hydroxy-3-[(2-chloroacetyl)aminomethyl]phenyl]sulfonyl]phenoxy]acetate, 93135-32-1; ethyl[2,3-dichloro-4-[[4-hydroxy-3-(hydroxymethyl)phenoxy]methyl]phenoxy]acetate, 93135-33-2; ethyl [2,3-dichloro-4-[[3-(methyliminohydroxy)-4-(benzyloxy)phenoxy]methyl]phenoxy]acetate, 93135-34-3; 2,3-dichloro-4-[(4-nitrophenylacetyl]phenol 1,2-propylene ketal, 93135-35-4; [2,3-dichloro-4-[(4-aminophenylacetyl]phenoxy]acetic acid hydrochloride, 93135-36-5; 4-(carboxymethoxy)-2,3-dichloro-4′-hydroxy-3-[(chloroacetyl)aminomethyl]benzil, 93135-37-6; ethyl 4-(carboxymethoxy)-2,3-dichloro-4′-hydroxy-3-[(chloroacetyl)-aminomethyl]benzil, 93135-38-7; 2-[(trifluoroacetamido)-methyl]-4-nitrophenol, 93135-39-8; 3-[4-hydroxy-3-[(2-chloroacetyl)aminomethyl]phenyl]-6-(carboxymethoxy)-7-chloro-1,2-benzisoxazole, 93135-40-1; ethyl 3-[4-hydroxy-3-[(2-chloroacetyl)aminomethyl]phenyl]-6-(carboxymethoxy)-7-chloro-1,2-benzisoxazole, 93135-41-2; methyl 3-(2,3-dichloro-4-methoxyphenyl)oxirane-2-carboxylate, 93135-42-3; sodium 3-(2,3-dichloro-4-methoxyphenyl)oxirane-2-carboxylate, 93135-43-4; 1-morpholino-2-(2,3-dichloro-4-methoxyphenyl)ethene, 93135-44-5; 2,3-dichloro-4-ethoxybenzenesulfonyl chloride, 93135-45-6; gentisyl alcohol, 495-08-9; *N*-(hydroxymethyl)trifluoroacetamide, 50667-69-1; ethyl 3-oxo-4-pentenoate, 22418-80-0.

Diterpenoid Sweeteners. Synthesis and Sensory Evaluation of Stevioside Analogues with Improved Organoleptic Properties

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Congeneric series of stevioside (1) and rebaudioside A (3) analogues have been prepared. It was found that the bitter-taste component endogenous in the natural compounds 1 and 3 may be eliminated by increase in molecular hydrophilic character. Through the series of compounds prepared, bitter-taste character was correlated with k', a chromatographic indicator of gross hydrophilicity. An analogue (11) of stevioside, shown chromatographically to be of increased hydrophilicity, was prepared and found to exhibit no bitter-taste character. Similarly an analogue (13) of rebaudioside A, having increased polarity, was prepared and found not to exhibit any bitter taste. The rebaudioside A analogue 13 was determined to have higher potency than 11 and is suggested as a potential nonnutritive sweetener for food applications.

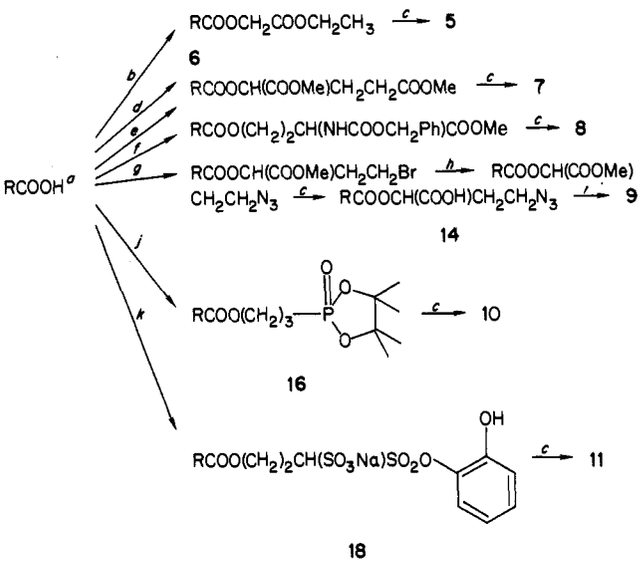
Interest in safe, high-sweetness quality, nonnutritive sweeteners is very high. The record 1983 sales of the dipeptide sweetener, aspartame, document the public's willingness to pay a premium price for a very good sucrose mimic.[1] In our sensory investigations on the well-known nonnutritive sweeteners,[2] only sodium cyclamate and aspartame were found to consistently exhibit the high sweet-taste quality mandated by the consumer. Recently, we reported that the marginal taste quality of the sweet diterpenoid triglucoside, stevioside (1), could be improved dramatically by replacement of the 19-*O*-glucosyl substituent by a (sodiosulfo)propyl moiety to give **2**.[3] Although this stevioside analogue 2 exhibits taste quality similar to that of sodium cyclamate, it reproducibly exhibits a weak, bitter-taste component. In the interest of obtaining a nonnutritive sweetener devoid of bitter taste, we have prepared a congeneric series of 19-*O*-substituted analogues of 1 and also of the related diterpenoid tetraglucoside, rebaudioside A (3). This work provides the subject for the following report.

Sensory Evaluation. The experimental compounds described below were evaluated by a human sensory panel. The same criteria, regarding purity and absence of toxicity which were applied in our earlier work,[4] were applied to these materials. Since none of them showed any toxicity, they were subjected to sensory analysis by a trained panel of judges. Panelists were required to carry out magnitude estimation (vs. 10% sucrose) and taste quality determination (percent sweet, sour, salty, bitter, and other) in one sensory session. From this analysis, comparative taste potency data, calculated on both weight (P_w) and molar (P_m) bases, and taste quality data were obtained.

Results

Analogue Design, Synthesis, and Sensory Evaluation. The mechanism responsible for the substantially improved taste quality of 2 over stevioside (1) is not known.

Scheme I



[a] RCOOH = steviolbioside (4). [b] K_2CO_3-DMF-$ClCH_2COOCH_2CH_3$. [c] NaOH. [d] Potassium *tert*-amyl oxide/toluene-DMF-1,4-butanesultone. [e] K_2CO_3-DMF-$COOMeCHBrCH_2CH_2COOMe$. [f] K_2CO_3-DMF-$Br(CH_2)_2CH(NHCOOCH_2Ph)COOMe$. [g] Potassium *tert*-amyl oxide/toluene-DMF-$Br(CH_2)_2CHBrCOOMe$. [h] NaN_3-DMF. [i] $NaBH_4$-$NiCl_2 \cdot 6H_2O$-MeOH. [j] K_2CO_3-DMF-**15**. [k] Potassium *tert*-amyl oxide/toluene-DMF-**17**.

Clearly, however, the 19-*O*-glucosyl substituent in 1 is not involved in any essential receptor binding interaction. Evidence has been put forth by Koyama and Kurihara[5]

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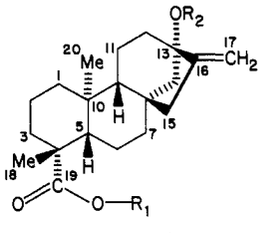
Table I. Sensory and Chromatographic Evaluation of Stevioside, Stevioside Analogues, and Other Sweeteners

compd	sensory evaluation: judgments	concn, ppm	I_p[b]	P_w[c]	P_m[c]	sweet	bitter	other	sweet/bitter, other	chromatographic[d] evaluation: k'
1 (stevioside)	12	500	0.9 (0.1)	190 (10)	440 (30)	62 (10)	30 (10)	8 (5)	62/38	6.6
2	12	534	0.8 (0.1)	160 (10)	360 (20)	92 (6)	4 (6)	4 (4)	92/8	5.9
3 (rebaudioside A)	12	638	1.1 (0.1)	170 (10)	470 (20)	85 (5)	12 (6)	3 (2)	85/15	6.6
4 (steviolbioside (Na))	12	1000	1.0 (0.1)	100 (10)	190 (20)	65 (9)	35 (10)	0 (1)	65/35	7.6
5	12	634	0.9 (0.06)	140 (10)	310 (20)	80 (9)	19 (9)	1 (1)	80/20	7.4
6	12	650	0.8 (0.1)	120 (20)	290 (30)	79 (11)	17 (11)	4 (3)	79/21	6.2
7 (Na)	12	550	0.9 (0.06)	160 (10)	380 (30)	84 (6)	2 (2)	10 (7)	84/16	7.0, 7.2[e]
8	12	615	1.2 (0.1)	200 (20)	420 (40)	60 (7)	35 (9)	5 (3)	60/40	7.5
9	12	650	1.1 (0.1)	170 (10)	360 (40)	79 (7)	18 (6)	3 (2)	79/21	5.6
10	12	650	0.8 (0.1)	120 (20)	280 (40)	87 (5)	8 (4)	5 (5)	87/13	5.8
11	12	631	0.8 (0.04)	120 (6)	310 (10)	96 (2)	0 (0)	4 (2)	96/4	5.5[f]
12 (rebaudioside B (Na))	12	650	1.0 (0.03)	150 (5)	370 (10)	88 (7)	4 (4)	8 (5)	88/12	7.7
13	12	595	1.0 (0.03)	170 (5)	470 (10)	96 (2)	1 (2)	3 (2)	96/4	6.6
sucrose	12	100000	1.0 (0)	1.0 (0)	1.0 (0)	100 (0)	0 (0)	0 (0)	100/0	
saccharin (Na)	12	330	1.0 (0.1)	300 (30)	180 (20)	85 (6)	12 (8)	3 (2)	85/15	
acesulfam (K)	12	1000	1.0 (0.05)	100 (5)	55 (3)	83 (8)	16 (8)	1 (1)	83/17	
cyclamate (Na)	12	5000	1.1 (0.1)	22 (2)	13 (1)	94 (3)	2 (2)	4 (3)	94/6	
aspartame	12	750	1.0 (0)	130 (0)	85 (0)	100 (1)	0 (1)	0 (0)	100/0	
neohesperidin dihydrochalcone	12	250	1.2 (0.1)	480 (40)	860 (70)	81 (8)	3 (2)	16 (8)	81/19	
monoammonium glycyrrhizzinate	12	3000	1.0 (0.1)	33 (3)	90 (8)	84 (8)	3 (4)	13 (8)	84/16	

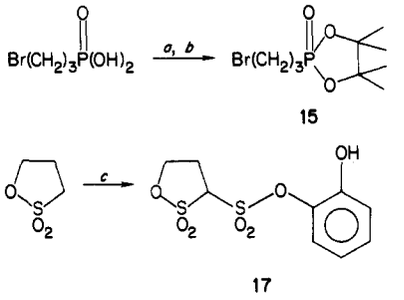
[a] Sensory data are reported as follows: mean value ($2S_m$). [b] Sample intensity relative to 10% sucrose; compound concentrations were chosen, when possible, by the panel supervisor to yield solutions having taste intensity comparable to the 10% sucrose reference. [c] P_w = compound potency calculated on a weight basis; P_m = compound potency calculated on a molar basis. [d] k' values are calculated by formula $k' = (t_R - t_0)/t_0$, where t_R is the compound's HPLC retention time in minutes and t_0 is the time for elution of the column void volume; a 30-cm μ-Bondapak C-18 reverse-phase column was employed, eluting with a 15-min linear gradient of 10–40% MeCN in 0.005 M KH_2PO_4 (pH 3.4). [e] Diastereomeric mixture. [f] HPLC elution carried out with 10–40% MeCN in 0.005 M $Ca(OAc)_2$.

that suggests that the mechanism of bitter-taste sensation involves partitioning of tastant molecules into the taste-cell membranes. Bitterness thus correlates in a very general way with molecular hydrophilicity. It therefore seems likely that the 19-O ester substituent appended to steviolbioside (**4**), the carboxylic acid obtained on saponification of stevioside, may function to modulate molecular hydrophobicity and that proper choice may result in a compound with no bitter-taste character. For this reason, we prepared the congeneric series (**5–11**) of steviolbioside esters in which the 19-O substituent is varied in a manner so as to modulate hydrophobicity. The syntheses of **5–11** were accomplished as illustrated in Scheme I, and their sensory properties are presented in Table I.



1 (stevioside), R_1 = β-D-glucosyl; R_2 = β-D-sophorosyl
2, $R_1 = (CH_2)_3SO_3Na$; R_2 = β-D-sophorosyl
3 (rebaudioside A), R_1 = β-D-glucosyl; R_2 = 3-*O*-β-D-glucosyl-β-D-sophorosyl
4 (steviolbioside), R_1 = H; R_2 = β-D-sophorosyl
5, $R_1 = CH_2COOH$; R_2 = β-D-sophorosyl
6, $R_1 = (CH_2)_4SO_3Na$; R_2 = β-D-sophorosyl
7, $R_1 = CH(COOH)CH_2CH_2COOH$; R_2 = β-D-sophorosyl
8, $R_1 = (CH_2)_2CH(NH_2)COOH$; R_2 = β-D-sophorosyl
9, $R_1 = CH(COOH)CH_2CH_2NH_2$; R_2 = β-D-sophorosyl
10, $R_1 = (CH_2)_3PO(OH)(ONa)$; R_2 = β-D-sophorosyl
11, $R_1 = (CH_2)_2CH(SO_3Na)_2$; R_2 = β-D-sophorosyl
12 (rebaudioside B), R_1 = H; R_2 = 3-*O*-β-D-glucosyl-β-D-sophorosyl
13, $R_1 = (CH_2)_3SO_3Na$; R_2 = 3-*O*-β-D-glucosyl-β-D-sophorosyl

Scheme II



[a] PCl_5. [b] Et_3N-CH_2Cl_2-pinacol. [c] *n*-BuLi-THF (−78 °C)-catechol sulfate.

Of interest from a synthetic point of view is the preparation of **9**. Although the azido acid **14** was easily prepared, reduction of **14** to the amino acid **9** was at first problematical. Hydrogenation over Lindlar catalyst[6] and $NaBH_4$ in MeOH[7] were completely unsuccessful. However, the method of Satoh and co-workers for reduction of nitro compounds[8] was found to be very useful for affecting a very mild and selective reduction of the azide moiety of **9**. Thus, this method may be complementary to other selective methods of azide reduction, recent samples of which include $Cr(II)/H^+$[9] Ph_3P/NH_4OH,[10] water,[11] and 1,3-propanedithiol/Et_3N.[12]

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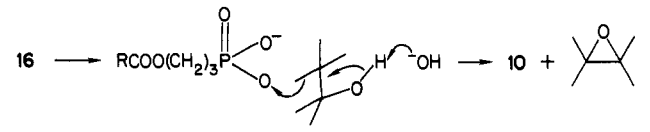

Figure 1. Proposed mechanism for alkaline hydrolysis of 16.

The synthesis of the phosphonic acid derivative **10** also merits comment. The intermediate phosphonate ester **16** was designed to permit hydrolysis under reasonably mild alkaline conditions. Conditions commonly employed for phosphonate ester hydrolysis are strong acid treatment[13] and bromotrimethylsilane-mediated hydrolysis.[14] Both of these methods are inconsistent with the acid-labile functionality present in **16**. It is known[13] that, under alkaline conditions, phosphonate esters hydrolyze easily to a monoester–monoacid and that this intermediate is nearly inert to further hydrolysis. Phosphonate diester **16** obtained from **15** (Scheme II) was designed such that the intermediate half ester–half acid could fragment via a 1,3-elimination rather than by the unfavorable nucleophilic attack of hydroxide anion on phosphorus. In fact, the hydrolysis of **16** to **10** occurs smoothly under alkaline conditions. It is likely that the mechanism illustrated in Figure 1 is responsible for the relatively mild saponification of **16**.

The preparation of disulfonic acid **11** is also noteworthy. The required alkylating agent **17** (Scheme II) was prepared by sulfonation of the lithium salt of 1,3-propanesultone with catechol sulfate.[15] This reaction may be exemplary of a very general method for the preparation of sulfonic acids in protected form. Deprotection when desired (i.e., **18** → **11**) is then achieved by alkaline hydrolysis. This latter step likely proceeds by a sulfene mechanism as has been postulated to account for the facile base hydrolysis of phenolic esters of alkanesulfonic acids.[16]

Rebaudioside A (**3**) exhibits a higher quality sweet taste than does stevioside (**1**). In order to determine if the sensory properties of **3** could be improved by substitution of (sodiosulfo)propyl for the 19-*O*-β-D-glucosyl moiety of **3**, as was observed for **1**, we prepared **13**. The synthesis of **13** was accomplished by chemistry analogous to that employed for preparation of **2**,[3] and the sensory properties of **13** are reported in Table I.

Discussion

At the outset of this work, the available SAR information on steviolbioside esters suggested that the 19-O ester substituent was not involved in specific receptor interactions. Rather, it was felt that this polar moiety served to potentiate gross molecular hydrophobic character to control partitioning of the compound between rather specific sweet-taste receptors and less discriminatory bitter-taste receptors. In a general way, molecular hydrophobicity can be quantitated by the chromatographic parameter k'. In fact, k' values have been employed in rationalization of the taste properties of some zwitterionic dihydrochalcone sweeteners.[17] k' values determined for the compounds prepared in this study are given in Table I and represent a ratio of the amount of time a compound spends interacting with a nonpolar, stationary phase to the amount of time spent in the aqueous phase. Thus, within a congeneric series, k' values provide an index of gross hydrophobicity.

On inspection of the sensory and k' data for steviolbioside esters **1**, **2**, and **5**–**11**, it is of interest to note that, with the exception of carboxylic acids **5** and **7**, the amount of bitter taste character correlates very well with k'. More specifically, the amount of bitter-taste character reaches a minimum for the most polar analogue **11** ($k' = 5.5$). These findings are consistent with the mechanism of bitter taste suggested by Koyama and Kurihara, where bitterness is suggested to derive from a general partitioning phenomenon of molecules into taste-cell membranes.[5] Thus, in the case of the dianionic disulfonic acid salt **11**, the compound can be considered to have become too hydrophilic to partition into the taste-cell membrane but to still retain the necessary hydrophobicity in defined regions for interaction with sweet-taste receptor functionality. The k' data for the carboxylic acids **4**, **5**, and **7** does not correlate well with bitter taste character relative to the compounds described above. This may be explained by the fact that the k' values given were determined under conditions (pH 3.4) in which the carboxylic acids would be unionized while sensory evaluation is carried out under conditions (pH ~7) in which they would be ionized and therefore somewhat more polar. It is interesting to note, however, that within the series **4** ($k' = 7.6$) → **5** ($k' = 7.4$) → **7** ($k' = 7.0, 7.2$) of increasing polarity, bitter-taste component decreases in the same order (35% → 19% → 2%). A similar correlation is noted for the two zwitterionic steviolbioside esters **8** and **9**. Here with a k' decrease of 7.5 (**8**) to 5.6 (**9**), the bitter-taste character decreases from 35% to 18%.

The highest quality sweetener prepared in the present work is the (sodiosulfo)propyl rebaudioside B ester **13**, which may be considered simply the rebaudioside A analogue of **2**. The data indicate this compound to be superior to sodium cyclamate and very close to aspartame in sweet-taste quality. No bitter taste component whatsoever was observed for **13**. Unfortunately, the HPLC-derived k' parameter does not distinguish the polarity difference between stevioside (**1**) and rebaudioside A (**3**) derivatives. Thus, in spite of the fact that the rebaudioside A compounds contain an additional polar glucose moiety, the k' values for the **1** (6.6)/**3** (6.6), **4** (7.6)/**12** (7.7), and **2** (5.9)/**13** (6.6) pairs are either the same or increase in a direction opposite from that anticipated. Intuitively, however, it is clear that the gross hydrophilicities of **3**, **12**, and **13** are greater than that of **1**, **4**, and **2**, respectively, and it is important to note that bitter-taste character decreases with hydrophilicity increase. Thus, **30** → **12**, **35** → **4**, and **4** → **1** percent changes in bitter taste character are observed for the **1**–**3**, **4**–**12**, and **2**–**13** pairs, respectively.

Rebaudioside A analogue **13** exhibits sweet-taste character indistinguishable from stevioside analogue (**11**). It should be noted, however, that the potency of **11** is significantly less than that of **13**. It is reasonable to suggest that while bitter-taste character can be eliminated by hydrophilicity increase to an optimum level, further increase may result in diminished interaction with the sweet-taste receptor. Thus, rebaudioside A analogue **13** may well represent an optimum molecular polarity that minimizes interaction leading to bitter taste and optimizes the polarity for interaction with sweet-taste receptors. On the other hand, stevioside analogue **11**, although similar to **13** in having a minimum of interactions leading to bitter taste, may have an effective hydrophilicity that results in diminished interaction with the sweet-taste receptor, which

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is then reflected in the lower taste potency.

In summary, it has been shown that the two polar moieties that are appended to the aglycon portion of stevioside (1) and rebaudioside A (3) can be modified to minimize the bitter-taste character endogenous in the natural members of this class of diterpenoid glycosides. To be specific, stevioside analogue 11 and rebaudioside A analogue 13 were prepared, neither of which exhibit any bitter-taste character. The rebaudioside A analogue, however, is of higher sweet-taste potency and thus may be of real utility for use as a nonnutritive sweetener in food systems.

Experimental Section

Sensory Evaluation. 19-*O*-[(Sodiosulfo)propyl]steviolbioside (2) was obtained as described earlier.[3] The remainder of the compounds that were evaluated were either obtained from Sigma Chemical Co. or prepared as described in the synthetic procedures given below except for Acesulfam-K (Hoechst Pharmaceutical Co.), neohesperidin dihydrochalcone (Nutrilite Products, Inc., Buena Park, CA), and monoammonium glycyrrhizzinate (Maruzen Pharmaceutical Co., Ltd., Japan).

Synthetic Procedures. All organic starting materials and reagents were obtained from Aldrich Chemical Co. except for Steviron F (Morita Kagako Kogyo Co., Ltd., Japan). Steviolbioside (4) was prepared from stevioside by the method of Wood and co-workers.[18] Solvents used were reagent grade and obtained from either J. T. Baker Chemical Co. or Fisher Scientific Co. Dimethylformamide (DMF) was distilled in vacuo from CaH_2 and stored over activated (400 °C, 3 h) 3-Å molecular sieves (J. T. Baker Chemical Co.) prior to use.

Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Perkin-Elmer Model 137 infrared spectrometer. Proton magnetic resonance spectra were recorded on either a Varian T-60A spectrometer or a Brüker 100-MHz instrument and are reported as parts per million (ppm) relative to tetramethylsilane. Combustion analyses were performed by the Microanalysis Laboratory, Stanford University, Stanford, CA. Neutralization equivalents were obtained by potentiometric titration vs. 0.100 N NaOH (compounds 6, 9, and 10–13) or vs. 0.100 N $HClO_4$ in glacial acetic acid (compounds 5 (Na) and 8). Sulfonic acid or phosphonate salts were first converted to the protic form by ion exchange on Bio-Rad AG MP-50(H) cation-exchange resin. Compounds not readily soluble in water were titrated in dimethyl sulfoxide/water (15:1). Glucose esters 1 and 3 were saponified (2.0 equiv of 0.050 M KOH, 100 °C, 1.5 h) to the potassium salts followed by titration with 0.100 N HCl. The titrations were carried out on a Brinkman Metrohm Herisau Potentiograph E576. The results obtained were calculated for the Na salts and are corrected for water content, which was determined by Karl Fischer titration.

Analytical thin-layer chromatography (TLC) was carried out on prelayered silica gel F-254 plates (E. Merck, Darmstadt, West Germany) visualizing with either UV light or sulfuric acid charring. Preparative radial chromatography was carried out on a Harrison Research (Palo Alto, CA) Chromatotron using 4-mm silica gel PF-254 rotors. High-pressure liquid chromatography was carried out on a Waters Associates instrument equipped with a Model 660 solvent programmer and two Model 6000A pumps. Analytical work was carried out on a μ-Bondapak C-18 reverse-phase column (30 cm × 3.9 mm i.d.) eluting with a linear gradient (15 min, 2 mL/min) of 10–40% MeCN in 0.005 M KH_2PO_4 (pH 3.4) unless otherwise indicated. The detector employed was a Schoeffels Model SF-770 spectroflow monitor equipped with a Model GM-770 monochrometer. Detection was carried out at 200 nm.

Unless otherwise indicated, all reactions were carried out under an inert atmosphere of argon with vigorous magnetic stirring. Concentrations of solutions were carried out in vacuo unless otherwise noted. The final products were assayed for purity by a combination of (1) proton titration, (2) HPLC, and (3) Karl Fischer analyses.

Stevioside (1) and Rebaudioside A (3). The two steviol glycosides 1 and 3 were obtained in pure form by isolation from Steviron F. Ten grams of Steviron F was extracted with 800 mL of CH_3OH. Crystallization in the cold gave 3.63 g of pure 1: TLC ($CHCl_3/CH_3OH/H_2O$, 15:10:2), R_f 0.40; HPLC, t_R 15.2 min; neutralization equivalents (after saponification), calcd, 804.9; found, 817.8. The mother liquor was concentrated to give 6.21 g of a viscous oil. Preparative radial chromatography ($CHCl_3/CH_3OH/H_2O$) of this material followed by recrystallization (CH_3OH) yielded 1.42 g of pure 3: mp 218–223 °C (lit.[19] mp 242–244 °C); TLC ($CHCl_3/CH_3OH/H_2O$, 15:10:2), R_f 0.32; HPLC, t_R = 16.6 min; neutralization equivalents (after saponification), calcd, 967.0; found, 976.8; Karl Fischer analysis, 1.9% water.

19-*O*-(Carboxymethyl)steviolbioside (5). To a solution of 1.29 g (2.00 mmol) of steviolbioside in 20 mL of DMF was added 380 mg (2.5 mmol) of K_2CO_3 and 337 mg (0.30 mL, 2.5 mmol) of ethyl chloroacetate. The resultant suspension–solution was stirred vigorously at 40 °C for 16 h. After allowing to cool, the reaction mixture was poured into 180 mL of ice-cold 5% HCl. The white, precipitated product was filtered, washed with ice water, and dried in vacuo to give 1.15 g of crude 19-*O*-(carboethoxymethyl)steviolbioside. The impure ester was dissolved in 20 mL of dry pyridine and cooled to 0 °C. To this solution was added 3.9 g (38 mmol) of acetic anhydride dropwise over 5 min. After warming to ambient temperature with stirring overnight, the pyridine solution was poured into 100 mL of 5% HCl with agitation. The resulting heterogeneous mixture was extracted with ether (3 × 50 mL), the combined portions of which were washed with 5% HCl (6 × 40 mL), water (3 × 50 mL), and brine (1 × 50 mL), dried ($MgSO_4$), and concentrated to yield 1.48 g of a white solid. Purification by preparative radial chromatography (hexane/ethyl acetate) gave 1.20 g of the pure heptaacetate derivative of 5 ethyl ester: TLC (hexane/EtOAc, 1:2), R_f 0.43. This ester was dissolved in 15 mL of CH_3OH and treated with 2.3 mL of 1 M NaOH at reflux for 3 h. The CH_3OH was then evaporated, yielding a residue, which was dissolved in water. The pH was adjusted to 7 by addition of dilute H_2SO_4. The aqueous solution was then evaporated to dryness to give a residue which was triturated with CH_3OH. The methanol-soluble product was then allowed to crystallize in the cold to give 625 mg of colorless granules: mp 230–240 °C dec; IR (KBr) 2.92 (OH), 5.84 (C=O), 6.21 (C=C) μm; NMR (CD_3SOCD_3) δ 0.70 (s, 3 H, 20-CH_3), 1.15 (s, 3 H, 18-CH_3); Neutralization equivalents: calcd, 700.8; found, 713.2. A sample of 5 was titrated potentiometrically with 0.100 N NaOH to the endpoint to give the sodium salt. Lyophilization yielded 5 (Na) as a flocculent, white solid. Anal. ($C_{34}H_{51}O_{15}Na \cdot H_2O$) C, H.

19-*O*-[(Sodiosulfo)butyl]steviolbioside (6). To a solution of 1.93 g (3.00 mmol) of steviolbioside in 45 mL of DMF was added 5.88 mL of 0.51 M potassium *tert*-amyl oxide in toluene (3.0 mmol) and 408 mg (3.0 mmol) of 1,4-butanesultone. The resulting homogeneous solution was heated at 65–70 °C for 48 h. One and one-half millimoles of additional alkylating agent was then added and heating continued for 20 h. HPLC analysis of an aliquot removed at this point indicated a reaction mixture composition of 14% starting material (t_R = 17.2 min) and 86% 6 (t_R = 14.4 min). The hydrolysis of excess sultone was then ensured by addition of 9 mL of 1 M KOH and 50 mL of CH_3OH followed by heating at 65 °C overnight. After cooling, the reaction mixture was neutralized by addition of 10% HCl and concentrated to dryness to yield 4.13 g of a viscous oil. Attempts to separate steviolbioside from the sulfobutyl ester by recrystallization were unsuccessful. The crude product was then dissolved in 25 mL of DMF and reacted with 207 mg (1.5 mmol) of K_2CO_3 and 0.35 mL (3.0 mmol) of benzyl chloride at 40 °C for 16 h. TLC analysis ($CHCl_3/CH_3OH/H_2O$, 15:8:1) showed all steviolbioside (R_f 0.37) to have been converted to a benzyl ester (R_f 0.52). The reaction mixture was then diluted with 15 mL of water and concentrated to dryness. The residue was dissolved in 50 mL of water and the solution neutralized by addition of 5% HCl. Extraction with EtOAc (3 × 25 mL) removed all steviolbioside benzyl ester. The purified steviolbioside sulfobutyl ester was converted to the Na

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salt by passage through a 400-g column of Bio-Rad AG MP 50 (Na) ion-exchange resin and desalted by chromatography over a column of Bio-Rad AG 11A8 ion-retardation resin to give 2.30 g of a viscous oil. Recrystallization from 75 mL of 98:2 ethanol/water yielded 602 mg (26%) of white granules: mp 185–230 °C; TLC ($CHCl_3/CH_3OH/H_2O$, 15:8:1), R_f 0.12; HPLC, t_R = 14.0 min; IR (KBr) 2.90 (OH), 5.84 (C=O), 6.05 (C=C), 8.5 (S=O), 9.5 (S=O) μm; NMR (CD_3SOCD_3) δ 0.81 (s, 3 H, 20-CH_3), 1.13 (s, 3 H, 18-CH_3), 4.93 (br s, 2 H, C=CH_2); neutralization equivalents, calcd, 800.9; found, 824.4. Anal. ($C_{36}H_{57}NaO_{16}S\cdot 2H_2O$) C, H.

19-*O*-(1,3-Dicarboxypropoxy)steviolbioside (7). Potassium carbonate (0.86 g, 6.2 mmol) and dimethyl 2-bromoglutarate (1.48 g, 6.2 mmol) were added to a solution of 3.22 g (5.0 mmol) of steviolbioside in 40 mL of DMF. After the solution was stirred at ambient temperature for 16 h, TLC analysis ($CHCl_3/CH_3OH/H_2O$, 15:5:0.8) indicated nearly all starting material (R_f 0.31) to be consumed to give one major product (R_f 0.58). The reaction mixture was poured into 70 mL of ice water and the resultant mixture neutralized by addition of 5% HCl. This solution–suspension was concentrated to dryness. Extraction of the residue with CH_3OH gave 5.56 g of the dimethyl ester of **7** as a crude product. The dimethyl ester was then chromatographed over 100 g of grade IV silica gel ($CHCl_3/CH_3OH$) to give 3.25 g (81%) of the pure dimethyl ester of **7**. To a solution of the ester in 50 mL of CH_3OH was added 50 mL of 10% NaOH. After the solution was stirred at ambient temperature for 30 min, TLC ($CHCl_3/CH_3OH/H_2O$, 15:5:0.8) indicated the saponification to have proceeded cleanly to give one product (R_f 0.10). The reaction mixture was then diluted with 100 mL of water and neutralized with 10% HCl. The neutral solution was concentrated to remove all CH_3OH and was then desalted by chromatography on a Bio-Rad AG 11A8 ion-retardation resin column. Fractions containing pure R_f 0.10 component were combined, concentrated, and dried to yield 0.67 g (16%) of **7** (Na) as a hygroscopic white solid: mp 152–165 °C; IR (KBr) 2.93 (OH), 5.81 (C=O) μm; NMR (CD_3SOCD_3) δ 0.82 (s, 3 H, 20-CH_3), 1.17 (s, 3 H, 18-CH_3); neutralization equivalents, calcd, 386.4; found, 392.2.

19-*O*-(3-Amino-3-carboxypropyl)steviolbioside (8). Two and one-half millimoles (345 mg) of K_2CO_3 was added to a solution of 1.28 g (2.00 mmol) of steviolbioside and 825 mg (2.5 mmol) of methyl 2-[(benzyloxycarbonyl)amino]-4-bromobutanoate.[17] The resultant suspension–solution was stirred vigorously at ambient temperature. After 16 h, TLC analysis ($CHCl_3/CH_3OH/H_2O$, 15:5:0.8) indicated the consumption of all starting material (R_f 0.21) to give one product (R_f 0.43). The reaction mixture was then poured into 250 mL of water and the resultant aqueous DMF solution neutralized by addition of 5% HCl. Extraction with EtOAc (3 × 150 mL) followed by washing the combined extracts with water (6 × 100 mL) and brine (1 × 200 mL), then drying ($MgSO_4$), and concentrating yielded 1.56 g of crude 19-*O*-[3-[(benzyloxycarbonyl)amino]-3-carbomethoxypropyl]steviolbioside. This product was combined with 30 mL of CH_3OH and 30 mL of 10% NaOH. The resultant solution was refluxed for 18 h. HPLC analysis at this point indicated conversion to one product (t_R = 13.6 min). The reaction mixture was then neutralized by addition of 2 N H_2SO_4 while cooling in an ice bath. The resulting solution was concentrated to dryness and the residue extracted (4 × 200 mL) with hot CH_3OH. The combined CH_3OH extracts were concentrated to dryness to give crude **8**, which was then recrystallized twice from CH_3OH to give 495 mg (38%) of colorless clusters: mp 198–203 °C dec; IR (KBr) 2.92–4.2 (br s, OH, NH_2), 5.85 (ester C=O), 6.14 (acid C=O) μm; NMR (CD_3SOCD_3) δ 0.80 (s, 3 H, 20-CH_3), 1.13 (s, 3 H, 18-CH_3); neutralization equivalents, calcd, 372; found, 369.5. Anal. ($C_{36}H_{57}NO_{15}\cdot H_2O$) C, H, N.

19-*O*-(1-Carboxy-3-aminopropyl)steviolbioside (9). To a solution of 1.29 g (2.00 mmol) of steviolbioside in 20 mL of DMF was added 3.92 mL of 0.51 M (2.00 mmol) of potassium *tert*-amyl oxide in toluene solution. After 5 min, 572 mg (2.20 mmol) of methyl 2,4-dibromobutyrate[4] was added as a neat liquid. The resulting homogeneous reaction mixture was stirred at ambient temperature for 10 h, at which point TLC analysis ($CHCl_3/CH_3OH/H_2O$, 15:8:1) of an aliquot showed consumption of nearly all starting material (R_f 0.47) to give one major product (R_f 0.70). Sodium azide (260 mg, 4.00 mmol) was then added and the resulting solution–suspension stirred at ambient temperature overnight. The reaction mixture was then poured into 200 mL of water and the resulting aqueous DMF solution neutralized by addition of 5% HCl. This mixture was then extracted with EtOAc (3 × 50 mL), the combined portions of which were washed with 5% NaCl (6 × 50 mL), then dried ($MgSO_4$), and concentrated to give 1.13 g (72%) of crude 19-*O*-(1-carbomethoxy-3-azidopropyl)steviolbioside as a viscous oil: TLC ($CHCl_3/CH_3OH/H_2O$, 15:8:1), R_f 0.70. The ester was dissolved in 25 mL of CH_3OH and reacted with 10 mL of 10% KOH for 1 h. The reaction mixture was then neutralized by addition of 5% HCl and concentrated to remove CH_3OH. Filtration then yielded 712 mg (64%) of the acid. The azido acid (712 mg, 0.91 mmol) and 433 mg (1.82 mmol) of $NiCl_2\cdot 6H_2O$ were dissolved in 45 mL of CH_3OH. To the resultant green solution was added 344 mg (9.1 mmol) of $NaBH_4$ in small portions over a 5-min period. After the solution was stirred at ambient temperature overnight, TLC analysis ($CHCl_3/CH_3OH/H_2O$, 15:10:2) indicated clean formation of one product (R_f 0.18). The reaction mixture was first made acidic (pH ~1–2) by addition of 10% HCl and then neutralized by addition of saturated $NaHCO_3$ solution. A flocculent black precipitate formed, which was removed by filtration. The resulting green solution was then desalted by chromatography over a column of 25 mL of Bio-Rad AG 11A8 ion-retardation resin. Combination of fractions containing pure R_f 0.18 material yielded 0.57 g of **9** as a white solid. Recrystallization from CH_3OH/water yielded 497 mg (74%) of pure **9** as large flocculent white clusters: mp 194–204 °C dec; IR (KBr) 2.95 (OH, NH), 5.85 (ester C=O), 6.20 (acid C=O) μm; NMR (CD_3SOCD_3) δ 0.87 (s, 3 H, 20-CH_3), 1.13 (s, 3 H, 18-CH_3), 4.75 (br s, 2 H, 17-CH_2); HPLC, t_R = 13.4 min; neutralization equivalents, calcd, 371.8; found, 368.0. Anal. ($C_{38}H_{57}NO_{15}\cdot 2H_2O$) C, H. N.

19-*O*-[3-(Sodiophospho)propyl]steviolbioside (10). To a suspension of 10.1 g (50 mmol) of 3-bromopropane-1-phosphonic acid[20] in 500 mL of dry benzene was added portionwise 20.8 g (100 mmol) of PCl_5. The resultant solution was refluxed for 90 min after which the solvent was distilled from the reaction mixture to reduce the volume to ca. 25 mL. Fractional distillation of the residue then gave 10.8 g (90%) of 3-bromopropane-1-phosphonyl chloride as a colorless liquid: bp 79–81 °C (0.03 mm); NMR ($CDCl_3$) δ 1.90–3.20 (m, 4 H, $BrCCH_2CH_2P$), 3.54 (t, J = 6 Hz, 2 H, $BrCH_2$).

To a solution of 960 mg (4.00 mmol) of 3-bromopropane-1-phosphonyl chloride and 520 mg (4.40 mmol of pinacol in 10 mL of dry CH_2Cl_2 was added dropwise 1.24 mL (890 mg, 8.8 mmol) of Et_3N with stirring at 0 °C. After warming to ambient temperature over 2 h, the reaction mixture was poured into 50 mL of 5% HCl and extracted with EtOAc (3 × 25 mL). The combined extracts were washed with water (3 × 10 mL) and brine (1 × 10 mL), dried ($MgSO_4$), and concentrated to give 804 mg (70%) of pinacolyl 3-bromopropane-1-phosphonate as an amber oil. Preparative radial chromatography yielded a colorless viscous oil for an analytical sample: TLC ($CHCl_3/CH_3OH$, 95:5), R_f 0.38; IR (KBr) 7.96 (P=O) μm; NMR ($CDCl_3$) δ 1.37 (s, 6 H, cis OC-(CH_3)C(CH_3)O), 1.50 (s, 6 H, cis OC(CH_3)C(CH_3)O), 1.77–2.52 (m, 4 H, $BrCCH_2CH_2P$), 3.54 (t, J = 5 Hz, 2 H, $BrCH_2$). Anal. ($C_9H_{18}BrO_3P$) C, H, P.

Two millimoles (1.28 g) of steviolbioside was added to a solution–suspension of 305 mg (2.20 mmol) of K_2CO_3 and 627 mg (2.20 mmol) of pinacolyl 3-bromopropane-1-phosphonate in 20 mL of DMF and the resultant reaction mixture stirred at 40 °C for 24 h. Additional portions of K_2CO_3 and alkyl bromide were added, and stirring continued at 40 °C until all steviolbioside (R_f 0.33) had been consumed as shown by TLC analysis ($CHCl_3/CH_3OH/H_2O$, 15:8:1). The reaction mixture was then diluted with 50 mL of water, neutralized by addition of 5% HCl, and concentrated to dryness to yield the phosphonic acid ester as a tan solid. This intermediate was then dissolved in 55 mL of 10% KOH and the resultant solution refluxed until (40 h) HPLC analysis of an aliquot indicated presence of one product (t_R = 13.7 min). After cooling, the reaction mixture was then neutralized with 5% HCl and concentrated to dryness. The crude product was fractionated and converted to the Na salt by chromatography over

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400 g of Bio-Rad AG MP 50 (Na) ion-exchange resin. This product was desalted by chromatography over Bio-Rad AG 11A8 ion-retardation resin and recrystallized (EtOH) to yield 491 mg of colorless clusters: mp 200–260 °C dec; TLC ($CHCl_3/CH_3OH/H_2O$, 15:10:2), *Rf* 0.22; IR (KBr) 2.90 (OH), 5.86 (C=O) μm; NMR (CD_3SOCD_3) δ 0.82 (s, 3 H, 20-CH_3), 1.12 (s, 3 H, 18-CH_3), 4.78 (br s, 2 H, 17-CH_2); neutralization equivalents, calcd, 786.8; found, 789. Anal. ($C_{35}H_{56}NaO_{16}P\cdot 5H_2O$) C, H, P.

19-*O*-[3,3-Bis(sodiosulfo)propyl]steviolbioside (11). To a solution of 1.22 g (10.0 mmol) of 1,3-propanesultone in 20 mL of dry THF was added 4.4 mL of 2.4 M *n*-butyllithium in hexane (10.5 mmol) with stirring at −78 °C. After 45 min, a solution of 1.89 g (11.0 mmol) of catechol sulfate[15] in 10 mL of THF was added dropwise. The resultant reaction mixture was stirred at −78 °C for 30 min and was then poured onto a mixture of 250 mL of 10% H_2SO_4 and 250 g of ice. Extraction of the resulting aqueous mixture with ether (3 × 100 mL) followed by drying the combined extracts ($MgSO_4$) and concentrating yielded 2.93 g of crude catecholyl 3-sulfo-1,3-propanesultone as a viscous oil. Preparative radial chromatography yielded 1.19 g (40%) of this pure compound as a light yellow oil: IR (KBr) 2.86 (OH), 7.30 (S=O) μm; NMR ($CDCl_3$) δ 3.15 (q, *J* = 7 Hz, 2 H, $OCCH_2CS$), 4.23–4.90 (m, 2 H, OCH_2), 5.16 (t, *J* = 7 Hz, 1 H, CHS), 5.90 (br s, 1 H, OH), 6.76–7.53 (m, 4 H, Ar H).

To a solution of 1.72 g (2.68 mmol) of steviolbioside in 20 mL of DMF was added 5.2 mL of 0.51 M potassium *tert*-amyl oxide in toluene solution (2.68 mmol). To the potassium salt solution–suspension thus obtained was added 1.05 g (2.68 mmol) of catecholyl 3-sulfo-1,3-propanesultone as a solution in 5 mL of DMF. After stirring of the resultant reaction mixture for 24 h, it was concentrated to dryness. The residue was dissolved in 25 mL of water to give a solution, which was neutralized by addition of 5% HCl. Concentration yielded 4.30 g of an amber solid. Preparative radial chromatography ($CHCl_3/CH_3OH/H_2O$) of this crude product yielded 1.41 g (49%) of pure catecholyl 19-*O*-(3-sulfo-3-kaliosulfopropyl)steviolbioside. Recrystallization from water/CH_3OH yielded an analytical sample: mp 185–190 °C dec; IR (KBr) 2.95 (OH), 5.86 (C=O), 6.02 (C=C) μm; NMR (CD_3SOCD_3) δ 0.76 (s, 3 H, 20-CH_3), 1.07 (s, 3 H, 18-CH_3), 4.14 (m, 1 H SCHS), 4.47 (t, *J* = 6 Hz, 2 H, $COOCH_2$), 4.75 (br s, 1 H, 17-H), 4.84 (br s, 1 H, 17-H), 6.7–7.4 (m, 4 H, Ar H), 9.85 (s, 1 H, Ar OH). Anal. ($C_{41}H_{59}KO_{20}S_2$) C, H, S.

To a suspension-solution of 878 mg (0.90 mmol) of catecholyl 19-*O*-(3-sulfo-3-kaliosulfopropyl)steviolbioside in 88 mL of distilled water was added 1.5 mL of 1.00 M KOH. The resulting solution was refluxed for 8 h at which point TLC analysis ($CHCl_3/CH_3OH/H_2O$, 15:10:2) indicated complete consumption of starting material (R_f 0.60) to yield one product (R_f 0.24). After cooling, the solution was neutralized with 10% H_2SO_4 and concentrated to dryness. The product was extracted from the residue with hot CH_3OH. The CH_3OH extract was concentrated to dryness and triturated with EtOAc to remove catechol. Preparative radial chromatography of the resultant material gave 0.70 g of crude 11 (K salt). Ion-exchange chromatography [Bio-Rad AG MP 50 (Na)] of the potassium salt then yielded the sodium salt. Finally, recrystallization (CH_3OH/H_2O) yielded 480 mg (60%) of pure 11 as white granules: mp 200–225 °C dec; HPLC (10–40% MeCN in 0.005 M $Ca(OAc)_2$) t_R = 8.8 min; IR (KBr) 2.93 (OH), 5.87 (C=O), 6.10 (C=C), 8.3 (S=O), 9.6 (S=O) μm; NMR (CD_3SOCD_3) δ 0.82 (s, 3 H, 20-CH_3), 1.13 (s, 3 H, 18-CH_3), 4.75 (br s, 1 H, 17-H), 4.88 (br s, 1 H, 17-H). Anal. ($C_{35}H_{54}Na_2O_{19}S_2$) C, H, S.

19-*O*-[(Sodiosulfo)propyl]rebaudioside B (13). A solution–suspension of 553 mg (0.687 mmol) of rebaudioside B,[21] 104 mg (0.75 mmol) of K_2CO_3, and 105 mg (0.86 mmol) of 1,3-propanesultone in 5 mL of DMF was stirred at ambient temperature for 64 h. TLC analysis ($CHCl_3/CH_3OH/H_2O$, 15:10:2) of an aliquot removed at this time indicated the complete consumption of starting material (R_f 0.38) to give one product (R_f 0.22). Ten milliliters of 10% KOH was then added and the resulting solution stirred at 40 °C overnight. After neutralization with 5% HCl, the solution was concentrated to dryness. Extraction of the residue with CH_3OH yielded 556 mg of a white solid. This product was converted to the Na salt by ion-exchange chromatography over a column of 400 g of Bio-Rad AG MP 50 (Na) ion-exchange resin. Recrystallization (CH_3OH) then yielded 399 mg (61%) of **13** as colorless granules: mp 235–250 °C dec; IR (KBr) 2.93 (OH), 5.84 (C=O), 6.04 (C=C), 8.6 (S=O), 9.5 (S=O) μm; NMR (CD_3SOCD_3) δ 0.81 (s, 3 H, 20-CH_3), 1.13 (s, 3 H, 18-CH_3), 4.02 (t, *J* = 7 Hz, 2 H, $COOCH_2$); neutralization equivalents, calcd, 949; found, 939. Anal. ($C_{41}H_{65}NaO_{21}S\cdot 2H_2O$) C, H, S.

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Registry No. **1**, 57817-89-7; **2**, 79184-06-8; **3**, 58543-16-1; **4**, 41093-60-1; **4**·Na, 79200-40-1; **4** (sulfobutyl ester), 93000-21-6; **5**·Na, 92206-66-1; **5** (ethyl ester, heptaacetate derivative), 93000-20-5; **6**, 92206-59-2; **7**·2Na (isomer 1), 93060-53-8; **7**·2Na (isomer 2), 93060-54-9; **7** (dimethyl ester), 92206-63-8; **8**, 92206-65-0; **9**, 93000-17-0; **10**, 93000-18-1; **11**, 92206-68-3; **11**·2K, 93000-27-2; **12**, 58543-17-2; **12**·Na, 85071-21-2; **13**, 93000-19-2; **15**, 93000-25-0; **17**, 84311-62-6; ethyl chloroacetate, 105-39-5; 19-*O*-(carboethoxymethyl)steviolbioside, 92206-67-2; 1,4-butane sultone, 1633-83-6; dimethyl 2-bromoglutarate, 760-94-1; methyl 2-[(benzyloxycarbonyl)amino]-4-bromobutanoate, 76338-91-5; 19-*O*-[3-[(benzyloxycarbonyl)amino]-3-carbomethoxypropyl]steviolbioside, 93000-22-7; methyl 2,4-dibromobutyrate, 29547-04-4; 19-*O*-(1-carbomethoxy-3-azidopropyl)steviolbioside, 93000-23-8; 19-*O*-(1-carboxy-3-azidopropyl)steviolbioside, 93000-24-9; 3-bromopropane-1-phosphonic acid, 1190-09-6; 3-bromopropane-1-phosphonyl chloride, 64371-20-6; pinacol, 76-09-5; 1,3-propanesultone, 1120-71-4; catechol sulfate, 4918-96-1; catecholyl 19-*O*-(3-sulfo-3-kaliosulfopropyl)steviolbioside, 93000-26-1.

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