Easy Access to Derivatives of 2-(Hydroxymethyl)propane-1,2,3-triol (Isoerythritol) with up to Four Separately Addressable Functionalities

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Keywords: Allylic compounds / Alcohols / Sulfur heterocycles / Hydroxylation / Nucleophilic substitution

5-Methylene-2-oxo[1,3,2]dioxathiane (**2**) was obtained in 91% yield from 2-methylenepropane-1,3-diol (**1**) and thionyl chloride. The cyclic sulfite **2** reacts with a variety of nucleophiles to give formally monosubstituted products **3** of the diol **1** in 62–77% yield. Oxidation of **2** with $RuCl_3/NaIO_4$ yields the diprotected tetraol 5-(hydroxymethyl)-2,2-dioxo[1,3,2]-dioxathian-5-ol (**7**) in 86% yield, which can be used to easily access tetrafunctional derivatives of 2-(hydroxymethyl)propane-1,2,3-triol (isoerythritol); for example, acetylation with acetic anhydride furnishes in 96% yield the primary acetate **11**, which reacts with potassium cyanide and sodium azide to give the 2-cyano- and 2-(azidomethyl)propane-1,2,3-triol monoacetates **12a**,**b** (78 and 82% yield, respectively).

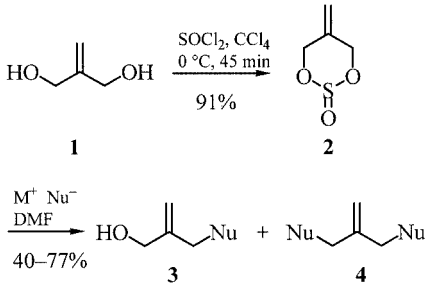
Introduction

Trifunctional building blocks obtained by formal monosubstitution of one hydroxy group in 2-methylenepropane-1,3-diol[1] (**1**) have been applied for a variety of synthetic purposes. 3-Amino-2-methylenepropan-1-ol has been used as a starting material in the synthesis of carbapenem antibiotics.[2] A monoester of **1** has served as a precursor to type I and IV cyanolipids,[3] and monocarbonates have served[4] as bis(allylic) templates for Pd^0-catalyzed solid-phase syntheses of tertiary amines. A monosulfone derived from **1** can be transformed into a dianion, which reacts with electrophiles chemoselectively.[5] A diethyl allylmalonate derivative of **1** has been subjected to a ring-closing metathesis (RCM) reaction.[6] In most cases,[3,4,6] the syntheses were achieved in moderate yields by the reaction of an appropriate derivative of **1** with 1 equiv. of the reagent and subsequent separation from the disubstitution product. Only a few examples of selective syntheses of formally monosubstituted products of **1**[7] are known. 4-Methylene[1,2]oxasilolanes, generated by radical ring closure of propargyl silyl ethers, undergo ring opening to formal monosilyl-substitution products of **1**, and the cyclic carbonate[8] of **1** — which has been reported to be accessible from the diol, although without any experimental details having been reported, including the yield[9] — has been used to prepare the monosulfonyl derivative in a palladium-catalyzed substitution reaction with sodium *p*-toluenesulfinate. Despite the wide use, however, of formal monosubstitution products of 2-methylenepropane-1,3-diol (**1**), no general method for their selective preparation has been described.

Results and Discussion

The most frequently applied selective functionalization of one hydroxy group in a 1,3-diol proceeds via the corresponding cyclic sulfate.[10] Attempts to prepare the cyclic sulfate of **1** directly by reaction with sulfuryl chloride[11] or *N*,*N*′-sulfuryldiimidazole[12] proved to be futile. Routinely, cyclic sulfates of 1,3-diols are prepared by oxidizing the corresponding cyclic sulfite.[13] Indeed, we found that the cyclic sulfite of **1**, 5-methylene-2-oxo[1,3,2]dioxathiane (**2**), is easily accessible, and it turned out to react readily with a variety of nucleophilic reagents in a selective manner.

Treatment of the commercially available 2-methylenepropane-1,3-diol[1] (**1**) with thionyl chloride in tetrachloromethane gave 5-methylene-2-oxo[1,3,2]dioxathiane (**2**) in 91%



Scheme 1. Preparation of 5-methylene-2-oxo[1,3,2]dioxathiane (**2**) and its reaction with different nucleophiles; for details, see Table 1

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  DOI: 10.1002/ejoc.200200099

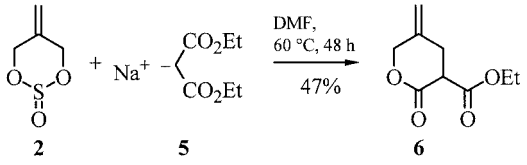
Table 1. Reaction of 5-methylene-2-oxo[1,3,2]dioxathiane (**2**) in DMF with various nucleophiles

Reagent	Temp. [°C] (time [h])	Product	Nu	Yield (%)
NaN_3	80 (0.25)	**3a**	N_3	77
KNPhth[a]	100 (1)	**3b**	NPhth	69
NaOPh	50 (2.5)	**3c**	OPh	69[b]
NaOAc	100 (1)	**3d**	OAc	69[c]
$NaCH(CO_2Et)$	60 (3)	**3e**	$CH(CO_2Et)_2$	40[d]
$NaCH(CO_2Et)$	60 (48)	**6**	$CH(CO_2Et)_2$	47[e]

[a] Phth = phthalimidoyl. [b] Plus 6% of disubstitution product **4c**. [c] Plus 9% of disubstitution product **4d**. [d] Plus 14% of δ-lactone **6**. [e] 2 equiv. of diethyl sodiomalonate were used, 9% of **3e** was also isolated.

yield. This clean transformation of **1** into **2** could be achieved only in tetrachloromethane (Scheme 1), because the use of other solvents, as well as the addition of a base, led mainly to the formation of oligomers and chlorides. Only in tetrachloromethane is the solubility of the evolving hydrogen chloride low enough[14] to prevent these side reactions. The reaction of **2** with a number of nucleophiles proceeded best in dimethylformamide (DMF) to yield the monosubstitution products **3** cleanly in most cases (Scheme 1 and Table 1).

With sodium azide and potassium phthalimide, only the desired monosubstitution products **3a**,**b** were formed in good yields. The reactions with sodium phenolate and sodium acetate gave the products **3c**,**d** in similar yields, but they were accompanied by the corresponding disubstitution products **4c**,**d** (6 and 9%, respectively). When **2** was treated with the sodium enolate of diethyl malonate **5** at 60 °C for 3 h, a mixture of the expected monosubstitution product **3e** and the δ-lactone **6** was obtained. The latter was apparently formed by subsequent intramolecular transesterification of **3e**. By extending the reaction time to 48 h at 60 °C, the δ-lactone **6** was isolated in 47% yield (Scheme 2).

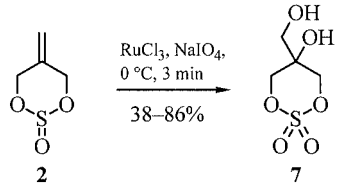


2 **5** **6**

Scheme 2. Reaction of 5-methylene-2-oxo[1,3,2]dioxathiane (**2**) with diethyl sodiomalonate

Thus, the cyclic sulfite **2** of 2-methylenepropane-1,3-diol (**1**), which is easily obtained from the diol **1** in high yield, can be used to prepare formal monosubstitution products of **1**.[15] These products **3** all contain an allylic alcohol moiety that is accessible to further elaboration, e.g., by palladium-catalyzed nucleophilic substitution[16] of an appropriate ester derived from them. Even the previously unknown δ-lactone **6** is an ester that should be prone to undergo further selective transformations.

In an attempt to oxidize the cyclic sulfite **2** to the corresponding sulfate by treatment with in situ generated ruthenium tetroxide,[13] we achieved both oxidation of the sulfur atom and dihydroxylation of the double bond[17] at the same time.[18] The yield of this transformation turned out to depend highly on the solvent system used.[19] Routinely, a two-phase solvent system is employed to extract the formed product into the organic phase where it will be protected from further oxidation.[17a] In the case of 5-(hydroxymethyl)-2,2-dioxo[1,3,2]dioxathian-5-ol (**7**) — which, because of its high polarity, is soluble in water, but not in a majority of organic solvents — the best yield of **7** (86%) was obtained in a homogeneous mixture (6:1) of acetonitrile and water (Scheme 3, Table 2).[19]



2 **7**

Scheme 3. Oxidation of 5-methylene-2-oxo[1,3,2]dioxathiane (**2**) to 5-(hydroxymethyl)-2,2-dioxo[1,3,2]dioxathian-5-ol (**7**); for details, see Table 2

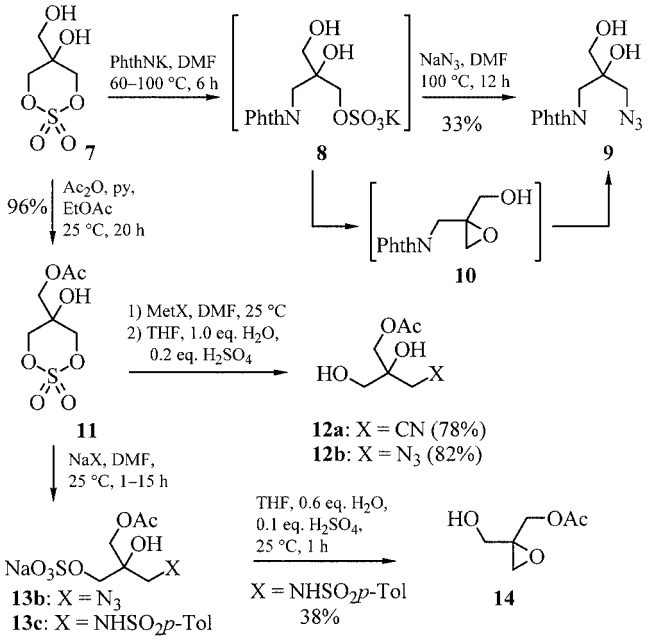
Table 2. Optimization of the solvent system for the oxidation of **2** to yield **7**

Entry	Solvents (ratio)	Yield of **7** (%)
1	CCl_4/MeCN/H_2O (3:3:1)[a]	54
2	CCl_4/MeCN/H_2O (1:1:1)	38
3	MeCN/H_2O (1:1)	41
4	MeCN/Et_2O/H_2O (3:3:1)	54
5	MeCN/H_2O (6:1)	86

[a] Solvent mixture routinely employed for the oxidation of sulfites.[13]

To demonstrate some possible further selective transformations, **7** was sequentially treated with various combinations of two nucleophiles (PhthNK, NaN_3, NaOAc, NaOPh), but the only successful reaction sequence that we achieved was with potassium phthalimide and sodium azide in DMF to furnish the phthalimidoazide **9**, albeit in only 33% yield (Scheme 4). This formal double-substitution product may well have been formed via the epoxide **10**. When the primary hydroxy group was protected by acetylation with acetic anhydride in pyridine/ethyl acetate, the opening of the cyclic sulfate moiety in the resulting acetate **11** with potassium cyanide and sodium azide led to the corresponding monosubstitution products, with a sulfate group

on one primary hydroxy group, that were hydrolyzed upon aqueous workup to give the monoacetylated triols **12a**,**b** in 78 and 82% yield, respectively.



Scheme 4

Nucleophilic ring opening with a number of nucleophiles yielded the corresponding open-chain sulfates **13** almost quantitatively, but the selective hydrolysis of the sulfate moiety turned out to be difficult in certain cases.[20] Thus, the sulfate **13** resulting from **11** and sodium *p*-toluenesulfonylamide gave (acetoxymethyl)glycidol (**14**)[21] unexpectedly as the only product in 38% isolated yield. Apparently, the *p*-toluenesulfonylamide moiety is protonated under the acidic conditions and then acts as a leaving group in an intramolecular substitution by a hydroxy group. Therefore, investigations of possible functionalizations of **11** will require further elaboration.

Conclusion

The 5-(hydroxymethyl)-2,2-dioxo[1,3,2]dioxathian-5-ol (**7**) is a formal derivative of 2-(hydroxymethyl)propane-1,2,3-triol, also called isoerythritol.[22] Derivatives of isoerythritol have come to prominent attention as acyclic nucleoside analogues[23] and as GABA analogues.[24] With use of the formal isoerythritol derivative **11**, each of the primary hydroxy functions of isoerythritol may selectively be addressed.

Experimental Section

General Remarks: ^{1}H and ^{13}C NMR: Spectra were recorded with a Bruker AM 250 instrument at 250 MHz (^{1}H) and 62.9 MHz [^{13}C, additional DEPT (Distortionless Enhancement by Polarization Transfer)]. Chemical shifts in $CDCl_3$ are reported in δ values relative to tetramethylsilane (δ = 0.00 ppm), with residual $CHCl_3$ (δ = 7.26 ppm) and $CDCl_3$ (δ = 77.0 ppm) used as internal standards for ^{1}H and ^{13}C NMR spectra, respectively, unless otherwise stated. IR spectra were recorded with a Bruker IFS 66 instrument, measured as KBr pellets or oils between KBr plates. Low-resolution EI mass spectra were obtained with a Varian-MAT 731. Elemental analyses were performed by the Mikroanalytisches Laboratorium, Institut für Organische Chemie, Universität Göttingen. Melting points are uncorrected. TLC analyses were performed using Macherey−Nagel precoated plates, 0.25 mm Sil G/UV_{254}. Preparative column chromatography was performed on Merck silica gel 60 (63−200 μm). All reactions were carried out under dry nitrogen or argon in oven- and/or flame-dried glassware. Solvents were dried according to commonly used procedures.

5-Methylene-2-oxo[1,3,2]dioxathiane (2): A solution of thionyl chloride (8.33 g, 70.0 mmol) in tetrachloromethane (15 mL) was added under vigorous stirring to an emulsion of 2-methylenepropane-1,3-diol (**1**, 4.15 g, 47.2 mmol) in tetrachloromethane (30 mL) at 0 °C. When the evolution of hydrogen chloride had ceased after approximately 30 min, the solution was stirred for an additional 15 min. Evaporation of the solvent at 0 °C and 5 mbar, followed by kugelrohr distillation (b.p. 90−110 °C/10 Torr) yielded **2** as a colorless liquid (5.77 g, 43.1 mmol, 91%). IR (film): $\tilde{\nu}$ = 3088, 2991, 2938, 2873, 1461, 1446, 1416, 1342, 1300, 1239, 1195, 1177, 982, 958, 926, 870, 759, 717, 692, 663 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 4.24 [d, ^2J = 12.9 Hz, 2 H, 4(6)-H], 5.14 (s, 2 H, =CH_2), 5.35 [d, ^2J = 12.9 Hz, 2 H, 4(6)-H] ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ = 61.6 [−, C-4(6)], 114.4 (−, =CH_2), 135.5 (C_{quat}, C-5) ppm. MS (EI, 70 eV): *m*/*z* (%) = 134 (6) [M^+], 70 (50), 69 (24), 42 (100), 41 (82). $C_4H_6O_3S$ (134.15): calcd. C 35.81, H 4.51; found C, 36.11, H 4.51.

2-(Azidomethyl)prop-2-en-1-ol (3a): Sodium azide (233 mg, 3.58 mmol) was added to a solution of **2** (400 mg, 2.98 mmol) in DMF (3 mL), and then the mixture was heated to 80 °C. After 15 min, the reaction was quenched by addition of water (20 mL). The aqueous phase was extracted with diethyl ether (3 × 10 mL), the combined organic extracts were washed with water, dried with anhydrous $MgSO_4$, and concentrated under reduced pressure. Flash chromatography (25 g of silica gel, light petroleum ether/ethyl acetate, 65:35, R_f = 0.23) then gave **3a** as a colorless liquid (258 mg, 2.28 mmol, 77%). IR (film): $\tilde{\nu}$ = 3270 (OH), 2937, 2877, 2100, 1659, 1455, 1440, 1244, 1068, 1033, 915, 883 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.72 (s, 1 H, OH), 3.86 (s, 2 H, CH_2N_3), 4.19 (s, 2 H, 1-H), 5.18 (s, 1 H, 3-H), 5.28 (s, 1 H, 3-H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ = 53.3 (−, CH_2N_3), 64.0 (−, C-1), 114.6 (−, C-3), 142.7 (C_{quat}, C-2) ppm. MS (CI, NH_3): *m*/*z* (%) = 148 (72) [M + NH_4^+ + NH_3], 131 (100) [M + NH_4^+]. $C_4H_7N_3O$ (113.11): calcd. C 42.47, H 6.24, N 37.15; found C, 42.67, H 6.18, N 37.00.

***N*-[2-(Hydroxymethyl)allyl]phthalimide (3b):** Potassium phthalimide (1.38 g, 7.45 mmol) was added to a solution of **2** (500 mg, 3.73 mmol) in DMF (2 mL), and then the resulting suspension was stirred at 100 °C. After 1 h, the reaction was quenched with water (14 mL). The aqueous phase was extracted with diethyl ether (3 × 10 mL), and the combined organic extracts were washed with water, dried with anhydrous $MgSO_4$, and concentrated under reduced pressure. Flash chromatography (60 g of silica gel, petroleum ether/ethyl acetate, 70:30, R_f = 0.17) then gave **3b** as colorless crystals (558 mg, 2.57 mmol, 69%), m.p. 83 °C. IR (KBr): $\tilde{\nu}$ = 3509 (OH), 3103, 2924, 2799, 1764, 1699, 1435, 1397, 1331, 1174, 1116, 1090, 1061, 950, 911, 729, 712 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ =

2.44 (t, ^3J = 6.2 Hz, 1 H, OH), 4.13 (d, ^3J = 6.2 Hz, 2 H, CH_2OH), 4.36 (s, 2 H, 1-H), 5.11 (d, ^2J = 0.5 Hz, 1 H, 3-H), 5.18 (d, ^2J = 0.5 Hz, 1 H, 3-H), 7.71−7.76 (m, 2 H), 7.83−7.88 (m, 2 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ = 39.5 (−, C-1), 64.2 (−, CH_2OH), 114.1 (−, C-3), 123.4 (+), 131.9 (C_{quat}), 134.2 (+), 142.9 (C_{quat}), 168.3 (C_{quat}) ppm. MS (EI, 70 eV): *m/z* (%) = 217 (5) [M^+], 160 (37), 130 (40), 104 (58), 77 (72), 76 (100) [$C_6H_4^+$], 50 (50), 41 (45). $C_{12}H_{11}NO_3$ (217.22): calcd. C 66.35, H 5.10, N 6.45; found C, 66.13, H 4.93, N 6.38.

2-(Phenoxymethyl)prop-2-en-1-ol (3c) and 3-Phenoxy-2-(phenoxymethyl)propene (4c): A suspension of sodium hydride (64.4 mg, 2.68 mmol) in THF (3 mL) was cooled to 0 °C and treated with phenol (253 mg, 2.69 mmol). After the evolution of hydrogen had ceased, the solvent was evaporated under reduced pressure, and the resulting sodium phenolate was dissolved in DMF (2 mL). This solution was added to a solution of **2** (300 mg, 2.24 mmol) in DMF (1 mL), and the reaction mixture was stirred at 50 °C. After 2.5 h, the reaction was quenched with water (20 mL). The aqueous phase was extracted with diethyl ether (3 × 10 mL), and the combined organic extracts were washed with water, dried with anhydrous $MgSO_4$, and concentrated under reduced pressure. Flash chromatography (30 g of silica gel, petroleum ether/ethyl acetate, 75:25) yielded two fractions. Fraction I (R_f = 0.22) provided **3c** as a colorless liquid (255 mg, 1.55 mmol, 69%). IR (film): ṽ = 3346 (OH), 3064, 3040, 2923, 2868, 1599, 1587, 1496, 1457, 1400, 1241, 1172, 1079, 1060, 1031, 916, 754, 691 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.74 (s, 1 H, OH), 4.27 (s, 2 H, 1-H), 4.60 (s, 2 H, CH_2OPh), 5.29 (s, 2 H, 3-H), 6.92−7.00 (m, 3 H), 7.26−7.32 (m, 2 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ = 63.9 (−, C-1), 68.9 (−, CH_2OPh), 113.7 (−, C-3), 114.6 (+), 121.0 (+), 129.4 (+), 144.1 (C_{quat}, C-2), 158.4 (C_{quat}) ppm. MS (EI, 70 eV): *m/z* (%) = 164 (30) [M^+], 145 (29), 133 (32), 131 (23), 95 (30), 94 (100) [$C_6H_6O^+$], 77 (20), 43 (18), 41 (30). $C_{10}H_{12}O_2$·0.5H_2O (173.21): calcd. C 69.34, H 7.57; found C 69.16, H 7.63. Fraction II (R_f = 0.67) provided **4c** as a colorless liquid (21 mg, 87 μmol, 6%). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 4.65 (s, 4 H, 3-H), 5.42 (s, 2 H, 1-H), 6.90−7.02 (m, 6 H, Ph-H), 7.25−7.37 (m, 4 H, Ph-H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ = 68.5 (−, C-3), 114.7 (+), 115.7 (−, C-1), 121.00 (+), 129.4 (+), 140.4 (C_{quat}, C-2), 158.5 (C_{quat}) ppm. $C_{16}H_{16}O_2$ (240.30): calcd. C 79.97, H 6.71; found C 79.74, H 7.02.

2-(Acetoxymethyl)prop-2-en-1-ol (3d) and 1,3-Diacetoxy-2-methyleneпropane (4d): Sodium acetate (367 mg, 4.47 mmol) and 18-crown-6 (6.0 mg, 23 μmol) was added to a solution of **2** (300 mg, 2.24 mmol) in DMF (3 mL). The reaction mixture was stirred for 1 h at 100 °C. The mixture was cooled to room temp. and then hydrolyzed with water (10 mL). The aqueous phase was extracted with ethyl acetate (3 × 10 mL), and the combined organic extracts were washed with water, dried with anhydrous $MgSO_4$, and concentrated under reduced pressure. Flash chromatography (20 g of silica gel, petroleum ether/ethyl acetate, 50:50) yielded two fractions. Fraction I (R_f = 0.45) provided **3d** as a colorless liquid (201 mg, 1.55 mmol, 69%). IR (film): ṽ = 3433 (OH), 3095, 2936, 2875, 1744, 1660, 1455, 1376, 1243, 1029, 951, 916, 844 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.91 (br. s, 1 H, OH), 2.10 (s, 3 H, COCH_3) 4.14 (s, 2 H, 1-H), 4.64 (s, 2 H, CH_2OAc), 5.18 (s, 1 H, 3-H), 5.24 (s, 1 H, 3-H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ = 20.9 (+, CO*C*H$_3$), 63.7 (−, C-1), 64.7 (−, *C*H$_2$OAc), 114.4 (−, C-3), 143.3 (C_{quat}, C-2), 171.0 (C_{quat}, *C*OMe) ppm. MS (CI, NH_3): *m/z* (%) = 165 (15) [M + NH_4^+ + NH_3], 148 (100) [M + NH_4^+], 131 (5) [M + H^+]. Fraction II (R_f = 0.65) provided **4d** as a colorless liquid (35 mg, 203 μmol, 9%). Spectral data are in agreement with those reported previously.[15b]

Diethyl 2-[2-(Hydroxymethyl)allyl]malonate (3e) and Ethyl 5-Methylene-2-oxotetrahydropyran-3-carboxylate (6): A suspension of sodium hydride (168 mg, 7.00 mmol) in THF (5 mL) was treated at 0 °C with a solution of diethyl malonate (1057 mg, 6.60 mmol) in THF (2 mL). After the evolution of hydrogen had ceased, the solvent was removed under reduced pressure, and the resulting diethyl sodiomalonate was dissolved in DMF (5 mL). This solution was added to a solution of 5-methylene[1,3,2]dioxathian-2-one (**2**, 737 mg, 5.50 mmol) in DMF (2.5 mL), and then the reaction mixture was stirred at 60 °C. After 3 h, the reaction was quenched with water (50 mL). The aqueous phase was extracted with diethyl ether (3 × 10 mL), and the combined organic extracts were washed with water, dried with anhydrous $MgSO_4$, and concentrated under reduced pressure. Flash chromatography (50 g of silica gel, hexane/ethyl acetate, 75:25) gave two fractions. Fraction I (R_f = 0.19) provided diethyl 2-[2-(hydroxymethyl)allyl]malonate (**3e**) as a colorless liquid (505 mg, 2.19 mmol, 40%). IR (film): ṽ = 3448 (OH), 3081, 2984, 2938, 2874, 1734, 1653, 1466, 1447, 1393, 1370, 1335, 1234, 1153, 1036, 908, 860, 790 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.26 (t, ^3J = 7.1 Hz, 6 H) 1.75 (br. s, 1 H, OH), 2.69 (d, ^3J = 7.8 Hz, 2 H, 1-H), 3.65 (t, ^3J = 7.8 Hz, 1 H, C*H*CO$_2$Et), 4.10 (br. s, 2 H, CH_2OH), 4.22 (q, ^3J = 7.1 Hz, 4 H), 4.93 (s, 1 H, 3-H), 5.10 (s, 1 H, 3-H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ = 14.0 (+), 31.7 (−, C-1), 50.7 (+, *C*HCO$_2$Et), 61.5 (−, CO$_2$*C*H$_2$), 65.8 (−, CH_2OH), 112.4 (−, C-3), 145.1 (C_{quat}, C-2), 169.0 (C_{quat}, *C*O$_2$Et) ppm. MS (EI, 70 eV): *m/z* (%) = 230 (1) [M^+], 185 (35), 160 (90), 139 (40), 111 (100), 82 (27), 67 (20), 55 (22), 41 (15). $C_{11}H_{18}O_5$ (230.26): calcd. C 57.38, H 7.88; found C 57.12, H 7.62. Fraction II (R_f = 0.29) provided ethyl 5-methylene-2-oxotetrahydropyran-3-carboxylate (**6**) as a colorless liquid (141 mg, 766 μmol, 14%). IR (film): ṽ = 3085, 2986, 2939, 1735, 1660, 1467, 1444, 1379, 1345, 1244, 1203, 1149, 1042, 913, 857, 831, 749 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.26 (t, ^3J = 7.1 Hz, 3 H) 2.84 (dd, ^2J = 16.1, ^3J = 6.9 Hz, 1 H, 4-H), 3.05 (dd, ^2J = 16.1, ^3J = 8.5 Hz, 1 H, 4-H), 3.66 (dd, ^3J = 8.5, ^3J = 6.9 Hz, 1 H, 3-H), 4.19−4.31 (m, 2 H, CH_2Me), 4.79 (s, 2 H, 6-H), 5.11−5.14 (m, 2 H, =CH_2) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ = 14.0 (+), 29.3 (−, C-4), 47.2 (+, C-3), 62.1 (−), 71.9 (−, C-6), 113.4 (−, =CH_2), 135.7 (C_{quat}, C-5), 167.6 (C_{quat}), 168.0 (C_{quat}) ppm. MS (EI, 70 eV): *m/z* (%) = 184 (3) [M^+], 138 (17), 111 (100), 82 (17), 67 (20), 55 (12). $C_9H_{12}O_4$ (184.19): calcd. C 58.69, H 6.57; found C 58.92, H 6.55. According to the procedure above — starting with sodiomalonate, prepared as described above from diethyl malonate (721 mg, 4.50 mmol) in DMF (4.5 mL), and compound **2** (300 mg, 2.24 mmol) in DMF (1 mL) — the reaction mixture after 48 h was diluted with EtOAc (50 mL) and poured into 10% aqueous H_2SO_4 (50 mL). The organic phase was washed with H_2O (30 mL), brine (30 mL), and dried with $MgSO_4$. Evaporation of the solvent and chromatography (30 g of silica gel, hexane/ethyl acetate, 75:25) gave two fractions. Fraction I (R_f = 0.19) provided diethyl 2-[2-(hydroxymethyl)allyl]malonate (**3e**) as a colorless liquid (45 mg, 196 μmol, 9%). Fraction II (R_f = 0.29) provided ethyl 5-methylene-2-oxotetrahydropyran-3-carboxylate (**6**) as a colorless liquid (193 mg, 1.05 mmol, 47%).

5-(Hydroxymethyl)-2,2-dioxo[1,3,2]dioxathian-5-ol (7): A solution of ruthenium(III) chloride (15 mg, 72 μmol) and sodium periodate (1.59 g, 7.45 mmol) in water (10 mL) was added to a solution of 5-methylene-2-oxo[1,3,2]dioxathiane (**2**, 500 mg, 3.73 mmol) in acetonitrile (60 mL) at 0 °C. After 3 min, the mixture was filtered through Celite (1 cm), and the solvent was evaporated under reduced pressure. Flash chromatography (15 g of silica gel, light petroleum ether/EtOAc, 35:65, R_f = 0.26) gave **7** as colorless crystals (591 mg, 86%), m.p. 94−96 °C. IR (KBr): ṽ = 3399 (OH),

2959, 1453, 1391, 1354, 1316, 1197, 1152, 1111, 1032, 997, 979, 921, 901, 847, 806, 782, 690 cm^{-1}. ^1H NMR (250 MHz, [D$_6$]DMSO): δ = 3.34 (s, 2 H, CH_2OH), 4.42 [d, ^2J = 10.6 Hz, 2 H, 4(6)-H], 4.79 [d, ^2J = 10.6 Hz, 2 H, 4(6)-H], 5.24 (br. s, 1 H, OH), 5.73 (br. s, 1 H, OH) ppm. ^{13}C NMR (62.9 MHz, [D$_6$]DMSO, DEPT): δ = 62.4 (−, CH_2OH), 66.4 (C_{quat}, C-5), 79.0 [−, C-4(6)] ppm. MS (CI, NH_3): *m/z* (%) = 403 (3) [2 M + NH_3 + NH_4^+], 386 (10) [2 M + NH_4^+], 236 (22) [M +2 NH_3 + NH_4^+], 219 (100) [M + NH_3 + NH_4^+], 202 (16) [M + NH_4^+]. $C_4H_8O_6S$ (184.16): calcd. C 26.09, H 4.38; found C 26.20, H 4.32.

***N*-[2-(Azidomethyl)-2,3-dihydroxypropyl]phthalimide (9):** Potassium phthalimide (185 mg, 1.0 mmol) was added to a solution of 5-(hydroxymethyl)-2,2-dioxo[1,3,2]dioxathian-5-ol (**7**, 94 mg, 0.51 mmol) in DMF (1.5 mL), and the resulting mixture was stirred at 60 °C for 4 h and then at 100 °C for 2 h. Sodium azide (65 mg, 1.0 mmol) was then added and the mixture was stirred at 100 °C. After 2 h, the reaction was quenched by adding a mixture of water and brine (1:1, 20 mL). The aqueous phase was extracted with ethyl acetate (3 × 10 mL), and the combined organic extracts were washed with brine, dried with anhydrous $MgSO_4$, and concentrated under reduced pressure. The solid residue (129 mg) was recrystallized from ether/hexane to provide **9** as colorless crystals (45 mg, 33%), m.p. 80−81 °C. IR (KBr): ṽ = 3478, 3400, 3333, 3099, 3045, 3029, 2182, 2104, 1776, 1701, 1402, 1384, 1236, 1038, 922, 909, 888, 726, 714 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 2.90 (br. s, 2 H, 2 OH), 3.39 (d, *J* = 12.7 Hz, 1 H), 3.49 (s, 2 H, CH_2N_3), 3.50 (d, *J* = 12.6 Hz, 1 H), 3.83 (d, ^2J = 14.6 Hz, 1 H, CH_2OH), 3.90 (d, ^2J = 14.6 Hz, 1 H, CH_2OH), 7.74−7.78 (m, 2 H), 7.86−7.90 (m, 2 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ = 41.5 (−, CH_2N_3), 55.3 (−, C-1), 63.9 (−, C-3), 75.1 (C_{quat}, C-2), 123.8 (+), 131.5 (C_{quat}), 134.6 (+), 169.5 (C_{quat}, C=O) ppm. MS (CI, NH_3): *m/z* (%) = 294 (100) [M + NH_4^+], 237 (20). $C_{12}H_{12}N_4O_4$ (276.25): calcd. C 52.17, H 4.38; found C 52.55, H 4.27.

5-Hydroxy-2,2-dioxo[1,3,2]dioxathian-5-ylmethyl Acetate (11): Pyridine (607 mg, 7.67 mmol) and acetic anhydride (783 mg, 7.67 mmol) were added to a solution of **7** (706 mg, 3.83 mmol) in anhydrous EtOAc (10 mL), and the mixture was stirred at room temp. for 20 h. Evaporation of the solvent under reduced pressure, followed by filtration through silica gel (15 g; light petroleum ether/EtOAc, 50:50, R_f = 0.44) gave the title compound mixed with pyridine. Evaporation of the pyridine under reduced pressure (10^{-3} mbar) overnight gave **11** as colorless crystals (832 mg, 3.68 mmol, 96%), m.p. 67−68 °C. IR (KBr): ṽ = 3378 (OH), 2957, 1717 (CO), 1465, 1405, 1386, 1321, 1268, 1197, 1175, 1109, 1058, 1009, 988, 941, 823, 776, 706 cm^{-1}. ^1H NMR (250 MHz, [D$_6$]DMSO): δ = 2.05 (s, 3 H), 4.04 (s, 2 H), 4.49 [d, ^2J = 11.2 Hz, 2 H, 4(6)-H], 4.75 [d, ^2J = 11.2 Hz, 2 H, 4(6)-H], 6.10 (br. s, 1 H, OH) ppm. ^{13}C NMR (62.9 MHz, [D$_6$]DMSO, DEPT): δ = 20.8 (+), 63.9 (−), 65.0 (C_{quat}, C-5), 77.8 [−, C-4(6)], 170.2 (C_{quat}) ppm. MS (CI, NH_3): *m/z* (%) = 470 (10) [2 M + NH_4^+], 261 (43) [M + NH_3 + NH_4^+], 244 (100) [M + NH_4^+]. $C_6H_{10}O_7S$ (226.20): calcd. C 31.86, H 4.46; found C 32.20, H 4.35.

3-(Acetoxymethyl)-3,4-dihydroxybutyronitrile (12a): A solution of **11** (50 mg, 221 μmol) and potassium cyanide (16 mg, 246 μmol) in DMF (1.5 mL) was stirred at 25 °C for 18 h. The solvent was evaporated under reduced pressure, and the residue was dissolved in THF (5 mL). Water (8 μL) and concentrated sulfuric acid (12 μL) were added, and the mixture was stirred at room temp. for 1 h. Neutralization by addition of solid $NaHCO_3$, filtration, and evaporation of the solvent, followed by flash chromatography (5 g of silica gel, light petroleum ether/EtOAc, 25:75, R_f = 0.15) gave **12a** as a colorless liquid (30 mg, 78%). IR (film): ṽ = 3387 (OH), 2937, 2252, 1737, 1727, 1378, 1249, 1151, 989, 836 cm^{-1}. ^1H NMR (250 MHz, [D$_6$]DMSO): δ = 2.02 (s, 3 H, COCH_3), 2.63 (s, 2 H, 2-H), 3.25−3.42 (m, 2 H, CH_2OH), 3.90 (d, ^2J = 11.2 Hz, 1 H, CH_2OAc), 4.00 (d, ^2J = 11.2 Hz, 1 H, CH_2OAc), 5.07 (t, ^3J = 5.7 Hz, 1 H, CH_2OH), 5.40 (s, 1 H, 2-OH) ppm. ^{13}C NMR (62.9 MHz, [D$_6$]DMSO, DEPT): δ = 20.9 (+), 24.00 (−, C-2), 64.1 (−, CH_2OH), 66.2 (−, CH_2OAc), 71.6 (C_{quat}, C-3), 118.4 (C_{quat}, CN), 170.4 (C_{quat}) ppm. MS (CI, NH_3): *m/z* (%) = 364 (5) [2 M + NH_4^+], 191 (100) [M + NH_4^+]. An analytical sample was obtained by kugelrohr distillation, b.p. 140−150 °C/0.01 Torr. $C_7H_{11}NO_4 \cdot 0.5H_2O$ (182.17): calcd. C 46.15, H 6.64; found C 46.72, H 6.34.

2-(Azidomethyl)-2,3-dihydroxypropyl Acetate (12b): A solution of **11** (154 mg, 0.68 mmol) and sodium azide (65 mg, 1.00 mmol) in DMF (3 mL) was stirred at 25 °C for 16 h. The solvent was evaporated under reduced pressure and the residue was dissolved in a mixture of THF and Et_2O (1:1.5, 10 mL). Water (5 drops) and concentrated sulfuric acid (1 drop) were added, and the mixture was stirred at ambient temperature for 1 h. Neutralization with solid $NaHCO_3$, filtration, evaporation of the solvent, and subsequent kugelrohr distillation gave **12b** as a colorless liquid (106 mg, 0.56 mmol, 82%), b.p. 120−130 °C/0.01 Torr. IR (film): ṽ = 3420 (OH), 2943, 2886, 2107, 1728 (CO), 1445, 1378, 1243, 1118, 1047, 992, 927, 795 cm^{-1}. ^1H NMR (250 MHz, [D$_6$]DMSO): δ = 2.01 (s, 3 H, COCH_3), 3.24 (s, 2 H), 3.33 (d, ^3J = 5.6 Hz, 2 H, 3-H), 3.88 (d, ^2J = 11.1 Hz, 1 H, 1-H), 3.97 (d, ^2J = 11.1 Hz, 1 H, 1-H), 4.86 (t, ^3J = 5.6 Hz, 1 H, 3-OH), 5.12 (s, 1 H, 2-OH) ppm. ^{13}C NMR (62.9 MHz, [D$_6$]DMSO, DEPT): δ = 21.0 (+), 53.8 (−), 62.9 (−, C-3), 65.3 (−, C-1), 73.9 (C_{quat}, C-2), 170.51 (C_{quat}) ppm. MS (CI, NH_3): *m/z* (%) = 396 (34) [2 M + NH_4^+], 207 (100) [M + NH_4^+]. $C_6H_{11}N_3O_4$ (189.17): calcd. C 38.10, H 5.86; found C 37.89, H 5.71.

Sodium 2-(Acetoxymethyl)-2-hydroxy-3-azidopropyl Sulfate (13b): Sodium azide (29 mg, 446 μmol) was added to a solution of **11** (100 mg, 442 μmol) in DMF (5 mL), and the mixture was stirred at room temp. for 1 h. Evaporation of the solvent gave **13b** as a colorless solid (129 mg, 442 μmol, 100%). IR (KBr): ṽ = 3467 (OH), 2113, 1734 (CO), 1662, 1457, 1387, 1254, 1137, 1071, 1049, 1015, 936, 829 cm^{-1}. ^1H NMR (250 MHz, [D$_6$]DMSO): δ = 2.03 (s, 3 H), 3.28 (s, 2 H, 3-H), 3.72 (s, 2 H, 1-H), 3.88 (d, ^2J = 9.8 Hz, 1 H, CH_2OAc), 3.97 (d, ^2J = 9.8 Hz, 1 H, CH_2OAc), 5.51 (s, 1 H, OH) ppm. ^{13}C NMR (62.9 MHz, [D$_6$]DMSO, DEPT): δ = 20.9 (+), 53.9 (−, CH_2N_3), 65.2 (−, C-1), 67.4 (−, CH_2OAc), 72.8 (C_{quat}, C-2), 170.4 (C_{quat}) ppm. MS (ESI): anions: *m/z* (%) = 269 (100) [A$^-$], 560 (84) [M + A$^-$]; cations: *m/z* (%) = 314 (16) [M + Na^+], 605 (54) [2 M + Na^+], 896 (100) [3 M + Na^+].

Sodium 2-(Acetoxymethyl)-2-hydroxy-3-[(tolylsulfonyl)amino]propyl Sulfate (13c): Sodium *p*-toluenesulfonamide (44 mg, 221 μmol) was added to a solution of **11** (50 mg, 221 μmol) in THF (5 mL), and the mixture was stirred at room temp. for 15 h. Evaporation of the solvent gave **13c** (94 mg, 221 μmol, 100%) as a colorless solid. IR (KBr): ṽ = 3500 (OH), 3359, 3261, 1739 (CO), 1653, 1599, 1528, 1457, 1388, 1307, 1257, 1161, 1097, 1070, 1005, 904, 817, 704 cm^{-1}. ^1H NMR (250 MHz, [D$_6$]DMSO): δ = 2.02 (s, 3 H), 2.34 (s, 3 H), 2.76 (d, ^2J = 6.9 Hz, 1 H, 3-H), 2.78 (d, ^2J = 6.9 Hz, 1 H, 3-H), 3.76 (d, ^2J = 11.2 Hz, 1 H, 1-H), 3.84 (d, ^2J = 11.2 Hz, 1 H, 1-H), 4.01 (d, ^2J = 12.1 Hz, 1 H, CH_2OAc), 4.25 (d, ^2J = 12.1 Hz, 1 H, CH_2OAc), 6.90 (br. s, 1 H, OH), 7.32 (d, ^3J = 8.1 Hz, 2 H), 7.68 (d, ^3J = 8.1 Hz, 2 H) ppm. ^{13}C NMR (62.9 MHz, [D$_6$]DMSO, DEPT): δ = 20.8 (+), 21.2 (+), 48.8 (−, C-3), 56.2 (C_{quat}, C-2), 63.4 (−, C-1), 66.0 (−, CH_2OAc), 125.8 (+), 129.4 (+), 141.7 (C_{quat}), 142.5 (C_{quat}), 170.3 (C_{quat}) ppm. MS (ESI): anions: *m/z*

(%) = 397 (100) [A^-], 525 (17), 696 (22), 816 (8) [M + A^-]; cations: *m/z* (%) = 443 (54) [M + Na^+], 622 (86), 741 (76), 861 (100) [2 M + Na^+].

[2-(Hydroxymethyl)oxiranyl]methyl Acetate (14): H_2O (1.0 μL, 55.5 μmol) and concentrated sulfuric acid (0.92 mg, 9.41 μmol) were added to a solution of **13c** (40 mg, 95.4 μmol) in THF (1 mL), and then the mixture was stirred at room temp. for 1 h. Neutralization with solid $NaHCO_3$, filtration, evaporation of the solvent, and subsequent flash chromatography (2 g of silica gel, petroleum ether/EtOAc, 25:75) gave **14** as a colorless liquid (5.3 mg, 36.3 μmol, 38%), the spectra of which are in agreement with the ones reported in the literature.[21]

Acknowledgments

This work was supported by E. Merck KGaA, Darmstadt, and the Fonds der Chemischen Industrie, Frankfurt. We are grateful to Dr. Burkhard Knieriem (Göttingen) for his careful proofreading of the final manuscript.

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Received February 22, 2002

