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REGIOSELECTIVE PROTECTION OF TRIOLS TO CYCLIC CARBONATES

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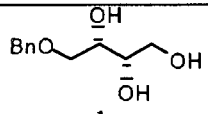
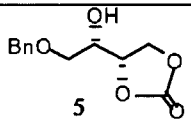
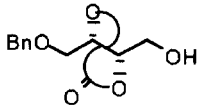
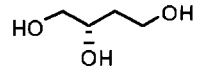
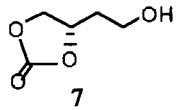
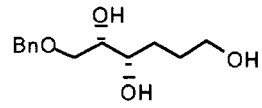
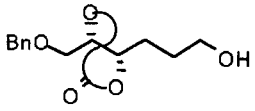
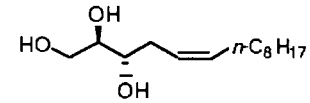
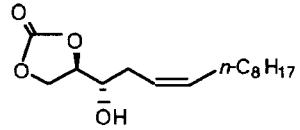
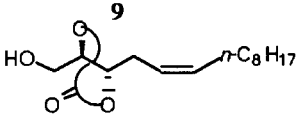
ABSTRACT: Regioselective protection of 1,2,3-, 1,2,4-, and 1,2,5-triols to 5-membered cyclic carbonates with triphosgene, dimethyl carbonate, or carbonyldiimidazole is described.

Conversion of diols to cyclic carbonates is a method of protection in organic synthesis.[1] In connection with our research programs, we needed to use protected cyclic carbonates as activating groups,[2] and we were interested in the regioselective preparation of cyclic carbonates. Here we report regioselective preparation of 5-membered cyclic carbonates by treatment of 1,2,3-, 1,2,4-, or 1,2,5-triols with triphosgene, dimethyl carbonate, or carbonyldiimidazole.

The results are summarized in Table 1. The substituted 1,2,3-triol **1**[3] reacted with triphosgene[4] in the presence of pyridine (Method A) to afford 5-membered 1,2-cyclic carbonate **5** as the sole product (entry 1). However, 1,2,3-triol **1** with dimethyl carbonate (Method B) afforded the more stable

Table 1. Regioselective Protection of Triols to Cyclic Carbonates.

Entry	Substrate	Reaction Conditions[a]	Product[b]	Isolated Yield(%)
1	 **1**	A	 **5**	77
2	**1**	B	 **6**	65
3	 **2**	A	 **7**	66
4	**2**	B	**7**	76
5	**2**	C	**7**	79
6	 **3**	A	 **8**	80
7	 **4**	A	 **9**	60
8	**4**	B	 **10 + 9** (1 : 1)	63

[a]A: $(Cl_3CO)_2CO$, CH_2Cl_2, pyridine, -70 °C, 15 min. B: NaH, Me_2CO_3, r.t., 30 min. C: $CO(Im)_2$, CH_2Cl_2, r.t., 30 min. [b]$[\alpha]_D^{25}$ values in $CHCl_3$; **5**: +40.3 (*c* 0.82). **6**: -33.6 (*c* 4.20). **7**: -39.6 (*c* 2.50). **8**: -47.80 (*c* 1.30). **9**: -1.16 (*c* 0.87).

internal cyclic carbonate **6** (entry 2). The structure of 5-membered cyclic carbonate **6** was confirmed by comparison with ^{1}H NMR spectrum of the authentic compound prepared from (*2S, 3S*)-2,3-*O*-isopropylidenedioxy-1,4-butanediol monobenzyl ether by deprotection (Dowex 50Wx8 resin, MeOH, r.t., 76%), monosilylation (*t*-BuPh$_2$SiCl, DMAP, DMF, 55%), protection of diol (carbonyldiimidazole, CH_2Cl_2, r.t., 74%) followed by deprotection of silyl group (*n*-Bu$_4$NF, THF, r.t., 65%). For the (*S*)-1,2,4-butanetriol **2**, treatment with triphosgene (Method A), dimethyl carbonate (Method B), or carbonyldiimidazole (Method C) provided the 5-membered 1,2 cyclic carbonate **7**[5] as the only isolated product without formation of 6-membered cyclic carbonate (entries 3-5). The 1,2,5- triol **3** with triphosgene yielded **8** (entry 6). Reaction of triphosgene with the *cis*-substituted triol **4** provided the external cyclic carbonate **9**[6] (entry 7). However, the *cis*-substituted triol **4** with dimethyl carbonate gave a mixture of cyclic carbonates **9** and **10** in the ratio of 1 : 1 (entry 8).

In summary, 1,2,3-, 1,2,4-, or 1,2,5-triols were regioselectively protected to cyclic carbonates by suitable choice of reagents.

EXPERIMENTAL

^{1}H NMR spectra(200 MHz) were recorded on a Varian GEMINI-200 and (300 MHz) were recorded on a Bruker WP-300 instrument with TMS as internal standard. IR spectra were recorded on a Nicolet 205 FT-IR spectrometer and MS spectra were obtained on a VG-Trio 2000 instrument. Combustion analyses were performed on a Carlo Erba EAGER 200 CHN elemental analyzer. Optical rotations were measured on a Rudolph AUTOPOL III polarimeter.

(2S,3S)-4-Benzyloxy-1,2,3-butanetriol 1,2-cyclic carbonate (5):

General Procedures:

Method A: To a stirred solution of triphosgene(104 mg, 0.35 mmol) in CH_2Cl_2(1 ml) at -70 °C was added pyridine(0.29 ml, 3.59 mmol) and triol **1** (125 mg, 0.59 mol) in CH_2Cl_2(1 ml). Once addition was complete, the reaction mixture was then allowed to warm to room temperature. The resultant homogeneous solution was quenched with saturated aqueous ammonium chloride and washed with 1N HCl, saturated aqueous $NaHCO_3$, brine, and dried over anhydrous $MgSO_4$. The organic layer was filtered and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel using EtOAc/hexanes 1 : 1 as eluent to afford **5** (108 mg, 77%). TLC; SiO_2, EtOAc/hexanes 1 : 1, R_f = 0.34. $[\alpha]_D^{25}$ +40.3 (*c* 0.82, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 2.55 (bs, 1H), 3.61 (m, 2H), 3.85 (m, 1H), 4.50 (m, 2H), 4.61 (s, 2H), 4.82 (m, 1H), 7.35 (m, 5H). IR (neat): 3500, 2980, 2900, 2700, 1786, 1380 cm^{-1}. Anal. Calcd for $C_{12}H_{14}O_5$: C, 60.49 ; H, 5.92. Found: C, 60.13 ; H, 5.95. MS(m/e): 238(M^+), 176, 167, 159, 133, 107, 91(base peak), 69, 43.

(2S,3S)-4-Benzyloxy-1,2,3-butanetriol 2,3-cyclic carbonate (6):

Method B: To a stirred solution of triol **1** (130 mg, 0.61 mmol) in dimethyl carbonate (1 ml), was added NaH (60% dispersion in mineral oil, 34 mg, 1.42 mmol) at room temperature and stirred for 30 min. The reaction mixture was quenched with brine and then extracted with ether. The organic layer was washed with brine, and dried over anhydrous $MgSO_4$, and evaporated *in vacuo*. The crude product was purified by column chromatography on silica gel using ethyl acetate as eluent to afford **6** (95 mg, 65%). TLC; SiO_2, EtOAc, R_f = 0.43. $[\alpha]_D^{25}$ - 33.6 (*c* 4.20, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 2.25 (bs,

1H), 3.72 (m, 3H), 4.00 (dd, 1H, J = 12, 2 Hz), 4.65 (m, 4H), 7.35 (m, 5H). IR (neat): 3500, 2962, 2873, 1800 cm^{-1}. Anal. Calcd for $C_{12}H_{14}O_5$: C, 60.49 ; H, 5.92. Found: C, 59.79 ; H, 5.92. MS(m/e): 238(M^+), 158, 145, 133, 91(base peak).

(S)-1,2,4-Butanetriol-1,2-cyclic carbonate (7)

Method A: To a stirred solution of triphosgene (151 mg, 0.51 mmol) in CH_2Cl_2(2 ml) at -70 °C was added pyridine (0.49 ml, 6.1 mmol) and triol **2** (108 mg, 1.02 mmol) in CH_2Cl_2 (1 ml). Once addition was complete, the reaction mixture was then allowed to warm to room temperature. The resultant homogeneous solution was quenched with saturated aqueous ammonium chloride and washed with 1N HCl, saturated aqueous $NaHCO_3$, brine, and dried over anhydrous $MgSO_4$. The organic layer was filtered and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel using EtOAc/hexanes 2 : 1 as eluent to afford **7** (89 mg, 66%). TLC; SiO_2, EtOAc/hexanes 1 : 2, R_f = 0.13, $[\alpha]_D^{25}$ -38.3 (*c* 0.52, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$) δ 1.85 (bs, 1H), 2.05 (m, 2H), 3.85 (m, 2H), 4.23 (dd, 1H, J = 8.6, 7.5 Hz), 4.61 (dd, 1H, J = 8.6, 7.5 Hz), 4.95 (m, 1H). IR (neat): 3743, 2830, 1797, 1777 cm^{-1}. Anal. Calcd for $C_5H_8O_4$: C, 45.46 ; H, 6.10. Found: C, 44.65 ; H, 6.20. MS(m/e): 132(M^+), 71, 57, 43(base peak).

Method B: To a stirred solution of triol **2** (200 mg, 1.88 mmol) in dimethyl carbonate (5 ml) was added NaH (60% dispersion in mineral oil, 160 mg, 4.14 mmol) at room temperature and stirred for 30 min. The reaction mixture was quenched with brine and then extracted with ether. The organic layer was washed with brine, and dried over anhydrous $MgSO_4$, and evaporated *in vacuo*. The crude product was purified by column chromatography on silica gel using EtOAc/hexanes 2 : 1 as eluent to afford **7** (189 mg, 76%). $[\alpha]_D^{25}$ - 40.5 (*c* 3.01, $CHCl_3$).

Method C: To a stirred solution of triol **2** (150 mg, 1.41 mmol) in CH_2Cl_2 (2 ml) was added carbonyldiimidazole (340 mg, 1.55 mmol) at room temperature under nitrogen atmosphere. After stirring about 30 min., the reaction mixture was filtered on silica gel and CH_2Cl_2 was evaporated *in vacuo*. The crude product was purified by column chromatography on silica gel using EtOAc/hexanes 2 : 1 as eluent to afford **7** (147 mg, 79%). $[\alpha]_D^{25}$ - 39.6 (*c* 2.50, $CHCl_3$).

***(4S,5S)*-6-Benzyloxy-1,4,5-hexanetriol 4,5-cyclic carbonate (8):**

Method A: To a stirred solution of triphosgene (80 mg, 0.27 mmol) in CH_2Cl_2 (2 ml) at -70 °C was added pyridine (0.2 ml, 2.7 mmol) and triol **3** (109 mg, 0.45 mmol) in CH_2Cl_2 (1 ml). Once addition was complete, the reaction mixture was then allowed to warm to room temperature. The resultant homogeneous solution was quenched with saturated aqueous ammonium chloride and washed with 1N HCl, saturated aqueous $NaHCO_3$, brine, and dried over anhydrous $MgSO_4$. The organic layer was filtered and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel using ethyl acetate as eluent to afford **8** (96 mg, 80%). TLC; SiO_2, EtOAc, R_f = 0.41. $[\alpha]_D^{25}$ -47.80 (*c* 1.3, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$) δ 1.75 (m, 5H), 3.69 (m, 4H), 4.41 (m, 1H), 4.62 (m, 3H), 7.35 (m, 5H). IR (neat): 3500, 2960, 2850, 2700, 1793 cm^{-1}. Anal. Calcd for $C_{14}H_{18}O_5$: C, 63.10 ; H, 6.81. Found: C, 63.15; H, 6.96. MS (m/e): 266 (M^+), 204, 91(base peak).

***(2R,3S)*-(*Z*)-5-Tetradecene-1,2,3-triol 1,2-cyclic carbonate (9):**

Method A: To a stirred solution of triphosgene (84 mg, 0.28 mmol) in CH_2Cl_2 (2 ml) at -70 °C was added pyridine (0.22 ml, 2.82 mmol) and triol **4** (115.2 mg, 0.48 mmol) in CH_2Cl_2 (1 ml). Once addition was complete, the

reaction mixture was then allowed to warm to room temperature. The resultant homogeneous solution was quenched with saturated aqueous ammonium chloride and washed with 1N HCl, saturated aqueous $NaHCO_3$, brine, and dried over anhydrous $MgSO_4$. The organic layer was filtered and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel using EtOAc/hexanes 1 : 1 as eluent to afford **9** (76 mg, 60%). TLC; SiO_2, EtOAc/hexanes 1 : 1, R_f = 0.61. $[\alpha]_D^{25}$ -1.16 (*c* 0.87, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$) δ 0.90 (t, 3H, J = 6.7 Hz), 1.35 (m, 12H), 2.05 (m, 2H), 2.30 (m, 2H), 2.51(bs, 1H), 3.95 (m, 1H), 4.55 (m, 3H), 5.40 (m, 1H), 5.65 (m, 1H) IR (neat): 3500, 2962, 2873, 1800 cm^{-1}. Anal. Calcd for $C_{15}H_{26}O_4$: C, 66.63 ; H, 9.69. Found: C, 66.28; H, 9.67. CIMS (CH_4, m/e): 271 (M^++1), 209, 191(base peak), 135, 121, 109, 95, 83, 81, 69, 67.

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3. The 1,2,3-triol **1** was prepared from (*2S, 3S*)-2,3-*O*-isopropylidenedioxy-1,4-butanediol monobenzyl ether by deprotection (Dowex 50Wx8 resin, MeOH, r.t., 81%).
4. Burk, R.M.; Roof, M. B. *Tetrahedron Lett.* **1993**, *34*, 395.
5. The structure of **7** was confirmed by comparison with the authentic sample prepared from (*S*)-1,2,4-butanetriol by (1) protection of diol (acetone, *p*-TsOH, r.t., 81%), (2) benzylation (NaH, $PhCH_2Br$, DMF, 88%), (3) deprotection (Dowex 50Wx8 resin, MeOH, r.t., 93%), (4) protection of diol (carbonyldiimidazole, CH_2Cl_2, r.t., 86%) and (5) debenzylation (H_2, Pd/C, EtOAc, r.t., 57%).
6. The structure of **9** was also confirmed by comparison with the authentic compound prepared from triol **4** by monobenzylation (NaH, $PhCH_2Br$, DMF, 89%), deprotection (HOAc, THF, 82%), protection of diol (carbonyldiimidazole, CH_2Cl_2, r.t., 76%) followed by debenzylation (H_2, Pd/C, EtOAc, r.t., 92%). For the preparation of the triol **4** from (-)-2-deoxy-D-ribose, see, Kang, S-K.; Lee, D-H.; Lee, J-M. *Synlett* **1990**, 591.

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