Tetrahedron Letters,Vol.25,No.5,pp 569-572,1984
Printed in Great Britain

0040-4039/84 $3.00 + .00

A NEW SYNTHESIS OF N-BENZOYL L-ACOSAMINE

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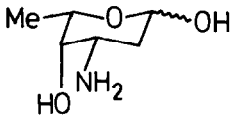
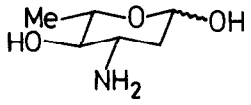
Reaction of (2R,3S)-2,3-(cyclohexylidenedioxy)butanenitrile, derived from ethyl (S)-lactate, with the magnesium enolate of t-butyl acetate gave the corresponding (Z)-β-amino acrylate derivative, which was transformed into N-benzoyl acosamine by acetylation, stereoselective hydrogenation, acidic hydrolysis, and ring-formation followed by reduction with diisobutylaluminium hydride.

Anthracycline antibiotics adriamycin, daunomycin, and carminomycin are highly effective against a wide range of tumors[1,2] and contain commonly an amino sugar moiety, called L-daunosamine. Changing the sugar part of adriamycin with its 4-epimer, L-acosamine, lowers the cardiotoxicity while retaining the anti-tumor activity,[3] and therefore extensive studies are recently concerned with the synthesis of this amino sugar.[4] We wish to report a new chiral synthesis of L-acosamine, starting with readily available ethyl (S)-lactate (Scheme 1) and employing a nitrile-acetate coupling reaction[5] and stereoselective hydrogenation (Scheme 2).



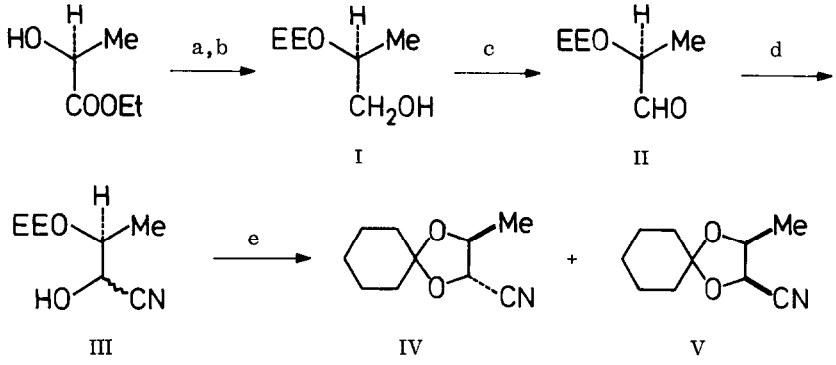
L-daunosamine



L-acosamine

A key intermediate (2R,3S)-2,3-(cyclohexylidenedioxy)butanenitrile (V) was prepared by the process summarized in Scheme 1. Ethyl (S)-lactate was protected with ethyl vinyl ether and reduced with lithium aluminium hydride to give (S)-2-ethoxyethyl-1,2-propanediol (I)[6] (bp 77-9°C/17 Torr, $[\alpha]_D^{29}$ +42.2° (c 5.87, $CHCl_3$)) in 91% overall yield. Oxidation of I by the Swern's method[7] gave the aldehyde II[6] (bp 53-4°C/17 Torr, $[\alpha]_D^{23}$ -56.9° (c, 6.31, $CHCl_3$), IR 1735 cm^{-1}, ^1H NMR ($CDCl_3$) δ 9.59 (d, J = 3.0 Hz) and 9.64 (d, J = 1.5 Hz), totally 1 H) in 78% yield after distillation. II was stirred with excess acetone cyanohydrin and a catalytic amount of triethylamine. After evaporation of the volatile material the residue was purified briefly by column chromatography to give the cyanohydrin III, which was stirred at room temperature in dichloromethane with cyclohexanone dimethyl acetal and

Scheme 1

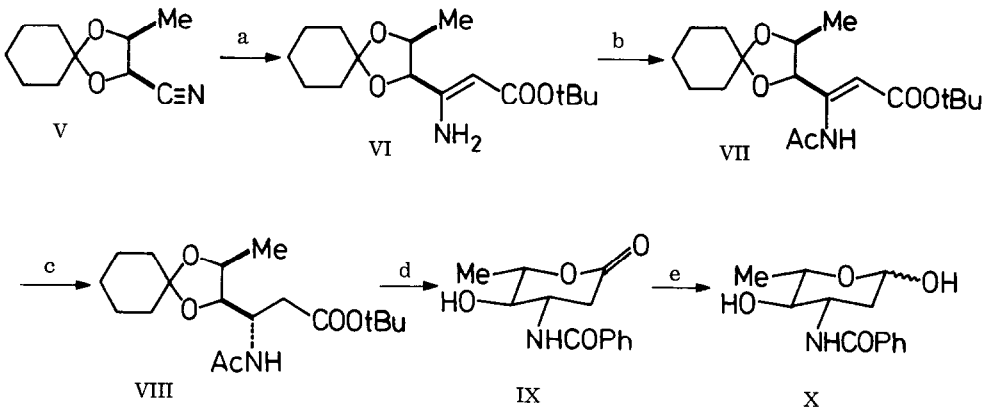


a: CH_2=CHOEt, PyHOTs, CH_2Cl_2, 0°C - r.t.
b: $LiAlH_4$, ether, reflux
c: DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, -65 - -70°C
d: $Me_2C(OH)CN$, Et_3N, 0°C
e: $(CH_2)_5C(OMe)_2$, $(Me_3SiO)_2SO_2$, Molecular Sieve 4 A, 0°C - r.t.

bis(trimethylsilyl) sulfate catalyst[8] in the presence of Molecular Sieve 4 A to give a 45:55 mixture of (2S,3S)-2,3-(cyclohexylidenedioxy)butanenitrile (IV)[6] (bp 60-1°C/0.25 Torr, $[\alpha]_D^{24}$ +15.5° (c 8.84, $CHCl_3$), IR (neat) 2250 cm^{-1}, ^1H NMR (CCl_4) δ 1.38 (d, J = 6.0 Hz, 3 H), 4.02 (d, J = 7.5 Hz, 1 H), 4.36 (dq, J = 7.5, 6.0 Hz, 1 H)) and its (2R,3S)-derivative V[6,9] (bp 74-5°C/0.25 Torr, $[\alpha]_D^{23}$ + 26.4° (c 5.57, $CHCl_3$), IR (neat) 2250 cm^{-1}, ^1H NMR (CCl_4) δ 1.45 (d, J = 6.0 Hz, 3 H), 4.21 (dq, J = 5.3, 6.0 Hz, 1 H), 4.58 (d, J = 5.3 Hz, 1 H)) in 96% overall yield. These two nitriles were separated by column chromatography. Careful ^1H NMR study using Eu(TFC)$_3$ showed >95% optical purity of these nitriles.[11] Thus, no trace of racemization occurred during the oxidation of I, cyanohydrin formation or acetalization leading to IV and V. Apparently, the protected lactaldehyde[12] and the cyanohydrins[13] are versatile synthetic intermediates.

Condensation of the nitrile V with the magnesium enolate of t-butyl acetate[5] in ether at 0°C gave VI[6] (bp 112-3°C/0.3 Torr, $[\alpha]_D^{26}$ -7.40° (c 3.59, $CHCl_3$), IR (neat) 3525, 3350, 1670, 1620 cm^{-1}, ^1H NMR ($CDCl_3$) δ 1.21 (d, J = 6.0 Hz, 3 H), 1.48 (s, 9 H), 4.30-4.60 (m, 3 H)) in a 54% yield after distillation. Attempted reduction of the C=C bond in VI under various conditions resulted in vain. However, the catalytic hydrogenation of the N-acetyl derivative VII was proved to be feasible.[14] Thus, VI was acetylated with acetic anhydride in pyridine at 50-60°C to give VII[6] (77%, $[\alpha]_D^{26}$ -131.7° (c 2.26, $CHCl_3$), IR (neat) 3525, 3250, 3000, 1720, 1670, 1635 cm^{-1}, ^1H NMR ($CDCl_3$) δ 1.10 (d, J = 6.0 Hz, 3 H), 1.50 (s, 9 H), 2.14 (s, 3 H), 4.73 (quinted, J = 6.0 Hz, 1 H), 5.55 (d, J = 1.0 Hz, 1 H), 5.74 (dd, J = 6.0, 1.0 Hz, 1 H), 11.34 (br s, 1 H, NH)) along with the (E)-isomer (20%). Reduction of VII was carried out in an autoclave[15] (H_2, 70 kg/cm^2, 5% Rh/C catalyst, THF, 55°C, 24 h) to give a single product VIII[6,16] ($[\alpha]_D^{26}$ +21.2° (c 2.04, $CHCl_3$), IR (neat) 3450, 3200, 1730, 1660 cm^{-1}, ^1H NMR ($CDCl_3$)

Scheme 2



a: CH_2=C(OtBu)CMgX, ether, 0°C,
b: Ac_2O, Py, 50 - 60°C
c: H_2, 70 kg/cm^2, Rh/C, THF, 55°C
d: (i) 2 N HCl, reflux, (ii) PhCOCl, sat aq $NaHCO_3$-acetone (5:2), r.t., (iii) 2 N HCl
e: iBu_2AlH, THF, -60 - -50°C

δ 1.25 (d, J = 6.0 Hz, 3 H), 1.47 (s, 9 H), 1.95 (s, 3 H), 2.48 (d, J = 6.7 Hz, 2 H), 4.1-4.5 (m, 3 H), 5.93 (br d, J = 7.5 Hz, 1 H, NH)) in 84% yield. The structure of this product was proved by conversion to a known lactone IX[17] by acidic hydrolysis, benzoylation under Schotten-Baumann conditions followed by lactonization with hydrochloric acid (73% overall yield). The spectral data as well as $[\alpha]_D^{20}$ +11.5° (c 0.80, EtOH) were identical with the reported values, e.g. $[\alpha]_D^{20}$ +11.5° (c 1.1, EtOH).[17] Final reduction with diisobutylaluminium hydride (5 eq) in THF gave N-benzoyl acosamine in 98% yield having consistent spectral properties.[17]

As ethyl (S)-lactate in optically pure form is now readily available, the present approach to L-acosamine will be applicable to large-scale synthesis. Furthermore, in view of the possible inversion of the configuration at C(4),[4] L-daunosamine also is accessible. In addition, by applying the sequence of the reactions in Scheme 2 to the nitrile IV, we could prepare the C(4) epimer of IX, a precursor of N-benzoyl daunosamine.

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9. The nitrile was alternatively prepared from dimethyl L(+)-tartrate by (i) $(CH_2)_5C(OMe)_2$, TsOH; $LiAlH_4$, 80% yield, (ii) monotosylation (TsCl/Py); $NaBH_4$ in DMSO, 59% yield, (iii) DMSO, $(COCl)_2$, Et_3N, 87% yield, to give (2R,3S)-2,3-(cyclohexylidenedioxy)butanal (ref 10) which was led to the oxime (NH_2OH, Py) and then to IV (CCl_4-PPh_3, Et_3N) (83% yield). In a similar way we prepared (2S,3S)-2,3-(2',2'-propylidenedioxy)butanenitrile also.

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11. Racemic V was prepared starting with ethyl (±)-lactate according to the procedures in Scheme 1. Separation of the methine doublet (δ 4.58, J = 5.3 Hz) of racemic V was best realized with 1.2 mol of $Eu(TFC)_3$ in carbon tetrachloride to give two doublets at δ 4.46 and 4.50. The optically active sample gave the former peak only within the error of 5%.

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15. Although the reduction can be carried out with PtO_2 at atmospheric pressure of hydrogen in ethanol or at 10 kg/cm^2 hydrogen pressure in ethyl acetate with complete stereocontrol, it took much longer reaction time.

16. The high stereoselectivity may be attributed to the steric bulk of the dioxolane ring as well as the orbital effect of the allylic alkoxy group as discussed in R. W. Franck, T. V. John, and K. Olejniczak, J. Am. Chem. Soc., 104, 1106 (1982).

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(Received in Japan 2 November 1983)