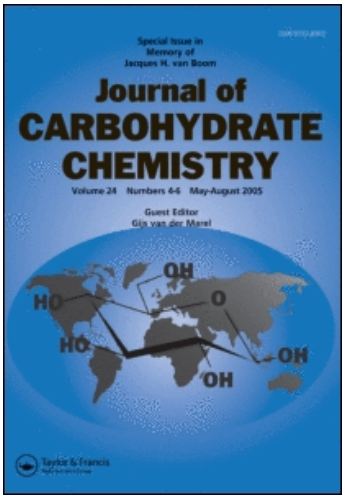

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SYNTHESIS OF STREPTAZOLINE GLUCOPYRANOSIDES

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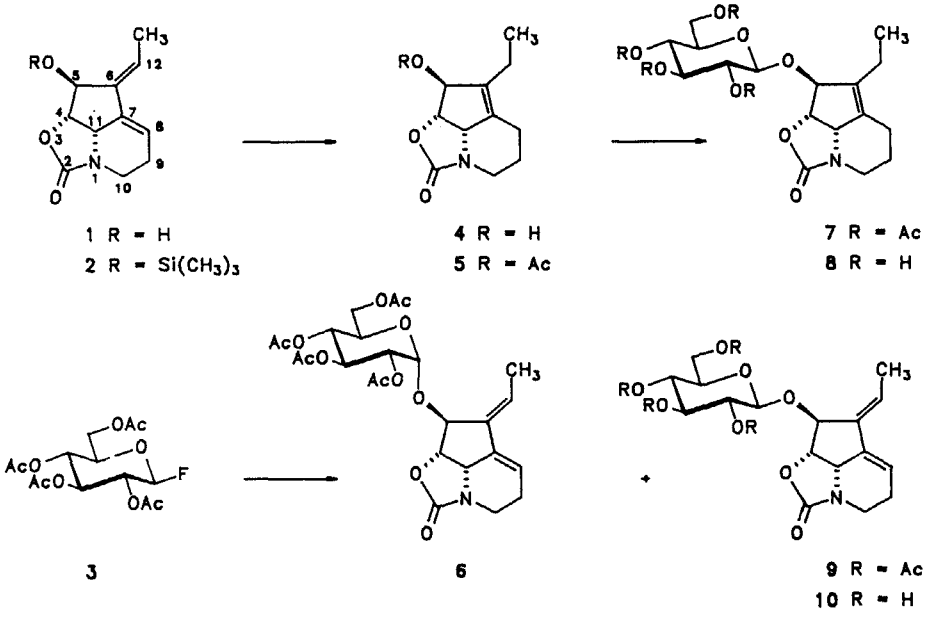
INTRODUCTION

The antibacterial properties of streptazoline (**1**),[2] isolated as a lipophilic neutral component from *Streptomyces viridochromogenes*,[3] were recognized to be attributed to the formation of chartreusine.[4] The pure compound **1** is rather labile due to the presence of the diene part, which enhances its polymerization. However, it may be kept for some time in diluted solutions at low temperatures. Recently, the total synthesis of streptazoline (**1**) was reported,[5] based on an aza-analogue Ferrier rearrangement.[6] The catalytic hydrogenation of the compound **1** afforded the stable dihydrostreptazoline (**4**) which possessed lower antibacterial and antifungal activities than streptazoline (**1**) itself.[7] X-ray studies of 5-acetoxydihydrostreptazoline (**5**) showed that it contained an internal urethane structure.

RESULTS AND DISCUSSION

There was interest to enhance the stability and solubility of these compounds by glycosylation of the 5-hydroxy group, and study the biological properties of such glycosides.

By treatment of 2,3,4,6-tetra-*O*-acetyl-*β*-D-glucopyranosyl fluoride (3)[8] and the dihydro component **4** in anhydrous acetonitrile at 0 °C with titanium tetrafluoride, the solid glucopyranoside **7** was obtained in 75 % yield. It was be completely characterized by ^{1}H NMR spectroscopy and proved to be the *β*-glycoside ($J_{1',2'}$ = 8.0 Hz) exclusively. Zemplén deacetylation quantitatively led to the unblocked derivative **8** obtained as a syrup.



This type of glycosylation caused problems with streptazoline owing to its limited stability and extended polymerization reactions in the presence of Lewis acid. However, the 5-*O*-trimethylsilyl derivative **2**, obtained in the conventional way (72 %), was more stable and could be glucosylated with **3** under similar conditions (CH_3CN, 0 °C, TiF_4). In this case a mixture of the anomers **6** and **9** resulted (71 %, **6** : **9** = 15 : 85).

Whereas the β-glucoside **9** was the main product as expected for a neighbouring group assisted glycosylation, a considerable amount of the α-anomer **6** resulted. Its formation may be understood by a double inversion reaction caused by the particular stereoelectronic prerequisites of the aglycone. As discussed previously in other transformations[8] and for this case, the formation of an intermediate octahedral titanium complex may be assumed. The amorphous α-anomer **6** and the crystalline β-anomer **9** could be completely separated by column chromatography. By ^{1}H NMR assignment the α-anomer **6** showed the typical small coupling ($J_{1',2'}$ = 3.9 Hz), and for the β-anomer **9** $J_{1',2'}$ = 7.9 Hz was observed. In contrast to streptazoline (**1**) both the purified glucosides **6** and **9** proved completely stable, and could be kept at low temperature without decomposition or polymerization. Finally, the β-derivative **9** was deesterified mildly (Zemplén procedure) to give the amorphous unblocked β-glucoside **10** as a monohydrate.

These results gave evidence that an approach using Lewis acid-catalyzed glycosylations with glycosyl fluorides[8-14] may be successfully applied to rather complex and labile polycyclic aglycones. Further studies of the properties of these conjugates were reported elsewhere.[15]

EXPERIMENTAL

General Prodedures. Compare references.[8,16]

8,12-Dihydrostreptazoline 2,3,4,6-Tetra-O-acetyl-β-D-glucopyranoside (7). A solution of 8,12-dihydrostreptazoline (**4**, 45 mg, 0.22 mmol) and 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl fluoride (**3**, 83 mg, 0.24 mmol) in anhydrous acetonitrile (5 mL) was treated with titanium tetrafluoride (30 mg, 0.14 mmol) for 2 h at room temperature. The reaction mixture was filtered over silica gel (approximately 3 g), poured into iced water, neutralized with sodium hydrogen carbonate, and extracted with ethyl acetate. After concentration the crude material was purified by chromatography on silica gel (toluene/ethyl

acetate, 1:1) to give 88 mg (74 %) of compound **7** as an amorphous solid, $[\alpha]_D^{20}$ +58.0° (*c* 1.61, acetone); ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.65 (dd ≈ d, H-4), 4.77 (bs, H-5), 2.70 (m, H-8a), 1.81 (m, H-9a), 1.40 (m, H-9b), 3.87 (dd, H-10a), 3.06 (ddd, H-10b), 4.38 (bd, H-11), 2.06 (mc, 3H, H-8b, H-12a, H-12b), 1.01 (t,3H, CH_3-13), 4.59 (d, H-1'), 4.98 (dd, H-2'), 5.14 (dd ≈ t, H-3'), 5.04 (dd ≈ t, H-4'), 4.05 (ddd, H-5'), 4.18 (d, 2H, H-6a', H-6b'), 2.00, 2.04, 2.05, 2.10 (4s, each 3H, OAc); $J_{4,5} < 0.5$, $J_{4,11} = 6.8$, $J_{9a,10b} = 12.7$, $J_{9b,10a} = 4.5$, $J_{9b,10b} = 3.2$, $J_{10a,10b} = 14.0$, $J_{1',2'} = 8.0$, $J_{2',3'} = 9.7$, $J_{3',4'} = 9.6$, $J_{4',5'} = 9.9$, $J_{5',6a'} = 3.4$, $J_{5',6b'} = 4.8$ Hz.

Anal. Calcd for $C_{25}H_{33}NO_{12}$ (539.5) : C, 55.65; H, 6.17; N, 2.60. Found: C, 55.87; H, 6.28; N, 2.12.

8,12-Dihydrostreptazoline β-D-Glucopyranoside (8). A solution of **7** (88 mg, 0.16 mmol) in anhydrous methanol (5 mL) was treated with 2 drops of a solution of sodium methoxide in methanol (1 %) for 2 h at room temperature. Following neutralization with ion exchange resin (Amberlite IR 120, H^+) the solution was concentrated to give 60 mg (98 %) of compound **8** as a syrup $[\alpha]_D^{20}$+ 68.4° (*c* 2.11, methanol); ^{1}H NMR (300 MHz, acetone-d_6): δ 4.36 (d, H-1'); $J_{1',2'} = 7.7$ Hz.

5-O-Trimethylsilylstreptazoline (2). A solution of streptazoline (**1**, 145 mg, 0.70 mmol) in anhydrous pyridine (5 mL) was treated at -30 °C with 1,1,1,3,3,3-hexamethyldisilazane (0.4 mL, 0.31 g, 1.90 mmol) and chlorotrimethylsilane (0.2 mL, 0.17 g, 1.58 mmol). Under continous stirring the reaction mixture was allowed to reach room temperature within 3 h, and then concentrated in high vacuo at 10°C. The residue was dissolved in dichloromethane, filtered over silica gel (3 g) and purified by silica gel chromatography (n-hexane/ethyl acetate, 2:1) to give 141 mg (72 %) of compound **2** as a colourless syrup. ^{1}H NMR (300 MHz, $CDCl_3$) : δ 4.56 (d, H-4), 4.78 (bs, H-5), 5.95 (m, H-8), 2.44 (m, H-9a), 2.14 (m, H-9b), 3.35 (m, 2H, H-10a, H-10b), 4.23 (bd, H-11), 6.06 (q, H-12), 1.78 (d, 3H, CH_3-13), 0.19 (s, 9H, $Si(CH_3)_3$); $J_{4,5} < 0.5$, $J_{4,11} = 7.1$, $J_{12,13} = 7.4$ Hz.

Anal. Calcd for $C_{14}H_{21}NO_3Si$ (279.4) : C, 60.18; H, 7.58; N, 5.01. Found: C, 60.44; H, 7.29; N, 4.71.

Streptazoline 2,3,4,6-Tetra-O-acetyl-α- (6) and -β-D-glucopyranoside (9). A solution of 2 (128 mg, 0.46 mmol) and 3 (320 mg, 0.91 mmol) in anhydrous acetonitrile (10 mL) was treated with titanium tetrafluoride (115 mg, 0.91 mmol) for 4 h at 0 °C. After 2 h more titanium tetrafluoride (approx. 50 mg) was added. Following the workup described for compound 7, the excess of 3 was separated by silica gel chromatography (dichloromethane/ethyl acetate, 6:1) to give 176 mg (71 %) of the α/β-anomeric mixture, α-6 : β-9 = 15 : 85 (by ^{1}H NMR). The α-glycoside 6 was obtained as the slightly faster running spot.

Compound **6** : 16 mg (6.5 %), amorphous material, softening interval 120-125 °C, $[\alpha]_D^{20}$+ 73.4° (*c* 0.9, chloroform); ^{1}H NMR (300 MHz, C_6D_6) : δ 4.67 (bd, H-4), 4.56 (bs, H-5), 5.50 (m, H-8), 1.82 (mc, 2H, H-9a, H-9b). 3.40 (m,H-10a), 2.91 (m,H-10b), 3.57 (bd, H-11), 5.82 (bq, H-12), 1.54 (d, 3H, CH_3-13), 5.05 (d, H-1'), 5.01 (dd, H-2'), 5.74 (dd ≈ t, H-3'), 5.20 (dd, H-4'), 4.06 (ddd, H-5'), 4.22 (dd, H-6a'), 4.14 (dd, H-6b'), 1.59, 1.66, 1.69, 1.76 (4s, each 3H, OAc); $J_{4,5}$ < 0.5, $J_{4,11}$ = 6.5, $J_{12,13}$ = 7.4, $J_{1',2'}$ = 3.9, $J_{2',3'}$ = 9.9, $J_{3',4'}$ = 9.4, $J_{4',5'}$ = 10.4, $J_{5',6a'}$ = 6.2, $J_{5',6b'}$ = 2.5, $J_{6a',6b'}$ = 12.1 Hz.

Compound **9**: 106 mg (43 %), mp 72 °C, $[\alpha]_D^{20}$-1.5° (*c* 1.11, chloroform); ^{1}H NMR (300 MHz, C_6D_6) : δ 4.64 (d, H-4), 4.88 (bs, H-5), 5.48 (m, H-8), 1.85 (m, H-9a), 1.68 (m, H-9b), 3.46 (ddd, H-10a), 2.88 (ddd, H-10b), 3.90 (d, H-11), 5.91 (bq, H-12), 1.67 (d, 3H, CH_3-13), 4.31 (d, H-1'), 5.20 (dd, H-2'), 5.29 (dd ≈ t, H-3'), 5.12 (dd ≈ t, H-4'), 2.97 (ddd, H-5'), 4.03 (dd, H-6a'), 4.02 (dd, H-6b'), 1.65, 1.69 (2), 1.70 (4s, each 3H, OAc); $J_{4,5}$ < 0.5, $J_{4,11}$ = 6.8, $J_{9a,10a}$ = 7.9, $J_{9a,10b}$ = 3.6, $J_{9b,10a}$ = 8.0, $J_{9b,10b}$ = 9.0, $J_{10a,10b}$ = 12.4, $J_{12,13}$ = 7.2, $J_{1',2'}$ = 7.9, $J_{2',3'}$ = 9.5, $J_{3',4'}$ = 9.5, $J_{4',5'}$ = 9.9, $J_{5',6a'}$ = 2.9, $J_{5',6b'}$ = 4.6 Hz.

Anal. Calcd for $C_{25}H_{31}NO_{12}$ (537.5): C, 55.86; H, 5.81; N, 2.61. Found for **6**: C, 55.42; H, 5.43; N, 2.19. Found for **9**: C, 55.24: H, 5.40; N, 2.08.

Streptazoline β-D-Glucopyranoside Monohydrate (10). A solution of **9** (78 mg, 0.15 mmol) in anhydrous methanol (5 mL) was treated for 2 h at room temperature with 3 drops of a solution of sodium methoxide in

anhydrous methanol (1 %). Following neutralization with ion exchange resin (Amberlite IR 120, H^+), concentration and freeze-drying 50 mg (93 %) of compound **10** was obtained as an amorphous, hygroscopic syrup; mp 195-199 °C, $[\alpha]_D^{20}$ -3.7° (*c* 1.55, methanol); ^1H NMR (300 MHz, CD_3CN) : δ 4.87 (d, H-4), 4.99 (bs, H-5), 6.11 (m, H-8), 6.31 (q, H-12), 1.85 (d, 3H, CH_3-13), 4.42 (d, H-1'); $J_{4,5} < 0.5$, $J_{4,11} = 6.9$, $J_{12,13} = 7.5$, $J_{1',2'} = 7.9$ Hz.

Anal. Calcd for $C_{17}H_{23}NO_8 \cdot H_2O$ (387.4) : C, 52.71; H, 6.50; N, 3.62. Found: C, 52.97; H, 6.46; N, 3.39.

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REFERENCES AND FOOTNOTES

1. Present address: Hoechst AG, Hauptlaboratorium G 830, Postfach 80 03 20, D-6230 Frankfurt 80, FRG.
2. Rational name (used in this paper): (4S,5S,11S)-1-Aza-3-oxa-5-hydroxy-6(Z)-ethyliden-tricyclo[5.3.1.$0^{4,11}$]-dec-7-en-2-one; systematic name according to Chemical Abstracts 4-Ethyliden-2a,3,4,6,7a,7b-hexahydro-3-hydroxy-1H-2-oxa-7a-azacyclo-pent[c,d]-inden-1-on[2aS-(2aα,3α,4Z,7bα)].
3. H. Drautz, H. Zähner, E. Kupfer, and W. Keller-Schierlein, *Helv. Chim. Acta*, **64**, 1752 (1981).
4. E. Simonitsch, W. Eisenhuth, O. A. Stamm, and H. Schmid, *Helv. Chim. Acta*, **47**, 1459, (1964).
5. A. P. Kozikowski, and P. Park, *J. Am. Chem. Soc.*, **107**, 1763 (1985).
6. A. P. Kozikowski, and P. Park, *J. Org. Chem.*, **49**, 1674 (1984).
7. A. Karrer, and M. Dobler, *Helv. Chim Acta*, **65**, 1432 (1982).
8. M. Kreuzer, and J. Thiem, *Carbohydr. Res.*, **149**, 347 (1986).
9. T. Mukaiyama, Y. Murai, and S. Shoda, *Chem. Lett.*, 431 (1981).
10. T. Mukaiyama, Y. Hashimoto, and S. Shoda, *Chem. Lett.*, 935 (1983).

11. S. Hashimoto, M. Hayashi, and R. Noyori, *Tetradedron Lett.*, **25**, 1379 (1984).

12. K. C. Nicolaou, R. E. Dolle, A. Chucholowski, and J. L. Randall, *J. Chem. Soc., Chem. Commun.*, 1153 and 1155 (1984).

13. H. Kunz, and W. Sager, *Helv. Chim. Acta*, **68**, 283 (1985).

14. H. Kunz, and H. Waldmann, *J. Chem. Soc., Chem. Commun.*, 638 (1985).

15. H.-U. Hoppe, S. Grabley, H. Voelskow, M. Schlingmann, H.-P. Kraemer, M. Wiesner, and J. Thiem, DOS 3 616 180 A1 (14.5.1986; 19.11.1987); *Chem. Abstr.*, **109**, 37 687 (1988).

16. E. Kirchner, F. Thiem, R. Dernick, J. Heukeshoven, and J. Thiem, *J. Carbohydr. Chem.*, **7**, 453 (1988).