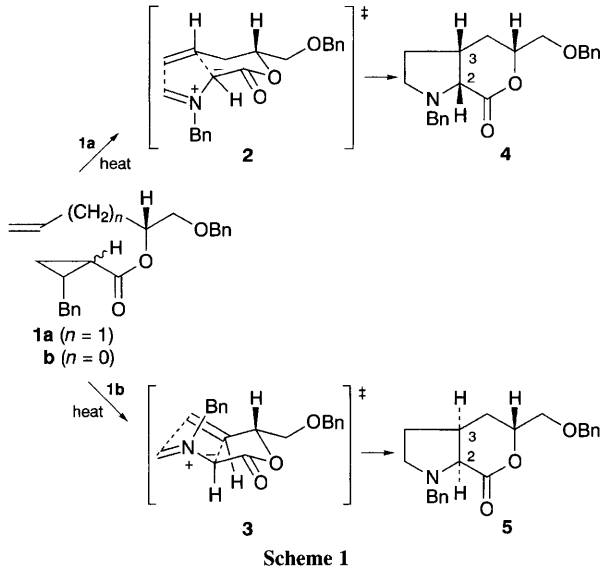
A Stereocontrolled Route to Both Enantiomers of the Necine Base Dihydroxyheliotridane *via* Intramolecular 1,3-Dipolar Addition Using the Same Chiral Precursor

Kazuya Hashimura, Shun'ichi Tomita, Kou Hiroya and Kunio Ogasawara*

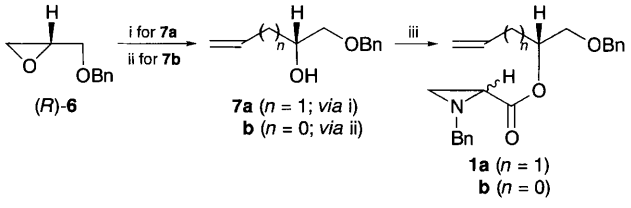
Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980-77, Japan

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 learned[1] 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*-benzylglycidol[2] **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 base[3] dihydroxyheliotridane[4–6] **19** from chiral *O*-benzylglycidol.



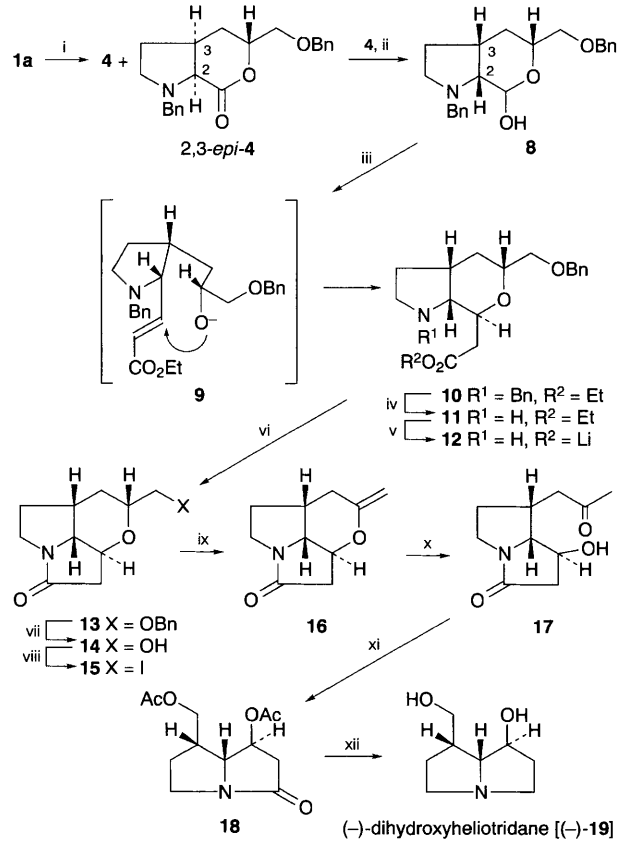
Scheme 1



Scheme 2 *Reagents and conditions*: i, vinylmagnesium bromide, CuI, THF, −20 °C (95%); ii, (*a*) $NaCH_2SOMe$, Me_2SO, (*b*) $CaCO_3$, 1,2-$Cl_2C_6H_4$, reflux (70%); iii, 2,3-dibromopropionyl chloride, Et_3N, then $BnNH_2$ (87% for **1a** and 77% got **1b**)

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

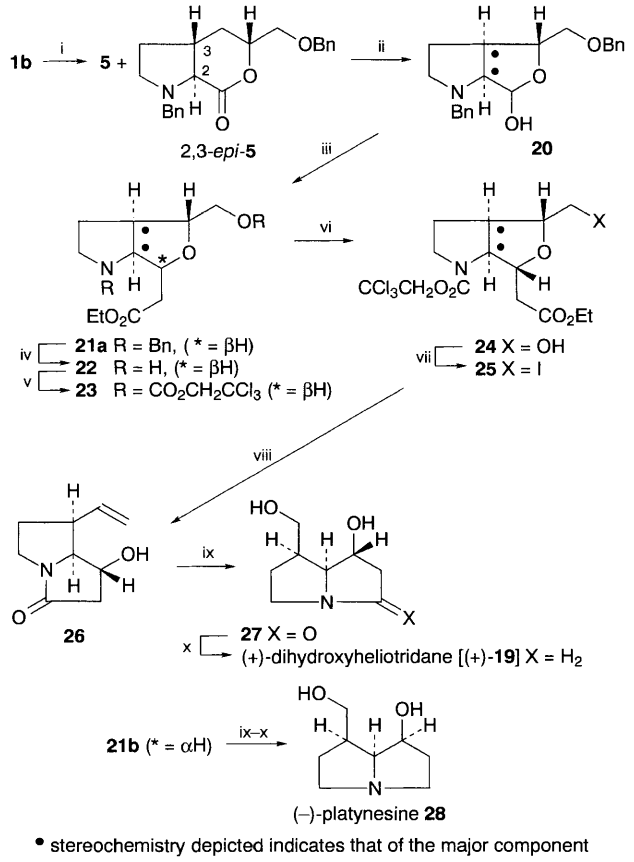
We first examined the themolysis of the homoallylic ester **1a** which afforded the readily separable isomeric products in the form of the expected **4** and its 2,3-epimer in 70 and 8% yields‡ within 5 min on heating at 260 °C in diphenyl ether. Since **4** and its epimer gave enantiomeric methyl 3-allyl-1-carbobenzoxyprolinate§ by sequential double debenzylation, *N*-carbobenzoxylation, 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 3 *Reagents and conditions*: i, diphenyl ether, 260 °C, *ca.* 5 min (**4**: 70% and 2,3-*epi*-**4**: 8% after SiO_2 column separation); ii, DIBAL-H, −40 °C, THF; iii, $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF (76% from **4a**); iv, H_2, $Pd(OH)_2$ (97%); v, LiOH, aq. THF; vi, $(PhO)_2P(O)N_3$, Et_3N, DMF (70% from **11**); vii, EtSH, $BF_3{\cdot}OEt_2$, CH_2Cl_2 (95%); viii, I_2, PPh_3, imidazole; ix, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), THF (70% from **14**); x, 1% HCl (94%); xi, Ac_2O, Et_3N, DMAP, then urea–H_2O_2 $(CF_3CO)_2O$ (54% from **17**); xii, $LiAlH_4$, 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, $CHCl_3$), 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, $CHCl_3$), *via* the secondary amine **11**, $[\alpha]_D^{26}$ −7.30 (*c* 1.36, MeOH), and the carboxylate **12**. After removal of the *O*-benzyl group[11] of **13**, the resulting alcohol **14**, $[\alpha]_D^{28}$ −6.06 (*c* 1.30, $CHCl_3$), was transformed into the bicyclic ketone **17**, $[\alpha]_D^{28}$ +62.67 (*c* 1.85, MeOH), *via* the iodide[12] **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 complex[13] to selectively give the diacetate **18**, $[\alpha]_D^{26}$ +21.73 (*c* 1.54, $CHCl_3$), 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 ^{1}H 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 phosphonate ester to give a mixture of the tetrasubstituted tetrahydrofurans, the more polar 2,5-*cis*-mixture **21a** (*βH) and the less polar 2,5-*trans*-mixture **21b** (*αH), in 72 and 11% yield respectively. The major mixture **21a** was sequentially double debenzylated, diacylated[14] and de-*O*-acylated to give the alcohol **24** in 82% overall yield *via* **22** and **23**. Conversion of **24** to the iodide[12] **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, EtOH) [lit.,[6] $[\alpha]_D^{21}$ + 32.0 (*c* 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, $CHCl_3$) [lit.,[16] $[\alpha]_D^{20}$ −65.5 (*c* 0.75, $CHCl_3$)], 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 ^{1}H NMR and the rotation values the diastereofacial selectivity of the cycloaddition was estimated to be about 50% de (Scheme **4**).



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, $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF (* = βH: 72% and * = αH: 11% overall from **5** after SiO_2 column separation); iv, H_2, Pd–C, *c* HCl, MeOH; v, CCl_3CH_2OCOCl, pyridine, CH_2Cl_2–DMF (1 : 2) (87% from **21**); vi, K_2CO_3, MeOH (94%); vii, I_2, PPh_3, imidazole, THF (99%); viii, Zn, EtOH, reflux (83%); ix, O_3, MeOH, −78 °C, then $NaBH_4$ (77%); x, $LiAlH_4$, THF (79%)

Received, 28th July 1995; Com. 5/05025A

Footnotes

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

‡ Both isomers were found to be diastereomerically pure by ^{1}H NMR (500 MHz) analysis.

§ Methyl (2*R*,3*S*)-3-allyl-1-carbobenzoxyprolinate, $[\alpha]_D^{30}$ −22.15 (*c* 0.81, $CHCl_3$) was obtained from the major adduct **4** and its 2*S*,3*R*-enantiomer, $[\alpha]_D^{28}$ +21.97 (*c* 1.08, $CHCl_3$), 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.

References

1 S. Takano, Y. Iwabuchi and K. Ogasawara, *J. Am. Chem. Soc.*, 1987, **109**, 5523; *J. Chem. Soc., Chem. Commun.*, 1988, 1204; S. Takano, S. Tomita, Y. Iwabuchi and K. Ogasawara, *Heterocycles*, 1989, **29**, 1473; S. Takano, K. Samizu and K. Ogasawara, *Chem. Lett.*, 1990, 1239.
2 S. Takano, Y. Sekiguchi, M. Setoh, T. Yoshimitsu, K. Inomata, M. Takahashi and K. Ogasawara, *Heterocycles*, 1990, **31**, 1715; A pertinent review, see: S. Takano and K. Ogasawara, *J. Synth. Org. Chem. Jpn.*, 1989, **47**, 813.
3 Pertinent reviews, see; D. J. Robins, *Nat. Prod. Rep.*, 1995, **12**, 413 and the preceding reports.
4 R. Adams and B. L. van Duuren, *J. Am. Chem. Soc.*, 1954, **76**, 6379.
5 J. M. Dener and D. J. Hart, *Tetrahedron*, 1988, **44**, 7037.
6 J. Mulzer and M. Scharp, *Synthesis*, 1993, 615.
7 P. DeShong, D. A. Kell and D. R. Sidler, *J. Org. Chem.*, 1985, **50**, 2309.
8 S. Takano, S. Tomita, Y. Iwabuchi and K. Ogasawara, *Synthesis*, 1988, 610.
9 S. Takano, Y. Iwabuchi and K. Ogasawara, *J. Chem. Soc., Chem. Commun.*, 1988, 1527.
10 T. Shioiri, K. Ninomiya and S. Yamada, *J. Am. Chem. Soc.*, 1972, **94**, 6203.
11 K. Fuji, K. Ichikawa, M. Node and E. Fujita, *J. Org. Chem.*, 1979, **44**, 1661.
12 P. J. Garegg and B. Samuelsson, *J. Chem. Soc., Chem. Commun.*, 1979, 978.
13 M. S. Cooper, H. Heaney, A. J. Newbold and W. R. Sanderson, *Synlett*, 1990, 533.
14 T. B. Windholz and B. R. Johnston, *Tetrahedron Lett.*, 1967, 2555.
15 R. Adams and E. F. Rogers, *J. Am. Chem. Soc.*, 1941, **63**, 537.
16 G. W. J. Fleet, J. A. Seijas and M. P. Vázquez-Tato, *Tetrahedron*, 1991, **47**, 525.