Tetrahedron Vol. 44, No. 23, pp. 7145 to 7153, 1988
Printed in Great Britain.

0040-4020/88 $3.00+.00

BIOMIMETIC TRANSFORMATIONS OF THE BIOGENETIC KEY INTERMEDIATE SECOLOGANIN. FIRST SYNTHESIS OF THE SECOIRIDOID SECOGALIOSIDE

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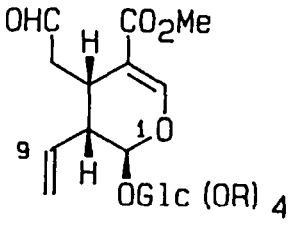
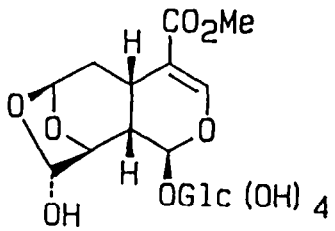
(*Received in Germany* 13 *June* 1988)

Abstract - Oxidation of secologanin tetraacetate 2 with osmium tetroxide afforded 45% of the bicyclic hemiacetal 3, which gave secogalioside tetraacetate 8 in a 29% yield and in addition 62% of the tricyclic acetal 6 by treatment with the *N*-chlorosuccinimide dimethyl sulfide complex. Sovolysis of 8 yielded 60% of secogalioside 9.

Secogalioside 9 is a tricyclic secoiridoid, which was isolated by Bock, Jensen and Nielsen[2] from *Galium album* Mitt. in 1976. One can assume that it is biosynthetically derived from secologanin 1,[3] the parent compound of the secoiridoids,[4] which in addition is a key intermediate in the biosynthesis of





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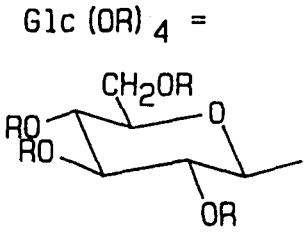
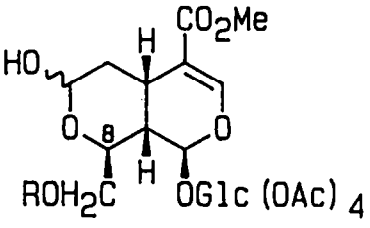


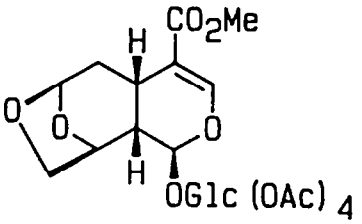
	R
1	H
2	Ac

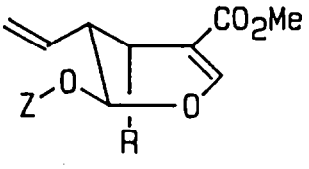
many alkaloids.[5] Secologanin 1 can be isolated in great quantity from the berries of *Symphoricarpos albus* (L.) S.F. Blake var. laevigatus (Fern.) and may therefore be employed as a substrate in the biomimetic synthesis of appropriate enantiomerically pure natural products.[6] *Lonicera tatarica* L.[7] can also be used as a plant material for the isolation of 1 but it has the disadvantage of containing large amounts of phenols of similar polarity, which are difficult to separate. Nowadays secologanin derivatives for the preparation of natural

products may also be obtained by total synthesis using a photochemical cycloaddition or a *hetero*-Diels-Alder reaction.[8]

For the synthesis of secogalioside 9 from secologanin 1 it was necessary to transform the vinyl group in 1 into a 1,2-diol-moiety, which has the (*S*)-configuration at C-9. Thus, the oxidation of secologanin tetraacetate 2 with a catalytic amount of osmium tetroxide in the presence of potassium chlorate[9] led to the bicyclic hemiacetal 3 in 45% yield and in addition by a non-chemoselective reaction at the endocyclic double bond to tetraacetylglucose (17%).[6,10] Furthermore 5% of 6, the cyclisation product of 3, and 20% of the educt were isolated. 3 can quantitatively be transformed into 6 by treatment with *p*-toluenesulfonic acid and phosphorus pentoxide in dichloromethane. The hydroxylation of the vinyl group in 2 occurs completely stereoselectively providing only the (9S)-diastereomer 3. It can be assumed, that 2 takes the conformation 7 in the transition state with the substituents at C-2 and C-3 in an equatorial and at C-4 in a pseudo-axial orientation. By ^{1}H NMR spectroscopy it has been shown that this conformation is also preferred in the ground state.[11]







Z= Glc (OAc) 4

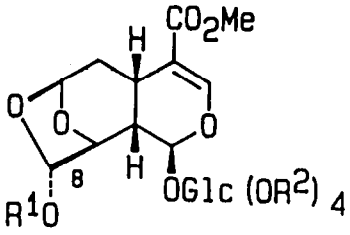
	R
3	H
4	⊕SMe2
5	Tos

6

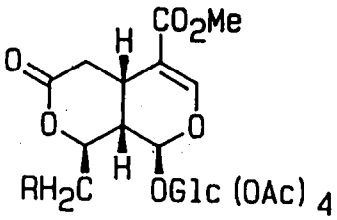
7

The most difficult part in the synthesis of 9 was the oxidation of the primary hydroxy function in the presence of the lactol moiety in 3. Treatment with pyridinium chlorochromate in the presence of sodium acetate in dichloromethane gave only 19% of secogalioside tetraacetate 8 and in addition 59% of the lactone 12, showing that the lactol moiety in 3 is oxidized faster than the primary hydroxy function. At prolonged reaction time also the lactone 11 was obtained, which is formed via an oxidation of 8. The lactone 12 can be transformed into 8-epikingiside[12] 14 via convertion of the hydroxymethyl to a methyl group; thus formation of the *p*-toluenesulfonate 13 and reduction with sodium cyanoborohydride afforded 14 in 34% yield.[13] Better results in the oxidation of 3 were obtained by treatment with *N*-chlorosuccinimide-dimethyl sulfide,[14] which leads to 8 in 29% yield as the only oxidation product, and in addition to 62% of the tricyclic compound 6. The formation of 6 may be explained by an

intramolecular substitution; thus, it can be assumed that in the reaction of 3 with N-chlorosuccinimide-dimethyl sulfide compound 4 is an intermediate, which either loses a proton and dimethyl sulfide to give 8 or undergoes a displacement reaction to 6 and dimethyl sulfoxide. The second possibility, that the oxidant attacks the hemiacetal moiety in 3 seems less likely, since the lactone 12, which should also be formed in this case, was not found. 8 can be transformed into the enantiomerically pure natural product secogalioside 9 by solvolysis with potassium carbonate in methanol in 60% yield. Interestingly, 9 exists only in the (*8R*)-configuration (> 95%); also, the crystalline pentaacetate 10, which was obtained from 9 by treatment with acetyl chloride and pydridine in 90% yield shows the same stereochemistry at C-8 (= 8S).

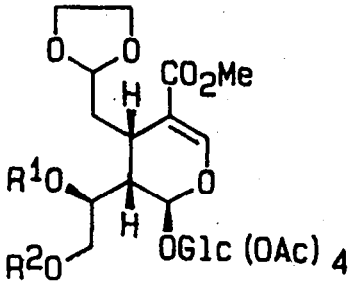


	R^1	R^2
8	H	Ac
9	H	H
10	Ac	Ac
11	=O on C-8	Ac

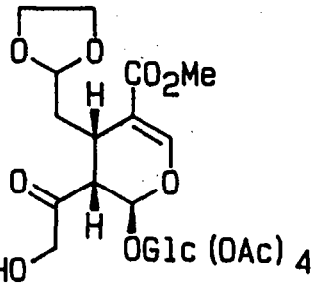


	R
12	OH
13	OTos
14	H

As already mentioned, the low yields of 8 in the oxidation of 3 were caused by side reaction at the hemiacetal moiety in 3. In order to avoid this, the diol 15 and its derivatives 16 and 17 with a protected aldehyde group were used as substrates. 15 is accessible from secologanin 1 by protection of the aldehyde function, acetylation and bishydroxylation.[6] Treatment of 15 with *p*-toluenesulfonyl chloride in the presence of a catalytic amount of dimethylaminopyridine gave 16 in 85% yield, which was quantitatively acetylated to 17. However, all attempts to oxidize the primary hydroxy function selectively in the presence of the secondary hydroxy group failed. Thus treatment of 15 with dimethyl sulfoxide in the presence of trifluoroacetic anhydride leads to ketone 18 in 84% yield; 18 was also obtained in the reaction of 15 with pyridinium dichromate, though in a lower yield. The oxidation of 16 with dimethyl sulfoxide (170°C, 3 min) gave the epoxide 19 as the main product in 36% yield and the oxidation of 17 using the same conditions also did not lead to the desired product. In addition, heating the toluenesulfonate 5, which was obtained from 16 by treatment with silica gel/sulfuric acid,[15] in dimethyl sulfoxide gave only the tricyclic compound 6.



	R^1	R^2
15	H	H
16	H	Tos
17	Ac	Tos



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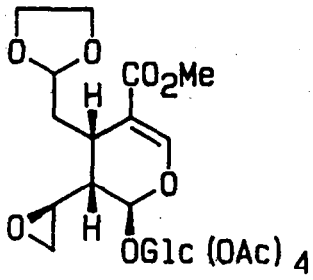

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These results show again, that in biomimetic syntheses the yields are generally better the closer to the biosynthetic pathway the transformations are carried out, even in non-enzymatic reactions.

EXPERIMENTAL

Melting points: Kofler micro-melting-point apparatus (uncorrected values). - IR: Perkin Elmer 297 - UV: Varian Cary 219. - Optical rotations: Perkin Elmer 241. - ^1H and ^{13}C NMR: Varian XL 200 (internal TMS). - MS: Varian MAT 311 A (70 eV). - Thin layer chromatography: SIL G/UV_{254} (Macherey, Nagel & Co.). - Column chromatography: Silica gel 60 (Macherey, Nagel & Co.) - Elementar analyses were carried out in the analytical laboratory of the University of Göttingen.

Isolation of Secologanin 1: Berries (40 kg) of *Symphoricarpos albus* (L.) were collected in the area around Göttingen in September, cut to pieces together with 30 l acetone and the obtained mixture was filtered. The filtrate was centrifuged to remove suspended particles, concentrated under reduced pressure at 30°C and freeze-dried. Column chromatography of the residue on silica gel with ethyl acetate-isopropanol (3:1) afforded 48 g (0.12%) of secologanin 1. - R_f = 0.39. - IR (KBr): ν = 3430 cm^{-1} (OH), 1704 (C=O), 1630 (C=C). - UV (methanol): λ_{max} (lg ϵ) = 229 nm (4.03). - ^1H NMR ([D_6]-acetone): δ = 2.22 (ddd, J = 1 Hz, J = 5 Hz, J = 17 Hz, 1 H; 7-H_a), 2.62-2.84 (m, 2H; 3-H, 4-H), 2.83 (dd, J = 6 Hz, J = 17 Hz, 1 H; 7-H_b), 3.20-3.96 (m, 6 H; 2'-H, 3'-H, 4'-H, 5'-H, 6'-H_2), 2.64 (s, 3 H; OCH_3), 4.72 (d, J = 8 Hz, 1 H; 1'-H), 5.18-5.26 (m, 2 H; 10-H_2), 5.48 (d, J = 4 Hz, 1 H; 2-H), 5.46-5.80 (m, 1 H; 9-H), 7.49 (d, J = 1.5 Hz, 1 H; 6-H), 9.73 (d, J = 1 Hz, 1 H; 8-H). - ^{13}C NMR (D_2O): δ = 26.72 (C-4), 43.76 (C-3), 43.90 (C-7), 51.78 (OCH_3), 60.64 (C-6'), 69.50 (C-4'), 72.53 (C-2), 75.58 (C-3'), 76.30 (C-5'), 96.97 (C-2), 98.72 (C-1'),108.76 (C-5), 120.79 (C-10), 132.84 (C-9), 153.22 (C-6), 169.37 (CO), 206.74 (CHO). - MS (DC I; isobutane): *m/z* (%) = 389 (100) $[M+1]^+$, 227 (60) $[M-C_6H_{10}O_5]^+$, 209 (33) $[C_6H_{10}O_5-H_2O]^+$.

Hydroxylation of Secologanintetraacetate 2: To a solution of 2 (2.00 g, 3.56 mmol) in dioxane (100 ml) and water (10 ml) were added under nitrogen 1 ml of a 0.02 M aqueous solution of osmium tetroxide. The mixture was heated to 90°C and than a solution of potassium chlorate (490 mg, 4.00 mmol) in water (10 ml) were dropped in slowly. It is important that the solution retains its brown colour during this procedure, otherwise 1 ml of the solution of osmium tetroxide has to be added. After complete transformation sodium hydrogen sulfite (300 mg) was added, the solution was cooled to room temperature and extracted with chloroform (3x100 ml). The combined organic layers were washed (saturated sodium

hydrogen carbonate solution and brine) and then dried (Na_2SO_4). Chromatography on silica gel (*tert*-butyl methyl ether) afforded three fractions beside 580 mg (20%) of 2. - A: 212 mg (17%) of *tetraacetyl-D-glucopyranose*. - B: 102 mg (50%) of *methyl (1S,4aS,6R,9S,9aS)-6,9-epoxy-1-(2',3',4',6'-tetraacetyl-ß-D-glucopyranosyloxy)-4a,9a-dihydro-1H-oxepano[4,5-c]pyran-4-carboxylate* 6. R_f (diethyl ether) = 0.29. - IR (KBr): ν = 1762 cm^{-1} (C=O), 1710 (C=O, conj.), 1635 (C=C). - UV (ether): λ_{max} (lg ϵ) = 235 nm (4.04). - $[\alpha]^{20}_D$ = -68° (c = 1 in chloroform). - ^1H NMR ($CDCl_3$): δ = 1.36 (dd, J = 11.5, J = 13.5 Hz, 1 H; 5-H_{ax}), 1.72 (ddd, J = 2 Hz, J = 6 Hz, J = 9 Hz, 1 H; 9a-H), 2.05, 2.06, 2.08, 2.10 (4 s, 12 H; 4 CH_3), 2.22 (ddd, J = 2.5 Hz, J = 5.5 Hz, J = 13.5 Hz, 1 H; 5-H_{eq}), 3.14 (ddd, J = 5.5 Hz, J = 6 Hz, J = 11.5 Hz, 1 H; 4a-H), 3.75 (s, 3 H; OCH_3), 3.78-4.00 (m, 3 H; 8-H_2, 5'-H), 4.02-4.49 (ABX, 2 H; 6'-H_2), 4.79 (dd, J = 2 Hz, J = 5 Hz, 1 H; 9-H), 4.88-5.34 (m, 4 H; 1'-H, 2'-H, 3'-H, 4'-H), 5.45 (d, J = 9 Hz, 1 H; 1-H), 5.50 (s, 1 H; 6-H), 7.46 (s, 1 H; 3-H). - ^{13}C NMR ($CDCl_3$): δ = 20.60, 20.69 (4 CH_3), 24.01 (C-4a), 36.05 (C-5), 39.78 (C-3a), 51.37 (OCH_3), 61.78 (C-6'), 68.16 (C-8), 68.39, 70.86, 71.84, 72.08, 72.50 (C-2',C-3', C-4', C-5', C-9), 96.46 (C-1), 98.42 (C-1'), 101.20 (C-6), 109.88 (C-4), 152.05 (C-3), 166.80 (4-CO), 169.40, 169.43, 170.14, 170.60 (4 CO, acetate). - MS (70 eV): *m/z* (%) = 331 (44) $[C_{14}H_{19}O_9]^+$, 271 (13) $[331-C_2H_4O_2]^+$, 229 (7) $[271-C_2H_2O]^+$, 225 (3) $[M-C_{14}H_{18}O_{10}]^+$, 169 (2) $[211-C_2H_2O]^+$, 139 (96) $[C_7H_7O_3]^+$, 109 (100) $[169-C_2H_4O_2]^+$. Anal. Calcd for $C_{11}H_{13}O_5$ (aglucone-OH): 225.0763. Found: 225.0763%. - C: 880 mg (42%) *methyl (1S,4aS,6RS,8S,8aS)-6-hydroxy-8-hydroxymethyl-1-(2',3',4',6'-tetraacetyl-ß-D-glucopyranosyloxy)-1,4a,5,6,8,8a-hexahydro-pyrano[3,4-c]pyran-4-carboxylate* 3. Ratio of diastereomers = 5:3. - R_f (chloroform/methanol = 4:1) = 0.64. - mp 148°C. - IR (KBr): ν = 3480 cm^{-1} (OH) 1760 (C=O), 1710 (C=O, conj.). 1640 (C=C). - UV (ether): λ_{max} (lg ϵ) = 232 nm (4.04). - $[\alpha]^{20}_D$ = -70.4° (c = 0.5 in chloroform). - ^1H NMR ($CDCl_3$): δ = 1.59-3.16 (m, 4 H; 4a-H, 5-H_2, 8a-H), 2.00, 2.01, 2.02, 2.03, 2.04, 2.05, 2.13, 2.14 (8s, 12 H; 4 CH_3, diast.), 3.56-4.04 (m, 4 H; 8-H, 9-H_2, 5'-H), 3.74 (s, 3 H; OCH_3), 4.08-4.18 (m, 2 H; 6'-H_2), 4.76-5.49 (m, 6 H; 1-H, 6-H, 1'-H, 2'-H, 3'-H, 4'-H), 7.39, 7.41 (2 d, J = 1.5 Hz, 1 H; 3-H). - ^{13}C NMR ($CDCl_3$): δ = 20.14, 20.45, 20.58, 20.74, 20.77 (CH_3, diast.), 24.74, 24.97 (C-4a, diast.), 37.76, 32.91 (C-5, diast.), 35.50, 36.23 (C-8a, diast.), 51.42 (OCH_3), 61.46, 61.45 (C-9, diast.), 63.58, 63.76 (C-6', diast.), 67.83, 68.06, 68.15, 68.34, 70.47, 70.62, 72.11, 72.39 (C-8, C-2'to C-5', diast.), 91.69, 92.51, 93.23, 94.89, 95.77, 96.69 (C-1, C-6, C-1', diast.), 110.18, 110.25 (C-4, diast.), 150.97, 151.02 (C-3, diast.), 166.70, 167.02 (CO, methyl ester, diast.), 169.07, 169.33, 169.43, 169.47, 170.21, 170.80, 171.21, 171.27 (CO, acetate, diast.). - MS (70 eV): *m/z* (%) = 331 (43) $[C_{14}H_{19}O_9]^+$, 271 (8) $[331-CH_3COOH]^+$, 169 (90), 109 (45), 43 (100). - Anal. Calcd for $C_{25}H_{34}O_{16}$ (590.8): C, 50.89; H, 5.80. Found: C, 50.98; H, 5.96%.

Oxidation of 3 *with Pyridinium Chlorochromate*: To a solution of pyridinium chlorochromate (39 mg, 0.18 mmol) and dry sodium acetate (40 mg) in dichloromethane (4 ml) were added 3 (100 mg, 0.17 mmol) in dichloromethane (2 ml). After stirring for 32 h at room temperature tert-butyl methyl ether (50 ml) was added, the reaction mixture filtered, and the solvent removed under reduced pressure; chromatography of the residue on silica gel (tert-butyl methyl ether) afforded three fractions. A: 10 mg (10%) of *methyl (1S,4aS,6S,9S,9aS)-6,9-epoxy-8-oxo-1-(2',3',4',6'-tetraacetyl-ß-D-glucopyranosyl)-4a-9a-dihydro-1H-oxepano-[4,5-c]pyran-4-carboxylate* 11. - R_f (ether) = 0.34. - IR (KBr): ν = 1810 cm^{-1} (C=O, lact.), 1750 (C=O, acetate), 1710 (C=O, conj.), 1640 (C=C). - UV (ether): λ_{max} (lg ϵ) = 230 nm (4.03). - $[\alpha]^{20}_D$ = -46.8° (c = 0.5 in chloroform). - ^1H NMR ($CDCl_3$): δ = 1.85 (ddd, J = 1 Hz, J = 12 Hz, J = 14 Hz, 1 H; 5-H_{ax}), 2.04, 2.05, 2.07, 2.09 (4 s, 12 H; 4 CH_3), 2.06 (m, 1 H; 9a-H), 2.29 (ddd, J = 1, J = 6, J = 14 Hz, 1 H; 5-H_{eq}), 3.00 (ddd, J = 6, J = 6 Hz, J = 12 Hz, 1 H; 4a-H), 3.73 (s, 3 H; O-CH_3), 3.73-3.84 (m, 1 H; 5'-H), 4.26 (ABX, $J_{A,B}$ = 12 Hz, 2 H; 6'-H_2), 4.70 (d, J = 2 Hz, 1 H; 9-H), 4.36-5.34 (m, 4 H; 1'-H, 2'-H, 3'-H, 4'-H), 5.48 (d, J = 9 Hz, 1 H; 1-H), 5.99 (s, 1 H; 6-H), 7.52 (s, 1 H; 3-H). - ^{13}C NMR ($CDCl_3$): δ = 20.59, 20.65, 20.70 (4 CH_3), 24.67 (C-4a), 31.94 (C-5), 35.94 (C-9a), 51.60 (OCH_3), 61.56 (C-6'), 70.70 (C-9), 68.15, 70.83, 72.10, 72.42 (C-2'to C-5'), 94.92 (C-1), 98.14 (C-1'), 103.46 (C-6), 108.74 (C-4), 152.48 (C-3), 166.15 (CO, ester), 169.23, 169.32, 170.21, 170.58, 171.76 (5 CO). - MS (70 eV): *m/z* (%) = 331 (35) $[C_{14}H_{19}O_9]^+$, 217 (5) $[331-C_2H_4O_2]^+$, 239 (3) $[M-C_{14}H_{19}O_9]^+$, 211 (4) $[271-C_2H_4O_2]^+$, 169 (78) $[211-C_2H_2O]^+$, 43 (100). - B: 19 mg (19%) of *methyl*

(1S,4aS,6S,8R,9S,9aS)-6,9-epoxy-8-hydroxy-1-(2',3',4',6'-tetraacetyl-ß-D-glucopyranosyloxy)-4a,9a-dihydro-1H-oxepano[4,5-c]pyran-4-carboxylate **8**. - R_f (ether) = 0.28. - IR (KBr): ν = 3475 cm^{-1} (OH), 1760 (C=O), 1710 (C=O, conj.), 1640 (C=C). - UV (ether): λ_{max} (lg ϵ) = 232 nm (4.12). - $[\alpha]^{20}_D$ = -53.6°C (c = 0.5 in chloroform). - ^{1}H NMR ($CDCl_3$): δ = 1.28 (ddd, J = 1 Hz, J = 12 Hz, J = 13 Hz, 1 H; 5-H_{ax}), 1.80 (ddd, J = 1 Hz, J = 6 Hz, J = 9 Hz, 1 H; 9a-H), 2.01, 2.04, 2.05, 2.08 (4 s, 12 H; 4 CH_3), 2.15 (ddd, J = 2 Hz, J = 6 Hz, J = 13 Hz, 1 H; 5-H_{eq}), 2.98 (ddd, J = 6 Hz, J = 6 Hz, J = 12 Hz, 1 H; 4a-H), 3.70 (s, 3 H; OCH_3), 3.70-3.86 (m, 1 H; 5'-H), 4.26 (ABX, $J_{A,B}$ = 12.5 Hz, 2 H; 6'-H_2), 4.49 (d, J = 1 Hz, 1 H; 9-H), 4.86-5.33 (m, 4 H; 1'-H, 2'-H, 3'-H, 4'-H), 5.38 (d, J = 9 Hz, 1 H; 1-H), 5.40 (s, 1 H; 8-H), 5.70 (s, 1 H; 6-H), 7.44 (s, 1 H; 3-H). - ^{13}C NMR ($CDCl_3$): δ = 20.60, 20.67, 20.85 (4 CH_3), 24.31 (C-4a), 34.80 (C-5), 36.91 (C-9a), 51.43 (OCH_3), 61.59 (C-6'), 68.28, 70.80, 72.20, 72.42 (C-2'to C-5'), 78.14 (C-9), 96.70 (C-8), 96.77 (C-1), 98.99 (C-1'), 102.38 (C-6), 109.42 (C-4), 152.23 (C-3), 166.71 (CO, methyl ester), 169.42 (2 CO, acetate), 170.23 (CO, acetate), 171.40 (CO, acetate). The spectrum shows the existence of the 8S-isomer (7%). - MS (70 eV): *m/z* (%) = 331 (25) $[C_{14}H_{19}O_9]^+$, 271 (7) $[331-CH_3COOH]^+$, 241 (1) $[M-C_{14}H_{19}O_9]^+$, 229 (2) $[271-C_2H_2O]^+$, 169 (71) $[229-CH_3COOH]^+$, 43 (100). - Anal. Calcd for $C_{25}H_{32}O_{16}$ (588.5): C, 51.00; H, 5.48. Found: C, 50.82; H 5.53% - C: 59 mg (59%) of *methyl (1S,4aS,8R,9S,9aS)-8-hydroxymethyl-6-oxo-1-(2',3',4',6'-tetraacetyl-ß-D-glucopyranosyloxy)-1,4a,5,6,8,8a-hexahydropyrano-[3,4-c]pyran-4-carboxylate* **12**. - R_f (ether) = 0.11. - IR (KBr): ν = 3510 cm^{-1} (OH), 1750 (C=O), 1710 (C=O, conj.), 1640 (C=C). - UV (ether): λ_{max} (lg ϵ) = 232 nm (4.09). - $[\alpha]^{20}_D$ = -45.4° (c = 0.5 in chloroform). - ^{1}H NMR ($CDCl_3$): δ = 2.00, 2.02, 2.04, 2.10 (4 s, 12 H; 4 CH_3), 2.38 (m, 1 H; 8a-H), 2.40 (dd, J = 9.2 Hz, 1 H; 5-H_{ax}), 3.00 (dd, J = 5,16 Hz, 1 H; 5-H_{eq}), 3.08 (m, 1 H; 4a-H), 3.68-3.84 (m, 2 H; 5'-H, 9-H_a), 3.96 (dd, J = 5.13 Hz, 1 H; 9-H_b), 4.14-4.33 (m, 3 H; 8-H, 6'-H_2), 4.88-5.30 (m, 4 H; 1'-H, 2'-H, 3'-H), 5.31 (d, J = 6.5 Hz, 1 H; 1-H), 7.51 (d, J = 1 Hz, 1 H; 3-H). - ^{13}C NMR ($CDCl_3$): δ = 20.37, 20.54, 20.70 (4 CH_3), 26.96 (C-4a), 33.49 (C-5), 35.24 (C-8a), 51.62 (OCH_3), 61.51 (C-9), 63.51 (C-6'), 68.14, 70.62, 72.20, 72.30 (C-2'to C-5'). 87.78 (C-8), 94.31 (C-1), 96.66 (C-1'), 109.37 (C-4), 152.04 (C-3), 166.16 (CO, ester), 169.19, 169.41, 170.14, 170.70, 171.00 (5 CO). - MS (70 eV): *m/z* (%) = 557 (0.5) $[M-CH_3O]^+$, 331 (29) $[C_{14}H_{19}O_9]^+$, 271 (4) $[331-C_2H_4O_2]^+$, 241 (2) $[M-C_{14}H_{19}O_{10}]^+$, 169 (70), 43 (100).- Anal. Calcd for $C_{25}H_{34}O_{10}$ (588.8): C, 51.02; H, 5.48. Found: C, 51.05; H, 5.62%. -

Oxidation of **3** *with N-Chlorosuccinimide-Dimethyl Sulfide*: To a vigorously stirred solution of N-chlorosuccinimide (40 mg, 0.3 mmol) in dry toluene (13 ml) dimethyl sulfide (30 µl, 0.41 mmol) was added at 0°C under argon. Stirring was continued for 30 min, then the reaction mixture was cooled to -25°C, and a solution of **3** (150 mg, 0.25 mmol) in dichloromethane (1 ml) was added and stirring was continued for 2 h at -25°C and 30 min at 0°C. Afterwards, a solution of triethylamine (30 mg, 0.30 mmol) in toluene (1 ml) was added dropwise to the solution. After allowing the mixture to warm up to room temperature, diethyl ether (50 ml) was added, and the organic layers were separated washed with 0.1 N hydrochloric acid (3x5 ml), saturated sodium hydrogen-carbonate solution (10 ml), and brine (2x10 ml) and then the organic layers were dried (Na_2SO_4). The solvent was removed under reduced pressure and the residue purified by chromatography on silica gel (diethyl ether) to give two fractions. A: 90 mg (62%) of **6**. - B: 43 mg (29%) of secogalioside tetraacetate **8**.

Secogalioside **9**: To a solution of **8** (50 mg, 0.08 mmol) in dry methanol (5 ml) was added potassium carbonate (5 mg) at 0°C. After strirring for 30 min, chloroform (20 ml) was added, the reaction mixture filtrated and the solvent removed under reduced pressure. Chromatography of the residue on silica gel (chloroform:methanol = 4:1) afforded 20 mg (60%) of **9**. - R_f = 0.26. - IR (KBr): ν = 1703 cm^{-1} (C=O, ester), 1642 (C=C). - UV (ethanol): λ_{max} (lg ϵ) = 238 nm (4.05). - $[\alpha]_D^\circ$ = -82° (c = 0.2 in ethanol). - ^{1}H NMR (D_2O): δ = 1.41 (dd, J = 12 Hz, J = 14 Hz, 1 H; 5-H_{ax}), 2.04 (m, 2 H; 6-H_{eq}, 9a-H), 2.96 (ddd, J = 5 Hz, J = 5 Hz, J = 12 Hz, 1 H; 4a-H), 3.67 (s, 3 H; OCH_3), 3.16-3.94 (m, 6 H; 2'-H, 3'-H, 4'-H, 5'-H, 6'-H_2), 4.54 (d, J = 1.5 Hz, 1 H; 9-H), 4.88 (d, J = 7 Hz, 1 H; 1'-H), 5.58 (d, J = 8 Hz, 1 H; 1-H), 5.61 (s, 1 H; 8-H), 5.76 (s, 1 H; 6-H), 7.54 (s, 1 H; 3-H). - ^{13}C NMR (D_2O): δ = 24.16 (C-4a), 33.62 (C-5), 36.17 (C-9a),

51.81 (OCH_3), 60.49 (C-6'), 69.42, 72.64, 75.69, 76.29 (C-2'to C-5'), 78.18 (C-9), 95.53 (C-8), 95.86 (C-1), 99.56 (C-1'), 102.64 (C-6), 109.08 (C-4), 153.61 (C-3), 169.28 (CO). - MS (FAB; sodium, glycerol): *m/z* (%) = 443 (6) $[M + Na]^+$, 421 (1.5) $[M+H]^+$, 403 (7), 241 (68), 139 (100). To a solution of **9** (60 mg, 0.10 mmol) in dry toluene (4 ml) and diethyl ether (1 ml) was added at 0°C acetyl chloride (35 µl, 0.40 mmol) and with stirring during 30 min pyridine (100 µl). Stirring was continued for 2 h, the precipitate was filtered off, the solvent removed under reduced pressure and the residue purified by chromatography on silicia gel (diethyl ether) to give 54 g (85%) of secogalioside pentaacetate **10**. mp 170-171°C (Lit.[2] mp 171-172°C). - Anal. Calcd for $C_{27}H_{34}O_{17}$ (630.6): C, 51.43; H, 5.43. Found: C, 51.61; H, 5.53%.

Methyl (1S,4aS,8S,8aS)-6-oxo-1-(2',3',4',6'-tetraacetyl-ß-D-glucopyranosyloxy)-8-tosyloxymethyl-1,4a,5,6,8,8a-hexahydro-pyrano[3,4-c]pyran-4-carboxylate **13**: A solution of **12** (29 mg, 0.05 mmol), *p*-toluenesulfonyl chloride (28 mg, 0.15 mmol) and dimethylaminopyridine (2 mg) in dry pyridine (5 ml) was stirred 12 h at room temperature. After removing the solvent under reduced pressure, chromatography of the residue on silica gel (diethyl ether:pentane = 3:1) afforded 30 mg (81%) of **13**. - R_f (diethyl ether) = 0.35. - IR (KBr): ν = 1750 cm^{-1}, (C=O), 1710 (C=O, conj.), 1635 (C=C), 1190 (S=O). - UV (ether): λ_{max} (lg ϵ) = 232 nm (4.39). - $[\alpha]^{20}_D$ = -34° (c = 0.5 in chloroform). - ^1H NMR ($CDCl_3$): δ = 2.02, 2.03, 2.04, 2.09 (4 s, 12 H; 4 CH_3), 2.33 (dd, J = 10 Hz, J = 16.5 Hz, 1 H; 5-H_{ax}), 2.37 (dd, J = 5.5 Hz, J = 7 Hz, 1 H; 8a-H), 2.48 (s, 3 H; CH_3-tosyl), 2.99 (dd, J = 4.5 Hz, J = 16.5 Hz, 1 H; 5-H_{eq}), 3.08 (m, 1 H; 4a-H), 3.70-3.82 (m, 1 H; 5'-H), 3.76 (s, 3 H; OCH_3), 4.14-4.24 (m, 5 H; 8-H, 9-H_2, 6'-H_2), 4.90-5.28 (m, 4 H; 1'-H, 2'-H, 3'-H, 4'-H), 5.30 (d, J = 7 Hz, 1 H; 1-H), 7.41 and 7.88, (2 d, 4 H; phenyl-H), 7.52 (d, J = 1 Hz, 1 H; 3-H). MS (70 eV): *m/z* (%) = 395 (2) $[M-C_{14}H_{19}O_{10}]^+$, 331 (14) $[C_{14}H_{19}O_9]^+$, 271 (6) $[331-C_2H_4O_2]^+$, 211 (5) $[271-C_2H_4O_2]^+$, 109 (80) $[211-C_2H_2O]^+$, 43 (100). - Anal. Calcd for $C_{18}H_{19}SO_8$: 395.0438. Found: 395.0438 (MS).

Methyl (1S,4aS,8R,8aS)-8-methyl-6-oxo-1-(2',3',4',6'-tetraacetyl-ß-D-glucopyranosyloxy)1,4a,5,6,8,8a-hexahydropyrano[3,4-c]pyran-4-carboxylate **14**: To a slurry of sodium cyanoborohydride 3 mg, 80 µmol) in hexamethyl phosphoric triamide (HMPA) (2 ml) under argon was added **13** (10 mg, 13 µmol) in 1 ml of HMPA. The reaction mixture was stirred for 2 h at 120°C, then water (5 ml) was added, the mixture extracted with diethyl ether/pentane (2:1, 3x10 ml) and the combined organic layers were dried (molecular sieve, 4 A). After removing the solvent under reduced pressure, the residue was crystallized form ether to give 2 mg (26%) of **14**. - mp 131-132°C (Lit.[12] 114.5-115°C). - R_f (ether) = 0.38. - IR (KBr): ν = 1750 cm^{-1} (C=O), 1705 (C=O, conj.), 1635 (C=C). - UV (ether): λ_{max} (lg ϵ) = 232 nm (4.41). - ^1H NMR ($CDCl_3$): δ = 1.50 (d, J = 6.5 Hz, 3 H; 9-H_3), 1.99, 2.04, 2.06, 2.12 (4 s, 12 H; 4 CH_3), 2.28-2.48 (m, 2 H; 5-H_{ax}, 8a-H), 2.98-3.20 (m, 2 H; 4a-H, 5-H_{eq}), 3.76 (s, 3 H; OCH_3), 4.12-4.34 (m, 2 H; 6'-H_2), 4.41 (dq, J = 1 Hz, J = 6,5 Hz, 1 H; 8-H), 4.88-5.30 (m, 4 H; 1'-H, 2'-H, 3'-H, 4'-H), 5.31 (d, J = 6 Hz, 1 H; 1-H), 7.44 (d, J = 1 Hz, 1 H; 3-H). - MS (70 eV): *m/z* (%) = 331 (14) $[C_{14}H_{19}O_9]^+$, 271 (5) $[331-C_2H_4O_2]^+$, 225 (3) $[M-C_{14}H_{19}O_{10}]^+$, 169 (79), 43 (100).

Oxidation of **15** *with Dimethyl Sulfoxide*: To a solution of **15** (64 mg, 0.10 mmol) and dimethyl sulfoxide (2 ml) in toluene (6 ml) was added under nitrogen at -20°C trifluoroacetic anhydride (23 mg, 0.11 mmol). After stirring for 1 h at this temperature and 2 h at room temperature, a saturated sodium hydrogencarbonate solution (5 ml) was added, and the solution was extracted with ether (3x10 ml). The combined organic layers were washed with brine (5 ml) and dried (Na_2SO_4). The solvent was removed under reduced pressure; chromatography of the residue on silica gel (tert-butyl methyl ether) afforded 52 mg (84%) of *methyl (2S,3R,4S)-4-(1,3-dioxolan-2-yl-methyl)-3-(2-hydroxy-1-oxoethyl)-2-(2',3',4',6'-tetraacetyl-ß-D-glucopyranosyloxy)-3,4-dihydro-2H-pyran-5-carboxylate* **18**. R_f (tert-butyl methyl ether) = 0.27. - IR (KBr): ν = 3480 cm^{-1} (OH), 1750 (C=O, acetate), 1712 (C=O, ketone), 1702 (C=O), 1635 (C=C). - UV (ether): λ_{max} (lg ϵ) = 230 nm (4.26). - $[\alpha]^{20}_D$ = -74° (c = 1 in chloroform. - ^1H NMR ($CDCl_3$): δ = 1.60 (br s, 1 H; 1.68-2.16 (m, 2 H; 7-H_2), 1.99, 2.00, 2.02, 2.13 (4 s, 12 H; 4 CH_3); 2.97 (dd, J = 5.5 Hz, J = 8 Hz, 1 H; 3-H), 3.15 (mc, J = 5.5

Hz, J = 6 Hz, 1 H; 4-H), 3.63 (s, 3 H; OCH_3), 3.64-3.98 (m, 5 H; 5'H, 2 OCH_2), 4.10-4.34 (m, 2 H; 6'-H_2), 4.14 (d, J = 19 Hz, 1 H; 10 H_a), 4.30 (d, J = 19 Hz, 1 H; 10-H_b), 4.82-5.30 (m, 5 H; 1'-H, 2'-H, 3'-H, 4'-H, 8-H), 5.63 (d, J = 8 Hz, 1 H; 2-H), 7.20 (s, 1 H; 6-H). - MS (FAB, xenon, glycerol): *m/z* (%): 633 (10) $[M+H]^+$, 331 (100) $[C_{14}H_{19}O_8]^+$. - Anal. Calcd for $C_{27}H_{36}O_{17}$: C, 51.16; H, 5.73. Found: C, 50.98; H, 5.96%.

Methyl (2S,3S,4S,9S)-3-(1-hydroxy-2-tosyloxyethyl)-4-(1,3-dioxolan-2-yl-methyl)-2-(2',3',4',6'-tetraacetyl-ß-D-glucopyranosyloxy)-3,4-dihydro-2H-pyran-5-carboxylate 16: To a solution of 15 (126 mg, 0.20 mmol) and N,N-dimethylaminopyridine (10 mg) in dry pyridine (3 ml) was added *p*-toluenesulfonyl chloride (40 mg, 0.21 mmol). After stirring for 4 h at room temperature toluene (20 ml) was added, and the solvent was removed under reduced pressure; chromatography of the residue on silica gel (diethyl ether) afforded 114 mg (85%) 16. R_f (ether) = 0.22. - IR (KBr): ν = 1750 cm^{-1} (C=O, acetate), 1705 (C=O, conj.), 1635 (C=C). - UV (ether): λ (lg ϵ) = 230 nm (4.09). - $[\alpha]_D^{20}$ = -68° (c = 1 in chloroform). - ^1H NMR ($CDCl_3$): δ = 1.65-2.20 (m, 3 H; 3-H, 7-H_2), 2.00, 2.06 (2 s, 12 H; 4 CH_3), 2.44 (br s, 3 H; CH_3), 2.80-3.06 (ddd, J = 5 Hz, J = 5 Hz, J = 2 Hz, 1 H; 4 H), 3.36 (br s, 1 H; OH), 3.68 (s, 3 H; OCH_3), 3.60-3.92 (m, 5 H; OCH_2CH_2O, 5'-H), 3.94-4.35 (m, 6 H; 5 H, 9-H, 10-H_2, 6'-H_2), 4.74-5.40 (m, 5 H; 1'-H, 2'-H, 3'-H, 4'-H, 7-H), 5.38 (d, J = 8 Hz, 1 H; 2-H), 7.31 (s, 1 H; 6-H), 7.30-7.86 (AA'BB', 4 H; phenyl-H). - MS (70 eV): *m/z* (%) = 4411 (0.5) $[M-C_{14}H_{19}O_{10}]^+$, 331 (6) $[C_{14}H_{19}O_9]^+$, 271 (2) $[331-C_2H_4O_2]^+$, 109 (100). - Anal Calcd for $C_{20}H_{25}SO_9$: 441.0745. Found: 441.0745.

Oxidation of 16 *with Dimethyl Sulfoxide*: A solution of 16 (40 mg, 0.05 mmol) in freshly distilled dimethyl sulfoxide (3 ml, CaH_2) under nitrogen was heated for 3 min at 170°C. After removing the solvent under reduced pressure, the residue was purified by chromatography on silica gel. This afforded 11 mg (36%) *methyl (2S,3S,4S,9S)-4-(1,3-dioxolan-2-yl-methyl-3-(1,2-epoxyethyl)-2-(2',3',4',6'-tetraacetyl-ß-D-glucopyranosyloxy)-3,4-dihydro-2H-pyran-5-carboxylate* 19. mp 93°C. - R_f (ether) = 0.41 - IR (KBr): ν = 1750 cm^{-1} (C=O, acetate), 1702 (C=O, conj.), 1642 (C=C). - UV (ether): λ_{max} (lg ϵ) = 229 nm (4.06). - ^1H NMR ($CDCl_3$): δ = 1.71 (m, 1 H; 3-H), 1.92-2.16 (m, 2 H; 7-H_2), 2.00, 2.03, 2.06, 2.12 (4 s, 12 H; 4 CH_3), 2.63 (dd, J = 2 Hz, J = 5 Hz, 1 H; 10-H_a), 2.89 (dd, J = 5 Hz, J = 5 Hz, 1 H; 10-H_b), 2.98 (m, 1 H; 9-H), 3.13 (m, 1 H; 4-H), 3.74 (s, 3 H; OCH_3), 3.74-4.04 (m, 5 H; 2 OCH_2, 5'-H), 4.06-4.16 (ABX, J = 12.5 Hz, 2 H; 6'-H_2), 4.86-5.30 (m, 5 H; 8-H, 1'-H, 2'-H, 3'-H, 4'-H), 5.47 (d, J = 7.5 Hz, 1 H; 2-H), 7.41 (s, 1 H; 6-H). - MS (70 eV): *m/z* (%) = 616 (0.5) $[M]^+$, 331 (87) $[C_{14}H_{19}O_9]^+$, 271 (25) $[331-C_2H_4O_2]^+$, 269 (32) $[M-C_{14}H_{19}O_{10}]^+$ 169 (100). - Anal. Calcd for $C_{27}H_{36}O_{16}$: 616.2003. Found: 616.2003.

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

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