PERKIN 1 COMMUNICATION

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

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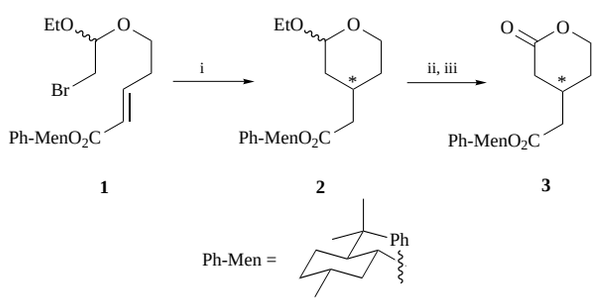
Radical cyclisation of the chiral α,β-unsaturated ester 1, carried out in the presence of MAD, gives six-membered cyclic acetal 2 diastereoselectively, which is transformed into (+)-12b-epidevinylantirhine 7.

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*-butyldimethylsilyloxypropanol[4] using standard procedures; oxidation with pyridinium dichromate (PDC), Wittig reaction using (−)-8-phenyl-*p*-menthan-3-yl (triphenylphosphoranylidene)acetate,[5] deprotection with Bu_4NF 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 diastereoisomeric excess (de), determined by ^{1}H NMR spectroscopy (300 MHz in C_6D_6) of **3**, are shown in Table 1.



Scheme 1 *Reagents and conditions:* i, see Table 1; ii, 10% $HClO_4$, THF, 20 °C, 12 h; iii, Ag_2CO_3–Celite, benzene, reflux, 1 h

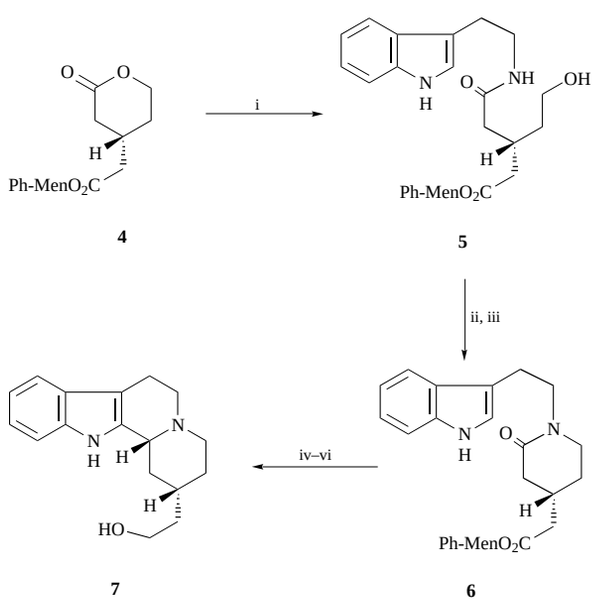
Heating with Bu_3SnH (entry 1) and $(Me_3Si)_3SiH$ (entry 2) in the presence of azoisobutyronitrile (AIBN) resulted in poor diastereoselectivities (13% de), while reaction with Bu_3SnH and Et_3B[7] at −40 °C gave 31% de (entry 3). The diastereoselectivity was improved by addition of a Lewis acid.[8] A moderate selectivity, 67% de, was obtained by reaction in the presence of 4.0 equiv. of Me_3Al (entry 4). However, no formation of the other stereoisomer was observed (>98% de) in the ^{1}H NMR spectrum of **3**, prepared by reaction in the presence of 2.0 equiv. of methylaluminium bis(2,6-di-*tert*-butyl-4-methylphenoxide) (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_3SnH, AIBN, benzene, reflux, 3.5 h	70	13
2	$(Me_3Si)_3SiH$, AIBN, benzene, reflux, 4 h	65	13
3	Bu_3SnH, Et_3B, toluene, −40 °C, 1.5 h	44	31
4	Bu_3SnH, Et_3B, Me_3Al, toluene, −40 °C, 2 h	51	67
5	Bu_3SnH, Et_3B, MAD, toluene, −40 °C, 1.5 h	38	>98

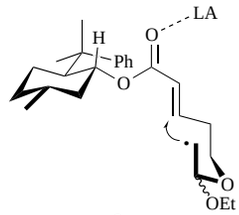
[a] Overall yield for three steps from **1**. [b] De was calculated based on the ^{1}H NMR spectrum of **3**.



Scheme 2 *Reagents and conditions:* i, tryptamine, toluene, 110 °C, 7.5 h, 72%; ii, $MeSO_2Cl$, Et_3N, benzene, 20 °C, 1 h; iii, KH, 18-crown-6, $MeOCH_2CH_2OMe$, 20 °C, 1.5 h, 69% for 2 steps; iv, $POCl_3$, MeCN, reflux, 1.5 h; v, $NaBH_4$, 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 $NaBH_4$, produced stereoselectively the indolo[2,3-*a*]quinolizine as a single stereoisomer, which was further reduced with DIBAL to provide (+)-**7**, $[a]_D^{21}$ +12.3 (*c* 0.50 in MeOH). The relative stereochemistry was deduced from the ^{1}H NMR spectroscopic data.[3a] The selective formation of the single isomer by the above reduction with $NaBH_4$ is explainable by stereoelectronic effects.[10] The *R* configuration at the 12b position was suggested by the circular dichroism (CD) spectrum, $[\theta]$ -3.14×10^3 (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**



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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 (4*S*)-2-oxo-3,4,5,6-tetrahydro-2*H*-pyran-4-ylacetate 4

To a mixture of **1** (42.6 mg, 0.089 mmol) and Bu_3SnH (0.036 cm^3, 0.133 mmol) in dry toluene (20 cm^3) at 20 °C was added 0.5 M MAD in toluene (0.186 cm^3, 0.093 mmol), and the mixture was stirred for 30 min at −40 °C. After addition of 1.0 M Et_3B in hexane (0.093 cm^3, 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 Et_2O, the resulting mixture was washed with 10% HCl, saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$) and the solvent evaporated. A mixture of the residue and 10% $HClO_4$ (2 cm^3) in THF (4 cm^3) was stirred for 12 h at 20 °C. After dilution with Et_2O, the organic layer was washed with saturated aqueous $NaHCO_3$ and brine and dried ($MgSO_4$). Evaporation of the solvents gave the crude cyclic hemiacetals, which were taken up into dry benzene (10 cm^3). After addition of Ag_2CO_3–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; $[a]_D^{24}$ +3.9 (*c* 1.05 in $CHCl_3$); ν_{max}/cm^{-1} 1735 and 1725 (C=O); δ_H(300 MHz, $CDCl_3$) 0.88 (3 H, d, *J* 6.6, 7′-H_3), 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 $M^+ - CMe_2Ph$, 253.1490. $C_{14}H_{21}O_4$ requires 253.1440).

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