A New Simple One-Pot Regioselective Preparation of Mixed Diesters of Carbonic Acid

Giorgio Bertolini,*,† Gianfranco Pavich, and Barbara Vergani

Italfarmaco Research Center, via dei Lavoratori 54, I-20092 Cinisello Balsamo, Milan, Italy

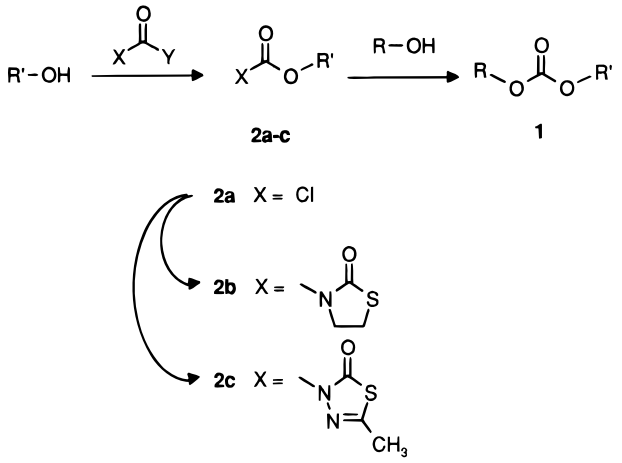
Received February 17, 1998

Introduction

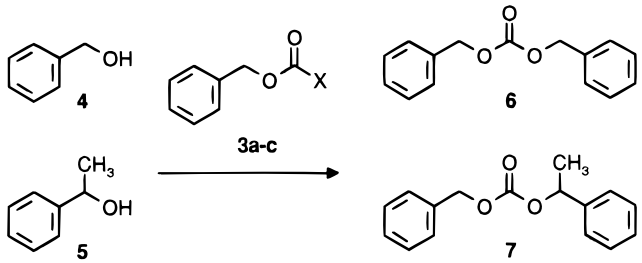
Diesters of carbonic acid (**1**) are frequently used in organic synthesis for the protection of sensitive functions.[1] Two of the most commonly used carbonates are the benzyl carbonate and the allyl carbonate which are removed under neutral conditions. In addition to protection, carbonates are also used for the reversible introduction of either hydrophobic moieties[2] or specific carrier systems for the targeting of drugs.[3] Recently it was reported that mixed carbonates of carbohydrates are useful starting materials for a novel intramolecular decarboxylative glycosylation reaction.[4] In general the acylation reaction of substrates containing primary and secondary hydroxy groups proceeds with low regioselectivity when using the most common methods for the synthesis of carbonates.

Improved regioselectivity is obtained when enzyme-based reactions are carried out.[5−8,14] Alternatively a two-step procedure can be used which involves the separate preparation of carbamates **2b**−**c** from the desired alkyl-chloroformates **2a** prior to their use as acylating agents[9,10] (Scheme 1). This approach however requires the purification of the intermediate **2b**−**c** and, in the case of carbohydrates, the use of dry pyridine as solvent to improve the yields.[9] Furthermore, alkyl chloroformates of unusual alcohols are not generally commercially available and a three-step procedure, which includes chloroformylation of the desired alcohol with either phosgene or phosgene substitutes, such as bis(trichloromethyl)-carbonates (Triphosgene),[11] is required. This further step may be aggravated by incompatibility between the chloroformylation conditions and functional groups present on the alcoholic residue. For this reason, only the synthesis of mixed carbonates with simple alkyl alcohols has been described using this method.

Scheme 1



Scheme 2



In this paper we report a general and efficient one-pot method for the selective preparation of mixed diesters of carbonic acid of primary alcohols.

Results and Discussion

It is well established that the selectivity of the acylation reactions toward primary alcohols increases with increasing the bulkiness of the R′ group (e.g., tBu) of the acylating agent (Scheme 1). Consequently the preparation of mixed carbonates having a non steric demanding R′ groups such as benzyl and allyl groups proceeds with low selectivity if both primary and secondary hydroxy groups are present. To develop a general and highly selective method for the synthesis of mixed carbonates, we decided to explore the role played by the nature of the leaving group X in the modulation of selectivity.

In the first experiment we used acylating agents characterized by X groups of different size such as *N*-hydroxysuccinimidyl ester **3a**, acyl chloride **3b**, and the imidazolide derivative **3c**. Their reactivity and selectivity were tested on a 1:1 mixture of simple primary and secondary alcohols (Scheme 2, Table 1). As described for other types of acylating agents,[12] increasing the steric hindrance of the carbonyl system, as it occurs in the series described here passing from *N*-hydroxysuccinimide ester, to chloride to the imidazolide derivative, the

† Address correspondence to Dr. Giorgio Bertolini, Italfarmaco Research Centre, Via Dei Lavoratori 54, 20092 Cinisello Balsamo, Milan, Italy. Phone: (39) 2-64.43.3022. Fax: (39) 2-66.011.579. E-mail: bertog@edith.sublink.org.

(1) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*; Wiley: New York, 1991: Vol. 2, pp 104−111.
(2) Tortolani, D. R.; Russel, J. W.; Whiterock, V. J.; Hitchcock, M. J. M.; Ghazzouli, I.; Martin, J. C.; Mansuri, M. M.; Starrett, J. E., Jr. *J. Pharm. Sci.* **1994**, *83*, 339−343.
(3) Pochet, S.; Kansal, V.; Destouesse, F.; Sarfati, S. R. *Tetrahedron Lett.* **1990**, *31*, 6021−6024.
(4) Iimori, T.; Shibazaki, T.; Ikegami, S. *Tetrahedron Lett.* **1996**, *37*, 2267−2270.
(5) Moris, F.; Gotor, V. *Tetrahedron* **1992**, *48*, 9869−9876.
(6) Moris, F.; Gotor, V. *Tetrahedron* **1993**, *49*, 10089−10098.
(7) Garcia-Alles, L. F.; Moris, F.; Gotor, V. *Tetrahedron Lett.* **1993**, *34*, 6337−6338.
(8) Pulido, R.; Gotor, V. *J. Chem. Soc., Perkin Trans. I* **1993**, 589−592.
(9) Allainmat, M.; L′Haridon, P.; Toupet, L.; Plusquellec, D. *Synthesis* **1990**, 27−32.
(10) Allainmat, M.; Plusquellec, D. *Tetrahedron Lett.* **1991**, *32*, 2751−2754.
(11) Eckert, H.; Forster, B. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 894−895.
(12) Katritzky, A. R.; Yang, B.; Semenzin, D. *J. Org. Chem.* **1997**, *62*, 726−728.

S0022-3263(98)00286-2 CCC: $15.00
Published on Web 07/25/1998

Table 1. Selective Acylation of a 1:1 Mixture of Primary and Secondary Alcohols Using Different Acylating Agents 3a−c

entry	acylating agent	X	*T*, °C	ratio **6**/**7**[a]	yield,[b] %
1	**3a**	succinimidyloxy	rt	2.4	72
2	**3b**	Cl	rt	3.7	75
3	**3c**	1-imidazolyl	rt	7.8	68
4	**3c**	1-imidazolyl	0	11.3	74

[a] Products ratios are based on analysis by HPLC. [b] Yields refer to isolated mixtures of the two carbonates and are the average of two runs.

Scheme 3

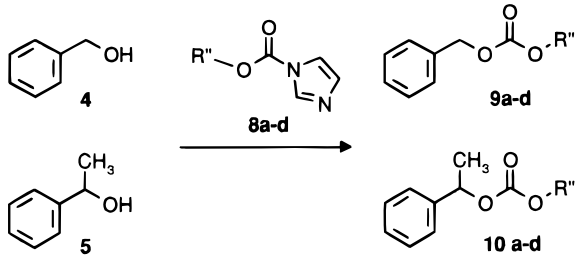


Table 2. Selective Acylation of a 1:1 Mixture of Primary and Secondary Alcohols Using Imidazolides 8a−d

entry	acylating agent	R″	ratio **9**/**10**[a]	yield,[b] %
1	**8a**	$PhCH_2CH_2$	6.5	79
2	**8b**	allyl	9.4	81
3	**8c**	3-pyCH_2	7.3	62
4	**8d**	$CH_3OCH_2CH_2$	8.9	73
5	**8a**	$PhCH_2CH_2$	7.4	83[c]
6	**11**−**12**[d]	$PhCH_2CH_2$	11.7	46[e]

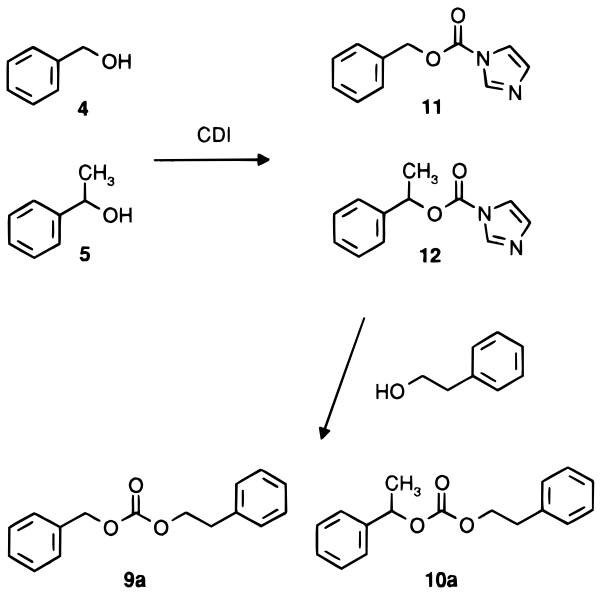
[a] Products ratios are based on analysis by HPLC. [b] Yields refer to isolated mixtures of the two carbonates and are the average of two runs. [c] Acylation reaction without isolating the intermediate imidazolide **8a**. [d] See Scheme 4. [e] 18% of symmetric **6** and 10% of asymmetric **7** were observed.

selectivity of the acylating reaction toward the primary alcohol was improved (Table 1, entries 1−3), although a non steric demanding R′ such as a benzyl group was used. As expected the reaction temperature played a crucial role in this reaction (Table 1, entries 3 and 4).

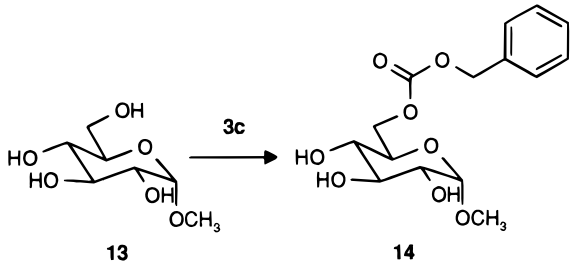
To investigate whether this approach can be applied to an acylating intermediate having an R′ group other than benzyl, the reactivity and selectivity of the imidazolides **8a**−**d** were tested (Scheme 3). These compounds were prepared by reacting the appropriate alcohol with 1,1-carbonyldiimidazole in THF for 1−2 h. After a simple workup procedure (see Experimental Section) the pure acylating agent was used in the next reaction without further purification. The results (Table 2) were similar to those of the previous reaction, suggesting therefore that the selectivity achieved was independent of the R′ group. Furthermore, when the same acylating reaction was repeated without isolating the intermediate imidazolide **8a** the yields were unaffected (Table 2, entry 5 vs entry 1) and the regioselectivity improved slightly. Therefore, under the above conditions the regioselective derivatization of primary alcohols in the presence of secondary alcohols can be carried out by a one-pot reaction.

To verify whether steric hindrance by the imidazolyl moiety is a factor governing the observed regioselectivity, an equimolar mixture of alcohols **4** and **5** was reacted at 0 °C with 1,1-carbonyldiimidazole where the carbonyl

Scheme 4



Scheme 5



system is shielded by two imidazolyl moieties (Scheme 4). Consistent with our hypothesis, imidazolide **11** and **12** were formed with high selectivity (ratio **11**/**12** = 12.1). Direct condensation without purification of the mixture of imidazolides with activated phenethyl alcohol gave **9a** and **10a** with higher selectivity compared to the previous sequence of reactions (entry 6 vs entry 5). However, in this case, yields were lower due to the presence in the mixture of unreacted alcohols **4** and **5** which reacted with **11** and **12** causing the formation of **6** (yield 18%) and **7** (yield 10%).

Using this simple method we synthesized with high regioselectivity the benzyl carbonate of the primary hydroxy of methyl α-D-glucopyranoside (Scheme 5) with yields comparable[13] with those obtained with **2b**[9] but using DMF as reaction solvent instead of dry pyridine.

In conclusion, we have identified a selective method for the synthesis of a primary diester of carbonic acid. This method seems to be general and gives good selectivity for primary alcohols even when the acylating agent contains a nonsterically demanding alcoholic group.

Experimental Section

General. ^1H and ^{13}C NMR spectra were recorded respectively at 200 and 50.3 MHz. The solutions were dried over Na_2SO_4, and the solvent was removed under reduced pressure. The

(13) Isolated yield of primary carbonate **14** was 49%, and the remaining 51% of the starting glycoside was lost as both unreacted starting material and the six-membered cyclic carbonate between the primary hydroxy group and the secondary alcohol in position 4 of methyl α-D-glucopyranoside. Only traces of carbonates on secondary hydroxy groups of the glycoside were detected.

(14) Bisht, K. S.; Deng, F.; Gross, R. A.; Kaplan, D. L.; Swift, G. *J. Am. Chem. Soc.* **1998**, *120*, 1363−1367.

mixture of carbonates was purified by flash chromatography on silica gel 60 (230−400 mesh ASTM) (E. Merck & Co) using *n*-hexanes−ethyl acetate (for **6**, **7**, **9a**−**d**, and **10a**−**d**) or chloroform−methanol (for **14**) as the eluent system. HPLC analysis was performed using a Supelcosil LC8DB (25 cm × 4.6 mm, 5 μm) column, acetonitrile−water 6:4, flow 1 mL/min, UV detector 220 nm.

General Procedure for the Synthesis of Imidazolide (3c, 8a−d). A solution of the desired alcohol (4.5 mmol) in THF (5 mL) was slowly added at 0 °C to a solution of 1,1-carbonyldiimidazole (730 mg, 4.5 mmol) in THF (5 mL). The solution was stirred at room temperature for 1 h; then the solvent was removed under reduced pressure and the crude product was dissolved in Et_2O and washed with a phosphate buffer solution pH 7. The solvent was removed to give pure imidazolide.

Benzyl carbonylimidazolide (3c): yield 84%; t_R = 4.58 min; ^{1}H NMR (DMSO-d_6) δ 8.32 (s, 1H), 7.64 (s, 1H), 7.51−7.32 (m, 5H), 7.10 (s, 1H), 5.46 (s, 2H); ^{13}C NMR (DMSO-d_6) δ 148.58, 137.55, 134.97, 130.66, 128.89 (3C), 128.60 (2C), 117.84, 69.50. Anal. Calcd for $C_{11}H_{10}N_2O_2$: C, 65.33; H, 4.98; N, 13.86. Found: C, 64.98; H, 4.87; N, 13.64.

2-Phenylethyl carbonylimidazolide (8a): yield 74%; t_R = 4.93 min; ^{1}H NMR (DMSO-d_6) δ 8.22 (s, 1H), 7.56 (s, 1H), 7.56−7.29 (m, 5H), 7.09 (s, 1H), 4.59 (t, 2H, *J* = 6.7 Hz), 3.08 (t, 2H, *J* = 6.7 Hz); ^{13}C NMR (DMSO-d_6) δ 148.49, 138.02, 137.39, 130.62, 129.26 (2C), 128.72 (2C), 126.86, 117.68, 68.70, 34.33. Anal. Calcd for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.60; N, 12.96. Found: C, 66.47; H, 5.51; N, 12.76.

Allyl carbonylimidazolide (8b): yield 79%; t_R = 3.70 min; ^{1}H NMR (DMSO-d_6) δ 8.31 (s, 1H), 7.64 (s, 1H), 7.10 (s, 1H), 6.13−5.96 (m, 1H), 5.48 (dt, 1H, *J* = 17.3 and 1.4 Hz), 5.34 (dd, 1H, *J* = 10.5 and 1.4 Hz), 4.91 (dd, 2H, *J* = 5.5 and 1.4 Hz); ^{13}C NMR (DMSO-d_6) δ 148.40, 137.54, 131.64, 130.64, 119.43, 117.81, 68.42. Anal. Calcd for $C_7H_8N_2O_2$: C, 55.25; H, 5.30; N, 18.42. Found: C, 55.13; H, 5.34; N, 18.15.

Pyrid-3-ylmethyl carbonylimidazolide (8c): yield 91%; t_R = 3.22 min; ^{1}H NMR (DMSO-d_6) δ 8.72 (s, 1H), 8.58 (dd, 1H, *J* = 4.8 and 1.7 Hz), 8.30 (s, 1H), 7.93 (dd, 1H, *J* = 7.9 and 1.7 Hz), 7.62 (s, 1H), 7.44 (dd, 1H, *J* = 7.9 and 4.8 Hz), 7.06 (s, 1H), 5.48 (s, 2H); ^{13}C NMR (DMSO-d_6) δ 150.04, 149.79, 148.48, 137.60, 136.57, 135.39, 130.62, 123.92, 117.85, 67.17. Anal. Calcd for $C_{10}H_9N_3O_2$: C, 59.11; H, 4.46; N, 20.68. Found: C, 58.93; H, 4.42; N, 20.55.

2-Methoxyethyl carbonylimidazolide (8d): yield 70%; t_R = 3.24 min; ^{1}H NMR (DMSO-d_6) δ 8.28 (s, 1H), 7.62 (s, 1H), 7.10 (s, 1H), 4.53 (m, 2H), 3.69 (m, 2H), 3.32 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 148.65, 137.49, 130.65, 117.79, 69.59, 67.26, 58.40. Anal. Calcd for $C_7H_{10}N_2O_3$: C, 49.40; H, 5.92; N, 16.47. Found: C, 49.51; H, 5.79; N, 16.27.

General Procedure for the Synthesis of Carbonates (6/7 and 9a−d/10a−d). An equimolar solution of **4** (207 μL, 2 mmol) and **5** (242 μL, 2 mmol) in THF (6 mL) was added to a suspension of NaH (6 mg, 0.2 mmol) in THF (6 mL). The reaction mixture was cooled to 0 °C; then a solution of the desired alkyl carbonylimidazolide (2 mmol) in THF (12 mL) was slowly added. The mixture was stirred at 0 °C for 30 min and then was diluted with Et_2O (50 mL) and washed with a saturated aqueous solution of NH_4Cl. The solvents were removed, and the ratio between primary and secondary carbonates was determined on the crude product by HPLC by comparison with authentic samples of pure compounds. The crude product was purified by flash chromatography giving the mixture of the two carbonates. The amount of the obtained mixture was used for the determination of the yield of the reaction (Tables 1 and 2).

Analytical data of pure compounds used as authentic samples are reported.

Dibenzyl carbonate (6): t_R = 9.33 min; IR (cm^{-1}, KBr) 1735; ^{1}H NMR (DMSO-d_6) δ 7.41−7.38 (m, 5H), 5.18 (s, 2H); ^{13}C NMR (DMSO-d_6) δ 154.70, 135.73, 128.77 (2C), 128.66, 128.47 (2C), 69.32.

Benzyl (α-methylbenzyl) carbonate (7): t_R = 10.95 min; IR (cm^{-1}, KBr) 1735, 1050; ^{1}H NMR (DMSO-d_6) δ 7.41−7.34 (m, 10H), 5.71 (q, 1H, *J* = 6.6 Hz), 5.13 (s, 2H), 1.52 (d, 3H, *J* = 6.6 Hz); ^{13}C NMR (DMSO-d_6) δ 154.07, 141.34, 135.74, 128.76 (4C), 128.63, 128.42 (2C), 128.30, 126.14 (2C), 76.21, 69.13, 22.40.

Benzyl (2-phenylethyl) carbonate (9a): t_R = 10.31 min; IR (cm^{-1}, KBr) 1735; ^{1}H NMR (DMSO-d_6) δ 7.34−7.23 (m, 10H), 5.10 (s, 2H), 4.30 (t, 2H, *J* = 6.8 Hz), 2.90 (t, 2H, *J* = 6.8 Hz); ^{13}C NMR (DMSO-d_6) δ 154.68, 137.82, 135.75, 129.09 (2C), 128.72 (2C), 128.61 (3H), 128.40 (2C), 126.67, 69.05, 68.28, 75.60.

α-Methylbenzyl (2-phenylethyl) carbonate (10a): t_R = 11.93 min; IR (cm^{-1}, KBr) 1735, 1050; ^{1}H NMR (DMSO-d_6) δ 7.40−7.22 (m, 10H), 5.66 (q, 1H, *J* = 6.6 Hz), 4.28 (t, 2H, *J* = 6.9 Hz), 2.91 (t, 2H, *J* = 6.9 Hz), 1.50 (d, 3H, *J* = 6.6 Hz); ^{13}C NMR (DMSO-d_6) δ 154.09, 141.36, 137.85, 129.11 (2C), 128.75 (2C), 128.65 (2C), 128.26, 126.70, 126.11 (2C), 75.92, 68.11, 34.53, 22.32.

Benzyl allyl carbonate (9b): t_R = 6.79 min; IR (cm^{-1}, KBr) 1740, 1640, 955; ^{1}H NMR (DMSO-d_6) δ 7.42−7.39 (m, 5H), 5.95 (m, 1H), 5.34 (dd, 1H, *J* = 17.5 and 1.7 Hz), 5.26 (dd, 1H, *J* = 10.6 and 1.4 Hz), 5.17 (s, 2H), 4.64 (d, 2H, *J* = 5.5 Hz); ^{13}C NMR (DMSO-d_6) δ 154.57, 135.77, 132.42, 128.77 (2C), 128.65, 128.45 (2C), 118.67, 69.24, 68.22.

α-Methylbenzyl allyl carbonate (10b): t_R = 7.82 min; IR (cm^{-1}, KBr) 1740, 1645, 1055, 955; ^{1}H NMR (DMSO-d_6) δ 7.42−7.34 (m, 5H), 5.95 (m, 1H), 5.70 (q, 1H, *J* = 6.6 Hz), 5.31 (m, 2H), 4.59 (d, 2H, *J* = 5.5 Hz), 1.53 (d, 3H, *J* = 6.6 Hz); ^{13}C NMR (DMSO-d_6) δ 153.94, 141.34, 132.45, 128.77 (2C), 128.29, 126.12 (2C), 118.60, 76.10, 68.03, 22.36.

Benzyl (pyrid-3-ylmethyl) carbonate (9c): t_R = 5.03 min; IR (cm^{-1}, KBr) 1740, 1590, 1425; ^{1}H NMR (DMSO-d_6) δ 8.63 (d, 1H, *J* = 2.2 Hz), 8.57 (dd, 1H, *J* = 4.9 and 1.8 Hz), 7.84 (m, 1H), 7.46−7.38 (m, 6H), 5.23 (s, 2H), 5.18 (s, 2H); ^{13}C NMR (DMSO-d_6) δ 154.57, 149.91, 149.78, 136.49, 135.63, 131.36, 128.77 (2C), 128.69, 128.50 (2C), 123.89, 69.46, 67.01.

α-Methylbenzyl (pyrid-3-ylmethyl) carbonate (10c): t_R = 5.54 min; IR (cm^{-1}, KBr) 1740, 1595, 1425, 1050; ^{1}H NMR (DMSO-d_6) δ 8.57 (d, 1H, *J* = 2.0 Hz), 8.54 (dd, 1H, *J* = 4.8 and 1.7 Hz), 7.79 (m, 1H), 7.42−7.30 (m, 6H), 5.68 (q, 1H, *J* = 6.6 Hz), 5.15 (s, 2H), 1.49 (d, 3H, *J* = 6.6 Hz); ^{13}C NMR (DMSO-d_6) δ 153.92, 149.85, 149.71, 141.19, 136.43, 131.35, 128.74 (2C), 128.31, 126.12 (2C), 123.85, 76.37, 66.81, 22.32.

Benzyl (2-methoxyethyl) carbonate (9d): t_R = 5.01 min; IR (cm^{-1}, KBr) 1735, 1115; ^{1}H NMR (DMSO-d_6) δ 7.40−7.32 (m, 5H), 5.16 (s, 2H), 4.22 (m, 2H), 3.54 (m, 2H), 3.27 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 154.80, 135.77, 128.77 (2C), 128.64, 128.45 (2C), 69.85, 69.16, 66.95, 58.27.

α-Methylbenzyl (2-methoxyethyl) carbonate (10d): t_R = 5.71 min; IR (cm^{-1}, KBr) 1735, 1115, 1050; ^{1}H NMR (DMSO-d_6) δ 7.40−7.32 (m, 5H), 5.69 (q, 1H, *J* = 6.6 Hz), 4.20 (m, 2H), 3.53 (m, 2H), 3.26 (s, 3H), 1.52 (d, 3H, *J* = 6.6 Hz); ^{13}C NMR (DMSO-d_6) δ 154.18, 141.34, 128.75 (2C), 128.28, 126.15 (2C), 76.00, 69.83 66.76, 58.27, 22.36.

One-Pot Synthesis of Carbonates 9a and 10a. A solution of 2-phenylethanol (358 μL, 3 mmol) in THF (10 mL) was slowly added to solution of 1,1-carbonyldiimidazole (486 mg, 3 mmol) in THF (5 mL) at 0 °C. The solution was stirred at 0 °C for 2 h and then was added without any further purification to an equimolar solution of **4** (311 μL, 3 mmol) and **5** (362 μL, 3 mmol) in THF (15 mL) at 0 °C, previously treated with NaH (9 mg, 0.3 mmol). The mixture was stirred at 0 °C for 30 min and then was diluted with Et_2O (50 mL) and washed with a saturated aqueous solution of NH_4Cl. The solvents were removed, and the ratio **9a**/**10a**, determined on the crude product by HPLC, was 7.4. The product was purified by flash chromatography giving 640 mg of mixture of the two carbonates (yield 83%).

One-Pot Synthesis of Carbonates 9a and 10a by Inverted Addition. An equimolar solution of **4** (311 μL, 3 mmol) and **5** (362 μL, 3 mmol) in THF (10 mL) was slowly added to solution of 1,1-carbonyldiimidazole (486 mg, 3 mmol) in THF (5 mL) at 0 °C. The solution was stirred at 0 °C for 2 h with the selective formation of the primary carbonylimidazolide (ratio **11**/**12** by HPLC = 12.1). Then a solution of 2-phenylethanol (358 μL, 3 mmol) in THF (15 mL) previously treated with NaH (9 mg, 0.3 mmol) was added at 0 °C. The mixture was stirred at at this temperature for 30 min and then was diluted with Et_2O (50 mL) and washed with a saturated aqueous solution of NH_4Cl. The solvents were removed, and the ratio **9a**/**10a**, determined on the crude product by HPLC, was 11.7. The product was purified by flash chromatography giving 571 mg of mixture of carbonates. Using the ratio among the carbonates determined by both ^{1}H NMR and HPLC the yields of carbonates were 46% of the mixture of **9a** and **10a**, 18% of symmetric carbonate **6**, and 10% of asymmetric carbonate **7**.

Synthesis of 6 and 7 Using Benzyl Chloroformate or *N*−(Benzyloxycarbonyloxy)succinimide. An equimolar solution of **4** (207 μL, 2 mmol) and **5** (242 μL, 2 mmol) in THF (6 mL) was added to a suspension of NaH (6 mg, 0.2 mmol) in THF (6 mL). The reaction mixture was cooled to 0 °C; then a solution of benzyl chloroformate or *N*-(benzyloxycarbonyloxy)succinimide (2 mmol) in THF (12 mL) was slowly added. The mixture was stirred either overnight (in the case of benzyl chloroformate) or for 48 h (in the case of benzyl succinimidyl carbonate) at room temperature and then was diluted with Et_2O (50 mL) and washed with a saturated aqueous solution of NH_4Cl. The solvents were removed, and the ratio between **6** and **7** was determined on the crude product by HPLC.

Synthesis of Benzyl Carbonate of Methyl α-D-glucopyranoside (14). A solution of benzyl alcohol (373 μL, 3.6 mmol) in THF (6 mL) was slowly added to solution of 1,1-carbonyldiimidazole (583 mg, 3.6 mmol) in THF (3 mL) at 0 °C. The solution was stirred at room temperature for 1 h; then the solution was added without any further purification to a solution of **13** (582 mg, 3 mmol) in DMF (15 mL) at 0 °C, previously treated with NaH (9 mg, 0.3 mmol). The mixture was stirred at 0 °C for 30 min; then the solvents were removed under high vacuum. The crude product was dissolved in THF (200 mL) and washed with a saturated aqueous solution of NH_4Cl (3 mL). The organic phase was dried, and the solvent was removed. The crude product was purified by flash chromatography (eluent chloroform−methanol 90:10) giving 480 mg of pure **14** (yield 49%): HPLC t_R = 4.01 min; IR (cm^{-1}, KBr) 1740, 740, 695; ^1H NMR (DMSO-d_6) δ 7.37 (s, 5H), 5.12 (s, 2H),, 4.51 (d, 1H, J = 3.7 Hz), 4.23 (m, 2H), 3.53 (m, 1H), 3.39 (dd, 1H, J = 9.4 and 8.8 Hz), 3.22 (m, 1H), 3.20, (s, 3H), 3.09 (dd, 1H, J = 10.0 and 8.8 Hz); ^{13}C NMR (DMSO-d_6) δ 154.80, 135.78, 128.77 (2C), 128.66, 128.51 (2C), 100.00, 73.37, 72.01, 70.34, 69.64, 69.17, 54.68. Anal. Calcd for $C_{15}H_{20}O_8$: C, 54.87; H, 6.14. Found: C, 54.63; H, 6.12.

JO980286E