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REVERSAL OF DIASTEREOFACIAL SELECTIVITY IN THE INTRAMOLECULAR MICHAEL ADDITION OF δ-CARBAMOYLOXY-α,β-UNSATURATED ESTERS. SYNTHESIS OF N-BENZOYL-D,L-DAUNOSAMINE

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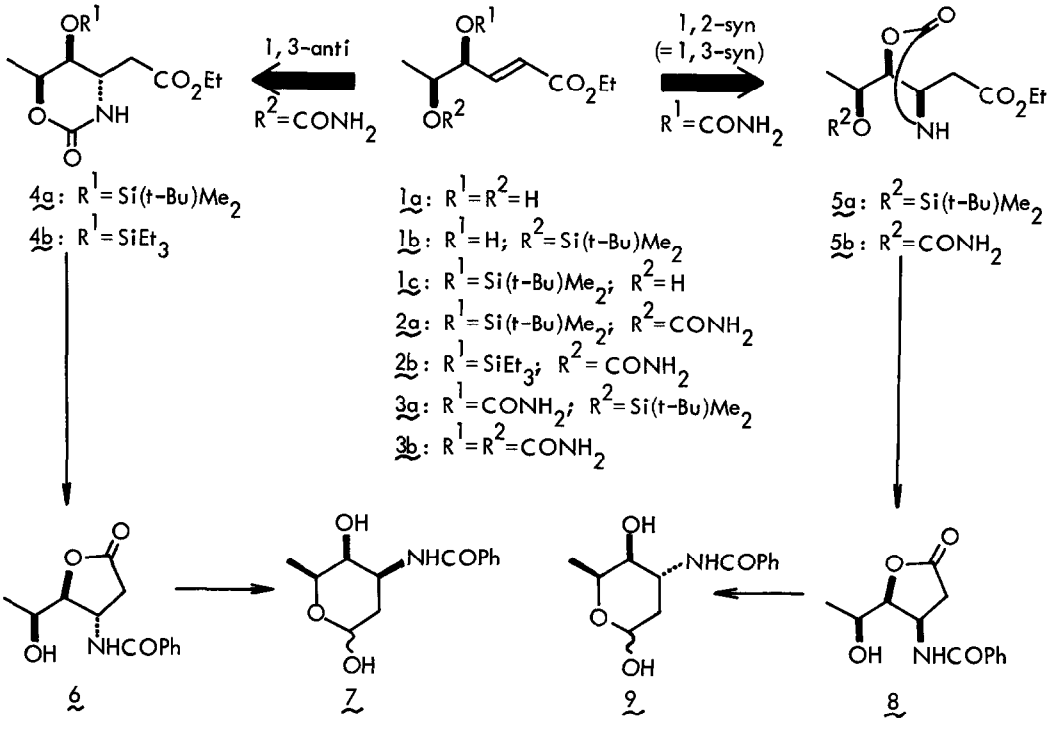
Abstract: Contrary to the precedents, 1,3-anti stereoselection was found in the intramolecular Michael addition of ethyl threo-5-carbamoyloxy-4-trialkylsilyloxy-2-hexenoate to culminate in a synthesis of N-benzoyl-D,L-daunosamine. The antiperiplanar effect due to the group at 4-position was revealed to play a major role in the stereoselection in this type of reactions. N-benzoyl-D,L-3-epidaunosamine was also synthesized by 1,2-syn asymmetric induction.

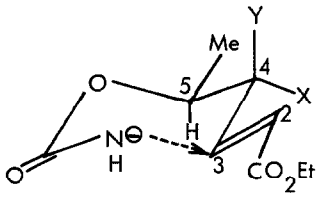
In the preceding paper[1], we have revealed complementary stereoselection by changing the site of carbamoyl group in the intramolecular conjugate addition of the carbamoyl derivatives of ethyl erythro-4,5-dihydroxy-2-hexenoate, and achieved stereoselective synthesis of N-acyl derivatives of acosamine and ristosamine. Diastereoface selectivity in these reactions was found to be the same (1,2-syn or 1,3-syn) as that of the derivatives of the corresponding monohydroxy unsaturated esters[2]. In this paper, we describe 1,3-anti selection occurring in the reaction of ethyl threo-4,5-dihydroxy-2-hexenoate derivatives, witnessed by the synthesis of D,L-daunosamine derivative, and discuss the factors controlling such stereoselection in these Michael addition reactions.

Homoallylic carbamates 2a and 2b were prepared by the following sequence starting from ethyl sorbate. Selective oxidation of sorbate with OsO_4 (1 mole %) N-methylmorpholine oxide[3] (1.1 eq.) for 4 h gave the desired threo diol 1a[4] in 60% yield based on ca. 50% conversion[5]. Silylation with t-butyldimethylsilyl chloride (1.1 eq./imidazole/DMF) afforded a mixture of monosilylethers 1b[4] (48%) and 1c[4a](27%), easily separable by SiO_2 chromatography. While the minor isomer 1c was directly converted to the carbamate 2a[4a] with CCl_3CONCO and subsequent hydrolysis[1], 2b[4] was prepared from the major 1b in four steps (48% overall yield): (i) protection of γ-hydroxyl (DHP/p-TsOH), (ii) deprotection of silylether (n-Bu_4NF), (iii) carbamation of δ-hydroxyl and concomitant deprotection of THP ether ($ClSO_2NCO$; $H_2O/70^oC$)[1], and (iv) protection (Et_3SiCl/imidazole/DMF). Cyclization of the homoallylcarbamates 2a and 2b was accomplished with t-BuOK (1.0 eq.) in THF (0^oC/20 min.).

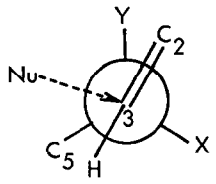
While the t-BuMe$_2$Si ether 2a gave a 2:1 mixture of the cyclic carbamate 4a and its diastereomer in 74% yield, 2b with Et$_3$Si group showed a higher selectivity (4b[4]: diastereomer=5:1, 75% yield)[6]. Each diastereomeric pair was separable by SiO_2 chromatography. The 1,3-anti relationship[7] in the major product 4b[8], opposite to the previous results[1,2], was determined by its transformation to the γ-lactone 6[4a] in two steps (53% overall), hydrolysis (1N-NaOH/EtOH/60°C) followed by benzoylation. The physical data of the synthetic 6 are identical with those reported by Hauser[9] (m.p. 135-137°C, lit[9]: m.p. 136-138°C). Since 6 was converted to N-Benzoyl-D,L-daunosamine 7[9], a formal total synthesis of 7 has thus been completed.



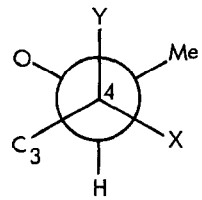
The origin of the diastereofacial selectivity in the kinetically controlled[2] conjugate addition of the homoallylic carbamates is quite intriguing. We believe two factors, steric and stereoelectronic, be operating. Two transition state models A and B may be most plausible for the formation of 4 and their *diastereomers, respectively, considering the conformational stability of carbon chain*[10] *and the trajectory of nucleophilic attack to a double bond*[11]. When X and Y are Hs, nonbonded interaction around C_3-C_4 is identical between A and B [compare A (3,4) and B (3,4)], and therefore the larger gauche interaction (Me-C_3) around C_4-C_5 in B [see B (4,5)] than that (Me-H, C_3-H) in A [A (4,5)] should be responsible for the observed (10:1) selectivity[2]. Introduction of an oxygen function in erythro configuration (X=OSiR$_3$, Y=H) would cause extra stabilization to the transition state A by stereoelectronic effect, while gauche interaction remains nearly the same: in A, LUMO of the unsatu-



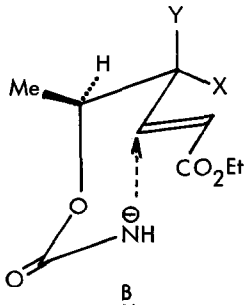
A



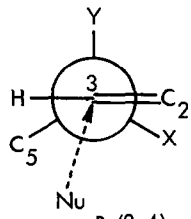
A (3,4)



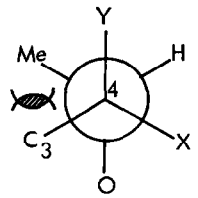
A (4,5)



B



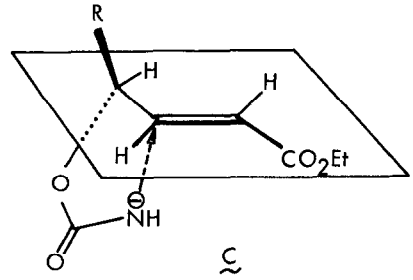
B (3,4)



B (4,5)

rated ester part would be stabilized by its perturbation with σ^* of the C-O bond at C_4 and result in the better interaction with HOMO of nucleophile (antiperiplanar effect)[11b], where as such an effect can not be expected in B. Thus, the higher stereoselectivity (up to > 50:1) in ethyl erythro-5-carbamoyloxy-4-trialkylsilyloxy-2-hexenoate[1] can be explained as cooperation of the steric and stereoelectronic effects. On the other hand, in the case of 2 where X=H, Y=$OSiR_3$, two effects counteract each other: while steric effect still favors A, stereoelectronic stabilization operates only in B. The relatively low 1,3-anti selection (up to 1:5) indicates the latter effect has a larger contribution.

The 1,2-syn selectivity in the reactions of allylic carbamates[2] is explicable on the basis of steric effect. The preferred conformation C[12] of the transition state also satisfies the required trajectory of nitrogen nucleophile for 5-Exo-Trig closure[11a]. From consideration of the model C, the synthesis of 3-epidaunosamine derivative can be envisaged starting from 1a or 1b. Thus, allyl carbamates 3a[4] and 3b[4], prepared by direct carbamation of 1b and 1a, respectively, cyclized smoothly on treatment with t-BuOK (1.0 eq./THF/0°C) leading to the oxazolidinones 5a[4] (27:1, 90% yield) and 5b[4] (23:1, 98%), respectively. Alkaline hydrolysis and subsequent benzoylation[1] of 5a and 5b, followed by deprotection of t-$BuMe_2Si$ group for 5a [AcOH-THF-H_2O (1:1:1)/r.t./overnight], gave the known γ-lactone 8[4a] (m.p. 154-156°C, lit[9]: m.p. 155-156°C), precursor of N-benzoyl-D,L-3-epidaunosamine 9[9], in 72% and 61% yields, respectively.



C

Thus, utilizing the carbamate-mediated intramolecular Michael addition, all possible diastereomers

of 2,3,6-trideoxy-3-aminohexose can be prepared starting from ethyl sorbate. The method should be useful for the preparation of various oxygenated amines. The effort is being made to improve the 1,3-anti diastereoselectivity disclosed in the present paper.

References and Notes

1) M. Hirama, T. Shigemoto and S. Itô, Tetrahedron Letters, the preceding paper.

2) M. Hirama, T. Shigemoto, Y. Yamazaki and S. Itô, J. Am. Chem. Soc., 107, 1797 (1985).

3) V. Van Rheenen, R.C. Kelly and D.Y. Cha, Tetrahedron Letters, 1973 (1976).

4) (a) Satisfactory spectral data (IR, ^{1}H NMR) and elemental analyses were obtained for all compounds reported herein. (b) Characteristic physical data: 1a: δ (90 MHz, $CDCl_3$) 1.24 (3H, d, J=6.4 Hz), 1.30 (3H, t, J=7.1 Hz), 3.72 (1H, dq, J=6.2, 6.4 Hz), 3.9-4.3 (1H, m), 4.20 (2H, q, J=7.1 Hz), 6.14 (1H, dd, J=1.5, 15.8 Hz), 6.91 (1H, dd, J=5.1, 15.8 Hz). 1b: δ (90 MHz, $CDCl_3$) 0.06 (3H, s), 0.08 (3H, s), 0.89 (9H, s), 1.21 (3H, d, J=6.1 Hz), 1.29 (3H, t, J=7.2 Hz), 2.58 (1H, d, J=5.8 Hz), 3.77 (1H, dq, J=4.9, 6.1 Hz), 3.8-4.2 (1H, m), 4.22 (2H, q, J=7.2 Hz), 6.13 (1H, dd, J=2.2, 15.7 Hz), 6.92 (1H, dd, J=4.9, 15.7 Hz). 2b: m.p. 70.5-72°C; ν (KBr) 1725, 1708 cm^{-1}; δ (90 MHz, $CDCl_3$) 0.4-1.1 (15H, m), 1.14 (3H, d, J=6.4 Hz), 1.30 (3H, t, J=7.2 Hz), 4.24 (2H, q, J=7.2 Hz), 4.48 (1H, ddd, J=1.8, 4.2, 5.2 Hz), 4.82 (1H, dq, J=5.2, 6.4 Hz), 4.96 (2H, m), 6.12 (1H, dd, J=1.8, 15.6 Hz), 6.95 (1H, dd, J=4.2, 15.6 Hz). 3a: m.p. 86-88°C; ν (KBr) 1736, 1704 cm^{-1}; δ (90 MHz, $CDCl_3$) 0.08 (6H, s), 0.89 (9H, s), 1.12 (3H, d, J=6.4 Hz), 1.29 (3H, t, J=7.2 Hz), 3.97 (1H, quint, J=6.4 Hz), 4.20 (2H, q, J=7.2 Hz), 4.80 (2H, m), 5.24 (1H, ddd, J=1.8, 4.6, 6.4 Hz), 6.02 (1H, dd, J=1.8, 15.8 Hz), 6.93 (1H, dd, J=4.6, 15.8 Hz). 3b: m.p. 128-130°C; ν (KBr) 1720, 1693 cm^{-1}. 4b: m.p. 92-94°C; ν ($CHCl_3$) 3380, 1716, 1700 cm^{-1}; δ (200 MHz, $CDCl_3$) 0.48-0.58 (6H, m), 0.90-1.08 (9H, m), 1.30 (3H, t, J=7.2 Hz), 1.40 (3H, d, J=6.6 Hz), 2.43 (1H, dd, J=9.5, 17.0 Hz), 2.62 (1H, dd, J=4.2, 17.0 Hz), 3.69 (1H, m), 3.75 (1H, m), 4.21 (2H, q, J=7.2 Hz), 4.35 (1H, dq, J=3.0, 6.6 Hz), 6.65 (1H, m). 5a: m.p. 88-90°C; ν (KBr) 3350, 1752 cm^{-1}; δ (200 MHz, $CDCl_3$) 0.08 (3H, s), 0.09 (3H, s), 0.88 (9H, s), 1.21 (3H, d, J=6.2 Hz), 1.29 (3H, t, J=7.2 Hz), 2.62 (2H, d, J=6.5 Hz), 4.07 (1H, dq, J=4.0, 6.2 Hz), 4.1 (2H, m), 4.22 (2H, q, J=7.2 Hz), 5.96 (1H, m). 5b: m.p. 116-119°C; ν ($CHCl_3$) 3530, 3430, 1765, 1718 cm^{-1}.

5) Attempts to improve the yield of 1a by using excess reagents and/or prolonged reaction times were unsuccessful, probably because further oxidation of the remaining double bond took place under such conditions.

6) Higher stereoselectivity of Et_3Si group than t-$BuMe_2Si$: See reference 9 in the preceding paper.

7) The similar reversal of stereoselectivity caused by changing stereochemistry of γ-substituent has been observed in the intermolecular benzyloxymercuration of derivatives of γ-alkyl-δ-hydroxy-α,β-unsaturated esters: S. Thaisrivongs and D. Seebach, J. Am. Chem. Soc., 105, 7407 (1983).

8) Although 4a has not been transformed to 6, its stereochemistry must be same as 4b, because its NMR spectral pattern resembles closely to that of 4b.

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