Enantioselective Synthesis and Absolute Configuration of (*R*)-(+)-Lunacridine and (*S*)-(+)-Lunacrine

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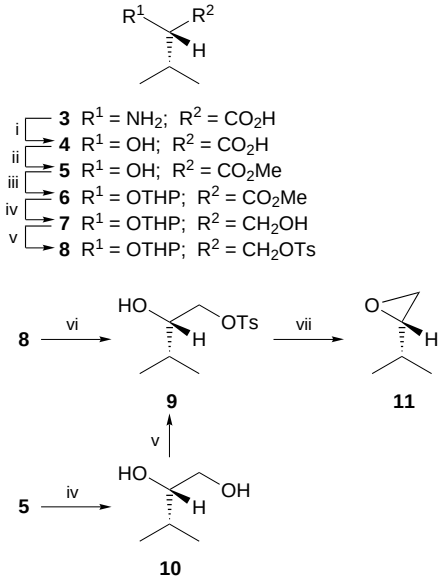
(*R*)-(+)-Lunacridine **1** has been synthesised in 97.3% e.e. using a chiron approach through L-valine and D-mannitol as the starting compounds in order to corroborate its absolute configuration.

The prenylated quinolinone alkaloids lunacridine and lunacrine have been isolated from *Lunasia* sp.[1] of different sources in optically active form and given structures **1** and **2** respectively on the basis of degradative studies, spectroscopic data[2] and a synthesis of the racemates (in extremely poor yield.[3] An attempt was also made by Grundon and coworkers[4] to assign absolute configurations to the title compounds through asymmetric synthesis in less than 1% e.e. The configurational assignments to compounds **1** and **2** were based on the assumption that (*S*)-peroxycamphoric acid on reaction with an olefin yields an (*S*)-epoxide and by comparison of the direction of specific rotation of their compound **1** with that reported for the natural product. In view of very low optical induction and magnitude of the specific rotation, $[\alpha]_D^{25} = -0.19$ for **1**, any assignment of absolute configuration to **1** and **2** needs further support to be unequivocal. Recently Barr *et al.*[5] have used a cumbersome resolution procedure to prepare the title compounds in poor overall yield. Therefore, the present studies were planned in order to accomplish an unambiguous and highly enantioselective synthesis of **1** and **2** so as to assign absolute configurations to these compounds on firm grounds. The strategy used for the present asymmetric synthesis is based on a chiron approach wherein optically pure (*S*)-(+)-valine and (*D*)-(+)-mannitol were used as the starting compounds. The synthetic investigations carried out are delineated below.

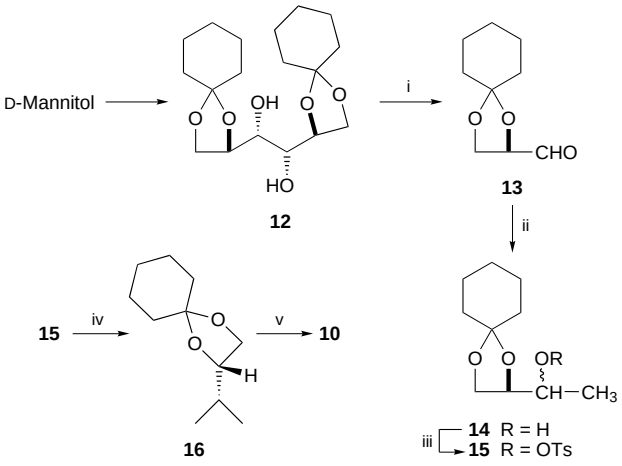
Synthesis of (S)-*Epoxide* **11**.—(i)(S)-*Valine as starting compound (Scheme 1)*.



Scheme 1 *Reagents and conditions:* i, HNO_2, 0 °C; ii, Amberlyst-15–MeOH; iii, DHP-H^+; iv, $LiAlH_4$; v, TosCl-py; vi, MeOH–H^+; vii, NaOMe

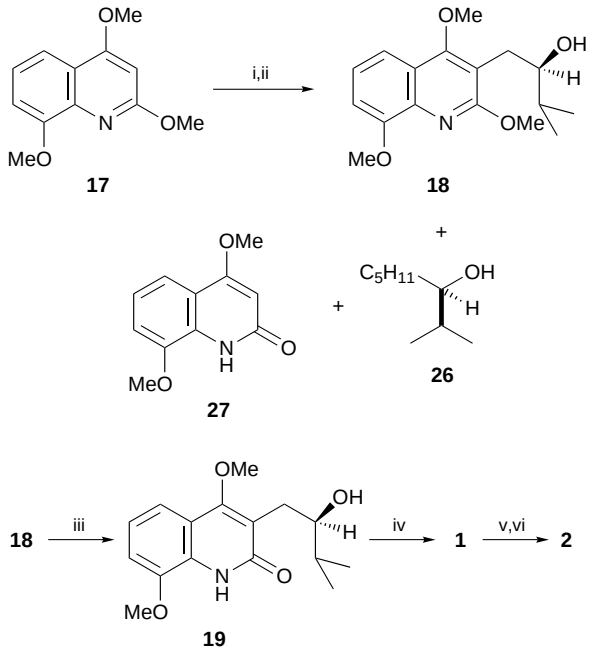
*To receive any correspondence.

(ii) D-*Mannitol as starting compound (Scheme 2).*



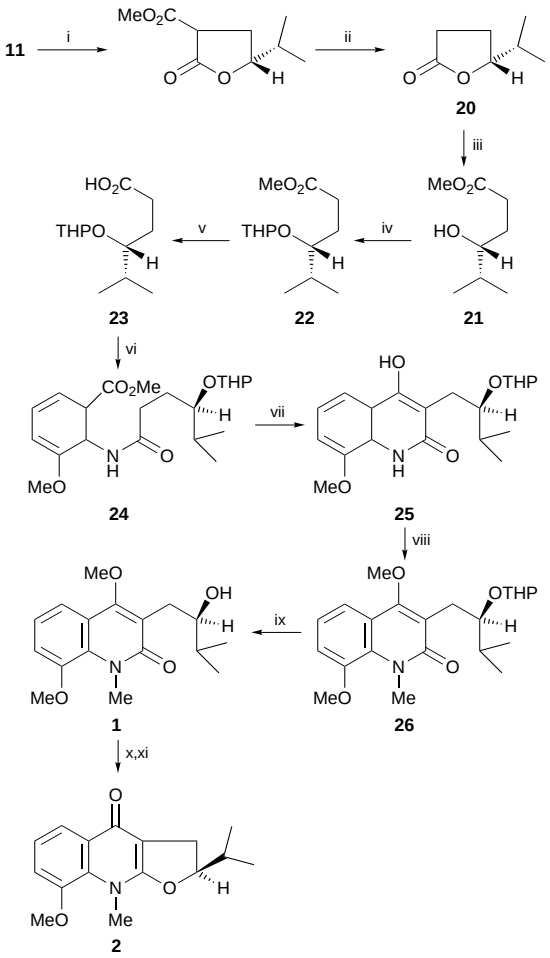
Scheme 2 *Reagents and conditions:* i, $NaIO_4$–aq. MeCN; ii, MeMgI; iii, TosCl–py; iv, $LiCuMe_2$; v, MeOH–H^+

Transformation of **11** *into Compounds* **1** *and* **2**.—*First approach (Scheme 3).*



Scheme 3 *Reagents and conditions:* i, BuLi at −78 °C; ii, **11**; iii, anhyd. HCl–OEt_2; iv, CH_2N_2; v, TosCl–py; vi, aq. NaOH

Second approach (Scheme 4).



Scheme 4 *Reagents and conditions:* i, $CH_2(CO_2Me)_2$; ii, NaCl–DMSO; iii, Amberlyst-15–MeOH; iv, DHP–H^+; v, aq. NaOH–H^+; vi, DCC followed by methyl 2-amino-3-methoxybenzoate; vii, 2 equiv. NaH–PhMe; viii, KOH–DMF–Me_2SO_4; ix, MeOH–H^+; x, TosCl–py; xi, aq. NaOH

The synthetic material had $[\alpha]_D^{30} = +28.47°$ (*c*, 1.5 in EtOH). Its mp and IR, UV and ^{1}H NMR data were identical with those reported for the natural product. Optical purity was also checked by derivatization of **1** with Mosher's reagent followed by ^{1}H NMR analysis of the resulting compounds. The transformation **1**→**2** has already been reported.[1]

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Techniques used: IR, ^{1}H NMR, UV spectroscopy, polarimetry

References: 9

Schemes: 4

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