Pergamon

Tetrahedron: Asymmetry, Vol. 7, No. 5, pp. 1273-1274, 1996

0957-4166/96 $15.00 + 0.00

S0957-4166(96)00141-3

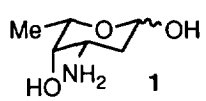
Asymmetric Synthesis of Methyl α-L-Daunosaminide Hydrochloride

Stephen G. Davies* and G. Darren Smyth

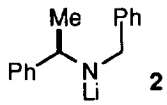
The Dyson Perrins Laboratory, University of Oxford, South Parks Road, Oxford, OX1 3QY, UK.

Abstract: Methyl α-L-daunosaminide hydrochloride was synthesised in five steps from methyl (*E,E*)-hexa-2,4-dienoate, *via* the conjugate addition of (*R*)-lithium *N*-benzyl-α-methylbenzylamide, and osmium tetroxide catalysed dihydroxylation of the resulting adduct.

Daunosamine **1**, the amino sugar constituent of the important anthracycline antibiotics daunorubicin[1] and doxorubicin,[2] has, since the discovery of these anticancer agents in the 1960s, attracted a great deal of synthetic interest.[3,4] Here we wish to report a relatively short synthesis of the daunosamine derivative **9**, in five steps from methyl (*E,E*)-hexa-2,4-dienoate **3**.

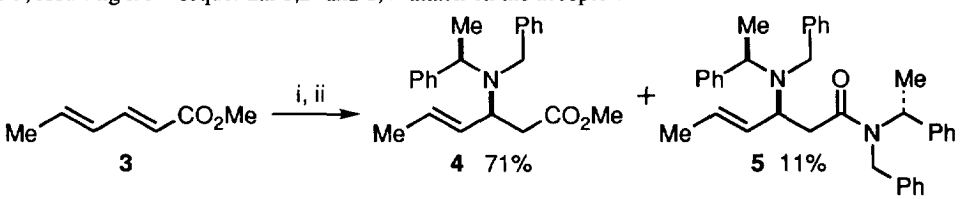


1



2

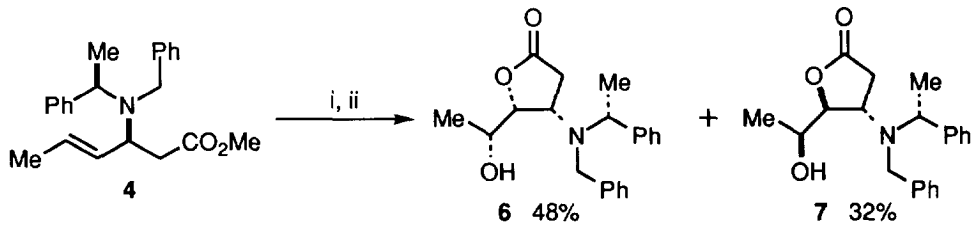
(*R*)-Lithium *N*-benzyl-α-methylbenzylamide[5] **2** adds in 95% d.e. to methyl (*E,E*)-hexa-2,4-dienoate **3**, to give pure adduct **4** in 71% isolated yield (Scheme 1).¶ The yield is somewhat compromised by the formation of the amide **5**, resulting from sequential 1,2- and 1,4- attack on the acceptor.



3 **4** 71% **5** 11%

Scheme 1 *Reagents:* i, **2**, THF, -78°C; ii, NH_4Cl (aq), -78°C to 20°C

The adduct **4** was treated with catalytic (5mol%) osmium tetroxide using the cooxidant developed by Yamamoto *et al.*[6] Under these conditions, dihydroxylation proceeded with concomitant cyclisation to give the two diastereomeric lactones **6** and **7** in the ratio 3:2, which were separable by column chromatography on silica gel, in isolated yields of 48% and 32% respectively (Scheme 2).



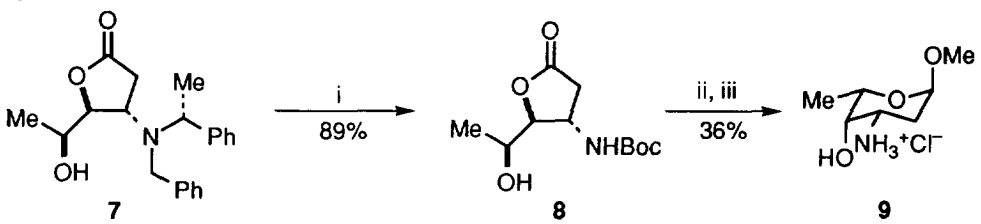
4 **6** 48% **7** 32%

Scheme 2: *Reagents :* i, OsO_4 (5mol%), $K_3Fe(CN)_6$ (3eq), K_2CO_3 (3eq), aq *t*-BuOH, 20°C; ii, Na_2SO_3 (s)

¶ All new compounds exhibited satisfactory spectroscopic (^1H and ^{13}C NMR, IR, MS) and combustion analysis data in accordance with the assigned structures.

Employing the Sharpless asymmetric dihydroxylation reaction[7,8] (osmium tetroxide 2%, chiral ligand 10% and methanesulfonamide 1 equiv.) gave in the presence of the ligand $(DHQ)_2PHAL$, **6** and **7** in the ratio 1:3, while in the presence of the ligand $(DHQD)_2PHAL$, the ratio of **6** to **7** was 9:2.

Hydrogenolysis of the two benzyl groups from the adduct **7** over palladium hydroxide on charcoal was achieved with *in situ* Boc protection, using a procedure developed by analogy with methods known for converting azides[9] or Z-protected amines[10] into the corresponding *N*-Boc compounds, to give the protected lactone **8** in 89% yield (Scheme 3). **8** was reduced with DIBAL-H in dichloromethane to give a complex mixture of the corresponding lactols. After purification by column chromatography on silica gel,[4c] the mixture of lactols was treated with methanolic hydrogen chloride, giving the title compound **9** in 36% yield from the lactone **8**. Data for this product: mp 184°C (dec; from MeOH/Et_2O); $[\alpha]_D^{23}$ = -146 (*c* 0.64 in MeOH) were in good agreement with those for the material obtained from the natural product:[1c] 188-190°C, (dec); $[\alpha]_D$ = -140 (*c* 1 in MeOH). Also, the synthetic material was shown, by mixed ^1H NMR spectroscopy, to be identical to authentic material (prepared from commercially available methyl β-L-daunosaminide hydrochloride by treatment with methanolic hydrogen chloride).



Scheme 3: *Reagents* i, H_2 (6atm), $Pd(OH)_2/C$, Boc_2O, EtOAc, 20°C; ii, DIBAL-H (3.5eq), CH_2Cl_2, -78°C; iii, HCl, MeOH

Thus a five step synthesis of the daunosamine derivative **9** from methyl (*E,E*)-hexa-2,4-dienoate **2** has been achieved. The low intrinsic diastereoselectivity of the the dihydroxylation reaction can be significantly improved using the Sharpless asymmetric dihydroxylation methodology.

References:

1. (a) F. Arcamone, G. Franceschi, P. Orezzi, G. Cassinelli, W. Barbieri and R. Mondelli, *J. Am. Chem. Soc.*, 1964, **86**, 5334; (b) F. Arcamone, G. Cassinelli, P. Orezzi, G. Franceschi and R. Mondelli, *J. Am. Chem. Soc.*, 1964, **86**, 5335; (c) F. Arcamone, G. Cassinelli, G. Franceschi, R. Mondelli, P. Orezzi and S. Penco, *Gazz. Chim. Ital.*, 1970, **100**, 949.
2. F. Arcamone, G. Franceschi, S. Penco and A. Selva, *Tetrahedron Lett.*, 1969, 1007.
3. Reviews: (a) F.M. Hauser and S.R. Ellenberger, *Chem. Rev.*, 1986, **86**, 35; (b) I.F. Pelyvás, C. Monneret and P. Herczegh, *Synthetic Aspects of Aminodeoxy Sugars of Antibiotics*, Springer-Verlag, Berlin, 1988.
4. More recent syntheses of daunosamine: (a) M. Hatanaka and I. Ueda, *Chem. Lett.*, 1991, 61; (b) L.-X. Dai, B.-L. Lou and Y.-Z. Zhang, *J. Am. Chem. Soc.*, 1988, **110**, 5195; (c) P.G. Sammes and D. Thetford, *J. Chem. Soc., Perkin Trans. I*, 1988, 111; (d) Y. St-Denis, J.-F. Lavallée, D. Nguyen and G. Attardo, *Synlett*, 1995, 272; (e) B. Abbaci, J.-C. Florent and C. Monneret, *Bull. Soc. Chim. Fr.*, 1989, 667; (f) P. Herczegh, M. Zsély, I. Kovács, G. Batta and F.J. Sztaricskai, *Tetrahedron Lett.*, 1990, **31**, 1195; (g) J. Jurczak, J. Kozak and A. Golebiowski, *Tetrahedron*, 1992, **48**, 4231; (h) S.-Y. Po and B.-J. Uang, *Tetrahedron: Asymmetry*, 1994, **5**, 1869.
5. S.G. Davies and O. Ichihara, *Tetrahedron: Asymmetry*, 1991, **2**, 183.
6. M. Minato, K. Yamamoto and J. Tsuji, *J. Org. Chem.*, 1990, **55**, 766.
7. K.B. Sharpless, W. Amberg, Y.L. Bennani, G.A. Crispino, J. Hartung, K.-S. Jeong, H.-L. Kwong, K. Morikawa, Z.-M. Wang, D. Xu and X.-L. Zhang, *J. Org. Chem.*, 1992, **57**, 2768.
8. Y.L. Bennani and K.B. Sharpless, *Tetrahedron Lett.*, 1993, **34**, 2079.
9. S. Saito, H. Nakajima, M. Inaba and T. Moriwake, *Tetrahedron Lett.*, 1989, **30**, 837.
10. M. Sakaitani, K. Hori and Y. Ohfune, *Tetrahedron Lett.*, 1988, **29**, 2983.

(*Received in UK* 18 *March* 1996)