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Enantiodivergent Synthesis of 2-Hydroxymethyl-3-hydroxy-4-nitro-pyrrolidines Through Tandem Michael-Henry Reaction Using L-Serine as the Chiral Educt.

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Abstract: By utilizing L-serine, both enantiomers of all *trans* 2-hydroxymethyl-3-hydroxy-4-nitro-pyrrolidine were efficiently prepared through tandem Michael-Henry methodology. Their stereochemistry has been assigned through conversion of one of them to *trans* 2-hydroxymethyl-3-hydroxypyrrolidine, a naturally occurring compound recently isolated from *Castanospermum australe*.

Naturally occurring and synthetic polyhydroxylated pyrrolidines and piperidines have recently received considerable attention due to their role as intermediates for the synthesis of more complex bioactive molecules or to their own biological activities.[1,2]

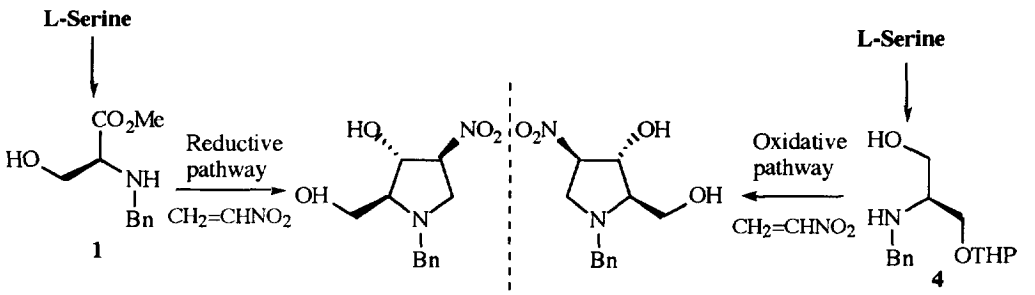
In connection with our program dealing with the tandem annulation chemistry of unsaturated nitro derivatives, we have recently[3] reported an efficient methodology for the synthesis of nitrohydroxylated pyrrolidine and piperidine ring systems entailing on easy intramolecular nitroaldol reaction (Henry reaction) of the nitroalkane adducts derived by the intermolecular Michael addition of nitrogen nucleophiles bearing at the α or β position a suitable precursor of an aldehyde function to the *in situ* generated nitroethylene.[4] In order to extend the efficiency of our own protocol, we decided to investigate the asymmetric version of tandem Michael-Henry reaction methodology.

We are here describing the preliminary results of these efforts in which 2-hydroxymethyl-3-hydroxy-4-nitro-pyrrolidine derivatives have been obtained in both the enantiomeric forms from a common chiral educt.

Considering that the crucial carbon-carbon bond forming reaction for the construction of the nitrogen heterocycles required the generation of an α-aminoaldehyde intermediate either by DIBAH reduction of an ester moiety or by Swern oxidation of a primary β-alcohol function, we turned our attention to the inexpensive L-serine, a widely used building block for natural product synthesis,[5] which possesses both these functionalities at the chiral carbon bearing the nitrogen atom. We anticipated that the alternative use of the two oxygenated substituents as an aldehyde precursor (Scheme I) through suitable modification of their oxidation state could allow us to invert the configuration,[6] avoiding, of course, a direct reduction of the ester group which would

result in the formation of an achiral aminodiol. Therefore, we searched for a careful combination of protecting groups and chemical manipulations.

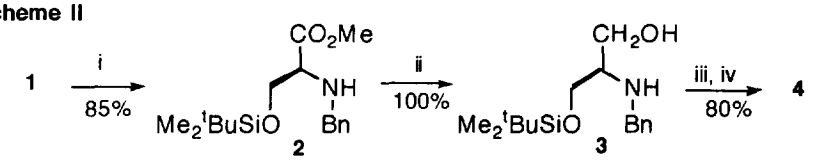
Scheme I



The required substrates **2** and **4** were efficiently obtained starting from the N-benzyl-protected derivative **1**, obtained as an oil, $[\alpha]^{22}_D$= -29.1 (c 8.18, $CHCl_3$), by reductive amination of L-serine methyl ester with benzaldehyde, following the protocol previously described[7] for the racemic compound. The benzyl protecting group has been selected in order to preserve the nucleophilic character of nitrogen, apart from being reductively removable at a later stage. The tert-butyldimethylsilyl ether **2** was smoothly obtained under standard conditions in 85% yield[8] and it served both as the fragment for the reductive pathway as well as a starting point for the preparation of the fragment **4**, required for the oxidative pathway.

The transformation of **2** to the primary alcohol **4** called for a $LiAlH_4$ reduction of the ester moiety to the corresponding primary alcohol **3**, which was transformed into the corresponding tetrahydropyranyl ether, obtained, as expected, as a diastereomeric mixture.[9] However, this protection was dictated by the concomitant presence of a nucleophilic nitrogen and of an additional differently hydroxy protected function, which could be selectively and quantitatively removed by fluoride ions to give the original primary alcohol **4** in 80% yield. The overall high-yield sequence is summarized in the following Scheme II.

Scheme II

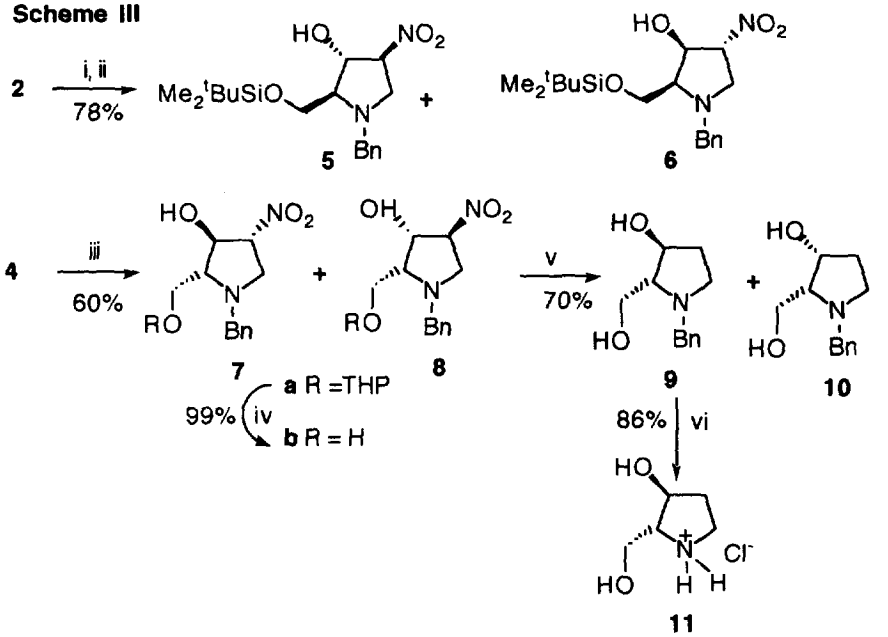


Reagents: i, $Me_2{}^tBuSiCl$, Et_3N, DMAP, CH_2Cl_2, rt, 4h; ii, $LiAlH_4$, THF, 0°C; iii, DHP, p-TosOH, CH_2Cl_2, -10 to 0°C; iv, $But_4N^+ F^-$, THF.

With **2** and **4** in hand, the stage was set for applying the one-pot tandem Michael-Henry protocol. Thus, DIBAH reduction of **2** at -78°C, followed by quenching with methanol and addition of 2-benzoyloxy-1-nitroethane, used as the safe precursor of nitroethylene, gave a 9 : 1 mixture of the two pyrrolidine derivatives **5** and **6** (75% yield), which were isolated through flash chromatography on silica gel (eluent: AcOEt : cyclohexane, 9 : 1). On the other hand, treatment of **4** with the usual nitroethylene precursor proceeded uneventfully to produce the expected Michael adduct, which was directly submitted to Swern oxidation to give a mixture of two pyrrolidine derivatives **7** and **8** in 60% yield. The reaction proceeded less stereoselectively than the reductive

pathway. In fact, after removal of the hydroxy protecting group by acid treatment, a 3 : 1 mixture of the pyrrolidine derivative **7b** and **8b** could be isolated after flash chromatography on silica gel (eluent: MeOH : AcOEt ; 1 : 9). (Scheme III).

Scheme III



Reagents: i, DIBAH, -78°C, then MeOH; ii, $BzOCH_2CH_2NO_2$; iii, $BzOCH_2CH_2NO_2$, then Swern oxidation; iv, H_3O^+; v, TBTH, AIBN, MeC_6H_5; vi, H_2, Pd/C, 3.5 atm.; MeOH, HCl.

In both cases the relative stereochemistry of the substituents on the pyrrolidine ring system could be determined by ^1H NMR, the all *trans* compound being the prevalent diastereomer. The absolute stereochemistry of **7a** had to be deduced from that of the (2R,3S)-2-hydroxymethyl-3-hydroxypyrrolidine **11**, a natural compound of known stereochemistry isolated from *Castanospermum australe* several years ago,[10] derived from a two-step sequence involving denitration of **7b** by Ono's procedure[11] to give (2R,3S)-N-benzyl-3-hydroxy-2-hydroxymethylpyrrolidine **9** $[\alpha]^{22}_D$= -43.3 (c 1, $CHCl_3$), which underwent hydrogenolysis of the benzyl protecting group to furnish **11**, isolated as its hydrochloride, mp 96-98°C, $[\alpha]^{22}_D$= +47 (c 0.5, H_2O), lit.[8], mp 108-110°C, $[\alpha]^{22}_D$ = +46.5 (c 0.5, H_2O), lit.[12], mp 63-65°C, $[\alpha]^{22}_D$ = +46 (c 0.3, H_2O), lit.[13], mp 120°C, $[\alpha]^{20}_D$ = +45.7 (c 0.21, H_2O). Moreover, denitration of **8b** produced (2R,3R)-N-benzyl-3-hydroxy-2-hydroxymethylpyrrolidine **10**, $[\alpha]^{22}_D$ = -58 (c 1.3, $CHCl_3$), lit.[12], $[\alpha]^{22}_D$ = -56.5 (c 0.5, $CHCl_3$).

In summary, we have developed an efficient one-pot procedure for the synthesis of optically active hydroxylated pyrrolidine ring systems in both enantiomeric forms employing L-serine as common and convenient starting material. The application of this strategy to more complex targets and the enantioselective synthesis of the homologuous polyhydroxylated piperidine ring systems are under active investigation.

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8. Satisfactory spectral and analytical data were obtained for all new compounds. Selected compounds: **2** , oil, $[\alpha]^{22}_D$= -11.25 (c 3.2, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 0.02 (s, 6H), 0.86 (s, 9H), 2.1 (sb, 1H), 3.4 (t, 1H, J=5.4), 3.65 (d, 1H, J=14.6), 3.71 (s, 3H), 3.85 (m, 2H), 3.9 (d, 1H, J=14.6), 7.5 (m, 5H). **3**, oil, $[\alpha]^{22}_D$ = +7.5 (c 1.5, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 0.05 (s, 6H), 0.9 (s, 9H), 2.3 (sb, 2H), 2.8 (quintet, 1H, J=5), 3.4-3.7 (m, 4H), 3.8 (s, 2H), 7.5 (m, 5H). **5**, oil, $[\alpha]^{22}_D$ = +27.5 (c 0.52, $CHCl_3$); IR (film): 3500-3200, 3050, 1535 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.06 (s, 6H), 0.9 (s, 9H), 2.6 (m, 1H), 2.8 (dd, 1H, J=13, J=7), 3.85 (dd, 1H, J=15, J=7), 3.95 (d, 1H, J=14), 4.7 (m, 2H), 7.5 (m, 5H). **6**, oil, $[\alpha]^{22}_D$ = +8.85 (c 0.13, $CHCl_3$); IR (film): 3500, 3050, 1535 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.06 (s, 6H), 0.9 (s, 9H), 2.8 (dd, 1H, J=13, J=6)), 3.15 (m, 1H), 3.35 (d, 1H, J=14), 3.4 (dd, 1H, J=13, J=7), 4.05 (d, 1H, J=14), 4.15 (dd, 1H, J=15, J=7), 4.75 (m, 1H), 4.85 (m, 1H), 7.3 (m, 5H). **7b**, oil, $[\alpha]^{22}_D$ = +13.2 (c 0.75, $CHCl_3$); IR (film): 3300, 1550 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.55 (dt, 1H, J=6.8, J=4)), 2.75 (dd, 1H, J=12.6, J=7.2), 3.3 (d, 1H, J=14), 3.55 (dd, 1H, J=12.6, J=2.5), 3.75 (dd, 1H, J=11, J=4), 4.1 (d, 1H, J=14), 4.2 (m, 1H), 4.65 (dt, 1H, J=7, J=2.4), 4.82 (dt, 1H, J=6.8, J=4), 7.3 (m, 5H). **8b**, oil, $[\alpha]^{22}_D$ = -8.4 (c 0.5, $CHCl_3$); IR (film): 3300, 1540 cm^{-1};^1H NMR ($CDCl_3$): δ 2.65 (dd, 1H, J=9, J=6.1), 2.9 (dt, 1H, J=6.5, J=4), 3.45 (dd, 1H, J=9.6, J=7.2), 3.49 (d, 1H, J=8, exchangeable with D_2O), 3.5 (d, 1H, J=14), 3.6 (dd, 1H, J=12, J=4), 3.8 (m, 1H), 4.0 (d, 1H, J=14), 4.75 (dd, 1H, J=6, J=4), 4.9 (dt, 1H, J=7, J=4), 7.3 (m, 5H).
9. **4**, oil, unseparable mixture of diastereomers; ^1H NMR ($CDCl_3$): δ 1.5-2 (m, 6H)), 2.9 (m, 1H), 2.51 (sb, 2H, exchangeable with D2O), 3.4-3.6 (m, 4H, 3.7 (m, 2H), 3.85 (m, 2H), 3.9 (s,2H), 7.3 (m, 5H).
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