

Radical cyclisation with high diastereofacial selectivity: asymmetric synthesis of (+)-12b-epidevinylantirhine

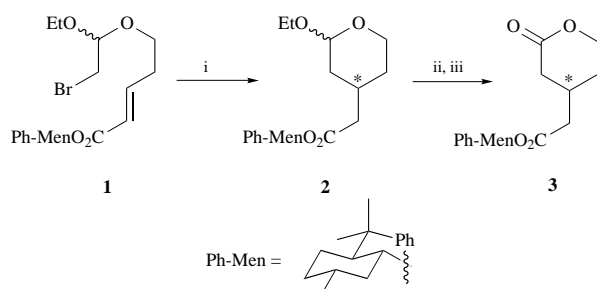
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Radical cyclisation of the chiral α,β -unsaturated ester **1**, carried out in the presence of MAD, gives six-membered cyclic acetal **2** diastereoselectively, which is transformed into (+)-12b-epidevinylantirhine **7**.

Radical cyclisation is well recognised as one of the most versatile methods for the creation of new carbon-carbon bonds.¹ Previously, we demonstrated the stereoselective formation of six-membered ring compounds with excellent 1,2-asymmetric induction.² As an extension of this work, a diastereofacially selective radical cyclisation of a chiral α,β -unsaturated ester has been investigated. We now report the highly selective outcome, as well as an asymmetric synthesis of (+)-12b-epidevinylantirhine, a cleaved product of geissoschizol.³

The substrate **1** was prepared from 3-*tert*-butyldimethylsilyloxypropanol⁴ using standard procedures; oxidation with pyridinium dichromate (PDC), Wittig reaction using (-)-8-phenyl-*p*-menthan-3-yl (triphenylphosphoranylidene)acetate,⁵ deprotection with Bu₄NF in the presence of acetic acid and acetal formation with ethyl vinyl ether and *N*-bromosuccinimide (NBS).⁶ Radical cyclisation of **1** was carried out under various conditions. Since purification of cyclic acetal **2** was difficult, the crude product was converted into the lactone **3** (Scheme 1). The overall yield for the three steps and the dia-



Scheme 1 Reagents and conditions: i, see Table 1; ii, 10% HClO₄, THF, 20 °C, 12 h; iii, Ag₂CO₃-Celite, benzene, reflux, 1 h

stereoisomeric excess (de), determined by ¹H NMR spectroscopy (300 MHz in C₆D₆) of **3**, are shown in Table 1.

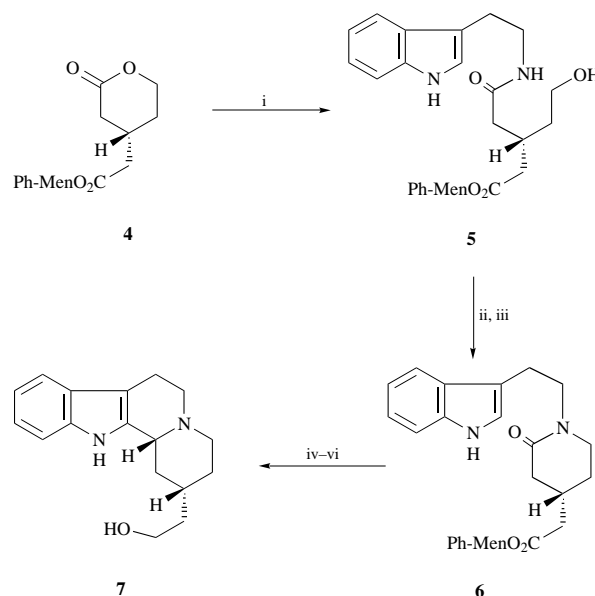
Heating with Bu₃SnH (entry 1) and (Me₃Si)₃SiH (entry 2) in the presence of azoisobutyronitrile (AIBN) resulted in poor diastereoselectivities (13% de), while reaction with Bu₃SnH and Et₃B⁷ at -40 °C gave 31% de (entry 3). The diastereoselectivity was improved by addition of a Lewis acid.⁸ A moderate selectivity, 67% de, was obtained by reaction in the presence of 4.0 equiv. of Me₃Al (entry 4). However, no formation of the other stereoisomer was observed (>98% de) in the ¹H NMR spectrum of **3**, prepared by reaction in the presence of 2.0 equiv. of methylaluminium bis(2,6-di-*tert*-butyl-4-methylphenoxy) (MAD)⁹ (entry 5).

The stereochemistry of the predominant isomer **4** was established by transformation into (+)-12b-epidevinylantirhine **7** (Scheme 2). Treatment of the product **4**, obtained using MAD (Table 1, entry 5), with tryptamine in hot toluene afforded **5**, which was cyclised to **6** in two steps. The Bischler-Napieralski

Table 1 Diastereofacially selective radical cyclisation of **1**

| Entry | Conditions | Yield of 3 (%) ^a | De (%) ^b |
|-------|--|------------------------------------|---------------------|
| 1 | Bu ₃ SnH, AIBN, benzene, reflux, 3.5 h | 70 | 13 |
| 2 | (Me ₃ Si) ₃ SiH, AIBN, benzene, reflux, 4 h | 65 | 13 |
| 3 | Bu ₃ SnH, Et ₃ B, toluene, -40 °C, 1.5 h | 44 | 31 |
| 4 | Bu ₃ SnH, Et ₃ B, Me ₃ Al, toluene, -40 °C, 2 h | 51 | 67 |
| 5 | Bu ₃ SnH, Et ₃ B, MAD, toluene, -40 °C, 1.5 h | 38 | >98 |

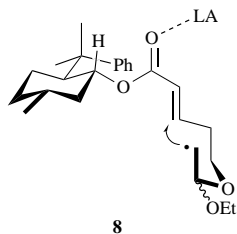
^a Overall yield for three steps from **1**. ^b De was calculated based on the ¹H NMR spectrum of **3**.



Scheme 2 Reagents and conditions: i, tryptamine, toluene, 110 °C, 7.5 h, 72%; ii, MeSO₂Cl, Et₃N, benzene, 20 °C, 1 h; iii, KH, 18-crown-6, MeOCH₂CH₂OMe, 20 °C, 1.5 h, 69% for 2 steps; iv, POCl₃, MeCN, reflux, 1.5 h; v, NaBH₄, MeOH, 0 °C, 1 h; vi, DIBAL, toluene, 0 °C, 0.5 h, 35% for 3 steps

reaction of **6**, followed by reduction of the resulting iminium salt with NaBH₄, produced stereoselectively the indolo[2,3-*a*]quinolizine as a single stereoisomer, which was further reduced with DIBAL to provide (+)-**7**, [α]_D²¹ +12.3 (*c* 0.50 in MeOH). The relative stereochemistry was deduced from the ¹H NMR spectroscopic data.^{3a} The selective formation of the single isomer by the above reduction with NaBH₄ is explainable by stereoelectronic effects.¹⁰ The *R* configuration at the 12b position was suggested by the circular dichroism (CD) spectrum, [θ] -3.14 × 10³ (269 nm in MeOH).¹¹ This indicates that the radical cyclisation proceeds *via* the *s-trans* conformation **8**, and is restricted by the presence of the Lewis acid.

It is expected that the above six-membered ring compounds **2**



and **4**, possessing newly created stereogenic centres with three differentiated C-2 units, will be useful as chiral intermediates.

Experimental

(+)-(1' R,3' R,4' S)-8'-Phenyl-*p*-menthan-3'-yl (4S)-2-oxo-3,4,5,6-tetrahydro-2H-pyran-4-ylacetate **4**

To a mixture of **1** (42.6 mg, 0.089 mmol) and Bu₃SnH (0.036 cm³, 0.133 mmol) in dry toluene (20 cm³) at 20 °C was added 0.5 M MAD in toluene (0.186 cm³, 0.093 mmol), and the mixture was stirred for 30 min at -40 °C. After addition of 1.0 M Et₃B in hexane (0.093 cm³, 0.093 mmol) at -40 °C, the mixture was stirred for 1.5 h at the same temperature. After evaporation of the solvents, followed by dilution with Et₂O, the resulting mixture was washed with 10% HCl, saturated aqueous NaHCO₃ and brine, dried (MgSO₄) and the solvent evaporated. A mixture of the residue and 10% HClO₄ (2 cm³) in THF (4 cm³) was stirred for 12 h at 20 °C. After dilution with Et₂O, the organic layer was washed with saturated aqueous NaHCO₃ and brine and dried (MgSO₄). Evaporation of the solvents gave the crude cyclic hemiacetals, which were taken up into dry benzene (10 cm³). After addition of Ag₂CO₃-Celite (17:15 w/w, 890 mg, 0.887 mmol), the mixture was heated for 1 h under reflux. Filtration through Celite, followed by evaporation of the filtrate, afforded a residue which was subjected to column chromatography on silica gel. Elution with hexane-AcOEt (3:1 v/v) provided **4** (12.6 mg, 38%) as an oil; [α]_D²⁴ +3.9 (*c* 1.05 in CHCl₃); ν_{max}/cm⁻¹ 1735 and 1725 (C=O); δ_H(300 MHz, CDCl₃) 0.88 (3 H, d, *J* 6.6, 7'-H₃), 0.93-1.01 (1 H, m), 1.10-1.26 (1 H, m), 1.18 (3 H, s, 8'-Me), 1.29 (3 H, s, 8'-Me), 1.33-1.59 (4 H, m), 1.62-1.76 (2 H, m), 1.80-1.90 (3 H, m), 1.94-2.13 (3 H, m), 2.53-2.65

(1 H, m), 4.16-4.24 (1 H, m, 6-H), 4.31-4.38 (1 H, m, 6-H), 4.81 (1 H, ddd, *J* 4.4, 10.7, 10.7, 3'-H), 7.09-7.31 (5 H, m, Ph) (HRMS: found M⁺ - CMe₂Ph, 253.1490. C₁₄H₂₁O₄ requires 253.1440).

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