Tetrahedron Vol 44, No. 23, pp. 7163 to 7169, 1988
Printed in Great Britain

0040-4020/88 $3.00 + .00

SHORT SYNTHESIS OF C-ARYL-GLUCOPYRANOSIDES OF THE PAPULACANDIN TYPE

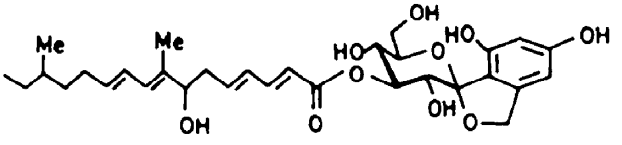
RICHARD R. SCHMIDT * and WENDELIN FRICK

Fakultät Chemie, Universität Konstanz
D-7750 Konstanz, Germany

(*Received in Germany* 20 *July* 1988)

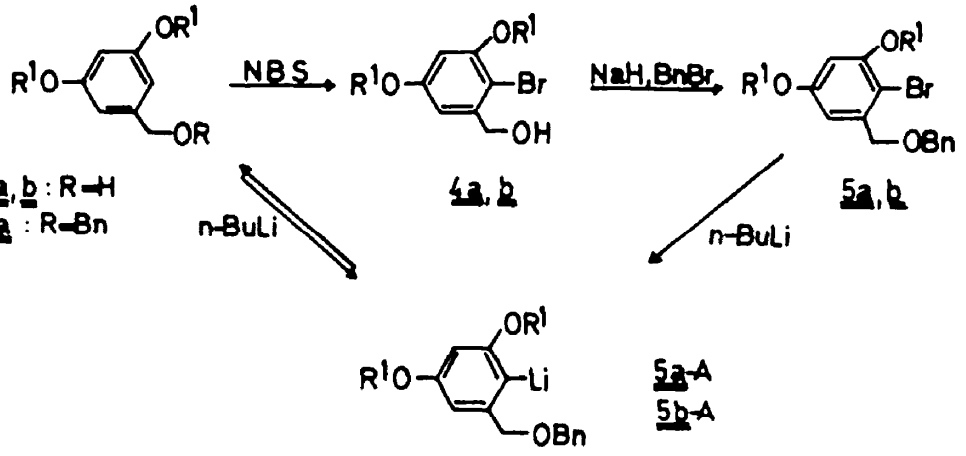
Abstract - The aryllithium species 5a-A and 5b-A generated via bromine/lithium exchange reaction, afforded with the per-O-benzylated D-glucose 6 the adducts 9a,b; subsequent oxidation furnished the corresponding ketones 10a,b. Compound 10a was also obtained from 5a-A and methyl D-gluconate 8. Hydrogenolytic debenzylation an treatment with acetic anhydride provided directly the tricyclic spiroketals 11 and 12, found in the papulacandins.

C-Arylglycosides are wide-spread in Nature. [1] They are of interest as natural dyestuffs[2] and as compounds having important physiological properties.[3] Most of the compounds are derivatives of oxysubstituted benzene and benzoquinone derivatives for which an interesting hypothesis of antitumor activity has been proposed.[4] The papulacandins, a family of antibiotics isolated from a strain of Papularia sphaerosperma whose structure was recently assigned,[5] show strong activity against Candida albicans and several other yeasts.[6] A representative example of these compounds with a tricyclic spiroketal structure is papulacandin D (1).

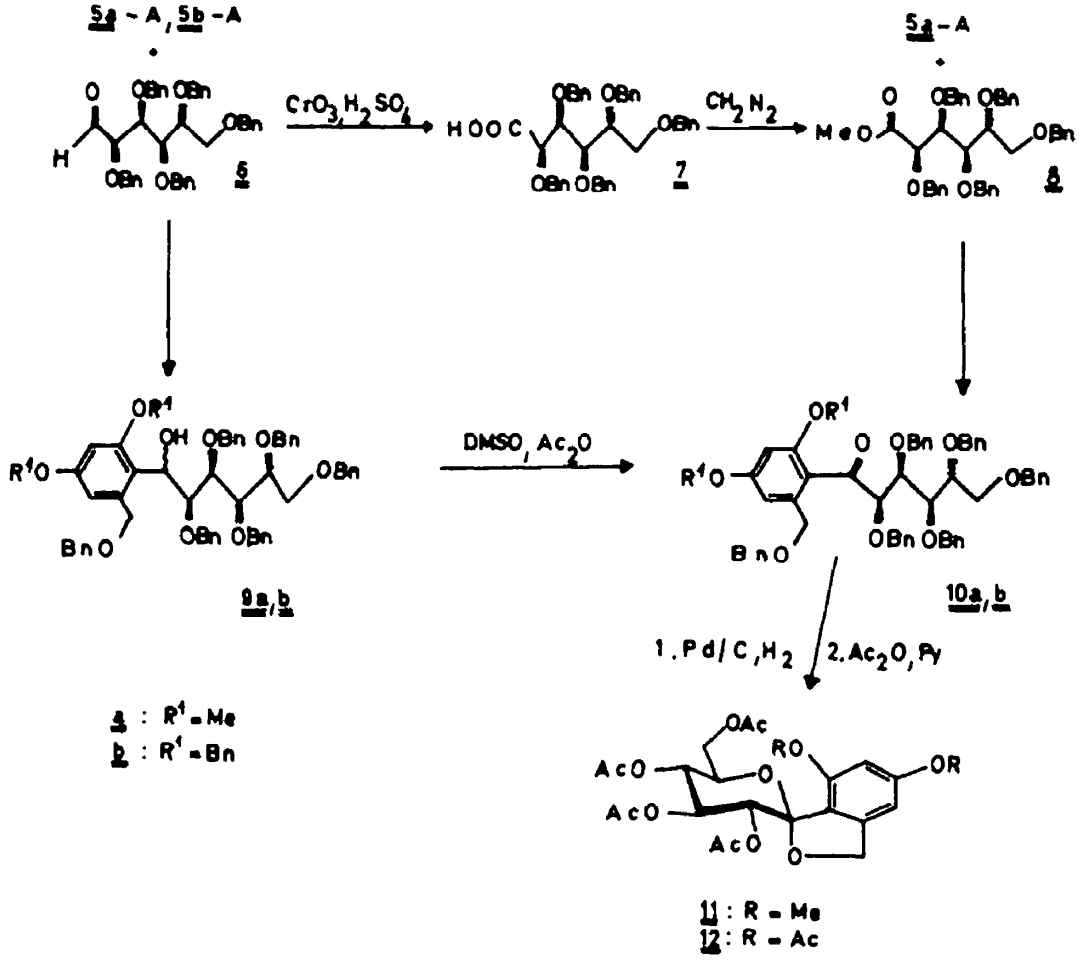


1

The synthesis of C-glycosides is mainly achieved with the sugar moiety as the electrophile and the aglycon as the nucleophile.[3,7] However, recently also C-glycoside syntheses with a nucleophilic[9] or a radical[10] sugar intermediate and de novo C-glycoside syntheses via hetero-Diels-Alder reactions[10,11] have become competitive.



A special case of the first method mentioned above is the reaction of carbanions with D-gluconolactone.[12] This method should be suitable for the construction of the essential tricyclic spiroketal moiety of the papulacandins. However, the direct lithiation of compounds 2a,b[13,14] and 3a and the subsequent reaction of the generated C-2 lithiated species with 2,3,4,6-tetra-O-benzyl-D-gluconolactone resulted only in low yields of the desired hemiketal intermediates.[15,16]



Therefore we prepared the D-glucose aldehyde derivative 6,[17] availabe from D-glucose diethyl dithioacetal[18] in two steps and transformed it also into the corresponding methyl gluconate 8 via the acid 7 obtained by CrO_3 oxidation of the aldehyde 6. Compounds 6 and 8 are better electrophiles than D-gluconolactone. In addition, because quantitative generation of the lithiated species from compounds 2a,b and 3a was not attained as indicated by deuteration experiments, a bromine/lithium exchange reaction was selected instead.[13,15] The required regioselective bromine introduction into 3,5-dimethoxy and 3,5-dibenzyloxy benzylalcohol 2a and 2b was carried out according to a known procedure[14] yielding compounds 4a[13] and 4b[19], respectively. Subsequent O-benzylation with sodium hydride/benzyl bromide gave the ethers 5a,b. Treatment of these compounds with n-butyllithium generated practically quantitatively the lithiated species 5a-A and 5b-A as evidenced by quenching the reaction mixture with water.

Addition of the aldehyde 6 as the electrophile to the lithiated species 5a-A and 5b-A afforded compounds 9a (68%) and 9b (62%), respectively. These compounds were obtained as 1:1-diastereomeric mixtures as indicated by their ^1H n.m.r. data. Oxidation with DMSO/acetic anhydride furnished as single products the corresponding ketones 10a,10b in high yields (10a: 95%; 10b: 85%) These ketones are also directly obtainable from the lithiated species 5-A and the gluconate 8: for instance, compound 10a was synthesized in a 55% yield. Hydrogenolytic debenzylation of compounds 10a,b and subsequent acetylation led directly to the desired tricyclic spiroketals 11 and 12, respectively. The structural elucidation of compound 11 was attained through comparison of the ^1H n.m.r. data with those of a sample obtained from the natural product.[20]

EXPERIMENTAL

General: ^1H n.m.r. spectra were obtained on a Bruker WM 250 spectrometer. Chemical shifts are reported as δ-values relative to internal $SiMe_4$. Optical rotations were measured in a Perkin-Elmer 241 ML polarimeter. All anion reactions were carried out under dry nitrogen. Flash chromatography was performed on Merck Kieselgel 60 (230-400 mesh). M.p. were measured on a Gallenkamp apparatus and are uncorrected.

Benzyl 3,5-dimethoxybenzyl ether (3a)

To a solution of 3,5-dimethoxy benzyl alcohol (5g, 29.7 mmol) (available from Aldrich Co) in dry dimethyl formamide (100 ml) is added benzyl bromide (8.6 g, 50 mmol) and then sodium hydride (1.2 g, 50 mmol) in portions at 10-15°C. After 1h excess sodium hydride is destroyed by careful addition of methanol. The mixture is diluted with water (50 ml) and extracted with ether (3 x 80 ml). The organic layer is dried over $MgSO_4$, concentrated and the resulting oil purified by flash chromatography (silica gel, petroleum ether/ethyl acetate, 9 : 1) to yield 6.5 g (85%) of 3a as a colorless oil.- T.l.c. (petroleum ether/ethyl acetate, 9 : 1) R_F 0.35. - ^1H n.m.r. (250 MHz, $CDCl_3$) δ = 7.35-7.27 (m,5,Ph), 6.53 (d,2,2-H,6-H,J = 2.2 Hz), 6.39 (t,1,4-H, J = 2.2 Hz), 4.53 (s,2,O-$C\underline{H}_2$-Ph), 4.49 (s,2,Ar-$C\underline{H}_2$-OBn), 3.76 (s,6,2-O-CH_3). (Found: C, 74.45; H, 7.02. Calc. for $C_{16}H_{18}O_3$: C, 74.40; H, 7.02%).

Benzyl 2-bromo-3,5-dimethoxybenzyl ether (5a)

As described for 3a, from 2-brom-3,5-dimethoxybenzyl alcohol (4a)[13] compound 5a is obtained in 73% yield as a colorless oil.- T.l.c. (petroleum ether/ethyl acetate, 4:1) R_F 0.50 - ^1H n.m.r. (250 MHz, $CDCl_3$) δ = 7.41-7.32 (m,5,Ph), 6.76 (d,1,4-H or 6-H, J = 2.8 Hz), 6.43 (d,1,4-H or 6-H, J = 2.8 Hz), 4.64 (s,2,O-$C\underline{H}_2$-

Ph), 4.63 (s,2,Ar-CH_2-O-Bn), 3.86 (s,3,O-CH_3), 3.80 (s,3,O-CH_3). (Found: C, 57,17; H, 5.04. Calc. for $C_{16}H_{17}BrO_3$: C, 56.99; H, 5.08%).

Benzyl 3,5-dibenzyloxy-2-bromobenzyl ether (5b)

As described for 3a, from 3,5-dibenzyloxy-2-bromo-benzyl alcohol (4b)[20] compound 5b is obtained in 75% yield as colorless crystals; m.p. 76°C.- T.l.c. (petroleum ether/ethyl acetate, 6:1) R_F 0,53.- ^{1}H n.m.r. (250 MHz, $CDCl_3$) δ = 7.47-7.29 (m,15,3-Ph), 6.86 (d,1,4-H or 6-H, J = 2.4 Hz), 6.55 (d,1,4-H or 6-H, J = 2.4 Hz), 5.10 (s,2,CH_2-Ph), 5,02 (s,2,CH_2-Ph), 4.63 (s,2,Ar-CH_2-O-Bn), 4.62 (s,2,O-CH_2-Ph).(Found: C, 68.72; H, 5.24. Calc. for $C_{28}H_{25}BrO_3$: C,68.72; H, 5.15%).

2,3,4,5,6,-Penta-O-benzyl-D-glucose (6)

a) Synthesis of 2,3,4,5,6-Penta-O-benzyl-D-glucose diethyl dithioacetal

To a solution of benzyl bromide (60 g, 347 mmol) in dry dimethyl formamide (250 ml) is added sodium hydride (9.0 g, 375 mmol). To this mixture is added (15.0 g, 50.6 mmol) D-glucose diethyl-dithioacetate[19] under vigorous stirring within 30 min. The reaction temperature should not exceed 30°C. After 2h excess sodium hydride is destroyed by careful addition of methanol. The mixture is diluted with water (100 ml) and extracted with ether (3 x 150 ml). The organic layer is washed with water (3 x 150 ml), dried over $MgSO_4$ and concentrated. The resulting oil (40 g) is directly used on the next step.- T.l.c. (petroleum ether/ethyl acetate, 6:1) R_F 0.58.- ^{1}H n.m.r. (250 MHz, $CDCl_3$) δ = 7.36-7.22 (m,35,5-Ph), 4.81-4.42 (m,11,5-O-CH_2-Ph,1-H), 4.25-3.70 (m,6,2-H,3-H,4-H,5-H,6-H, 6'-H), 2.78-2.42 (2 m,4,2 -S-CH_2-CH_3), 1.22-1.10 (2 t,6,2-S-CH_2-CH_3).

b) Transformation of the intermediate into compound 6

To a solution of 2,3,4,5,6-penta-O-benzyl-D-glucose diethyl dithioacetal (40g crude product, see procedure a)) in acetone (250 ml) and water (60 ml) is added $CdCO_3$ (43g). To this mixture is dropped a solution of $HgCl_2$ (43 g) in acetone (50 ml) under vigorous stirring within 10 min. After 30 min the mixture is filtered through silica gel, acetone removed under vacuum, and chloroform (300 ml) added. Residual salts are removed by extraction with warm water (4 x 200 ml). The organic layer is dried over $MgSO_4$, concentrated, and the residue purified by flash chromatography (silica gel; petroleum ether/ethyl acetate, 6:1) to yield 20.0g (64% overall yield) of 6 as a colorless oil.- T.l.c. (petroleum ether/ethyl acetate, 6:1) R_F 0.48.- ^{1}H n.m.r. (250 MHz, $CDCl_3$) δ = 9.73 (s,1, -CHO), 7.30-7.22 (m, 35, 5-Ph), 4.80-4.37 (m, 10, 5-O-CH_2-Ph), 4.19-3.62 (m, 6, 2-H, 3-H, 4-H, 5-H, 6-H, 6'-H). (Found: C, 78,37; H, 6.71. Calc. for $C_{41}H_{42}O_6$: C, 78.07; H, 6.71%).

2,3,4,5,6-Penta-O-benzyl-D-gluconcic acid (7)

To a solution of CrO_3 (7 g, 70 mmol) in diluted sulfuric acid (17 g H_2SO_4, 55 g H_2O) is added a solution of compound 6 (14.4 g, 22.8 mmol) in acetone (50 ml) at such a rate, that the reaction temperature does not exceed 30°C. After 1h (t.l.c. monitoring required) water (200 ml) is added to the mixture which is then extracted with ether (3 x 160 ml). The organic layer is dried over $MgSO_4$, concentrated, and the residual brown oil filtered through silica gel with petroleum ether/ethyl acetate, 2:1 to yield 13.2 g (90%) of compound 7 as a colorless oil which is directly used for ester formation.- T.l.c. (petroleum ether/ethyl acetate, 2:1) R_F 0.3.- ^{1}H n.m.r. (250 MHz, $CDCl_3$) δ = 10.2-9.7 (bs, 1, COOH), 8.10-7.15 (m, 25, 5-Ph), 4.81-4.39 (m, 10, 5-O-CH_2-Ph), 4.21 (d, 1, 2-H, J_{2-3} = 3.6 Hz), 4.16-4.12 (m, 2, 3-H, 4-H), 3.90-3.80 (m, 1, 5-H), 3.75-3.60 (m, 2, 6-H, 6'-H).

Methyl 2,3,4,5,6-penta-O-benzyl-D-gluconate (8)

To a solution of compound 7 (13.2 g, 20.4 mmol) in ether (50 ml) is dropped an etherel diazomethane solution (calculated amount). When nitrogen formation has

ceased, the solution is concentrated and the residue purified by flash chromatography (silica gel; petroleum ether/ethyl acetate, 6:1) to yield 9.2 g (70%) of compound 8 as a colorless oil.- T.l.c. (petroleum ether/ethyl acetate, 6:1) R_F 0.34. - ^{1}H n.m.r. (250 MHz, $CDCl_3$) δ = 7.36-7.21 (m, 25, 5-Ph), 4.84-4.26 (m, 10, 5-O-CH_2-Ph), 4.25 (d, 1, 2-H, J_{2-3} = 1.5 Hz), 4.13-4.09 (m, 2, 3-H, 4-H), 3.89-3.82 (m, 1, 5-H), 3.69-3.60 (m, 2, 6-H, 6'-H), 3.55 (S, 3, O-CH_3). (Found: C, 76.27; H, 6.73. Calc. for $C_{42}H_{44}O_7$: C, 76.34; H, 6.71).

5-Benzyloxy-1,3-dimethoxy-4-[(1RS, 2R, 3S, 4R, 5R)-1-hydroxy-2,3,4,5,6-penta-benzyloxyhexyl] benzene (9a).

To a solution of compound 5a (5 g, 15 mmol) in dry THF (100 ml) is added at -15°C n-butyllithium (10 ml of a 1.6 M solution in n-hexane). After 5 min a solution of compound 6 (6.3 g, 10 mmol) in dry THF (15 ml) is added. After 15 min the mixture is treated with water (100 ml) and ether (100 ml). The organic layer is separated, the water layer washed with ether (2 x 50 ml), the combined organic phases were dried over $MgSO_4$, and concentrated. The residue is purified by flash chromatography (silica gel; petroleum ether/ethyl acetate, 4:1) to yield 6.0 g (68%) of compound 9a as a colorless oil.- T.l.c. (petroleum ether/ethyl acetate, 4:1) R_F 0.26.- (Found: C, 76.78; H, 6.87. Calc. for $C_{57}H_{60}O_9$: C, 77.00, H, 6.80).

1,3-Dibenzyloxy-5-benzyloxymethyl-4-[(1RS,2R,3S,4R,5R)-1-hydroxy-2,3,4,5,6-penta-benzyloxyhexyl] benzene (9b)

As described for 9a, from compounds 5a and 6 compound 9b is obtained in 62% yield as a colorless oil.- T.l.c. (petroleum ether/ethyl acetate, 4:1) R_F 0.39.- (Found: C, 79.57; H, 6.74. Calc. for $C_{69}H_{68}O_9$: C, 79.59, H, 6.58).

5-Benzyloxymethyl-1,3-dimethoxy-4-[(2R,3S,4R,5R)-2,3,4,5,6-penta-benzyloxy-1-hexanonyl] benzene (10a)

a) From 9a: A solution of compound 9a (5.0 g, 5.6 mmol) in dry dimethyl sulfoxide (60 ml) and acetic anhydride (30 ml) is stirred at room temperature for 24h. The raction mixture is concentrated under vacuum (0.01 torr, 60°C) and the residual yellow oil purified by flash chromatography (silica gel; petroleum ether/ethyl acetate, 4:1) to yield 4.8 g (95%) of compound 10a as a colorless oil.- T.l.c. (petroleum ether/ethyl acetate, 4:1) R_F 0.38.- $(\alpha)^{22}$ + 32° (c=1, $CHCl_3$).- ^{1}H n.m.r. (250 MHz, $CDCl_3$) δ = 7.36-7.18 (m, 30, 6-Ph), 6.86 (d, 1, 4-H or 6-H, J = 2.2 Hz), 6.26 (d, 1, 4-H or 6-H, J = 2.2 Hz), 5.11 (d, 1, 2'-H, $J_{2',3'}$ = 4.3 Hz), 4.87-4.13 (m, 15, 6-O-CH_2-Ph, 3'-H, 4'-H, 5'-H), 3.80 (s, 3, O-CH_3), 3.80-3.65 (m, 2, 2-6'-H), 3.53 (s, 3, O-CH_3). (Found: C 77.09; H, 6.80. Calc. for $C_{57}H_{58}O_9$: C, 77.18; H, 6.59%).

b) From 5a and 8 : As described for 9a, from compound 5a (1.0 g, 3 mmol), n-butyllithium (2 ml of a 1.6 M solution in n-hexane), and compound 8 (1.3 g, 2 mmol) 1.0 g (55%) of compound 10a is obtained as a colorless oil.

1,3-Dibenzyloxy-5-benzyloxymethyl-4-[(2R,3S,4R,5R)-2,3,4,5,6-pentabenzyloxy-1-hexanonyl] benzene (10b)

As described for 10a, from compound 9b compound 10b is obtained in 85% yield as a colorless oil.- T.l.c. (petroleum ether/ethyl acetate, 4:1) R_F 0.50.- $(\alpha)^{22}$ + 26° (c=1, $CHCl_3$).- ^{1}H n.m.r. (250 MHz, $CDCl_3$) δ= 7.41-7.10 (m, 40, 8-Ph), 6.94 (d, 1, 4-H or 6-H, J = 1.8 Hz), 6.40 (d, 1, 4-H or 6-H, J = 1.8 Hz), 5.16 (d, 1, 2'-H, $J_{2',3'}$ = 3.7 Hz), 5.03-3.95 (m, 19, 8-CH_2-Ph, 3'-H, 4'-H, 5'-H), 3.90-3.79 (m, 2, 2-6'-H). (Found: C, 79.74; H, 6.65. Calc. for $C_{69}H_{66}O_9$: C, 79.74; H, 6.40%).

1,1^2-Anhydro-1-C-[2-(hydroxymethyl)-4,6-dimethoxyphenyl]-β-D-glucopyranose tetraacetate (11)

A solution of compound 10a (300 mg, 0.34 mmol) in a mixture of acetic acid/ethyl acetate/methanol (1:1:1, 30 ml) is hydrogenated in presence of palladium on carbon (20 mg) as a catalyst. After 1h the reaction mixture is filtered and the catalyst washed with methanol. The filtrate is concentrated and treated with acetic anhydride/pyridine (1:1, 10 ml) at room temperature. After 15h ice water (5 ml) is added and the mixture extracted with ether (3 x 20 ml). The organic layer is dried over $MgSO_4$, concentrated, and the residue purified by flash chromatography (silica gel; petroleum ether/ethyl acetate, 1:1) to yield 105 mg (62%) of compound 11 as colorless crystals, m.p. 70-72°C.- T.l.c. (petroleum ether/ethyl acetate, 1:1) R_F 0.41.- $[\alpha]_D^{22}$ + 5° (c=1, $CHCl_3$).- ^{1}H n.m.r. (250 MHz, $CDCl_3$) δ = 6.32-6.30 (2s, 2, 2Ar-H), 5.90 (d, 1, 2'-H, $J_{2',3'}$ = 10.1 Hz), 5.57 (t, 1, 3'-H, $J_{3',2'}$=$J_{3',4'}$ = 10.1 Hz), 5.32 (t, 1, 4'-H, $J_{4',3'}$=$J_{4',5'}$ = 10.1 Hz), 5,17 (d, 1, Ar-CH_2-O, J = 12.8 Hz), 5.05 (d, 1, Ar-CH_2-O, J = 12.8 Hz), 4.33-4.06 (2m, 3, 5'-H, 2-6'-H), 3.84 (s, 3, O-CH_3), 3.79 (s, 3, O-CH_3), 2.07 (s, 3, OAc), 2.05 (s, 3, OAc), 2.01 (s, 3, OAc), 1.76 (s, 3, OAc). (Found: C, 55.73; H, 5.77. Calc. for $C_{23}H_{28}O_{12}$: C, 55.64; H, 5.68%).

1,1^2-Anhydro-1-C-[4,6-diacetoxy-2-(hydroxymethyl)phenyl]-β-D-glucopyranose tetraacetate (12)

As described for 11, from compound 10b compound 12 is obtained in 45% yield as colorless crystals; m.p. 199°C.- T.l.c. (petroleum ether/ethyl acetate, 1:1) R_F 0.45.- $[\alpha]_D^{22}$ - 7.5° (c=1, $CHCl_3$) δ = 6.97 (d, 1, 4-H or 6-H, J = 1.8 Hz), 6.89 (d, 1, 4-H or 6-H, J = 1.8 Hz), 5.67 (d, 1, 2'-H, $J_{2',3'}$=10.1 Hz), 5.56 (t, 1, 3'-H, $J_{3',2'}$=$J_{3',4'}$=10.1 Hz), 5.21 (t, 1, 4'-H, $J_{4',3'}$=$J_{4',5'}$=10.1 Hz), 5.16 (bs, 2, O-CH_2-Ar), 4.28-4.23 (m, 2, 5'-H, 6'-H), 3.99 (dd, 1, 6"-H, $J_{6",6'}$=10 Hz, $J_{6",5'}$=1.8 Hz), 2.37 (s, 3, OAc), 2.25 (s, 3, OAc), 2.04 (s, 3, OAc), 2.02 (S, 3, OAc), 1.98 (s, 3, OAc), 1.76 (s, 3, OAc). (Found: C, 54.02; H, 5.11. Calc. for $C_{25}H_{28}O_{14}$: C, 54.35; H, 5.11%).

Acknowledgement - This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.

REFERENCES AND NOTES

1 L.J. Haynes, Adv. Carbohydr. Chem. 20 (1965) 357; J. Asakawa, Progr. Chem. Org. Nat. Prod. 42 (1982) 154; S.R. James, J. Carbohydr. Nucleosides Nucleotides 6 (1979) 417.

2 T. Eisner, S. Newicki, Science 208 (1980) 1039; M. C. Whiting, Chem.i.u. Zeit 15 (1981) 179.

3 R. R. Schmidt, G. Effenberger, Carbohydr. Res. 171 (1987) 59; and references cited therein.

4 H.W. Moore, R. Czerniak, Med. Res. Rev. 1 (1981) 249.

5 P. Traxler, H. Fritz, W.J. Richter, Helv. Chim. Acta 60 (1977) 578; P. Traxler, H. Fritz, H. Fuhrer, W.J. Richter, J. Antibiotics 33 (1980) 967; G. Römmele, P. Traxler, W. Wehrli, J. Antibiotics 36 (1983) 1539.

6 J. Gruner, P. Traxler, Experientia 33 (1977) 137; P. Traxler, J. Gruner,

7 J.A.L. Anden, J. Antibiotics 30 (1977) 289,

8 M. Hoffmann, R.R. Schmidt, Liebigs Ann. Chem. (1985) 2403; and references cited therin.

9 R. R. Schmidt, R. Preuss, R. Betz, Tetrahedron Lett. 28 (1987) 6591; and ref. 7-9, 12-14, 16.

10 B. Giese, J. Dupuis, Angew. Chem. 95 (1983) 633; Angew. Chem., Int. Ed. Engl. 22 (1983) 622; R.M. Adlington, J. E. Baldwin, A. Basak, R. P. Kozyrod, J. Chem. Soc., Chem. Commun. (1983) 944; F. Baumberger, A. Vasella, Helv. Chim. Acta 66 (1983) 2210.

11 R. R. Schmidt, W. Frick, B. Haag-Zeino, S. Apparao, Tetrahedron Lett. 28 (1987) 4045; R. R. Schmidt, Acc. Chem. Res. 19 (1986) 250; Pure Appl. Chem. 59 (1987) 415; and references cited therein.

S. J. Danishefsky, B. J. Wang, G. Quallich, J. Am. Chem. Soc. 107 (1985) 1285.

12 W. A. Bonner, Methods in Carbohydr. Chem. 2 (1963) 46; J. Kast, Diplomarbeit, Univ. Konstanz, (1982); M. D. Lewis, J. K. Cha, Y. Kishi, J. Am Chem. Soc. 104 (1982) 4976.
13 P. D. Noire, R. W. Franck, Synthesis (1980) 882.
14 E. Reimann, Chem. Ber. 102 (1969) 2881.
15 W. Frick, unpublished results.
16 Recently, we became aware of an abstract where the application of this approach was claimed: S. B. Rosenblum, H. A. Bates, 194 th ACS National
17 Meeting, New Orleans, Sept. 1987; Abstract of Papers: ORGN 188.
This compound is mentioned in Chem. Abstr. 95 (1981) 25499 u; 98 (1982)
18 68787 z, 107729 v. However, we could not find it in the original papers.
19 E. Fischer, Ber. Dtsch. Chem. Ges. 27 (1894) 673.
20 A. K. Sinhababu, R. T. Borchardt, J. Org. Chem. 48 (1983) 2356.
Kindly provided by Dr. P. Traxler, Ciba-Geigy AG, Basel.