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ACYCLIC STEREOCONTROL BY HETEROCONJUGATE ADDITION-----3[1]

DIASTEREOSELECTIVE SYNTHESIS OF EITHER SYN OR ANTI DIASTEREOISOMER

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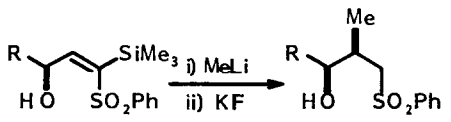
Summary: A stereoselective synthesis of both syn- and anti-diastereoisomers (3 and 4) was established by a method involving heteroconjugate addition, as the key step, with various nucleophiles such as alkoxyvinyllithiums which can be functionalized after the addition. Two examples with aliphatic and carboxylic groups are demonstrated in high specificity.

During the studies on maytansinoid synthesis we have developed a diastereoselective introduction of Me group into the vicinity of a secondary alcohol completely in syn-orientation (1 to 2).[2] This methodology for which we named 'heteroconjugate addition' was only known by addition of MeLi as nucleophile, although the other potentially useful nucleophiles will be important in the construction of chiral tertiary carbon bearing latent functionalizability (3 or 4). We herein describe a high diastereoselective synthesis of syn- and anti-isomers with different substituents on the asymmetric carbon.



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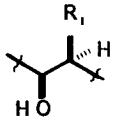

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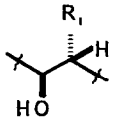

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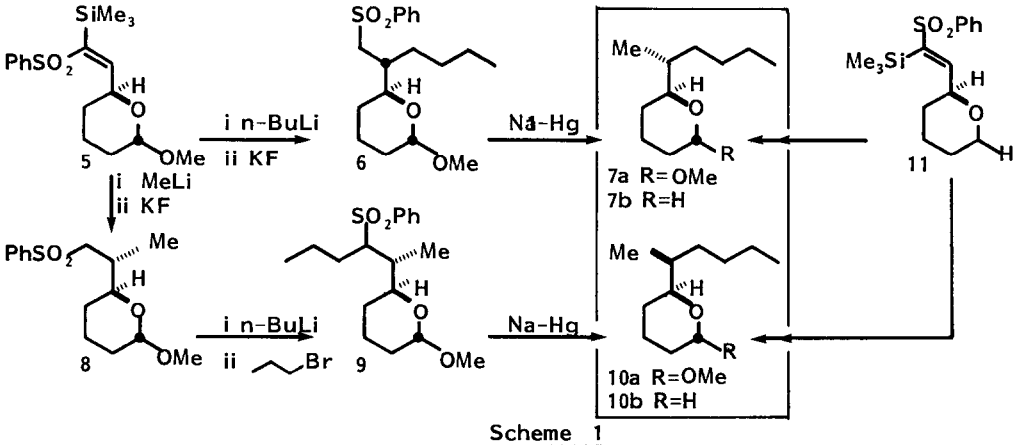
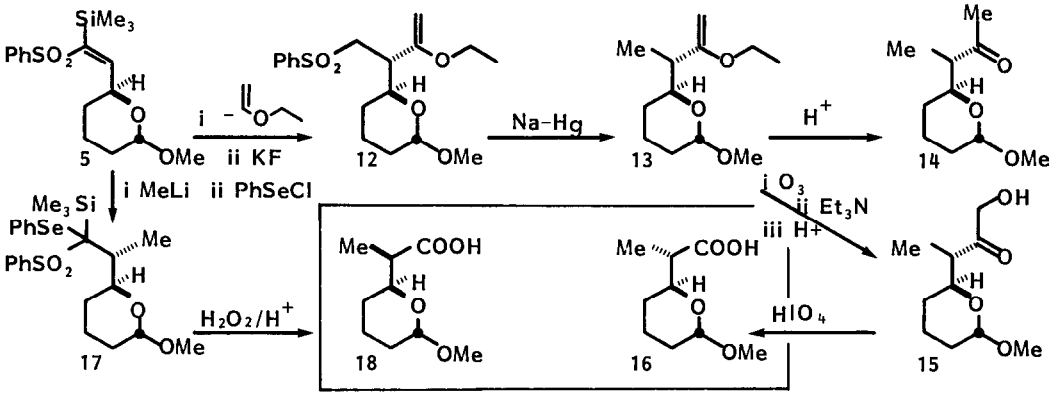
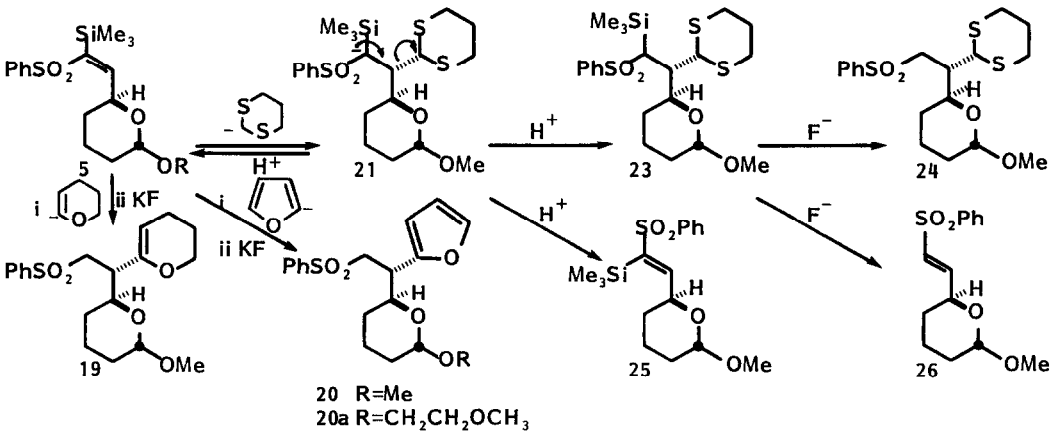
In addition to MeLi, three alkyllithiums (n-BuLi, sec-BuLi and t-BuLi) were examined to give readily the corresponding adducts. The first example used n-buty group to demonstrate the addition to the pyranosyl heteroolefin 5 [mp 66°C],[3] which was dissolved in THF (3% w/v) and stirred with n-BuLi (1.2 equiv. in n-hexane) at -78°C for 10 min. The adduct was treated with KF in hot MeOH to give 100%-pure 6 in 98% yield. The sulfonyl group of 6 was removed by stirring with Na-Hg in MeOH at rt for 40 hr to afford 7a [100%-anti, δ 0.87(d, J= 6.8Hz)ppm] in quantitative yield. First addition of MeLi to 5 in THF at -78°C for 10 min and second desilylation with KF in hot MeOH gave 8 (100%-pure, in 91% yield), which was subsequently alkylated with 1 equiv. n-BuLi and n-PrBr in THF at 0°C for 1 hr into 9 (60%). Subsequent amalgam reduction afforded 10a [100%-syn, δ 0.92(d, J= 6.9)] in 75% yield. Addition of n-BuLi to the



Scheme 1



Scheme 2



Scheme 3

simple tetrahydropyranosyl heteroolefin (11) [at -78°C for 10 min] followed by the same sequence afforded a mixture of compound 7b consisting 89% anti- [δ 0.86 ppm] and 11% syn- [δ 0.90 ppm] isomer in 93% yield (by nmr, and in 61% isolated overall yield). Addition of MeLi to 11 followed by propylation sequence produced 100%-pure 10b in 51% overall yield (Scheme 1).

Several nucleophiles, which are able to be converted into various functional groups after the addition, were searched by examining their nucleophilicity toward pyranosyl heteroolefin 5. Some alkoxyvinyllithiums exhibited excellent addition and high stereoselectivity. The following is the second example for selective preparation of anti and syn isomer of carboxylic acid 16 and 18 from 5 (Scheme 2). Anti-acid (16) was prepared in 4 steps commencing from the additon of ethoxyvinyllithium [generated by t-BuLi in THF at -78°C to 0°C] with stirring for 20 min at -78°C. Subsequent removal of the trimethylsilyl by KF in MeOH afforded the adduct 12 (in 98% yield and 77% crystalline yield, mp 85.5°C).[4] The ratio of the addition of ethoxyvinyllithium was 88%, which was estimated from the purity of 12.[4] Reduction of the sulfonyl group with 5 equiv. Na-Hg in MeOH for 20 hr at rt produced 13 [δ 1.05(d, J= 7)] in 89% yield.[5] It was further treated with ozone at -78°C in CH_2Cl_2 with Et_3N at low temperature and then with acetic acid (for acidification to avoid a possible epimerization) to give the hydroxymethylketone 15[6] and ethyl ester of 16 in 74% and 25% yield, respectively. Oxidation of 15 with a mixture of HIO_4 and n-Bu_4NIO_4 (4:1 molar ratio) in THF-H_2O at 0°C for 12 hr afforded the anti-carboxylic acid 16 in 75% yield.[7] On the other hand, the synthesis of the syn-carboxylic acid 18 via 17 was already studied in the synthesis of Prelog-Djerassi lactonic acid.[8] For the conversion of 5 into 17 were employed one-pot reactions involving (i) addition of MeLi in THF at -78°C for 5 min and (ii) trapping the intermediate carbanion with phenylselenenyl chloride at -45°C. Sila-pummerer rearrangement[9] of 17 was effected by H_2O_2 (30%)-THF at rt for 30 min to give 18[10] in 65% overall isolated yield. Incidentally, direct synthesis of the corresponding methyl ester was achieved by the rearrangement with anhydrous H_2O_2 in a mixture of MeOH and Et_2O. The carboxylic acid 16 and 18 were selectively prepared; thus, the heteroconjugate addition took place in the same syn-manner among these nucleophiles as well.

Lithium alpha-carbanion of dihydropyran [generated with t-BuLi at -78°C to 0°C in a mixture of pentane and THF] was stirred with 5 (R=Me) to produce, after subsequent removal of TMS, 19 (mp 100.0°C) in 85% yield and in 98% diastereoselectivity.[11] Alpha furyllithium [generated by t-BuLi at -78°C to 0°C] was also efficient nucleophile for the heteroolefin 5 (R=Me) to be converted into the adduct 20 (R=Me) in almost quantitative yield. In this case, the better diastereoselectivity was found in the less polar reaction media; thus, the ratios of syn:anti isomers in the mixture of THF and n-hexane varied with the polarity of the solvent as shown in Fig. 1. The major syn-isomer 20 was isolated as crystals (mp 93.5°C).[12] A higher selectivity of this chelation control was observed in a more oxygenated heteroolefin 5a (R= $CH_2CH_2OCH_3$) which gave 20a in the ratio of 98 : 2 in THF and n-hexane (2:1) [See Scheme 3].

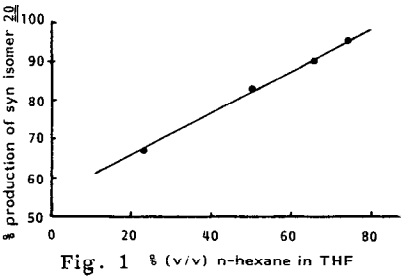


Fig. 1

Lithium carbanion of 1,3-dithiane showed some ability of the addition to 5 (R=Me) at -78°C. But the process of this addition was reversible under

this condition [for 1 hr in THF]: thus, pure Z-isomer of the heteroolefin (5, R=Me) was used as the starting material and was recovered as a mixture of 5 and 25 in a ratio of 1:2 with small amount of the adduct 23. The mixture was treated with n-Bu_4NF in MeOH to give low yield of 24 and E-unsaturated sulfone 26, inducating that 1,3-dithiane is on the boarder to work as a leaving group as well as a nucleophile [Scheme 3].

Above methodology will enable the general synthesis of various substituents on the asymmetric carbon both in syn and anti form in high selectivity.

Acknowledgements We thank the grant-in-aid for scientific research from the Ministry of Education, Science and Culture and the Suzuken Memorial Foundation for financial support.

References and Notes

1. Previous papers a) M. Isobe, M. Kitamura, T. Goto, Tetrahedron Lett., 3465 (1979); b) idem, ibid, 21, 4727 (1980).
2. a) M. Isobe, M. Kitamura, T. Goto, Tetrahedron Lett., 22, 239 (1981); b) idem, J. Am. Chem. Soc., 104, 4997 (1982).
3. See ref. #2a for preparation of 5 [pmr δ 0.30(9H, s), 3.05(3H, s), 4.60(1H, brs), 5.00(1H, ddd, J= 9,9,2), 6.40(1H, d, J=9); found C 57.56, H 7.33, calcd. C 57.59, H 7.39 for $C_{17}H_{26}O_4Si_1S_1$].
4. Mother liquor contained a mixture of ca. 50% of 12 and 50% an isomer; thus, the diastereoselectivity was 87%. 12: pmr(200 MHz) δ 1.10(3H, t, J=7), 1.5-1.7(6H, m), 2.81(1H, ddd, J=10.3, 6.4, 2.5), 3.12(1H, dd, J= 10,7), 3.28(1H, dd, J= 14.5, 2.5), 3.28(3H, s), 3.43 (1H, dd, J= 10,7), 3.62(2H, dd, J= 14.5, 10), 3.74(1H, d, J=2), 3.90(1H, d, J=2), 4.66 (1H, brs), 7.44-7.64(3H, m), 7.88(2H, dd, J=8,2); m/z 354(M+), 323, 213.
5. Compounds 12 and 13 are acid sensitive to be converted into 14 (from 13) with silica gel.
6. 15: pmr δ 1.05(3H, d, J=7), 3.19(3H,s), 3.85(1H, td, J=10,2), 4.29(2H, brs), 4.59 (1H, brs); cmr 12.6, 17.8, 28.7, 29.4, 47.3, 54.4, 69.3, 71.1, 98.2, 213.3; ir 3500, 1719 cm^{-1}.
7. 16: pmr δ 1.16(3H, d, J=7), 3.33(3H, s), 3.90(1H, brt), 4.71(1H, brs), 10.20(1H, br); cmr 13.3, 17.7, 28.0, 29.4, 45.6, 54.5, 70.2, 98.5, 181.1; ir 3520, 1720-1760 cm^{-1}.
8. M. Isobe, Y. Ichikawa, T. Goto, Tetrahedron Lett., 22, 4287 (1981). Pmr of 9 in this paper [δ 4.43(1H, s), and 4.61(2H, brs)] should be [δ 4.93 and 4.81], respectively.
9. a) I. Cutting, P.J. Parsons, Tetrahedron Lett., 22, 2021 (1981); b) R.D. Little, S.O. Myong, ibid, 3339 (1980); c) E. Vedejs, D.A. Engler, J.E. Telschow, J. Org. Chem., 43, 188 (1978); d) H.J. Reich, S.K. Shak, ibid, 42, 1773 (1977).
10. 18: pmr δ 1.14(3H, d, J=8), 3.34(3H, s), 4.00(1H, m), 4.74(1H, s), 9.70(1H, brs); cmr 12.0, 18.0, 28.3, 29.4, 44.7, 54.4, 69.4, 98.6, 180.0; ir 2800-3600, ∿ 1710 cm^{-1}.
11. 19: pmr δ 1.1-1.7(8H, m), 1.8(2H, m), 2.68(1H, ddd, J= 10.5, 6.0, 2.5), 3.22(1H, dd, J= 14.5, 2.5), 3.29(3H, s), 3.3(1H, m), 3.72(1H, dd, J= 14.5, 10.5), 3.76(2H, br-dd, J=10, 6), 4.47(1H, t, J=3.5), 4.67(1H, brs); HPLC analysis (Develosil 100-5) 99% purity.
12. 20: pmr δ 1.4-1.8(6H, m), 3.26(3H, s), 3.28(1H, m), 3.58(1H, dd, J=14.2, 11), 3.67(1H, m), 3.84(1H, dd, J=14.2, 2.8), 4.67(1H, brs), 5.92(1H,m), 6.06(1H,m),7.03(1H,m).

* Nmr was measured in $CDCl_3$ with JEOL FX-200 or 100. Crystalline new compounds [12, 19 & 20] showed sufficient combustion analyses.

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