

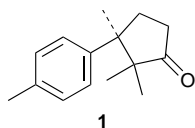
New asymmetric construction of the benzylic quaternary stereogenic centre: an enantiocontrolled access to (–)- α -cuparenone

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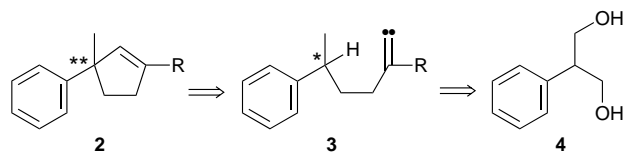
An efficient and enantiocontrolled formal total synthesis of (–)- α -cuparenone has been accomplished by employing a new asymmetric construction methodology for formation of the benzylic quaternary stereogenic centre.

Development of the methodology for assembling an asymmetric quaternary stereogenic centre has been a challenging and important target in organic synthesis.¹ Particularly, construction of benzylic quaternary centres has become of special interest² since it is involved in many biologically significant molecules. Here we present a new and efficient strategy for the asymmetric construction of the benzylic quaternary carbon centre by illustrating an enantiocontrolled formal total synthesis of (–)- α -cuparenone **1**.³ Our basic strategy is shown in Scheme 1.



We envisaged that a pivotal construction of the benzylic quaternary carbon in **2** might be realized by employing the diastereoselective [1,5] C–H insertion reaction of alkylidene carbene **3**,⁴ in which the benzylic tertiary asymmetric centre should be generated *via* a lipase-mediated asymmetric acetylation⁵ of the prochiral diol **4**. It is well known that the C–H insertion reaction proceeds with complete retention of configuration.^{4b,c}

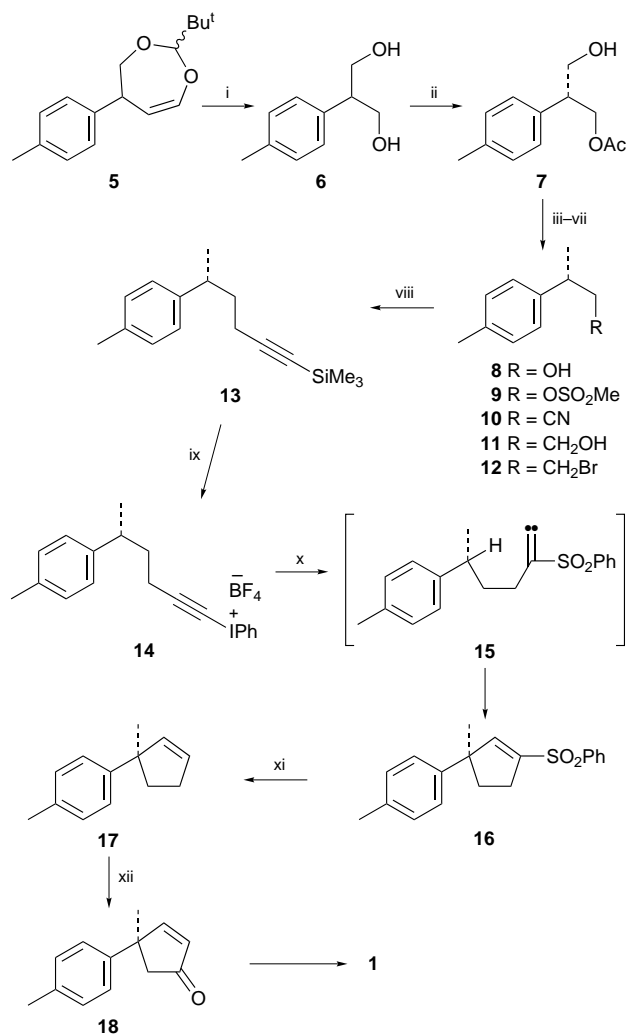
Treatment of 2-*tert*-butyl-4,5-dihydro-5-(4-methylphenyl)-1,3-dioxepine **5**,^{6a} prepared by the Heck reaction⁶ between 4-methyliodobenzene and 2-*tert*-butyl-4,7-dihydro-1,3-dioxepine,⁷ under ozonolytic cleavage conditions followed by reductive workup with NaBH₄ provided the prochiral 1,3-diol **6** in 84% yield (Scheme 2). It should be noted that the procedure is efficient and superior to the conventional method.⁸ With the prochiral diol in hand, we examined the optimum conditions for asymmetric acetylation using some lipases.⁹ Of these, porcine pancreatic lipase (PPL)-catalysed transesterification in diethyl ether using vinyl acetate as an acetyl donor at room temperature proved to be the best choice and (*R*)-monoacetate **7**, [α]_D + 15.6 (*c* 1.28, CHCl₃) {lit.⁹ for the (*S*)-isomer; [α]_D – 16.2 (*c* 1.20, CHCl₃)}, was obtained in 84% yield. The enantiomeric excess was 99% as determined by ¹H NMR analysis of its MTPA ester derivative. Removal of the hydroxy moiety in **7** by tosylation and subsequent reduction with NaBH₄ in Me₂SO⁹ furnished the alcohol **8**, which was mesylated to give **9** in 88% yield from **7**. Sequential cyanation, DIBAL-H reduction–acidic workup, and further reduction with NaBH₄ gave one-carbon elongated alcohol **11** in 75% overall yield. Reaction of the bromide **12**,



Scheme 1

prepared from **11** by a standard method, with lithium trimethylsilylacetylide produced the alkynylsilane **13** in 69% yield.

The stage was now set to explore the crucial construction of the quaternary stereogenic centre *via* the [1,5] C–H insertion reaction of the alkylidene carbene. For this purpose, we intended to use the procedure developed by Ochiai,^{4d,e,g} since the product obtained by this method is vinyl sulfone, which would be



Scheme 2 Reagents and conditions: i, O₃ then NaBH₄, CH₂Cl₂, –78 to 0 °C, 84%; ii, vinyl acetate, PPL, Et₂O, room temp., 84%; iii, TsCl, Et₃N, DMAP, CH₂Cl₂, room temp., then NaBH₄, Me₂SO, 60 °C, 73%; iv, MsCl, Pr₂NEt, CH₂Cl₂, room temp., 88%; v, KCN, 18-crown-6, Me₂SO, 60 °C, 90%; vi, DIBAL-H, hexane–CH₂Cl₂ (1 : 1), –78 °C then 1 M HCl, NaBH₄, MeOH, 75%; vii, Ph₃P, CBr₄, CH₂Cl₂, –40 °C, 94%; viii, Bu^tLi, HC≡CSiMe₃, THF, HMPA, –78–0 °C, 69%; ix, (PhIO)_n, BF₃·OEt₂, CH₂Cl₂, 0 °C; x, PhSO₂Na, H₂O, 0 °C, 83% for 2 steps; xi, Na–Hg (5%), MeOH, sonication, room temp., 70%; xii, PDC, Bu^tOOH, Celite, benzene, 10 °C–room temp., 72%

convenient for further transformations. Thus, treatment of **13** with iodosylbenzene in the presence of boron trifluoride–diethyl ether in CH₂Cl₂ at 0 °C followed by treatment with aqueous sodium tetrafluoroborate provided the iodonium tetrafluoroborate **14**, which was immediately exposed to aqueous sodium benzenesulfinate at 0 °C to give the cyclized vinyl sulfone **16**,[†] via the alkylidene carbene intermediate **15**, in 83% overall yield from **13** as the sole product. The absolute configuration at the newly-generated quaternary centre was deduced to be *R*, which was confirmed by the following conversion. Removal of the benzenesulfonyl moiety in **16** using Na–Hg under sonication¹⁰ afforded **17** in 70% yield. Finally, oxidation of the allylic methylene in **17** with pyridinium dichromate (PDC) in the presence of *tert*-butylhydroperoxide and Celite¹¹ produced the enone **18**, whose ¹H NMR data and optical rotation, [α]_D + 101 (*c* 1.28, EtOH) {lit.^{3a} [α]_D + 114 (*c* 1.36, EtOH)}, were identical with those reported. Since the compound **18** has already been converted into (–)-α-cuparenone **1** by a two-step sequence,^{3a} the present synthesis constitutes a formal total synthesis of **1**.

In summary, we have developed an efficient and unprecedented methodology for assembling benzylic quaternary stereogenic centres and demonstrated the formal total synthesis of (–)-α-cuparenone as an application of the procedure.

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Footnotes

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† Selected spectroscopic data for **16**: pale yellow oil; [α]_D +34.6 (*c* 0.38, CHCl₃); δ_H(200 MHz, CDCl₃) 1.45 (3 H, s), 2.14–2.21 (2 H, m), 2.31 (3 H, s), 2.54–2.73 (2 H, m), 6.82 (1 H, s), 7.09 (4 H, s), 7.55–7.61 (3 H, m), 7.91–8.43 (2 H, m); δ_C(100 MHz, CDCl₃) 20.9 (CH₃), 26.6 (CH₃), 30.0 (CH₂), 41.0 (CH₂), 52.9 (C), 124.5 (CH × 2), 128.0 (CH × 2), 129.2 (CH × 2), 129.3 (CH × 2), 133.5 (CH), 136.2 (C), 139.5 (C), 143.2 (C), 143.8 (C), 149.5 (CH); *m/z* (EI) 312 (M⁺); HRMS (EI) calc. for C₁₉H₂₀O₂S, 312.1184. Found: 312.1169. Anal. calc. for C₁₉H₂₀O₂S: C, 73.04; H, 6.45. Found: C, 72.89; H, 6.49%.

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