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SYNTHETIC STUDIES TOWARD MAYTANSINOIDS (2)[1]

A NEW STRATEGY BASED ON ASYMMETRIC INDUCTION BY HETEROCONJUGATE ADDITION OF METHYLLITHIUM ONTO PYRANOSYL HETERO-OLEFINS

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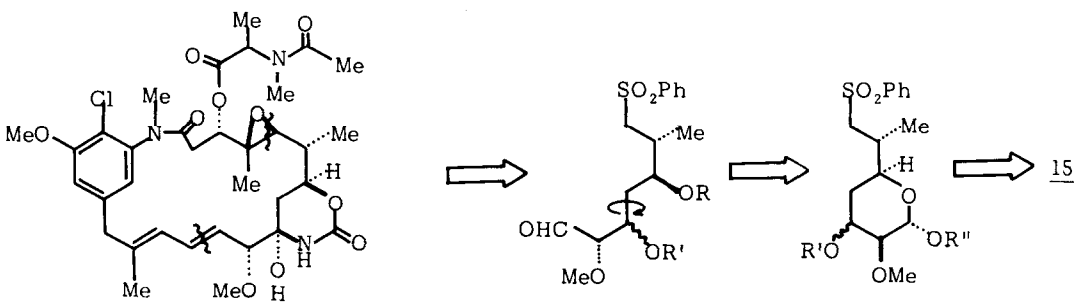
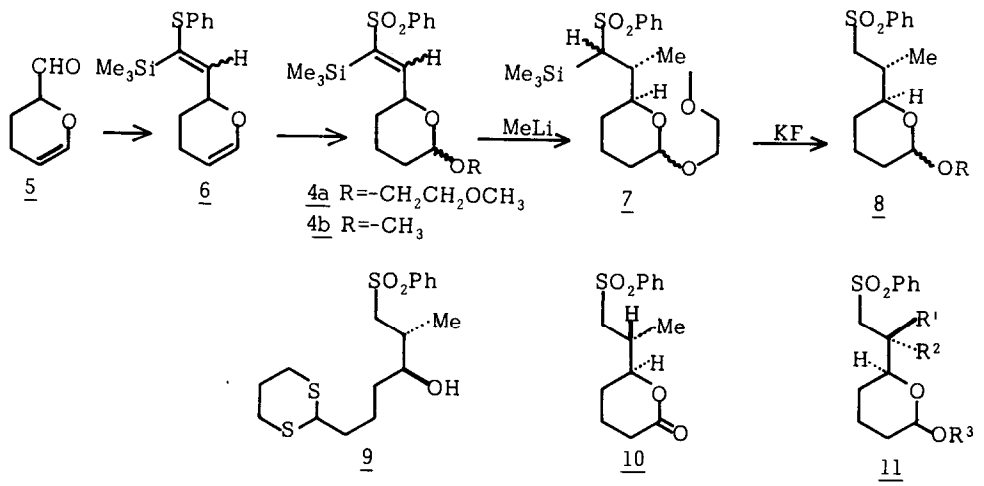
Summary : The functionalized pyranosyl hetero-olefins 4a, 13 and 15 received a remarkable diastereoselective addition of methyllithium to form threo adducts, one of which was introduced into a possible synthetic intermediate as 3 for maytansine (1) along Scheme I.

Maytansine (1), one of the most promising therapeutical agent with strong antitumor activity, has collected extensive attention of synthetic organic chemists.[2] We have recently explored a possibility of new synthetic strategy as shown in Scheme I, which involves acyclic asymmetric induction by heteroconjugate addition[3] of methyllithium onto pyranosyl hetero-olefins (3 vs 15). This methodology comprises a remarkable advantage for the formation of carbon-carbon bonds[4] and also does a potent applicability for the synthesis of optically active systems. Here is described our recent progress toward 1 along this line.



1 Scheme I 2 3

First of all, a simple model system of pyranosyl hetero-olefin was examined for the study on the diastereoselection. Thus, (±)-5-pyranosyl-hetero-olefin (4) was made from acrolein dimer (5) in 60 % overall yield by successive treatments with a) $PhS(Me_3Si)_2CLi$ [forming 6 as E/Z = 2/3], b) $HOCH_2CH_2OCH_3/PPTS/CH_2Cl_2$ and then c) mCPBA.[5] When 4 was treated with 1 eq. of methyllithium at -78℃ in THF for 5 min, it was converted into only a single product (9) in almost quantitative yield under the following treatments with KF and then with 1,3-propanedithiol/BF_3 to extinguish the undiscussed asymmetric centers. The chemical shift of the methyl signal in the cmr of the acyclic product (9) appeared at δ 13.9 ppm, which suggests the stereochemistry of 9 to be threo[6] as shown in the figure. When 8 (R=-$CH_2CH_2OCH_3$) was treated with 1N HCl (8, R=H) and then with bromine, it was also converted into a single γ-lactone (10) [ν 1735 cm^{-1}; δ 13.8 ppm (cmr-Me)]. These facts indicate the 1,2-asymmetric induction in methyl-addition to be completed in >99 %. Incidentally, the asymmetric induction of the corresponding methyl derivative (4b) [Z-α], for example, was tested under the same condition to reveal the ratio of threo(11a; R'=H, R^2=Me)/erythro(11b; R'=Me, R^2=H) to be 85/15.



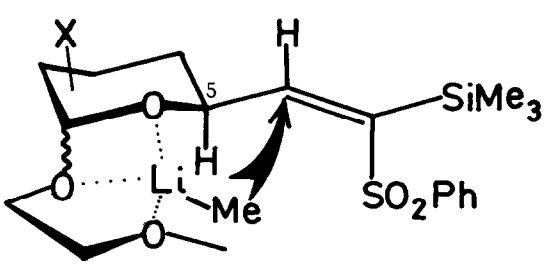
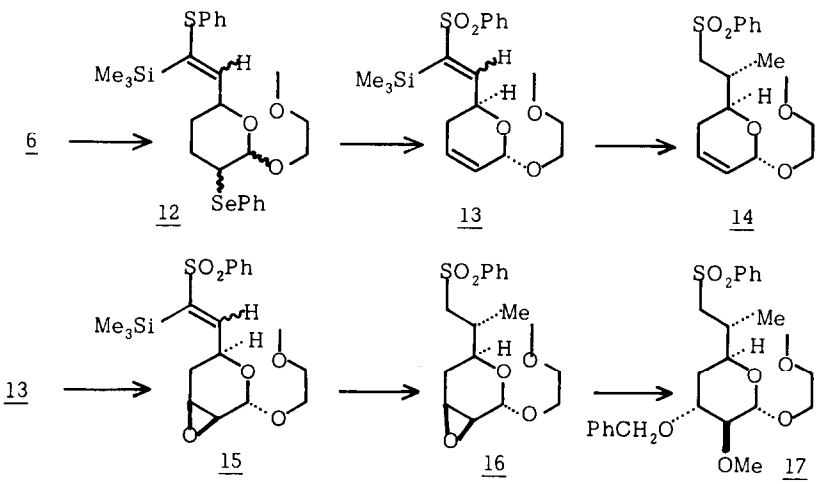


Fig. 1

The mechanism of this diastereoselectivity may be explained by a pseudo-intramolecular addition of methyllithium, chelated with the etherial oxygen atoms, onto the hetero-olefin which may exists in the eclipsed form to the C_5-H (see Fig. 1). Thus, the three etherial oxygen atoms of the methoxyethyl pyranoside (4a) can capture the lithium atom of the methyllithium to render its exclusive attack onto the hetero-olefin from one face, while the corresponding methyl pyranoside (4b) may slightly lack such complete effect. In spite of the absence of enough oxygen atoms in 4b, two oxygen atoms functioned similarly to convert it largely into the threo product (11a).

In order to proceed the synthetic work toward 1, we attempted the examination of the asymmetric inductivity on the further functionalized pyranoside system. Each of the Z-6 and E-6[5a] was treated with PhSeCl in CH_2Cl_2 in the presence of $HOCH_2CH_2OCH_3$ and pyridine at 0°C for 40 min to afford 12. The selenide (12), after the oxidation with 3.5 eq. of mCPBA, was heated in CH_2Cl_2 under reflux to give the unsaturated pyranoside (13)[7] in 75 % overall yield from 6. Addition of methyllithium at -78°C to the hetero-olefin (13) took place smoothly in 5 min as above cases to show the coincidental selectivity which was figured out by taking off the silyl group with KF in MeOH to afford 14 [δ 14.8 ppm (cmr-Me)][8] in 99.4 % overall yield.

Epoxidation of Z-13 with 1.5 eq. of mCPBA in CH_2Cl_2 in the dark at rt for 15 hr yielded the epoxides as a mixture of α/β = 18/82, and the major epoxide (Z-15) was separated in 74 % yield. E-13 was converted to E-15 similarly. Single product (16) [δ 14.6 ppm (cmr-Me)] was again obtained from either Z-15 or E-15 by addition of 1 eq. of MeLi and then with KF in 88 and 94 % yields, respectively.



All of the hetero-olefins attached to functionalized pyranosyls, 4a 13 and 15, exhibited complete diastereoselectivity when treated with methyllithium to afford the corresponding methyl adduct in threo orientation. For the initial purpose, the epoxide (16) was further treated with $NaOCH_2Ph$ in THF at 40°C and then with methyl iodide giving rise to 17[9] as an important synthetic intermediate (3) for maytansine (1).

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REFERENCES AND NOTES

1. For part 1; M. Isobe, M. Kitamura, T. Goto; Tetra. Lett., 3465 (1979).
2. For the structure; see a) S. M. Kupchan et al.; J. Am. Chem. Soc., 94, 1354 (1972), b) S. M. Kupchan et al.; J. Org. Chem., 42, 2349 (1977). For synthetic work; see c) E. J. Corey et al.; J. Am. Chem. Soc., 102, 1439 (1980), d) A. I. Meyers et al.; ibid, 101, 7140 (1979) and the references cited therein.
3. M. Isobe, M. Kitamura, T. Goto; Chem. Lett., 331 (1980).
4. About the chemical shifts of the corresponding methyl signals, see our preceeding paper: M. Isobe, M. Kitamura, T. Goto; Tetra. Lett., in press.
5. a) E and Z isomers of 6 could be separated by SiO_2/hexane to show the olefinic protons as doublets (J= 8 Hz) at δ 5.92 ppm and δ 6.5 ppm, respectively. b) Compound 4 comprised all possible four isomers respecting the olefin and the anomeric stereochemistry [α/β ≈ 1/1 (δ 4.8 ppm (brs) / δ 4.3 ppm (d, J= 8 Hz)].
6. Incidentally, erythro isomer of 9 prepared as 1:1 mixture of the alcohols (by oxidation of 9 with SO_3-Py in DMSO and then reduction of the corresponding ketone with $NaBH_4$) showed δ 17.4 ppm for the corresponding cmr-Me signal.
7. Because of the instability of this allylic glycoside (13), it was largely converted into the α-anomer by equilibration due to the acidity of meta-chlorobenzoic acid formed during the reaction. This equilibration could be facilitated by stirring the mixture in CH_2Cl_2 in the presence of dl-10-camphorsulfonic acid at rt for 20 hr to reach the constant ratio of α/β = 93/7.
8. Pmr signals : δ 5.92 ppm (brd, J= 12 Hz), δ5.68 (brd, J= 12 Hz) as olefinic 2H's; δ 4.90 ppm (brs) anomeric H; δ 1.12 ppm (d, J= 8 Hz) as for Me. Reduction of 14 with H_2/Pd-C gave 11c (R^1=H, R^2=Me, R^3= α-$CH_2CH_2OCH_3$) which was identical of α-isomer of 8 prepared from 4a, thus, the stereochemistry at C-1 position of 13 and 14 was assigned accordingly. Anomeric protons of α and β isomers of 8 appeared at δ 4.75 ppm (brs) and at δ 4.35 ppm (brd, J= 8 Hz), respectively.
9. Pmr signals : δ 4.78 ppm (brs, anomeric H); δ 4.6 ppm (ABq, OCH_2-Ph); δ 1.10 ppm (d, J= 7 Hz, Me).

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