A Stereocontrolled Route to Both Enantiomers of the Necine Base Dihydroxyheliotridane *via* Intramolecular 1,3-Dipolar Addition Using the Same Chiral Precursor

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Diastereofacial selectivity in an enantiospecific intramolecular 1,3-dipolar addition is controlled by adjusting the size of the tether between the dipole and the dipolarophile to give 2,3-disubstituted pyrrolidines enantiomeric with respect to the newly generated stereogenic 2,3-centres depending on the tether size; this leads to stereocontrolled synthesis of both enantiomers of the necine base dihydroxyheliotridane from chiral *O*-benzylglycidol.

We have learned1 that the enantiocontrolled intramolecular 1,3-dipolar cycloaddition of azomethine ylides 2 generated from aziridine precursors 1a proceeds in an excellent diastereofacial way with reflection of the existing stereogenic centre when the tether between the dipole and the dipolarophile is appropriately adjusted to form the δ -lactone moiety of the products 4. Because the observed high diastereoselectivity is attributable to the chair-like transition state 2, we were very interested in the reaction of 1b, having the envelope-like transition state 3 (because of the one carbon shorter tether), leading to the γ -lactone 5 with inversion of the diastereofacial selectivity (Scheme 1). We therefore examined the azomethine ylide-mediated intramolecular 1,3-dipolar cycloaddition reaction using two simple chiral substrates 1a and 1b, obtained from the same optically pure (R)-O-benzylglycidol² 6, expecting to generate the corresponding 2,3-disubstituted pyrrolidines, the δ -lactone 4 and the γ -lactone 5, enantiomeric to each other with respect to the 2,3-stereogenic centres. Here we report our result which leads to a new enantiocontrolled route to both enantiomers of the necine base³ dihydroxyheliotridane⁴⁻⁶ 19 from chiral O-benzylglycidol.



We prepared the homoallylic aziridine ester[†] 1a and the allylic aziridine ester[†] 1b from (*R*)-6 in satisfactory overall yields by following the established procedure⁷ via the known alcohols $7a^8$ and $7b^9$ as shown in Scheme 2.

We first examined the themolysis of the homoallylic ester 1a which afforded the readily separable isomeric products in the form of the expected 4 and its 2,3-epimer in 70 and 8% yields[‡] within 5 min on heating at 260 °C in diphenyl ether. Since 4 and its epimer gave enantiomeric methyl 3-allyl-1-carbobenzoxyprolinate§ by sequential double debenzylation, *N*-carbobenzoxyylation, iodination, reductive lactone ring-cleavage and esterification, they were confirmed to be enantiomeric at the 2,3-stereogenic centres. The diastereofacial selectivity of the cycloaddition was thus concluded to be 76% de based on the product ratio. The stereochemistry of the products were determined by transformation of the major product 4 into



Scheme 2 Reagents and conditions: i, vinylmagnesium bromide, CuI, THF, -20 °C (95%); ii, (a) NaCH₂SOMe, Me₂SO, (b) CaCO₃, 1,2-Cl₂C₆H₄, reflux (70%); iii, 2,3-dibromopropionyl chloride, Et₃N, then BnNH₂ (87% for 1a and 77% got 1b)

b (n = 0; via ii)

Β'n Ö

1a (n = 1)

b (n = 0)

Scheme 3 Reagents and conditions: i, diphenyl ether, 260 °C, *ca*. 5 min (4: 70% and 2,3-*epi*-4: 8% after SiO₂ column separation); ii, DIBAL-H, -40 °C, THF; iii, (EtO)₂P(O)CH₂CO₂Et, NaH, THF (76% from **4a**); iv, H₂, Pd(OH)₂ (97%); v, LiOH, aq. THF; vi, (PhO)₂P(O)N₃, Et₃N, DMF (70% from **11**); vii, EtSH, BF₃·OEt₂, CH₂Cl₂ (95%); viii, I₂, PPh₃, imidazole; ix, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), THF (70% from **14**); x, 1% HCl (94%); xi, Ac₂O, Et₃N, DMAP, then urea-H₂O₂ (CF₃CO)₂O (54% from **17**); xii, LiAlH₄, THF (80%)

(-)-dihydroxyheliotridane^{5,6} (-)-19. Thus, partial reduction of 4, followed by the Horner–Emmons reaction of the lactol 8 stereoselectively gave the bicyclic ester 10, $[\alpha]_D^{27} + 54.51$ (c 3.18, CHCl₃), in 76% yield. The reaction was presumed to proceed via an intramolecular Michael addition pathway involving the sterically most favourable transition state 9 giving rise to a single product. On sequential selective N-debenzylation, saponification and cyclization,¹⁰ 10 furnished the tricyclic lactam 13, $[\alpha]_{D}^{22}$ +16.92 (*c* 1.13, CHCl₃), *via* the secondary amine 11, $[\alpha]_{D}^{26}$ -7.30 (*c* 1.36, MeOH), and the carboxylate 12. After removal of the O-benzyl group¹¹ of 13, the resulting alcohol 14, $[\alpha]_D^{28}$ -6.06 (c 1.30, CHCl₃), was transformed into the bicyclic ketone 17, $[\alpha]_D^{28}$ +62.67 (c 1.85, MeOH), via the iodide¹² 15, and the enol ether 16. The overall yield of 17 from 10 was 42%. The ketone 17, after acetylation, was oxidised under Baeyer-Villiger conditions in the presence of a urea- H_2O_2 complex¹³ to selectively give the diacetate 18, $[\alpha]_D^{26}$ +21.73 (c 1.54, CHCl₃), in 54% yield. Finally, 18 was reduced with lithium aluminum hydride to give (-)-dihydroxyheliotridane¶ (-)-**19**, $[\alpha]_D^{28}$ -32.48 (c 0.60, EtOH) [lit., $[\alpha]_D^{20}$ -36.0 (c 0.67, EtOH)⁵ and $[\alpha]_D^{21}$ -31.7 (c 0.55, EtOH)⁶], in 80% yield. At this point the stereochemistry of the major adduct 4 as well as the minor adduct 2,3-epi-4 was determined unambiguously as shown in Scheme 3.

We next examined the thermolysis of the allylic ester **1b** which afforded an inseparable *ca*. 3:1 mixture containing the expected γ -lactone **5** as the major component and the minor 2,3-*epi*-**5** as the minor component (by ¹H NMR) in 70% yield on heating at 260 °C in diphenyl ether for 13 min. The mixture was reduced to the lactol **20** which was immediately treated with



• stereochemistry depicted indicates that of the major component

Scheme 4 Reagents and conditions: i, diphenyl ether, 260 °C, *ca.* 13 min (70%, inseparable *ca.* 3 : 1 mixture of 5 and 2,3-*epi*-5); ii, DIBAL-H, THF; iii, (EtO)₂P(O)CH₂CO₂Et, NaH, THF ($*=\beta$ H: 72% and $*=\alpha$ H: 11% overall from 5 after SiO₂ column separation); iv, H₂, Pd–C, *c* HCl, MeOH; v, CCl₃CH₂OCOCl, pyridine, CH₂Cl₂–DMF (1 : 2) (87% from 21); vi, K₂CO₃, MeOH (94%); vii, I₂, PPh₃, imidazole, THF (99%); viii, Zn, EtOH, reflux (83%); ix, O₃, MeOH, -78 °C, then NaBH₄ (77%); x, LiAlH₄, THF (79%)

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phosphonate ester to give a mixture of the tetrasubstituted tetrahydrofurans, the more polar 2,5-cis-mixture 21a (* β H) and the less polar 2,5-trans-mixture 21b (*aH), in 72 and 11% yield respectively. The major mixture 21a was sequentially double debenzylated, diacylated¹⁴ and de-O-acylated to give the alcohol 24 in 82% overall yield via 22 and 23. Conversion of 24 to the iodide¹² 25, followed by its exposure to zinc in refluxing ethanol allowed concurrent reductive ring-cleavage, N-deprotection and cyclization to afford the vinyl lactam 26 in a diastereoisomerically pure state in 82% yield with loss of the stereogenic centre that originated from the chiral starting material 6. Ozonolysis of the lactam 26 followed by reductive workup afforded the diol 27 which was finally reduced with lithium aluminum hydride to give (+)-dihydroxyheliotridane $[(+)-19], [\alpha]_D^{28} + 19.15 (c \ 0.56, \text{EtOH}) [lit., 6 \ [\alpha]_D^{21} + 32.0 (c \ 0.56, \text{EtOH}) [lit., 6 \ (\alpha]_D^{21} + 32.0 (c \ 0$ 0.50, EtOH)], in 61% overall yield. The minor less polar mixture 21b, on the other hand, afforded an epimeric necine base (-)-platynecine^{15,16}¶ [(-)-**28**], $[\alpha]_D^{28}$ -25.88 (c 1.18, CHCl₃) [lit., 16 [α]_D²⁰ -65.5 (c 0.75, CHCl₃)], in comparable overall yield with the same treatment. At this point the structures of the adduct components, the major 5 and the minor 2,3-epi-5, were clarified as shown. Based on the ¹H NMR and the rotation values the diastereofacial selectivity of the cycloaddition was estimated to be about 50% de (Scheme 4).

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Footnotes

[†] Satisfactory analytical (combustion and/or high resolution mass) and spectral (IR, ¹H NMR and MS) data were obtained for all new compounds.

 \ddagger Both isomers were found to be diastereomerically pure by ¹H NMR (500 MHz) analysis.

§ Methyl (2*R*,3*S*)-3-allyl-1-carbobenzoxyprolinate, $[\alpha]_D{}^{30} - 22.15$ (*c* 0.81, CHCl₃) was obtained from the major adduct **4** and its 2*S*,3*R*-enantiomer, $[\alpha]_D{}^{28} + 21.97$ (*c* 1.08, CHCl₃), was obtained from the minor adduct 2,3-*epi*-**4**.

¶ The ${}^{13}C$ NMR spectrum was also completely identical with that reported: (-)- and (+)-19 for ref. 5 and 6; (-)-28 for ref. 16.

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