

SYNTHETIC STUDIES TOWARD MAYTANSINOIDS¹

PREPARATION OF THE OPTICALLY ACTIVE INTERMEDIATES FROM D-MANNOSE

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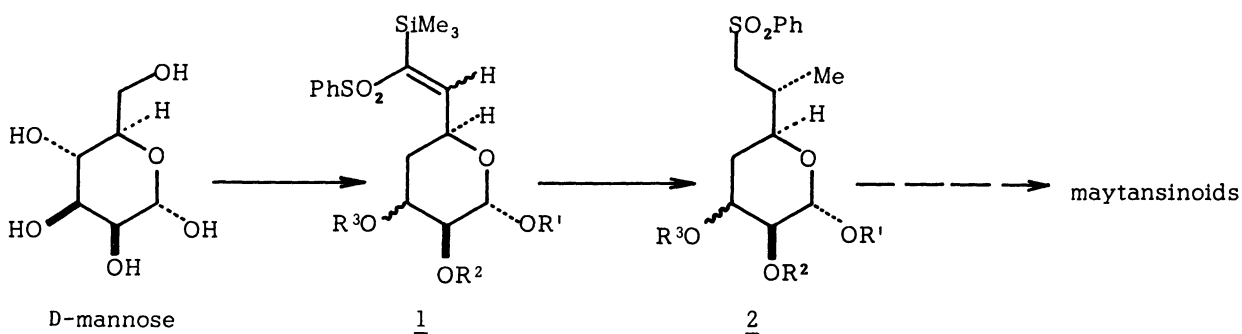
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Summary : Optically active intermediates (15 and 23) for maytansine were synthesized from D-mannose via heteroconjugate addition of methyllithium as a crucial step.

In our preceding paper on the synthetic studies toward maytansine, we have described a new possible synthetic strategy which involves an acyclic asymmetric induction when methyl group was introduced into racemic pyranosyl-hetero-olefins as 1 prepared from acrolein dimer¹. Here are described two syntheses of optically active 2 from D-mannose as a chiral starting material as shown in Scheme I and II.

Methyl D-mannopyranoside (3) [$\alpha_D = +78.8^\circ (c=1.00, H_2O)$] was treated in a mixture of 2,2-dimethoxypropane, acetone and dimethylformamide (2:5:16) in the presence of PPTS (pyridinium p-toluenesulfonate) at 5°C for 2 days affording 4,6-monoacetone (4) in 80 % yield [ca. half of the mass crystallized by standing was recrystallized from pet. ether-ether; mp 103°C; $\alpha_D = +73.6^\circ (c=1.00, CHCl_3)$].² Selective tosylation of 4 yielded the 3-O-tosyl alcohol (5) which was further converted



with NaH/MeI into 2-methyl ether (6) as crystalline mass [mp 116°C; $\alpha_D^{20} = +14.7^\circ$ (c=1.01, MeOH)] in 60 % overall yield. Acetonide group of 6 was hydrolyzed with Dowex 50W[H⁺] in methanol to give in 96 % yield the diol (7) [mp 99°C; $\alpha_D^{20} = +30.1^\circ$ (c=1.03, MeOH)]. Tritylation of 7 at 70°C afforded the 6-monotrityl alcohol (8) as white leaflets (86 % yield) [mp 156°C (decomp.); $\alpha_D^{20} = +20.0^\circ$ (c=1.02, CHCl₃)]. When 8 was treated with t-BuOK in THF at 0°C, it gave the epoxide (9). The oxirane ring in 9 was predominantly opened at the 4-position by an excess amount of lithium triethylborohydride in THF at 0°C for two overnights giving 4-deoxy (10) and 3-deoxy derivatives in 7:1 ratio. This ratio was measured by converting the products into the corresponding dimethyl-t-butylsilyl ether (11a) or benzyl ether (11b) and then by separating the ethers with Partisil (Whatman). Trityl group in 11b was hydrolyzed in CHCl₃ plus 0.2 % conc. HCl to afford 12 in 67 % overall yield from 8 as colorless oil which was successively treated with 1] CrO₃-2Py in CH₂Cl₂ [13, colorless oil], 2] PhS(Me₃Si)₂Cl in THF at -45°C, 3] purification by SiO₂ and then 4] 2.4 eq. of mCPBA to give the hetero-olefin (14) in 40 % overall yield. The ratio of Z/E geometry of 14 was ca. 2/1, and only Z-14 crystallized [mp 138°C; $\alpha_D^{20} = -64.3^\circ$ (c=1.00, MeOH)]. When this mixture (E and Z-14) was mixed with methyl-lithium at -78°C in THF and then treated with KF in methanol, one obtained 15³ [$\alpha_D^{20} = +40.0^\circ$ (c=1.60, CHCl₃)] as an only isolable product in 99 % yield.

We describe an alternative way (Scheme II) to make the optically active synthetic equivalent of 2 starting from α -methyl-D-mannopyranoside 2,3-monoacetonide (16).⁴ Selective protection of 16 [PPTS/dihydropyran] afforded 17, which was quantitatively converted into 18 by subsequent treatments in THF with NaH/CS₂ and then with MeI in the presence of a catalytic amount of imidazole. A toluene solution of 18 and tri-n-butyltin hydride (2.3 eq.)⁵ was heated overnight under reflux and the products were separated with a SiO₂ column to give 19 in 75 % yield.⁶ Selective deprotection of 19 occurred by stirring it in acetone containing MeOH and PPTS at 55°C for 4.5 hr to yield 78 % of 20, which was oxidized with CrO₃-2Py into the aldehyde 21 in 57 % yield. The hetero-olefin (22), similarly converted from 21 in 40 % overall yield, was successively treated with 1 eq. of MeLi in THF at -78°C and with KF in MeOH at rt to afford a single compound 23⁷ [$\alpha_D^{20} = +19.9^\circ$ (c=0.55, CHCl₃)] in 84 % overall yield.

In the heteroconjugate addition described above, complete asymmetric induction was observed even if methyl glycosides (14 and 22) lacked one oxygen atom as compared with the case of the methoxyethyl glycoside.¹ Introduction of a new asymmetric centers at the 6-position of deoxyhexoses implies that carbohydrates could be used in higher efficiency for the syntheses of optically active natural products.

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REFERENCES AND NOTES

1. Part 3 of this series. For Part 2, see M. Isobe, M. Kitamura, T. Goto; *Tetrahedron Lett.*, **22**, 239 (1981).
2. Use of PPTS [N. Miyashita, A. Yoshikoshi, P. Grieco; *J. Org. Chem.*, **42**, 3772 (1977)] instead of p-toluenesulfonic acid (see ref. #4) showed a better result for this kinetic mono-isopropylidene. Our method afforded crystalline mass without purification via the corresponding diacetate as reported by Evans et al.⁴ Optical rotation value in chloroform was the same as Evans [$\alpha_D = +73^\circ (c=0.99)$], however, the same crystalline sample showed $\alpha_D = +60.3^\circ (c=1.00)$ in MeOH which was different from the one [$\alpha_D = +68.3^\circ (c=1.15)$] reported by C. L. Stevens et al., in *J. Org. Chem.*, **35**, 592 (1970).
3. PMR of 15: δ 1.08 ppm (Me, d, $J = 7$ Hz), 1.55(2H₄, m), 2.20(H₆, m), 2.9(H₇, dd, $J = 14$ & 9), 3.26(OMe, s), 3.62(H₃, brq, $J = 3$), 3.90(H₅, ddd, $J_{4\beta} = 10$, $J_{4\alpha} = 3$, $J_6 = 4$), 4.5(2H, CH₂Ph), 4.51(H₁, brs), 7.2(5H, m), 7.5(3H, m), 7.8(2H, m). CMR : δ 14.6 ppm (Me).
4. M. E. Evans, F. W. Parrish; *Carbohydrate Research*, **54**, 105 (1977).
5. D. H. R. Barton, S. W. McCombie; *J. C. S. Perkin Trans. I*, **1975**, 1574.
6. Very recently, a similar report on the preparation of 4-deoxy-lyxo-hexose appeared [J. R. Rasmussen; *J. Org. Chem.*, **45**, 2725 (1980)] via Barton's radical process on the thiocarbonyl imidazol derivative corresponding to our 18. In our tetrahydropyranyl protection, it is easier to reduce the 4-hydroxy moiety via simpler xanthate as 18. Benzoate of 20 (in 80 % yield) showed properties consistent with those reported by Rasmussen.
7. PMR of 23: δ 1.10 ppm (Me, d, $J = 7$ Hz), 1.29 and 1.44 (acetamide Me₂), 1.73(H_{4\alpha'}, ddd, $J_{4\beta} = 12$, $J_3 = 6$, $J_5 = 2$), 2.28(H₆, m), 2.94(H₇, dd, $J = 14$ & 8), 3.28(OMe, s), 3.66(H₅, ddd, $J_{4\beta} = 10$, $J_6 = 3$, $J_{4\alpha} = 2$), 3.88(H₂, d, $J = 5$), 4.25(H₃, m), 4.84(H₁, s), 7.6(3H, m), 7.9(2H, m). CMR : δ 14.7 ppm (Me).

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