

Photomediated asymmetric synthesis of (–)-cuparene†

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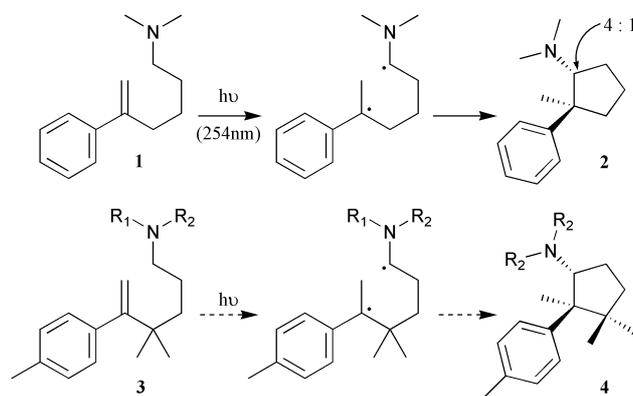
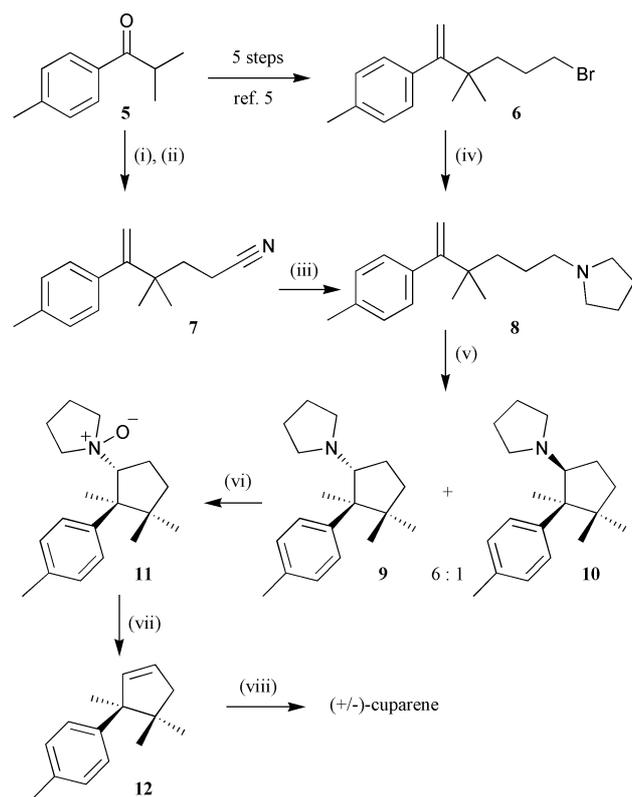
Generation of a benzylic quaternary stereocentre *via* the photomediated cyclisation of a chiral α -(aminobutyl)styrene followed by a microwave-assisted Cope elimination has led to a total synthesis of the sesquiterpene (–)-cuparene.

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 -(dimethylamino)butylstyrene **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** gave a slow but clean transformation to aminostyrene **8** (Scheme 2).

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) $h\nu$ (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%.

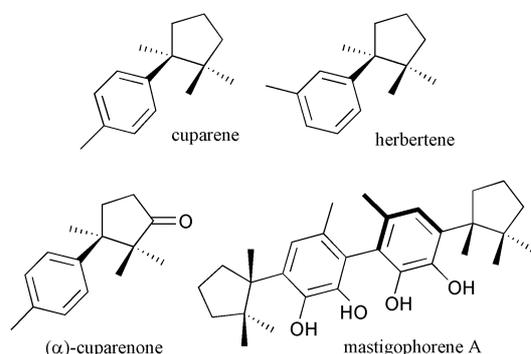


Fig. 1 Cuparene and herbertane sesquiterpenoids.

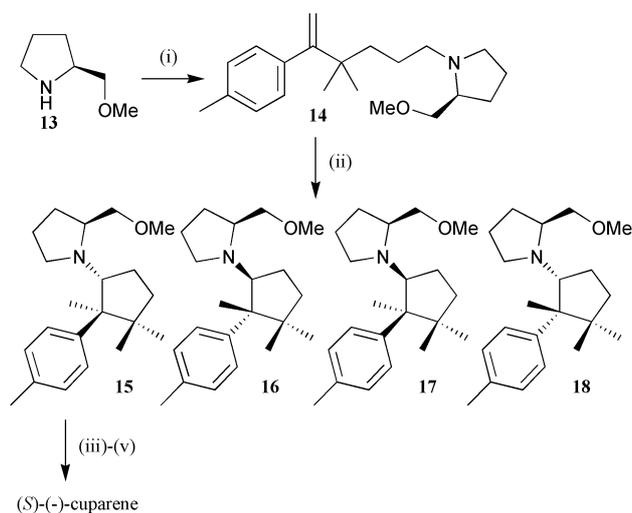
† Electronic supplementary information (ESI) available: experimental procedures and data including copies of $^1\text{H-NMR}$ and $^{13}\text{C-NMR}$ spectra for all new compounds, and NOESY spectra for compounds **9**, **10**, **11**, **15** and **16**. See <http://www.rsc.org/suppdata/cc/b3/b300815k/>

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 ¹H-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 slightly 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 ¹H-NMR) to a mixture of all four possible diastereomers in an approximate 10:5:2:1 ratio by ¹H-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**, Na₂CO₃, 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, CH₂Cl₂; (iv) μw (100 W), 200 °C, 1 min, DMSO; (v) 5% Pd/C, H₂, EtOAc, rt, 24% over 3 steps.

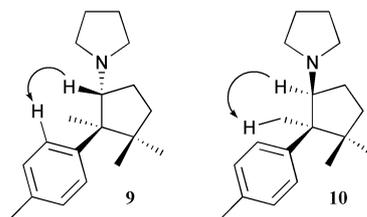
The absolute configuration of the major diastereomer **15** was ultimately established by correlation with the natural product, obtained via the same three step sequence developed in the racemic series. Hence oxidation to the amine oxide followed by Cope elimination and reduction of the double bond gave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

In conclusion, we have synthesised racemic and enantiomerically 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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