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THE CHEMISTRY OF O-SILYLATED KETENE ACETALS: AN EFFICIENT STEREOCONTROLLED SYNTHESIS OF N-BENZOYL L-DAUNOSAMINE

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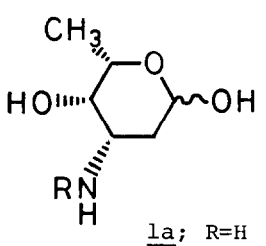
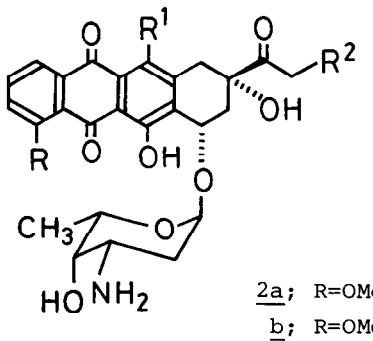
Summary: N-Benzoyl L-daunosamine was synthesized with high stereoselectivity utilizing a 1,3-addition of ketene silyl acetal (3a) to the chiral nitrone, (Z)-[(4R)-trans-2,2,5-trimethyl-1,3-dioxolan-4-yl]methylene[(1S)-1-phenylethyl]amine N-oxide (4c) accompanied by a silyl group-transfer in acetonitrile under mild conditions.

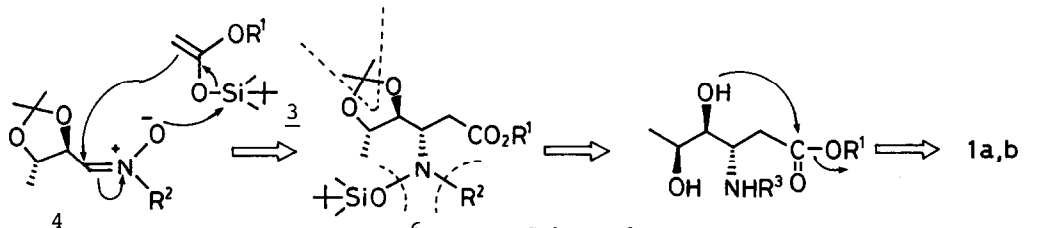
L-Daunosamine[1] (1a, 3-amino-2,3,6-trideoxy-L-lyxo-hexose), which is an essential component of natural and unnatural anthracycline antitumor agents daunomycin (2a), adriamycin (2b), 4-demethoxydaunomycin (2c), and 11-deoxydaunomycin (2d), has elicited a substancial interest as a synthetic target for organic synthesis.[2] In connection with our continuing efforts to establish new efficient methodology for the synthesis of anthracycline antibiotics,[3] we required a general practical route for the preparation of 1a. Recently, we have reported[4] a versatile method for the diastereoselective synthesis of 2-deoxy-D-ribose by utilizing aldol reaction of ketene silyl acetal (3) to 2,3-O-isopropylidene-D-glyceraldehyde accompanied by a silyl group transfer.[5] The method appeared to be aptly applicable to a synthesis of optically pure N-benzoyl-L-daunosamine (1b). We describe here an efficient stereocontrolled synthesis of 1b by a bond-forming strategy which engages the chiral Z-nitrone (4) and 3 in the silyl group-transfer 1,3-addition reaction (Scheme 1).



1a; R=H
b; R=COPh

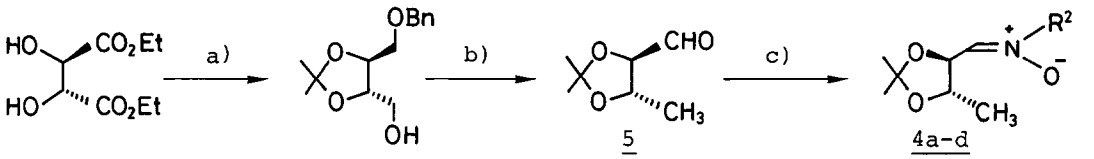


2a; R=OMe, R^1=OH, R^2=H
b; R=OMe, R^1=R^2=OH
c; R=R^2=H, R^1=OH
d; R=OMe, R^1=H, R^2=OH



Scheme 1

The starting chiral aldehyde (5) was obtained from commercially available diethyl L-tartrate by the modification of Fronza's[6] and Mukaiyama's methods[7] and reacted with achiral and chiral N-alkylhydroxylamines to give the corresponding chiral Z-nitrones (4a-d) in high yields (Scheme 2).



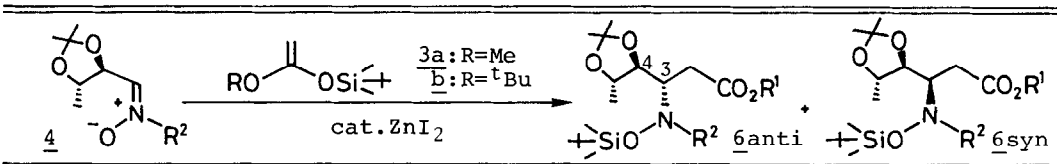
a): i) $Me_2C(OMe)_2$/p-TsOH, ii) $LiAlH_4$, iii) BnBr/NaH-DMF
b): i) TsCl/pyridine, ii) $NaBH_4$, iii) $[H_2]$, iv) $(COCl)_2$/DMSO-Et_3N
c): i) R^2NHOH/Na_2SO_4-CH_2Cl_2

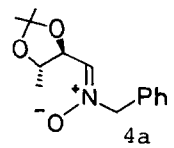
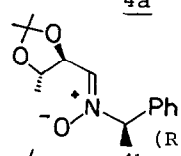
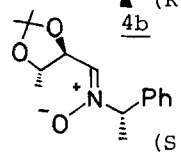
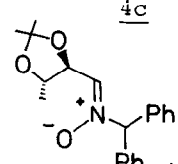
Scheme 2

DeShong and Leginus reported[8] that the achiral Z-nitrone (achiral-4a) underwent a diastereo- and regiospecific cycloaddition with ethyl vinyl ether to the isoxazolidine, which converted to racemic daunosamine involving a severe hydrogenolysis over Pearlman's catalyst.[9] We now found that the reaction of these chiral nitrones (4a-d) with ketene silyl acetals (3a,b) gave highly diastereoselective O-silylated 1,3-addition products (6a-g)[10] and the N-O bond in 6a-g proved to cleave smoothly under mild hydrogenolysis conditions to give the aminoesters, which were readily converted to optically pure N-benzoyl-L-daunosamine (1b). The best result was obtained by the reaction of (Z)-[(4R)-trans-2,2,5-trimethyl-1,3-dioxolan-4-yl]methylene[(1S)-1-phenylethyl]amine N-oxide (4c) [colorless oil, $[\alpha]_D^{28}$ +43.8° (c 0.54, $CHCl_3$), m/e 263 (M^+)] and O-methyl-O-t-butyldimethylsilyl ketene acetal (3a) at -78°C in the presence of a catalytic amount of zinc iodide in CH_3CN-CH_2Cl_2 (1:1) for 1 h (run 6). The O-silylated 1,3-addition product (6e) [colorless oil, $[\alpha]_D^{27}$ -5.98° (c 2.59, $CHCl_3$), m/e 451 (M^+)] was obtained in a quantitative yield with an anti relative stereochemistry at C-3 and C-4 (anti:syn=>100:1). The results are summarized in Table I.

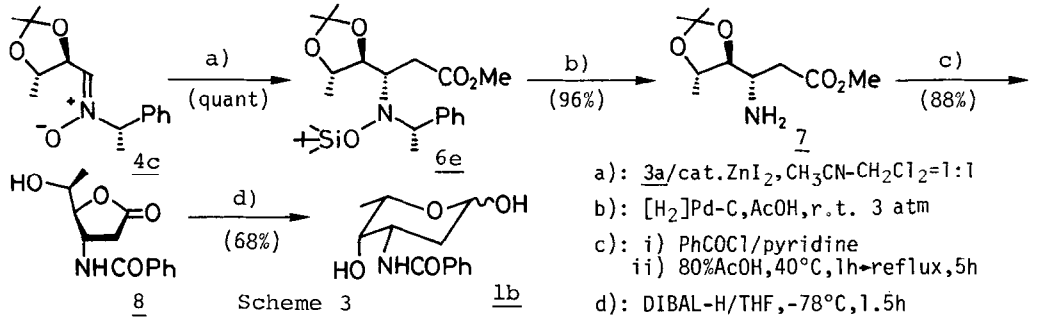
The stereochemical assignment of the adducts (6a-g) was established by the conversion of the adducts into the known γ-lactone (8)[2a,11]: Thus, the adduct (6e) was hydrogenated to give the amino ester (7), which was converted into 8 by a standard benzoylation followed by lactonization [8, ν_{max} (KBr) 3470, 3330, 1770, 1640 cm^{-1}, mp 148-149°C (AcOEt-hexane), $[\alpha]_D^{18}$ -19.7° (c 1.02, EtOH); lit.[11a] mp 147°C $[\alpha]_D^{23}$ -16° (c 1, MeOH); lit.[2a] mp 143-144°C, $[\alpha]_D^{26}$ -19.4° (c 1.0, EtOH); lit.[11b] 147.5-148°C

Table I Diastereoselective 1,3-Addition of the Chiral Nitrones (4a-d)



Runs	Nitrones	Silyl ketene Acetals	Reaction Conditions	Products	Yields	Diastereo Selectivity anti : syn
1	 4a	3a	-78°C, CH_3CN-CH_2Cl_2=1:1	6a	quant	60 : 40
2		3b	-78°C, CH_3CN-CH_2Cl_2=1:1	6b	99	83 : 17
3	 4b	3a	-78°C, CH_3CN-CH_2Cl_2=1:1	6c	89	88 : 12
4		3b	-78°C, CH_3CN-CH_2Cl_2=1:1	6d	77	94 : 6
5		3b	r.t., CH_3CN	6d	32	65 : 35
6	 4c	3a	-78°C, CH_3CN-CH_2Cl_2=1:1	6e	quant	100 : 0
7		3a	r.t., CH_3CN	6e	quant	95 : 5
8	 4d	3a	-78°C, CH_3CN-CH_2Cl_2=1:1	6f	90	93 : 7
9		3b	-78°C, CH_3CN-CH_2Cl_2=1:1	6g	85	100 : 0

$[\alpha]_D^{24}$ -20.1° (c 1.0, EtOH); lit.[11c] 138-140°C, $[\alpha]_D$ -24.9° (c 1, EtOH)]. The discrepancy of the physical data may be ascribed to the fact that the γ-lactone gradually isomerizes to the δ-lactone.[11d] The transformation of 8 into 1b was carried out according to the known method[11] [1b,[12] mp 154-156°C (acetone), $[\alpha]_D^{26}$ -108° (c 0.093, EtOH, after 30 min); lit.[13] mp 152°C, $[\alpha]_D^{20}$ -108° (c 0.5, EtOH); lit.[11d] mp 153-155°C, $[\alpha]_D^{20}$ -109° (c 0.1, EtOH, after 3h)]. The route is visualized in Scheme 3.

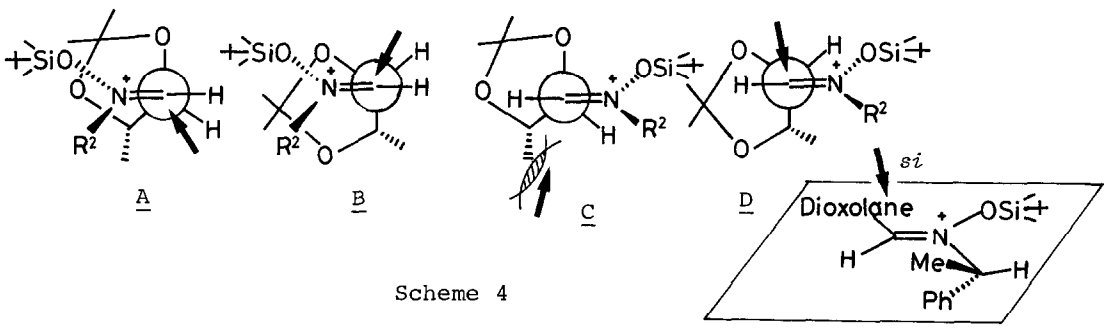


4c 6e 7 8 1b

Scheme 3

a): 3a/cat.ZnI_2, CH_3CN-CH_2Cl_2=1:1
b): [H_2]Pd-C, AcOH, r.t. 3 atm
c): i) PhCOCl/pyridine
ii) 80%AcOH, 40°C, 1h→reflux, 5h
d): DIBAL-H/THF, -78°C, 1.5h

While the details of the diastereoselection of the reaction of 4 and 3 remain unknown, a working model is given in Scheme 4. Addition to diastereotopic face of a π-system is usually explained in terms of the Felkin-Anh model.[14] For the reaction of 4, the following conformations (A-D) are considered. For conformations A and B, severe steric interactions are present between the dioxolane ring and the initially formed bulky siloxy group. For conformation C, unfavorable interactions between the incoming enolate anion and the methyl group on dioxolane ring are present. Molecular models suggest that the attack of enolate anion via conformation D is sterically demanded, and may explain the much more selection of the S-nitrone (4c) than the R-nitrone (4b) as pictured in Fig. (i).



Scheme 4

Fig. (i)

References and Notes

1) F. Arcamone, G. Cassinelli, P. Orezzi, G. Franceschi, and R. Mondelli, J. Am. Chem. Soc., 86, 5335 (1964); F. Arcamone, G. Franceschi, P. Orezzi, G. Cassinelli, W. Barbieri, and R. Mondelli, ibid., 86, 5334 (1964); A. DiMarco, F. Arcamone, and F. Zunio, "Antibiotics"; J. W. Corcoran and F. E. Hahn Eds.; Springer Verlag: New York, 1975; Vol. III pp 101-128.
2) For an excellent review, see: F. M. Hauser and S. R. Ellenberger, Chem. Rev., 86, 35 (1986) and references cited therein. Recent works after the review, see: a) M. Hirama, I. Nishizaki, T. Shigemoto, and S. Itô, J. Chem. Soc. Chem. Commun., 1986, 393; b) Y. Kimura, T. Matsumoto, M. Suzuki, and S. Terashima, Bull. Chem. Soc. Jpn., 59, 663 (1986); H. Iida, N. Yamazaki, and C. Kibayashi, J. Org. Chem., 51, 4245 (1986).
3) Y. Tamura, A. Wada, M. Sasho, K. Fukunaga, H. Maeda, and Y. Kita, ibid., 47, 4376 (1982); Y. Tamura, M. Sasho, S. Akai, A. Wada, and Y. Kita, Tet., 40, 4539 (1984); Y. Tamura, M. Sasho, H. Ohe, S. Akai, and Y. Kita, Tetrahedron Lett., 26, 1549 (1985); Y. Tamura, M. Sasho, S. Akai, H. Kishimoto, and Y. Kita, ibid., 27, 195 (1986).
4) Y. Kita, H. Yasuda, O. Tamura, F. Itoh, Y. Y. Ke, and Y. Tamura, ibid., 26, 5777 (1985).
5) For a review on the silyl group-transfer aldol and Michael reactions of ketene silyl acetals, see: Y. Kita, Yakugaku Zasshi, 106, 269 (1986).
6) G. Fronza, C. Fuganti, P. Grasselli, and G. Marinoni, Tetrahedron Lett., 1979, 3883, G. Fronza, C. Fuganti, and P. Grasselli, ibid., 21, 2999 (1980).
7) T. Mukaiyama, Y. Goto, and S.-I. Shoda, Chem. Lett., 1983, 671.
8) P. DeShong and J. M. Legius, J. Am. Chem. Soc., 103, 1686 (1983).
9) W. M. Pearlman, Tetrahedron Lett., 1967, 1663.
10) For the reaction of ketene silyl acetals with nitrones, see: S. Tomoda, Y. Takeuchi, and Y. Nomura, Chem. Lett., 1982, 1787.
11) a) F. M. Hauser, R. P. Rhee, and S. R. Ellenberger, J. Org. Chem., 49, 2236 (1984); b) S. Brandänge and B. Lindqvist, Acta Chem. Scand. B, 39, 589 (1985); c) S. Hanessian and J. Kloss, Tetrahedron Lett., 26, 1261 (1985); d) T. Hiyama, K. Nishide, and K. Kobayashi, Chem. Lett., 1984, 361.
12) L-Daunosamine was shown to exist in pyranose form (α:β=82:18) by the study of 500 MHz NMR.
13) C. Fuganti, P. Grasselli, and G. P.-Fantoni, J. Org. Chem., 48, 909 (1983).
14) M. Chérest, H. Felkin, and N. Prudent, Tetrahedron Lett., 1968, 2199; N. T. Anh and O. Eisentein, Nouv. J. Chim., 1, 61 (1977).

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