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TOTAL SYNTHESIS OF STEVIOSIDE[a,b]

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Abstract—Steviol **2** was transformed into stevioside **1** by applying the stereoselective methods of glycosidation.

Stevioside **1**, a diterpene glycoside, was isolated from *Stevia rebaudiana* Bertoni in 1931 by Bridel and Lavieille[1] and was shown to be 300 times sweeter than sucrose. The chemical structure of the aglycon, steviol **2**, was elucidated by Mosettig *et al.* in 1963.[2] The chemical structure of the sugar part was proposed by Fletcher *et al.* in 1956,[3] except the stereochemistry of the linkage between sophorose moiety and C_{13} tertiary OH group of steviol, which was assigned as β by Tanaka *et al.* in 1977[4] according to the ^{13}C NMR study.

Since the first total synthesis of **1** by Mori *et al.* was reported in 1970,[5] three alternate routes to steviol have been appeared.[6] However further transformation of steviol into stevioside, which should constitute a formal total synthesis of stevioside and also should give a synthetic support to the proposed stereochemistry, has remained to be achieved. We describe the first formal total synthesis of stevioside in this paper.

Chemical degradation of stevioside into steviol

Steviol had been obtained from stevioside by the use of several enzymes.[7] In order to prepare enough amount of steviol **2** as a key relay compound for the synthetic purpose, we prefer to develope an efficient way for the chemical degradation of stevioside into steviol under the condition which should prevent the proton-catalysed Wagner–Meerwein rearrangement of steviol into isosteviol **3** during the reaction. This prerequisite was readily solved by the application of oxidation and elimination sequence originally developed in the aminoglycoside field.[8] Periodate oxidation of stevioside in water gave hexaaldehyde **4** which without purification was refluxed in 10% KOHaq. Extractive work-up and crystallization afforded steviol in 75% yield. Starting from steviolbioside **5**, obtained by saponification of stevioside, same sequence of reactions also afforded steviol in 56% yield.

At the beginning of this project, only a few examples had been reported as for the glycosidation at tertiary hydroxyl group, especially at the bridgehead hydroxyl group[9] and also at sterically crowded carboxyl group,[10] both of these items should be carefully studied by using appropriate model systems from both preparative and stereochemical point of view.

Transformation of steviol into steviolbioside

The efficieny and the stereochemical outcome of the glycosidation at the teriary OH group was studied by using 3,4,6-tri-O-acetyl-2-O-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-α-D-glucopyranosyl bromide **7**.[11] As a model alcohol, 1-methyl cyclohexanol **8** was chosen. The glycosidation of **8** with **7** was studied in the presence of silver carbonate–celite,[9,12] silver triflate–collidine[13] or silver triflate–tetramethylurea.[14] Deacetylation of each products afforded α-sophoroside **9**, $[\alpha]_D^{25}$ + 36.7° (c = 0.48, MeOH), in 18, 90 and 94% yield respectively. α-Stereochemistry of glycosidation was assigned by ^{1}H and ^{13}C NMR data of **9**. Thus, ^{1}H NMR in D_2O showed $C_{1'}$-H at δ 5.42 as a doublet, J = 3 Hz and ^{13}C NMR showed $C_{1'}$ at δ 94.2 ppm with $^1J_{CH}$ = 168.4 Hz in good agreement with the empirical rule of Bock and Pedersen.[15] In these model experiments, β-isomer of **9** could not be isolated from the mixture. However, the reaction of steviol methyl ester **6** and glycosyl bromide **7** in the presence of silver triflate and 2,4,6-collidine, deacetylation by sodium methoxide in methanol, and subsequent chromatography on the column of silica gel afforded two isomers. The firstly eluted compound **10**, R_f 0.68 (chloroform: methanol: water = 30:20:2), $[\alpha]_D^{25}$ − 33.3° (c = 0.74, dioxane) was isolated in 3.1% yield. Secondly eluted compound **11**, R_f 0.64 (chloroform:methanol:water 30:20:2), $[\alpha]_D^{25}$ + 31.2° (c = 0.73, dioxane) was obtained in 86% yield. The stereochemistry of the former and the latter compound was assigned as β and α respectively according to the ^{13}C NMR data[15] [**10**: 97.3 ppm, $^1J_{CH}$ = 158 Hz for $C_{1'}$, and 105.9 ppm, $^1J_{CH}$ = 158 Hz for $C_{1''}$; **11**: 94.4 ppm, $^1J_{CH}$ = 168 Hz for $C_{1'}$ and 106.1 ppm, $^1J_{CH}$ = 158 Hz for $C_{1''}$].

Since the predominant formation of α-glycoside was observed in the above approach, a stepwise approach for the stereocontrolled transformation of steviol methyl ester into steviolbioside methyl ester **10** was then studied. Orthoester method[16] was chosen for this purpose for two reasons. First, stereochemical outcome of glycosidation is established as 1,2-*trans*.[16] Secondly, the use of orthoester derivatives such as **12** is quite suitable for further glycosidation at $C_{2'}$-OH group of the product such as **14**, having all other OH groups protected as benzyl ether.

Glycosidation of **6** with 3,4,6-tri-O-benzyl-1,2-O-(1-methoxy–ethylidene)-α-D-glucopyranoside **12**[17] in the presence of mercuric bromide[16,18] at 90° during 5 hr afforded **13**. Saponification of **13** into **14** and

[a]Experimental part of this paper was taken from a part of the Ph.D. thesis of M. N. (Univ. of Tokyo, 1979).

[b]This paper was orally presented at the 21*th Symp. on the Chemistry of Natural Products*, Sapporo, Aug. 1978.

subsequent glycosidation of **14** by using 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl bromide **20** and silver triflate–collidine afforded **15**, $[\alpha]_D^{25}$ − 19.6° (c = 0.81, $CHCl_3$), a derivative of steviolbioside methyl ester in 29% yield from **6**. Saponification of **15** into **16** and benzylation of **16** gave 13-O-[2-O-(2,3,4,6-tetra-O-benzyl-β-D-glucopyranosyl)-3,4,6-tri-O-benzyl-β-D-glucopyranosyl] steviol methyl ester **17**, $[\alpha]_D^{25}$ − 4.3° (c = 0.46, $CHCl_3$). Stereochemistry of two glycosidic linkages in **17** was deduced from the synthetic methods employed and was further supported by ^{13}C NMR data which showed two anomeric carbons at δ 96.1 ppm with $^1J_{CH}$ = 158 Hz for $C_{1'}$, and at δ 102.3 ppm with $^1J_{CH}$ = 158 Hz for $C_{1''}$. Deprotection of both benzyl ether and methyl ester function in the presence of exocyclic double bond was achieved by the treatment with Na metal in liquid ammonia and subsequent chromatography on the column of silica gel to afford a 45% yield of steviol bioside **5**, $[\alpha]_D^{25}$ − 32.7° (c = 0.46, MeOH) which was identified with the authentic sample obtained by the saponification[3] of stevioside through ^{13}C NMR comparison.

Transformation of steviolbioside **5** *into stevioside*

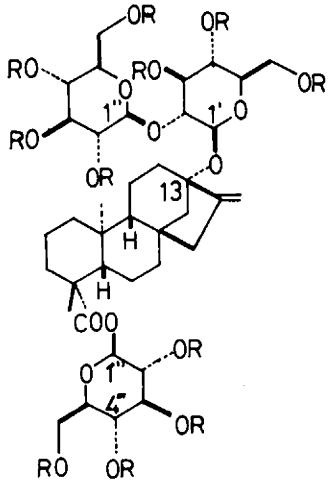
Several synthetic approaches toward glycosyl esters available so far[19] are not always suitable for the synthesis of sterically hindered glycosyl esters. For example, conventional glycosylation of gibberellic acid derivatives[10] such as **18** afforded only a low yield of the glycosyl ester **19**. The same situation was expected for the glycosidation of the carboxylic group of steviol derivatives. In order to circumvent these drawbacks, we developed a new approach to the synthesis of glycosyl esters by the use of tributyltin carboxylate.[20]

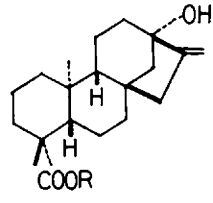
The reaction of 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl bromide **20** with tributyltin acetate did not proceed even on heating at 100°, but gave a good yield of 1,2,3,4,6-penta-O-acetyl-β-D-glucopyranose **24a** on heating at 60° in the presence of added bromide anion. Under essentially the same reaction condition, a variety of tributyltin carboxylates gave the corresponding 1,2-*trans* glucosyl esters in good yields (Table 1). The reaction may reasonably be explained as shown in Scheme 1. The acyloxonium ion **22**, derived from β-bromide **21**,[21] may be attacked either at C_1 to afford 1,2-*trans*-glycosyl ester **24** directly or at C* to afford acylorthoester **23** which subsequently rearranges to give 1,2-*trans*-glycosyl ester **24** in accordance with the observation of G. Wulff *et al.*[22]

As this approach was successfully applied to the synthesis of sterically crowded carboxylic acids, such as **24c** and **24e**, the application of this method to the transformation of steviol bioside into stevioside was undertaken.

Tributylstannylation of heptaacetyl steviolbioside **25**,[3] obtained by acetylation of steviolbioside, gave tributyltin carboxylate **26**, ν_{max}^{KBr} 1640 cm^{-1} for CO_2SnBu_3. Subsequent reaction of **26** with stoichiometric amount of **20** in toluene for 65 hr at 110° gave a high yield of a mixture of glucosyl esters **27** and **28**, which could not be separated on tlc. Deacetylation with methanolic sodium methoxide and subsequent chromatography on a column of silica gel afforded a 23% yield of α-D-glucosyl ester **29**, $[\alpha]_D^{25}$ + 7.0° (c = 0.61, pyridine) and a 61% yield of β-D-glucosyl ester **1**, $[\alpha]_D^{25}$ − 30.9° (c = 0.56, pyridine). Each structure was assigned according to ^{13}C NMR data. A newly introduced anomeric C atom of **29** appears at δ 93.2 ppm with $^1J_{CH}$ = 172.1 Hz, while that of **1** appears at δ 95.6 ppm with $^1J_{CH}$ = 163.2 Hz.[15]

This synthetic sequence, not only provides a synthetic support for the assigned stereochemistry of





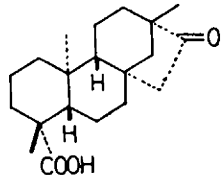
2 R = H

6 R = Me

1 R = H

27 R = Ac

30 $C_{4''}$ epimer of **1**



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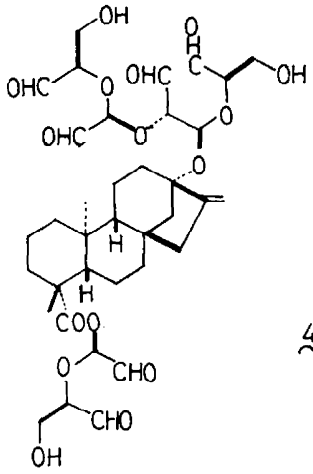

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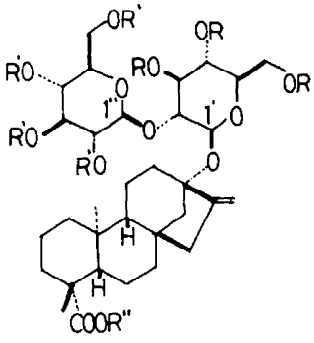
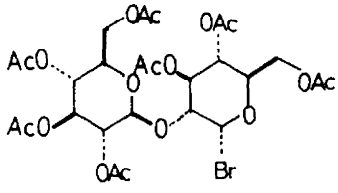


5 R = R' = R'' = H
10 R = R' = H, R'' = Me
15 R = Bn R' = Ac R'' = Me
16 R = Bn R' = H R'' = Me
17 R = R' = Bn R'' = Me
25 R = R' = Ac R'' = H
26 R = R' = Ac R'' = $SnBu_3$



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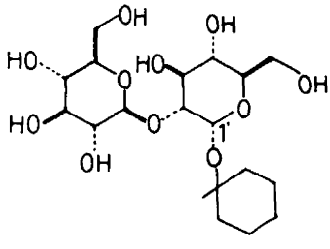

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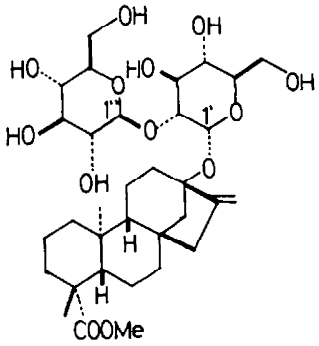

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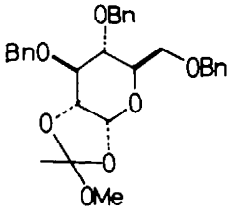

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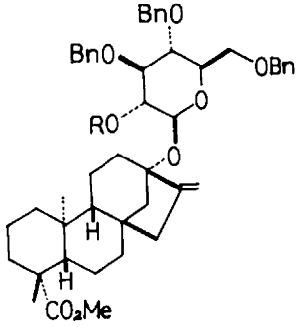
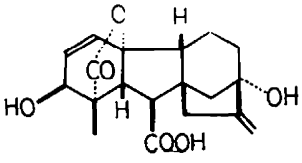


13 R=Ac

14 R=H



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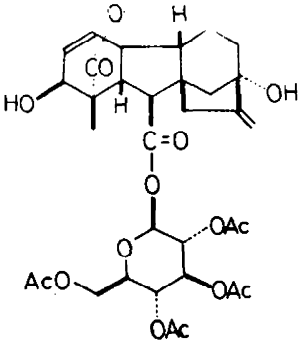

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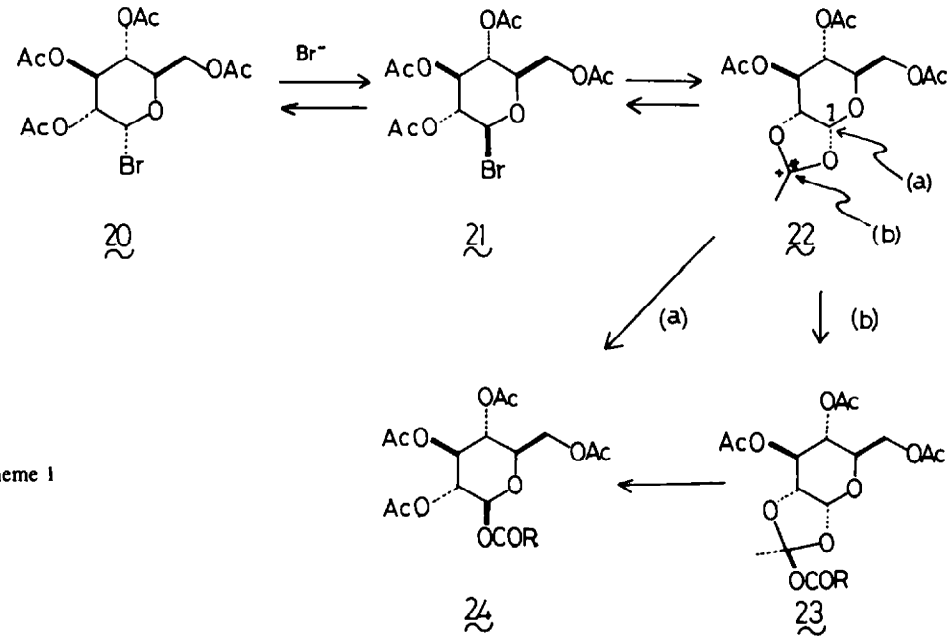
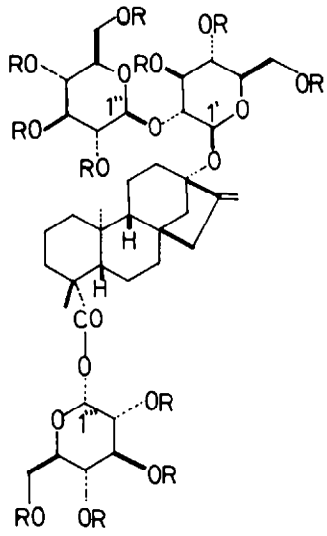


Scheme 1



stevioside but paves a way to prepare unnatural derivatives of stevioside, which should be of interest from the view point of sweetness.

For example, galactosyl derivative **30** of **1** could readily be synthesized by using 2,3,4,6-tetra-O-acetyl-α-D-galactopyranosyl bromide instead of **20** at the last step.

In conclusion, the transformation of steviol into stevioside was executed in a stereocontrolled manner, which constitute the first total synthesis of stevioside in a formal sense.

EXPERIMENTAL

M.ps were determined with a Yanagimoto micro melting point apparatus and were uncorrected. Optical rotations were determined with a Perkin–Elmer Model 141 polarimeter for solns in $CHCl_3$, unless otherwise noted. IR spectra were recorded with an EPI-G2 Hitachi spectrophotometer, as KBr discs for the crystalline samples and as neat films for the liquid samples. ^1H NMR spectra were recorded with a Varian HA-100 NMR spectrometre, using TMS as the internal standard. ^{23}C NMR spectra were recorded with a JNM-FX100 FT NMR spectrometer operated at 25.05 MNz. The values of δ_C and δ_H are expressed in ppm downward from the internal standard. Column chromatography was performed on columns of Silica Gel Merck (70–230 mesh; E. Merck, Darmstadt, Germany). Thin layer chromatography was performed on precoated plates (layer thickness, 0.25 mm; E. Merck, Darmstadt, Germany) of Silica Gel 60 F_{254}.

Steviol **2**

(a) Stevioside (**1**, 1 g) and $NaIO_4$ (1.5 g) in H_2O (75 ml) was stirred at room temp for 16 hr. Then KOH (7.5 g) was added

Table 1. The reaction of **20** with RCO_2SnBu_3 (R: same as that in 24) in the presence of tetrabutylammonium bromide

R in 24	Yield(%)	M.p.(°C)	$[\alpha]_D^{25}$	Reaction time (hr)	Reaction temp. (°C)	Chemical formula	Found (%) C	Found (%) H	Required (%) C	Required (%) H	δ_H
24a : Me	70.0	130 - 131	+3.9°	100	60	$C_{16}H_{22}O_{11}$	49.27	5.60	49.23	5.68	5.72 (1H, d, J=7 Hz)
24b : Me_2CH	44.3	106.5-107.5	+4.6°	10	80	$C_{18}H_{26}O_{11}$	51.52	6.16	51.67	6.26	5.72 (1H, d, J=7.5 Hz)
24c : Me_3C	64.1	136 - 137	+7.2°	100	80	$C_{19}H_{28}O_{11}$	52.33	6.58	52.77	6.53	5.70 (1H, d, J=8 Hz)
24d : C_6H_4OH-p	74.6	199 - 201	-31.8°	4	80	$C_{21}H_{24}O_{12}$	53.77	5.16	53.84	5.16	5.90 (1H, d, J=8 Hz)
24e :	62.1	101 - 102	+1.8°	100	80	$C_{20}H_{22}O_{11}$	56.08	6.83	55.92	6.83	5.72 (1H, d, J=7 Hz)

and the mixture was refluxed for 1 hr. After cooling to room temp, the mixture was carefully acidified with AcOH and extracted with ether. Organic layer was washed with water, dried ($MgSO_4$) and concentrated *in vacuo* to give crystalline residue (300 mg, 75%). Recrystallization (MeOH) gave 2 m.p. 246°. The IR and NMR spectra were identical with those of the authentic sample.[5]

(b) Steviolbioside **5** (100 mg) and $NaIO_4$ (100 mg) in H_2O (10 ml) was stirred at room temp. for 16 hr. Then $CaCO_3$ (100 mg) was added and the mixture was stirred at room temp. for 24 hr. The mixture was acidified with AcOH at 0° and extracted with ether. Organic layer was washed with water, dried ($MgSO_4$), and evaporated *in vacuo* to give crystalline residue (28 mg, 56%). $[\alpha]_D^{25}$ − 61.4° (c = 0.51). (Found: C, 71.81; H, 9.63. $C_{20}H_{30}O_3.CH_3OH$ requires: C, 71.96; H, 9.78%.)

1-*Methylcyclohexyl 2-O-β-D-glucopyranosyl-α-D-glucopyranoside* **9**

(a) CH_2ClCH_2Cl (40 ml) containing **8** (114 mg, 1.0 mM) and Fetizon reagent [12] (3 g) was distilled to the volume of 30 ml. To this mixture was added a soln of **7** (1.4 g, 20 mM) in CH_2ClCH_2Cl (10 ml) dropwise and the mixture stirred under reflux for 15 min. After cooling to room temp. inorganic substance was filtered off. The filtrate was concentrated *in vacuo* and chromatographed on silica gel (150 g). Elution with toluene–EtOAc (3:2) afforded an oil (130 mg) which was treated with 0.1 N NaOMe in MeOH (10 ml) at room temp overnight. MeOH was evaporated and the residue was chromatographed on silica gel (10 g). Elution with $CHCl_3$–MeOH–H_2O (45:12:2) afforded **9** (100 mg, 18% based on 1-methylcyclohexanol).

(b) To a mixture of **8** (456 mg, 4 mM), silver triflate (113 mg, 0.51 mM) and 2,4,6-collidine (0.06 ml, 0.54 mM) in CH_2ClCH_2Cl (2 ml) was added dropwise a soln of **7** (138 mg, 0.3 mM) in CH_2ClCH_2Cl (2 ml) at 0°. The mixture was further stirred at 0° for 1 hr. Then the mixture was directly applied to the column of silica gel (20 g). Elution with toluene–EtOAc (3:2) afforded a crude oil (130 mg) which was deacetylated and chromatographed on silica gel (10 g). Elution with $CHCl_3$–MeOH–H_2O (45:12:2) afforded **9** (79 mg, 90%).

(c) To a mixture of **8** (456 mg, 4 mM), silver triflate (113 mg, 0.51 mM), and tetramethylurea (0.07 ml, 0.59 mM) in CH_2ClCH_2Cl (2 ml) was added dropwise a soln of **7** (138 mg, 0.2 mM) in CH_2ClCH_2Cl (2 ml) at 0°. The mixture was further stirred at 0° for 1 hr and processed as described in (b) to give **9** (82 mg, 94%). $[\alpha]_D^{25}$ + 36.7° (c = 0.48, MeOH); δ_H (D_2O), 5.42 (1 H, d, J = 3 Hz), 4.02–3.02 (12 H), 1.86–1.20 (10 H), 1.22 (3 H, s): δ_C (CD_3OD), 94.2 ($C_{1'}$, $^1J_{CH}$ = 168.4 Hz), 106.0 ($C_{1''}$, $^1J_{CH}$ = 160.0 Hz), 82.5 ($C_{2'}$). (Found: C, 52.26; H, 7.71. $C_{19}H_{34}O_{11}$ requires: C, 52.05; H, 7.82%.)

13-*O-[2-O-(β-D-Glucopyranosyl)-β-D-glucopyranosyl]-steviol methyl ester* **10** and 13-*O-[2-O-(β-D-glucopyranosyl)-α-D-glucopyranosyl]-steviol methyl ester* **11**

To a mixture of **6** (628 mg, 1.9 mM), silver triflate (2.14 g, 9.7 mM), and 2,4,6-collidine (1.3 ml, 9.9 mM) in CH_2Cl_2 (7 ml) was added dropwise a soln of **7** (2.58 g, 3.8 mM) in CH_2Cl_2 (7 ml) at 0° under Ar. The mixture was further stirred at 0° for 1.5 hr and then filtered. The filtrate was evaporated and chromatographed on silica gel (400 g). Elution with toluene–EtOAc (3:1) gave an oil (1.6 g), which was treated with 0.01% NaOMe in MeOH (20 ml) at room temp for 3 hr. The mixture was evaporated and chromatographed on silica gel (100 g). Elution with $CHCl_3$–MeOH–H_2O (45:12:2) afforded **10** (38 mg, 3.1%), and **11** (1.072 g, 86%). **10**: R_f 0.68 in $CHCl_3$–MeOH–H_2O (30:20:2) $[\alpha]_D^{25}$ − 33.3° (c = 0,74, dioxane). δ_C (pyridine-d_5 at 60°), 97.3 ($C_{1'}$, $^1J_{CH}$ = 158.0 Hz), 105.9 ($C_{1''}$, $^1J_{CH}$ = 158.0 Hz), 83.9 ($C_{2'}$). ^{13}C NMR was identical with that of the authentic sample prepared from **5** by successive treatment with (i) Ac_2O–pyridine, (ii) CH_2N_2 in ether, and (iii) NaOMe in MeOH. **11**: R_f 0.64. $[\alpha]_D^{25}$ + 31.2 (c = 0.73, dioxane). δ_C (pyridine-d_5 at 60°), 94.4 ($C_{1'}$, $^1J_{CH}$ = 168.0 Hz), 106.1 ($C_{1''}$, 158.0 Hz), 82.1 ($C_{2'}$), 85.9 (C_{13}). (Found: C, 53.85; H, 7.43. $C_{33}H_{52}O_{13}.2H_2O$ requires: C, 54.28; H, 7.43%.)

13-*O-[2-O-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl)-3,4,6-tri-O-benzyl-β-D-glucopyranosyl] steviol methyl ester* **15**

Ester **6** (996 mg, 3 mM), **12** (7.0 g, 14 mM) and $HgBr_2$ (900 mg, 2.5 mM) was stirred at 95° for 5 hr under vacuum (5 mmHg). After cooling to room temp, the mixture was chromatographed on a silica gel (800 g). Elution with toluene–EtOAc (20:1) gave **13**. $[\alpha]_D^{25}$ − 7.46° (c = 0.67), R_f 0.59 in toluene–EtOAc (9:1). δ_H ($CDCl_3$), 2.00 (3 H, s). Treatment of **13** with 0.01% NaOMe in MeOH (15 ml) at room temp for 3 hr and subsequent chromatography on silica gel (300 g, toluene–EtOAc = 12:1) afforded crude **14** (2.4 g); R_f 0.35 in toluene–EtOAc (9:1). To a mixture of the crude **14** (2.32 g), silver triflate (3.40 g) and 2,4,6-collidine (1.68 ml) in CH_2Cl_2 (22 ml) was added dropwise at 0° a soln of **20** (5.5 g) in CH_2Cl_2 (30 ml). The mixture was further stirred at 0° for 5 hr and filtered. The filtrate was washed with water, dried over $MgSO_4$, concentrated, and chromatographed on silica gel (500 g, toluene–EtOAc = 9:1) to afford an oil (**15**, 840 mg, 29% from **6**). $[\alpha]_D^{25}$ − 19.6° (c = 0.81). δ_H ($CDCl_3$) 7.38–7.23 (15 H), 5.33–3.33 (25 H), 2.33–0.67 (38 H), 3.60 (3 H, s), 2.02 (12 H, bs), 1.18 (3 H, s), 0.88 (3 H, s). (Found: C, 67.85; H, 6.97. $C_{62}H_{78}O_{17}$ requires: C, 67.88; H, 7.17%.)

13-*O-[2-O-(2,3,4,6-Tetra-O-benzyl-β-D-glucopyranosyl)3,4,6-tri-O-benzyl-β-D-glucopyranosyl)-steviol methyl ester* **17**

Compound **15** (100 mg, 0.09 mM) was treated with 0.01% NaOMe in MeOH (10 ml) at room temp for 3 hr. MeOH was evaporated *in vacuo*. To the residue in DMF (5 ml) was added NaH (42 mg, 60%) at room temp and the mixture was stirred for 30 min. To the mixture was added dropwise benzyl bromide (175 mg) in DMF (2 ml) at 0° and the mixture was stirred at room temp for 3 hr. MeOH (1 ml) was added and the soln was concentrated *in vacuo*. The residue was dissolved in ether and ether layer was washed with water, dried ($MgSO_4$), evaporated, and chromatographed on silica gel (10 g, toluene–EtOAc = 20:1) to afford an oil (**17**, 91 mg, 81%). $[\alpha]_D^{25}$ − 4.3° (c = 0.46). δ_C ($CDCl_3$ at 60°). 96.1 ($C_{1'}$, $^1J_{CH}$ = 158 Hz), 102.3 ($C_{1''}$, $^1J_{CH}$ = 158 Hz), 86.7 (C_{13}). (Found: C, 74.62; H, 7.18. $C_{82}H_{94}O_{13}$ requires: C, 74.85; H, 7.36%.)

Steviolbioside **5**. To a soln of **17** (248 mg) in THF (5 ml) and liq. NH_3 (10 ml) was added Na metal (50 mg) piece by piece. The mixture was stirred at −30° for 3 hr. MeOH was added to the mixture and the solvent was evaporated. The residue was chromatographed on silica gel (10 g). Elution with $CHCl_3$–MeOH–H_2O (45:12:2) afforded **5** (55 mg, 45%). $[\alpha]_D^{25}$ − 32.7° (c = 0.46, MeOH). (Found: C, 58.07; H, 7.64. $C_{32}H_{50}O_{13}.H_2O$ requires: C, 58.17; H, 7.93%). δ_C (pyridine-d_6 at 60°): 106.1 ($C_{1''}$, $^1J_{CH}$ = 158 Hz), 97.6 ($C_{1'}$, $^1J_{CH}$ = 156 Hz), 86.2 (C_{13}), 84.1 ($C_{2'}$).

The general procedure for the synthesis of 2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl esters of carboxylic acids, **24a–24e**. Bis(tri-n-butyltin) oxide (29.8 g, 0.05 M) and carboxylic acid (0.1 M) in benzene (100 ml) was refluxed for 15 hr with continuous azeotropic removal of water. Evaporation of benzene gave tributyltin ester of carboxylic acid which is enough pure for the next step. 2,3,4,6-Tetra-O-acetyl-α-D-glucopyranosyl bromide (822 mg, 2 mM) and tributyltin ester of carboxylic acid (2 mM) in CH_2ClCH_2Cl (100 ml) was stirred at 80° in the presence of tetrabutylammonium bromide (322 mg, 1 mM). The mixture was evaporated *in vacuo*. The residue was chromatographed on silica gel (100 g) to give the product (Table 1).

Stevioside **1** *and its anomer* **29**. Compound **25** (2.5 g, 2.8 mM), bis(tributyltin)oxide (850 mg, 1.4 mM) in toluene (80 ml) was refluxed for 15 hr with continuous azeotropic removal of water. Toluene was evaporated to afford tributyltin ester of **26**, ν_{max} 2920, 1740, 1640 cm^{-1}. Compound

26 (1.44 g, 1.2 mM), **20** (510 mg, 1.2 mM), and tetrabutylammonium bromide (289 mg, 0.9 mM) in toluene (20 ml) was refluxed for 65 hr. The soln was evaporated *in vacuo*. The residue was chromatographed on a column of silica gel (200 g). Elution with toluene–EtOAc (3:1) gave a mixture of **27** and **28**. This mixture was stirred in 0.1 N NaOMe in MeOH (15 ml) at room temp for 3 hr and the solvent was evaporated *in vacuo*. The residue was chromatographed on silica gel (100 g). Elution with $CHCl_3$–MeOH–H_2O (45:12:2) afforded **1** (610 mg, 61%) and its α-anomer **29** (230 mg, 23%). **1**: R_f 0.43 in $CHCl_3$: MeOH: H_2O = 30:20:4. $[\alpha]_D^{25}$ − 30.9° (*c* = 0.56, pyridine). ν_{max} 3390, 2930, 1730, 1080 cm^{-1}. δ_C (pyridine-d_5 at 60°): 95.6 ($C_{1'''}$, $^1J_{CH}$ = 163.2 Hz), 176.7 (C_{19}). **29**: R_f 0.35 in $CHCl_3$:MeOH:H_2O = 30:20:4. $[\alpha]_D^{25}$ + 7.0° (*c* = 0.61, pyridine). ν_{max} 3390, 2930, 1730, 1080 cm^{-1}. δ_C (pyridine-d_5 at 60°) 93.2 ($C_{1'''}$, $^1J_{CH}$ = 172.1 Hz), 176.5 (C_{19}). (Found: C, 53.85; H, 7.48. $C_{38}H_{60}O_{18}.2H_2O$ requires: C, 54.28; H, 7.43%.)

13-*O*-[2-*O*-(*β-Glucopyranosyl-β-D-glucopyransyl*]-*steviol-β-D-galactopyranosyl ester* **30**. A soln of **26** (897 mg, 0.76 mM), acetobromogalactose (698 mg, 1.7 mM), and tetrabutylammonium bromide (250 mg, 0.77 mM) in toluene (10 ml) was refluxed for 70 hr. Toluene was evaporated *in vacuo*. The residue was chromatographed on silica gel (200 g). Elution with toluene–EtOAc (1:1) afforded a crude oil (958 mg), which was treated with 0.1 N NaOMe in MeOH (10 ml) at room temp for 3 hr. MeOH was evaporated and the residue was chromatographed on silica gel (50 g). Elution with $CHCl_3$–MeOH–H_2O = 45:12:2 afforded **30** (224 mg, 36%). $[\alpha]_D^{25}$ − 16.6° (*c* = 0.58, MeOH). δ_C (pyridine-d_5 at 60°): 96.1 ($C_{1'''}$, $^1J_{CH}$ = 160 Hz), 176.8 (C_{19}). (Found: C, 54.43; H, 7.29. $C_{38}H_{60}O_{18}.2H_2O$ requires: C, 54.28; H, 7.43%.)

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