Highly Stereoselective Synthesis of Carbocycles *via* a Radical Addition Reaction Using 2,2′-Azobis(2,4-dimethyl-4-methoxyvaleronitrile) [V-70L]

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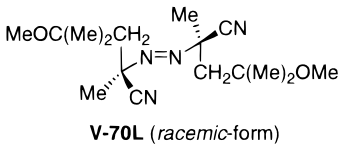
Received May 12, 1999

Carbocycles have widespread utility in organic synthesis since many bioactive compounds contain these structures. In this area, synthetic strategies of producing carbocycles from carbohydrate compounds have been developed over the past decade because of the easy accessibility to enantiomerically pure carbocycles and readily available starting materials.[1,2] In particular, the intramolecular radical cyclization reaction is one of the most powerful methods for the construction of various mono- and polycyclic compounds.[3−10] Furthermore, this strategy makes it possible to obtain high regio- and stereochemistries.[11]

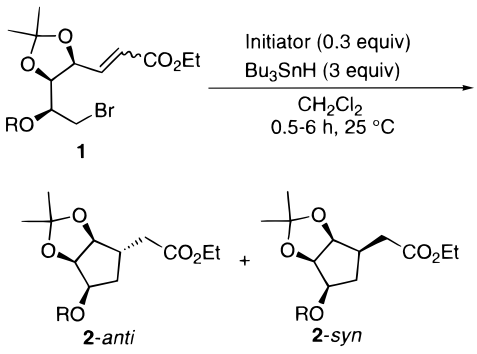
We have already reported that 2,2′-azobis(2,4-dimethyl-4-methoxyvaleronitrile) [V-70] can easily generate radical species under mild conditions such as room temperature (25 °C) or below.[12,13] We then applied this knowledge to the generation of anomeric radicals, and achieved the stereoselective and efficient synthesis of α-linked *C*-glycopyranosides.[14] Furthermore, we revealed that *racemic* V-70L (Figure 1) was a more active initiator at room temperature compared with *meso* V-70H[13] and established a practical synthetic method for pyrrolo[2,3-*d*]pyrimidine antifolate TNP-351 using V-70L.[15] We report here the highly stereoselective synthesis of polyhydroxylated carbocycles from carbohydrate derivatives[4] during radical addition reactions which occurred using V-70L as the initiator instead of AIBN.



V-70L (*racemic*-form)

Figure 1.

Table 1. Diastereoselective Radical Cyclization of Bromides 1



entry	bromide	R	initiator	yield (%)[a,b]	ratio[c] (*anti*:*syn*)[b]
1	(*Z*)-**1a**	H	V-70L	85	98:2
2[d]	(*Z*)-**1a**	H	AIBN	80	6:1
3[e]	(*Z*)-**1a**	H	*hν*	86	94:6
4[f]	(*Z*)-**1a**	H	Et_3B	69	99:1
5	(*Z*)-**1b**	COMe	V-70L	85 (80)	99:1 (5:1)
6	(*Z*)-**1c**	COPh	V-70L	94 (89)	99:1 (10:1)
7	(*E*)-**1a**	H	V-70L	80 (80)	30:70 (2:1)
8[f]	(*E*)-**1a**	H	Et_3B	73 (80)	26:74 (2:1)
9	(*E*)-**1b**	COMe	V-70L	85 (82)	33:67 (1:1)
10	(*E*)-**1c**	COPh	V-70L	70 (87)	24:76 (1:1.2)

[a] Total yields of stereoisomers. [b] Yields and ratios in parentheses are reported values using AIBN.[4] [c] The ratios were determined by ^1H NMR of crude products. [d] Reported value, and the reaction was carried out under reflux using benzene as a solvent.[4] [e] The reaction was carried out under reflux. [f] These reactions were carried out at −78 °C.

We applied stereocontrol to the intramolecular radical cycloaddition reactions of (*Z*)-**1a**[4] using various initiators (Table 1, entries 1−4). As a result, the reaction using V-70L gave the desired corresponding cyclized products **2** in higher yield and similar or higher diastereoselectivity than when using other initiators. In the case of using Et_3B as an initiator, the yields of the products were slightly low, probably due to decomposition of the starting material **1** by the acidic Et_3B (entries 4 and 8). Additionally, other (*Z*)- and (*E*)-bromides were examined. It is noteworthy that the stereochemistries of the cycloaddition products were almost completely controlled using V-70L, regardless of the structure of the R group in the substrate (*Z*)-isomers (entries 1, 5, and 6). By using AIBN, similar complete stereocontrol was not possible as shown in the parentheses.[4] Furthermore, in the case of the (*E*)-isomers, we found that V-70L could reverse the stereoselectivity during the cycloaddition process. Thus, using V-70L, (*E*)-isomers gave *syn*-**2** as the major product, while AIBN gave an equivalent amount of *anti*-**2** and *syn*-**2** or a slightly predominant *anti*-**2** (entries 7, 9, and 10).

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10.1021/jo990777e CCC: $18.00 © 1999 American Chemical Society
Published on Web 08/19/1999

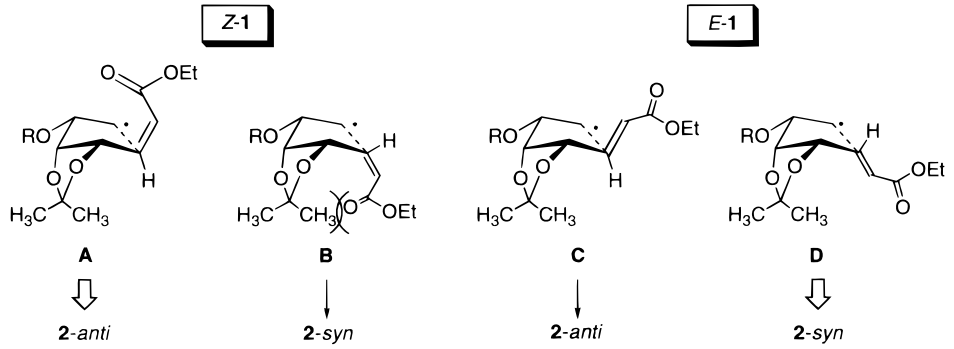
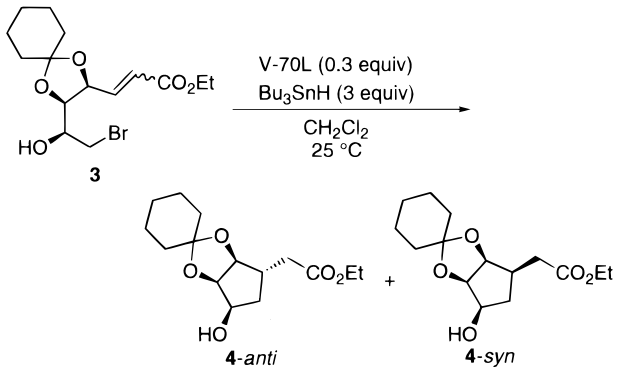


Figure 2. Transition state structures of the reaction of (*Z*)- and (*E*)-**1**.

Scheme 1



Z-**3**	4.5 h	81%	96 : 4
E-**3**	5 h	75%	30 : 70

We next examined the reaction of the (*Z*),(*E*)-bromides ((*Z*),(*E*)-**3**), in which the 1,2-diol was protected by cyclohexylidene using V-70L and obtained cyclized products **4** in good yields and with high diastereoselectivity under mild conditions (Scheme 1). In these cases, the reaction of (*Z*)-**3** gave the *anti*-**4** and the (*E*)-isomer predominantly gave *syn*-**4** similar to the reaction of the bromides **1**.

The stereoselectivity during these cyclization processes can be considered by the transition states in the reactions (Figure 2). In the case of the (*Z*)-bromides, the reaction proceeded through a favorable transition state **A**, since **B** was disfavored because of the steric interaction between the ester carbonyl oxygen and isopropylidene methyl, and afforded *anti*-products with extremely high selectivity. On the other hand, in the case of the (*E*)-bromides, it was considered that the reaction using V-70L was more kinetically controlled since it enabled the generation of radical species under mild conditions such as room temperature compared with AIBN, which requires elevated temperatures for the generation of the radicals. Thus, the reaction proceeded through **D** and gave predominantly *syn*-**2** (Figure 2).

We clarified that the use of V-70L made it possible to achieve the highly stereoselective radical addition reaction, which could not be achieved by AIBN under mild conditions. It is expected that the construction reaction of the carbon−carbon bond using V-70L will be applicable to various stereoselective reactions.

Experimental Section

All melting points are uncorrected. ^{1}H NMR spectra were measured in $CDCl_3$ on 300 and 500 MHz spectrometers with $SiMe_4$ as the internal standard. Infrared (IR) absorption spectra were recorded as a KBr pellet. E. Merck silica gel 60 (70−230 mesh ASTM) for column chromatography was used. V-70 is commercially available from Wako Pure Chemical Industries, Ltd., Japan. Bromides **1a**−**c** and **3** were prepared by the general procedure of Wilcox.[4] Unless otherwise noted, all experiments were carried out under an atmosphere of dry nitrogen using anhydrous solvents which were distilled and dried according to standard procedure.

Separation of the Diastereomers of V-70. V-70 (5.00 g) in Et_2O (25 mL) was stirred at 10 °C for 30 min to precipitate only V-70H (2.46 g; content of 100% from ^{1}H NMR). On the other hand, the filtrate, upon cooling to −10 °C for 2 days, gave crystallized V-70L (1.05 g; content of 100% from ^{1}H NMR). V-70L: mp 58 °C dec; ^{1}H NMR ($CDCl_3$) δ 1.29 (s, 6 H), 1.64 (s, 6 H), 2.26 (d, 2 H, J = 11.0 Hz), 2.42 (d, 2 H, J = 11.0 Hz), 3.21 (s, 6 H). V-70H: mp 100 °C dec; ^{1}H NMR ($CDCl_3$) δ 1.20 (s, 6 H), 1.27 (s, 6 H), 1.69 (s, 6 H), 2.19 (d, 2 H, J = 11.0 Hz), 2.59 (d, 2 H, J = 11.0 Hz), 3.19 (s, 6 H).

Typical Procedure for the Radical Addition Reaction of (*Z*)- and (*E*)-Bromides Using V-70L. To a stirred solution of bromide **1** (0.122 mmol) and V-70L (0.037 mmol) in dry CH_2Cl_2 (1.2 mL) was added Bu_3SnH (0.367 mmol) in one portion at 25 °C. A 1 mL sample of 15% aqueous KF was added, and the mixture was vigorously stirred at room temperature for 2 h. The organic layer was separated and extracted with CH_2Cl_2, dried over $MgSO_4$, and concentrated in vacuo, and the residue was chromatographed on silica gel (hexane−AcOEt) to give **2**.

Ethyl 2-[(3a*S*,4*S*,6*R*,6a*R*)-6-Hydroxy-2,2-dimethyltetrahydro-3a*H*-cyclopenta[*d*][1,3]dioxol-4-yl]acetate (*anti*-2a)[4,16] **and Ethyl 2-[(3a*S*,4*R*,6*R*,6a*R*)-6-Hydroxy-2,2-dimethyltetrahydro-3a*H*-cyclopenta[*d*][1,3]dioxol-4-yl]acetate (*syn*-2a).**[4,16] These products were isolated as a diastereo mixture. *anti*-**2a**: ^{1}H NMR ($CDCl_3$) δ 1.26 (3H, t, J = 7.2 Hz), 1.34 (3H, s), 1.51 (3H, s), 1.71 (1H, dt, J = 13.2, 4.8 Hz), 1.96 (1H, ddd, J = 13.2, 8.1, 7.2 Hz), 2.23 (1H, dd, J = 15.3, 8.1 Hz), 2.30 (1H, dd, J = 15.3, 7.8 Hz), 2.45 (1H, d, J = 7.8 Hz), 2.53 (1H, m), 4.03−4.18 (1H, m), 4.14 (2H, q, J = 7.2 Hz), 4.40 (1H, dd, J = 5.7, 1.7 Hz), 4.50 (1H, t, J = 5.7 Hz); ^{13}C NMR ($CDCl_3$) δ 14.2, 24.5, 26.1, 36.8, 37.0, 38.1, 60.5, 71.5, 79.9, 83.8, 112.0, 172.5. *syn*-**2a**: ^{1}H NMR ($CDCl_3$) δ 1.26 (3H, t, J = 7.2 Hz), 1.33 (3H, s), 1.47 (3H, s), 1.68−1.76 (1H, m), 1.90−2.08 (2H, m), 2.27 (1H, t, J = 7.5 Hz), 2.39 (1H, dd, J = 16.5, 6.6 Hz), 2.59 (1H, dd, J = 16.5, 7.5 Hz), 3.88 (1H, ddd, J = 16.2, 10.8, 6.0 Hz), 4.14 (2H, q, J = 7.2 Hz), 4.46 (1H, t, J = 5.4 Hz), 4.59 (1H, t, J = 4.8 Hz); ^{13}C NMR ($CDCl_3$) δ 13.6, 24.5, 25.6, 33.2, 34.7, 35.7, 60.3, 71.7, 78.5, 80.2.

Ethyl 2-[(3a*S*,4*S*,6*R*,6a*S*)-6-(Acetyloxy)-2,2-dimethyltetrahydro-3a*H*-cyclopenta[*d*][1,3]dioxol-4-yl]acetate (*anti*-2b):[4] colorless oil; $[\alpha]^{19}_D$ +58° (*c* 1.4, $CHCl_3$); IR 1738, 1732 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.26 (3H, t, J = 6.7 Hz), 1.30 (3H, s), 1.48 (3H, s), 1.76 (1H, ddd, J = 12.8, 6.1, 3.0 Hz), 2.10 (3H, s), 2.19 (1H, ddd, J = 12.8, 9.8, 7.3 Hz), 2.25 (1H, dd, J = 15.2, 7.9 Hz), 2.34 (1H, dd, J = 15.2, 7.3 Hz), 2.55 (1H, m), 4.15 (2H, q, J = 6.7 Hz), 4.38 (1H, d, J = 6.1 Hz), 4.68 (1H, t, J = 5.5 Hz), 4.92 (1H, dd, J = 9.8, 5.5 Hz); ^{13}C NMR ($CDCl_3$) δ 14.1, 20.8, 24.5, 26.1, 32.6, 36.9, 37.7, 60.6, 73.0, 78.1, 84.0, 111.7, 170.6, 171.6.

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Ethyl 2-[(3a*S*,4*R*,6*R*,6a*S*)-6-(Acetyloxy)-2,2-dimethyltetrahydro-3a*H*-cyclopenta[*d*][1,3]dioxol-4-yl]acetate (*syn*-2b):[4] colorless oil; $[\alpha]^{19}_{D}$ +35° (*c* 1.7, $CHCl_3$); IR 1738 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.26 (3H, t, *J* = 7.2 Hz), 1.30 (3H, s), 1.46 (3H, s), 1.64 (1H, t, *J* = 6.6 Hz), 1.69 (1H, dd, *J* = 12.9, 10.8 Hz), 1.93−2.00 (1H, m), 2.10 (3H, s), 2.41 (1H, dd, *J* = 16.5, 6.6 Hz), 2.62 (1H, dd, *J* = 16.5, 7.7 Hz), 4.14 (2H, dq, *J* = 1.2, 7.2 Hz), 4.58 (1H, dd, *J* = 5.1, 4.6 Hz), 4.65−4.73 (2H, m); ^{13}C NMR ($CDCl_3$) δ 14.2, 20.9, 24.2, 25.7, 31.5, 33.2, 34.4, 60.4, 73.4, 77.7, 79.7, 110.7, 170.7, 172.6.

(3a*S*,4*R*,6*S*,6a*S*)-6-(2-Ethoxy-2-oxoethyl)-2,2-dimethyltetrahydro-3a*H*-cyclopenta[*d*][1,3]dioxol-4-yl Benzoate (*anti*-2c):[4] colorless crystal; mp 42−44 °C (hexanes−Et_2O); $[\alpha]^{19}_{D}$ +49° (*c* 0.7, $CHCl_3$); IR 1732, 1728 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.28 (3H, t, *J* = 7.8 Hz), 1.29 (3H, s), 1.40 (3H, s), 1.88 (1H, ddd, *J* = 14.7, 6.6, 4.2 Hz), 2.27−2.43 (3H, m), 2.67 (1H, m), 4.17 (2H, q, *J* = 7.8 Hz), 4.45 (1H, dd, *J* = 6.3, 1.2 Hz), 4.80 (1H, t, *J* = 5.6 Hz), 5.18 (1H, dt, *J* = 8.6, 5.6 Hz), 7.44 (2H, t, *J* = 8.1 Hz), 7.56 (1H, t, *J* = 8.1 Hz), 8.08 (2H, d, *J* = 8.1 Hz); ^{13}C NMR ($CDCl_3$) δ 14.2, 24.6, 26.1, 33.2, 36.9, 37.9, 60.6, 73.5, 78.4, 84.2, 112.1, 128.3, 129.8, 130.1, 132.9, 166.1, 171.7.

(3a*S*,4*R*,6*R*,6a*S*)-6-(2-Ethoxy-2-oxoethyl)-2,2-dimethyltetrahydro-3a*H*-cyclopenta[*d*][1,3]dioxol-4-yl Benzoate (*syn*-2c):[4] colorless oil; $[\alpha]^{19}_{D}$ +26° (*c* 0.2, $CHCl_3$); IR 1732 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.27 (3H, t, *J* = 7.3 Hz), 1.30 (3H, s), 1.45 (3H, s), 1.86 (1H, br q, *J* = 11.6 Hz), 2.09 (1H, ddd, *J* = 11.6, 6.1, 5.5 Hz), 2.19 (1H, m), 2.47 (1H, dd, *J* = 16.5, 6.7 Hz), 2.67 (1H, dd, *J* = 16.5, 7.9 Hz), 4.16 (2H, dq, *J* = 3.1, 7.3 Hz), 4.64 (1H, t, *J* = 4.9 Hz), 4.80 (1H, t, *J* = 5.5 Hz), 4.93 (1H, ddd, *J* = 11.6, 6.1, 5.5 Hz), 7.43 (2H, m), 7.55 (1H, m), 8.07 (2H, dd, *J* = 7.9, 1.2 Hz); ^{13}C NMR ($CDCl_3$) δ 14.2, 24.4, 25.8, 31.9, 33.4, 34.5, 60.4, 73.9, 77.8, 80.1, 102.0, 128.3, 129.8, 132.9, 172.6.

Ethyl 2-[(3a*S*,4*S*,6*R*,6a*R*)-6-Hydroxy-2-1′-cyclohexanetetrahydro-3a*H*-cyclopenta[*d*][1,3]dioxol-4-yl]acetate (*anti*-4) and Ethyl 2-[(3a*S*,4*R*,6*R*,6a*R*)-6-Hydroxy-2-1′-cyclohexanetetrahydro-3a*H*-cyclopenta[*d*][1,3]dioxol-4-yl]acetate (*syn*-4). These products were isolated as a diastereo mixture. *anti*-**4**: ^1H NMR ($CDCl_3$) δ 1.26 (3H, t, *J* = 7.0 Hz), 1.40 (2H, br d, *J* = 4.9 Hz), 1.53−1.72 (9H, m), 1.95 (1H, dt, *J* = 13.1, 7.6 Hz), 2.22 (1H, dd, *J* = 15.2, 7.9 Hz), 2.31 (1H, dd, *J* = 15.2, 7.6 Hz), 2.48−2.57 (2H, m), 4.05 (1H, br m), 4.14 (2H, q, *J* = 7.0 Hz), 4.39 (1H, dd, *J* = 5.8, 1.5 Hz), 4.50 (1H, t, *J* = 5.8 Hz); ^{13}C NMR ($CDCl_3$) δ 14.1, 23.5, 23.9, 25.0, 33.7, 35.8, 36.6, 36.8, 38.1, 60.5, 71.0, 78.6, 83.7, 112.5, 171.8. *syn*-**4**: ^1H NMR ($CDCl_3$) δ 1.26 (3H, t, *J* = 7.0 Hz), 1.35−1.43 (2H, m), 1.52−1.73 (9H, m), 1.96−2.08 (2H, m), 2.40 (1H, dd, *J* = 16.5, 6.6 Hz), 2.47 (1H, br d, *J* = 9.9 Hz), 2.60 (1H, dd, *J* = 16.5, 7.2 Hz), 3.87 (1H, ddd, *J* = 16.2, 10.8, 5.7 Hz), 4.14 (2H, q, *J* = 7.0 Hz), 4.44 (1H, t, *J* = 5.5 Hz), 4.56 (1H, dd, *J* = 5.2, 4.6 Hz); ^{13}C NMR ($CDCl_3$) δ 14.1, 23.5, 24.9, 33.1, 33.6, 34.6, 35.3, 35.6, 60.2, 71.9, 78.3, 79.5, 111.0, 172.8.

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