Carbohydrate Research, 129 (1984) 267–270
Elsevier Science Publishers B.V., Amsterdam – Printed in The Netherlands

Note

Synthesis of methyl 3-*N*-benzoyl-4-*O*-benzoyl-β-L-daunosaminide*

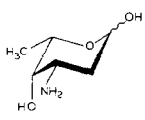
MUKUND K. GURJAR**, VIJAY J. PATIL, JHILLU S. YADAV, AND A. V. RAMA RAO
National Chemical Laboratory, Poona 411 008 (India)

(Received September 14th, 1983; accepted for publication, January 7th, 1984)

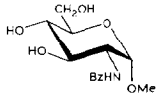
Several syntheses of L-daunosamine (**1**), the sugar unit of anthracycline antibiotics[1], have been reported, starting from both carbohydrate[2] and non-carbohydrate[3] precursors. We now report a new synthesis of the daunosamine derivative **11** from 2-amino-2-deoxy-D-glucose hydrochloride.

The strategy involved the migration of the 2-amino group of a 2-amino-2-deoxy-D-glucose derivative *via* an epimine to position 3, and the subsequent generation of a *C*-methyl group at C-5 with change of chirality at C-5.

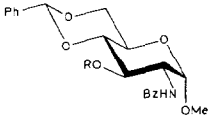
Methyl 3-benzamido-4,6-*O*-benzylidene-2-chloro-2,3-dideoxy-α-D-altropyranoside[4] (**6**) was chosen as the starting material and was prepared by the modified literature procedure[4]. Methyl 2-benzamido-4,6-*O*-benzylidene-2-deoxy-α-D-glucopyranoside (**3**) was obtained in excellent yield by treatment of **2** with α,α-dimethoxytoluene in acetonitrile in the presence of toluene-*p*-sulphonic acid. Conventional tosylation[4] (→**4**), followed by treatment with 1 molar equivalent of



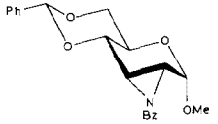
1



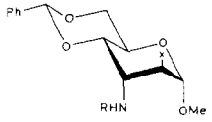
2



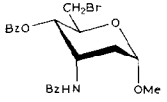
3 R = H
4 R = Ts



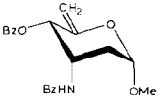
5



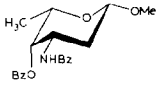
6 R = Bz, X = Cl
7 R = Bz, X = H
8 R = X = H



9



10



11

*NCL Communication No. 3363.
**To whom correspondence should be addressed.

0008-6215/84/$ 03.00

sodium hydride in dry tetrahydrofuran at room temperature, afforded the *N*-benzoylepimine **5**. Ring opening with ammonium chloride then gave **6**.

Dechlorination of **6** with 1 molar percentage of tri-*n*-butyltin chloride together with an excess of sodium borohydride in refluxing ethanol in the presence of light[5,6] gave 80% of the deoxy compound **7**, the structure of which was confirmed by ^{1}H-n.m.r. data [δ 4.76 (bs, H-1), 2.0 (m, H-2,2′)]. Compound **7** was also prepared by *N*-benzoylation of the known[2g] amine **8**.

Treatment of **7** with *N*-bromosuccinimide[7] in refluxing carbon tetrachloride opened the 1,3-dioxane ring and yielded methyl 3-benzamido-4-*O*-benzoyl-6-bromo-2,3,6-trideoxy-α-D-*ribo*-hexopyranoside (**9**, 76%). Dehydrobromination of **9** was accomplished by treatment with 1,5-diazabicyclo[5.4.0]undec-5-ene in hexamethylphosphoric triamide for 48 h under nitrogen at room temperature[2g] to afford the 5-hexenopyranoside **10** (97%). The ^{1}H-n.m.r. spectrum of **10** contained two narrow triplets for H-6,6′at δ 4.62 and 4.74, characteristic of the 5,6-ene group.

Hydrogenation of **10** and chromatography of the product gave 85% of methyl 3-*N*-benzoyl-4-*O*-benzoyl-β-L-daunosaminide (**11**, methyl 3-benzamido-4-*O*-benzoyl-2,3,6-trideoxy-β-L-*lyxo*-hexopyranoside). The L isomer was obtained as expected[2b,2g], and further confirmed by its large negative optical rotation ($[\alpha]_D$ −84°) and its ^{1}H-n.m.r. spectrum. The coupling constants $J_{1,2a}$ 9.5 and $J_{1,2e}$ 3.0 Hz were indicative of the $^1C_4$ conformation.

EXPERIMENTAL

All evaporations were performed under diminished pressure with a rotary evaporator. Melting points were recorded with a Kofler hot-plate and are uncorrected. ^{1}H-N.m.r. spectra were recorded for solutions in $CDCl_3$ (internal Me_4Si) with a Varian FT 80A spectrometer. All solvents were purified and dried. Light petroleum refers to the fraction b.p. 60–80°. Column chromatography was performed on silica gel (60–120 mesh, Acme Synthetic Chemicals).

*Methyl 2,3-*N*-benzoylepimino-4,6-*O*-benzylidene-2,3-dideoxy-α-*D*-allopyranoside* (**5**). — To a stirred solution of **4** (10 g, 18.56 mmol) in dry tetrahydrofuran (400 mL) under nitrogen was added sodium hydride (0.44 g, 18.56 mmol) at room temperature. The reaction was monitored by t.l.c. (ethyl acetate–light petroleum, 1:2). After 15 min, the mixture was diluted with dichloromethane, washed with water, dried, and concentrated, to afford **5** (5.85 g, 95%), m.p. 190°; lit.[8] m.p. 190–191°.

*Methyl 3-benzamido-4,6-*O*-benzylidene-2,3-dideoxy-α-*D*-*ribo*-hexopyranoside* (**7**). — (*a*) *From the 2-chloride* **6**. A mixture of **6** (3 g, 7.43 mmol), tri-*n*-butyltin chloride (24 mg), and ethanol (50 mL) was heated under reflux and irradiated with a 100-W tungsten lamp, whilst solid sodium borohydride (0.56 g, 14.86 mmol) was added in small portions. The reaction was monitored by t.l.c. (ethyl acetate–light petroleum, 1:1) and, after 6 h, the mixture was concentrated and a solution of the residue in ether was washed with water, dried, and concentrated. The re-

sidue was eluted from a short column of silica gel with ethyl acetate–light petroleum (1:10) to remove tri-*n*-butyltin material, and then with ethyl acetate to afford **7** (2.2 g, 80%) as a syrup, $[\alpha]_D$ +114° (*c* 0.9, chloroform). ^{1}H-n.m.r. data: δ 2.0 (m, 2 H, H-2,2′), 3.43 (s, 3 H, OMe), 3.4–4.5 (m, 4 H, H-4,5,6,6′), 4.76 (bs, 1 H, $W_{1/2}$ 6 Hz, H-1), 4.76 (m, 1 H, H-3), and 7.0–8.3 (m, 10 H, 2 Ph).

Anal. Calc. for $C_{21}H_{23}NO_5$: C, 68.3; H, 6.2; N, 3.8. Found: C, 68.1; H, 6.2; N, 3.7.

(*b*) *From the 3-amine*[2g] **8**. A mixture of **8** (0.2 g), pyridine (5 mL), and benzoyl chloride (0.2 mL) was stirred at 0° for 2 h and then left at room temperature overnight. Conventional work-up gave **7** (0.2 g), which was identical with the product in (*a*).

*Methyl 3-benzamido-4-O-benzoyl-6-bromo-2,3,6-trideoxy-α-*D-ribo-*hexopyranoside* (**9**). — A mixture of **7** (1.4 g, 3.79 mmol), dry carbon tetrachloride (40 mL), *N*-bromosuccinimide (1.1 g, 6.18 mmol), barium carbonate (1.5 g), and benzoyl peroxide (10 mg) was heated under reflux for 3 h. T.l.c. (ethyl acetate–light petroleum, 1:1) then indicated one major and one minor product, and no **7**. The mixture was filtered, washed with aqueous 5% sodium hydrogensulfite, aqueous 5% sodium hydrogencarbonate, and water, dried, and concentrated. The syrupy residue was subjected to chromatography on silica gel. Elution with ethyl acetate–light petroleum (1:4) afforded **9** (1.3 g, 76%), m.p. 149°, $[\alpha]_D$ +147° (*c* 0.82, chloroform). ^{1}H-N.m.r. data: δ 2.0 (m, 2 H, H-2,2′), 3.52 (s, 5 H, OMe + H-6,6′), 4.12 (m, 1 H, H-5), 5.0 (m, 3 H, H-1,3,4), and 7.0–8.0 (m, 10 H, 2 Ph).

Anal. Calc. for $C_{21}H_{22}BrNO_5$: C, 56.2; H, 4.9; Br, 17.85. Found: C, 55.5; H, 5.1; Br, 17.4.

*Methyl 3-benzamido-4-O-benzoyl-2,3,6-trideoxy-α-*D-erythro-*hex-5-enopyranoside* (**10**). — To a stirred solution of **9** (1 g, 2.23 mmol) in dry hexamethylphosphoric triamide (20 mL) under nitrogen was added 1,5-diazabicyclo[5.4.0]undec-5-ene (0.6 mL, 4.34 mmol) at room temperature. After 48 h, the mixture was diluted with ether, washed with aqueous 10% sodium hydrogensulfate, aqueous sodium hydrogencarbonate, and water, dried, and concentrated, to give **10** (0.80 g, 97%), m.p. 124°, $[\alpha]_D$ +162° (*c* 0.9, chloroform). ^{1}H-N.m.r. data: δ 2.0 (m, 2 H, H-2,2′), 3.52 (s, 3 H, OMe), 4.62 (t, 1 H, H-6), 4.74 (t, 1 H, H-6′), 4.8 (m, 2 H, H-1,3), 5.53 (m, 1 H, H-4), and 7.0–8.0 (m, 10 H, 2 Ph).

Anal. Calc. for $C_{21}H_{21}NO_5$: C, 68.6; H, 5.7. Found: C, 68.8; H, 5.9.

*Methyl 3-*N*-benzoyl-4-O-benzoyl-β-*L*-daunosaminide* (**11**). — A solution of **10** (0.7 g, 1.54 mmol) in ethyl acetate (25 mL) was hydrogenated in the presence of 10% Pd/C (0.2 g) at 40 p.s.i. for 8 h at room temperature, filtered through Celite, and concentrated. The residue was subjected to chromatography on silica gel. Elution with ethyl acetate–light petroleum (1:4) yielded **11** (0.6 g, 85%), m.p. 154°, $[\alpha]_D$ −84° (*c* 0.96, chloroform). ^{1}H-N.m.r. data: δ 1.19 (d, 3 H, *J* 6.5 Hz, H-6,6′,6″), 2.0 (m, 2 H, H-2,2′), 3.49 (s, 3 H, OMe), 3.66 (m, 1 H, H-5), 4.45 (m, 1 H, H-3), 4.45 (dd, 1 H, *J* 3 and 9.5 Hz, H-1), 5.20 (m, 1 H, H-4), 6.12 (d, 1 H, *J* 8.0 Hz, NH), and 7.0–8.2 (m, 10 H, 2 Ph).

Anal. Calc. for $C_{21}H_{23}NO_5$: C, 68.3; H, 6.2; N, 3.8. Found: C, 68.1; H, 6.15; N, 3.5.

REFERENCES

1 W. A. REMERS, *The Chemistry of Antitumor Antibiotics*, Vol. 1, Wiley International, New Jersey, 1979, Ch. 2.

2 (*a*) J. P. MARSH, JR., C. W. MOSHER, E. M. ACTON, AND L. GOODMAN, *Chem. Commun.*, (1967) 973–975; (*b*) D. HORTON AND W. WECKERLE, *Carbohydr. Res.*, 44 (1975) 227–240; (*c*) S. TAHAKA, Jpn. Kokai Tokkyo Koho, 79 14,913 (1979); *Chem. Abstr.*, 91 (1979) 5437m; (*d*) R. L. WHISTLER, U.S. Pat., 4,181,795 (1980); *Chem. Abstr.*, 92 (1980) 164255m; (*e*) G. MEDGYES AND J. KUSZMANN, *Carbohydr. Res.*, 92 (1981) 225–237; (*f*) T. YAMAGUCHI AND M. KOJIMA, *ibid.*, 59 (1977) 343–350; (*g*) A. CRUGNOLA, P. LOMBARDI, C. GANDOLFI, AND F. ARCAMONE, *Gazz. Chim. Ital.*, 111 (1981) 395–399.

3 (*a*) G. FRONGA, C. FUGANTI, AND P. GRASSELLI, *Chem. Commun.*, (1980) 442–444; (*b*) P. M. WOVKULICH AND M. R. USKOKOVIC, *J. Am. Chem. Soc.*, 103 (1981) 3956–3958; (*c*) C. FUGANTI, P. GRASSELLI, AND G. P. FANTONI, *Tetrahedron Lett.*, (1981) 4017–4020; (*d*) C. FUGANTI, P. GRASSELLI, AND G. P. FANTONI, *J. Org. Chem.*, 48 (1983) 909–910; (*e*) T. MUKAIYAMA, T. YAMADA, AND K. SUZUKI, *Chem. Lett.*, (1983) 5–8.

4 Y. ALI, A. C. RICHARDSON, C. F. GIBBS, AND L. HOUGH, *Carbohydr. Res.*, 7 (1968) 255–271; 1 (1965) 290–296.

5 E. J. COREY AND J. W. SUGGS, *J. Org. Chem.*, 40 (1975) 2554–2555.

6 M. K. GURJAR, J. S. YADAV, AND A. V. RAMA RAO, *Indian J. Chem.*, in press.

7 S. HANESSIAN, *Carbohydr. Res.*, 2 (1966) 86–88.

8 D. H. BUSS, L. HOUGH, AND A. C. RICHARDSON, *J. Chem. Soc.*, (1963) 5295–5301.