1}H-NMR) to a mixture of all four possible diastereomers in an approximate 10 : 5 : 2 : 1 ratio by ^{1}H-NMR of the crude reaction mixture. The two major diastereomers **15** and **16** could be separated by column chromatography, and were shown by NOESY experiments to have the amine and the aromatic ring *trans* to one another, as observed by Lewis in the case of **2** and by ourselves for **9**.



Scheme 3 *Reagents and conditions*: (i) **6**, Na_2CO_3, EtOH, sealed tube, 2 d, 150 °C, 77%; (ii) *hν* (265 nm), hexane, rt, 0.01 M, 1 h, 55% **15** (36% isolated yield); (iii) *m*-CPBA, CH_2Cl_2; (iv) μw (100 W), 200 °C, 1 min, DMSO; (v) 5% Pd/C, H_2, EtOAc, rt, 24% over 3 steps.

The absolute configuration of the major diastereomer **15** was ultimately established by correlation with the natural product, obtained *via* the same three step sequence developed in the racemic series. Hence oxidation to the amine oxide followed by Cope elimination and reduction of the double bond gave (*S*)-(−)-cuparene with an optical rotation identical to that reported for the natural product.[9]

In conclusion, we have synthesised racemic and enatiomerically pure cuparene *via* the photoelectron transfer initiated cyclisation of highly substituted α-(aminobutyl)styrenes **8** and **14** respectively. The 2 : 1 ratio of diastereomers **15** and **16** obtained upon irradiation of **14** establishes for the first time that a chiral amine can control (albeit with modest levels of selectivity) the absolute configuration at a hindered quaternary stereocentre formed in this cyclisation.[10]

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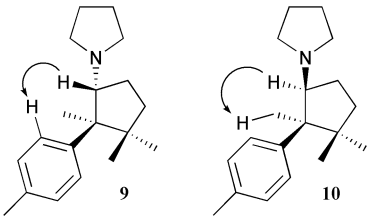
Notes and references

‡ In the NOESY spectrum of the major isomer **9**, the methine proton α to nitrogen shows a cross peak with the aromatic ring protons, but no correlation with the adjacent methyl group on the cyclopentane ring. In the NOESY spectrum of the minor isomer **10**, the methine proton α to nitrogen shows a cross peak with the adjacent methyl group on the cyclopentane ring, and no correlation with the aromatic ring protons. See ESI for details.



§ Although the double bond is simply reduced in this case, it offers a useful handle for further elaboration in the synthesis of other members of the cuparene class of sesquiterpenes. For example, we have also synthesised (±)-cuparenone as a mixture of α- and γ-isomers *via* allylic oxidation and double bond reduction.

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