Radical Cyclization of Sugar Derived β-(Alkynyloxy)acrylates: Synthesis of Novel Fused Ethers

Michiel A. Leeuwenburgh, Remy E.J.N. Litjens, Jeroen D.C. Codée, Herman S. Overkleeft, Gijsbert A. van der Marel and Jacques H. van Boom*

^{1}H- and ^{13}C-NMR spectra were recorded in $CDCl_3$ unless stated otherwise. ^{1}H-spectra were recorded on a Bruker DPX-300 (300 MHz). ^{13}C-spectra were recorded on a Jeol JNM-FX-200 (50 MHz). NMR shifts are reported in ppm (δ) relative to tetramethylsilane. Optical rotations were determined at 20 °C by means of a Propol polarimeter. Dichloromethane (Baker, p.a.) and tetrahydrofuran (THF, Baker, p.a.) were stored over molecular sieves (4 Å). Toluene was refluxed with CaH_2 for 2 h, distilled and stored over molecular sieves (4 Å). Column chromatography was performed on Baker silicagel (0.063-0.200 mm). TLC analysis was conducted on Merck TLC plastic sheets silicagel 60 F_{254}, with detection by UV absorption (254 nm) and charring with 20% H_2SO_4 in ethanol.

General procedure for the hetero-Michael reaction of alkynols **4**, **8**, **14a-d** *and* **24** *with ethyl propiolate.* A solution of the alkynol in CH_2Cl_2 (5 mL/mmol) was treated successively with *N*-methylmorpholine (1.5 equiv.) and ethyl propiolate (1.5 equiv.) and stirred for 1-2 h. Concentration, followed by column chromatography gave the pure β-(alkynyloxy)acrylate.

General procedure for the radical cyclizations of acrylates **5**, **9**, **15a-d** *and* **25** *and subsequent acidic destannylations.* A solution of the β-(alkynyloxy)acrylate in toluene (15 mL/mmol) was degassed by bubbling through with argon (20 min) and then heated (80 °C). Then, a degassed solution of Bu_3SnH (2 equiv.) and AIBN (0.25 equiv.) in toluene (5 mL/mmol acrylate) was added over 5 h (syringe pump). The reaction mixture was then stirred for another 12 h and concentrated. Silicagel column chromatography (5% EtOAc/light petroleum) yielded the pure vinylstannane. Then, the vinylstannane was

dissolved in CH_2Cl_2 (5 mL/mmol) and treated with *p*-toluenesulfonic acid (1.5 equiv.). The mixture was stirred for 1.5 h and then poured into sat. $NaHCO_3$ and extracted with Et_2O. Drying and concentration of the organic phase and silicagel chromatography gave the pure cyclic ether.

Cis-5,6-bicyclic ether **7**: colorless syrup. ^{13}C NMR: 170.1, 146.2, 138.4, 138.2, 128.2-127.5, 108.0, 80.4, 76.1, 75.7, 74.9, 74.7, 73.4, 72.1, 68.9, 60.1, 41.2, 14.1. ^{1}H NMR: 7.36-7.11 (m, 15H), 5.20 (t, 1H, *J* 2.7), 5.16 (t, 1H, 2.4 Hz), 4.98-4.94 (m, 1H), 4.96-4.74 (m, 3H), 4.88-4.84 (m, 1H), 4.64-4.48 (m, 3H), 4.31 (t, 1H, *J* 7.4 Hz), 4.18 (q, 2H, *J* 7.1 Hz), 3.74-3.56 (m, 5H), 2.63-2.61 (m, 2H), 1.27 (t, 3H). HRMS (FAB) calcd. for $C_{34}H_{38}O_7Na$ 581.2515, found: m/z 581.2525. α_D = +143 ° (*c* 1, $CHCl_3$).

Trans-6,6-bicyclic ether **11**: colorless syrup. ^{13}C NMR: 171.0, 142.8, 138.8, 138.1, 138.0, 128.3-127.5, 110.0, 83.6, 82.8, 78.9, 77.3, 76.5, 75.7, 75.2, 74.5, 73.4, 69.0, 60.6, 39.0, 37.5, 14.1. ^{1}H NMR: 7.36-7.11 (m, 15H), 4.95-4.80 (m, 4H), 4.68-4.43 (m, 4H), 4.34 (dd, 1H, J 4.3 Hz, 8.9 Hz), 4.06 (q, 2H, J 7.1 Hz), 3.72-3.46 (m, 5H), 3.41 (t, 1H, J 9.1 Hz), 3.17 (m, 1H), 2.82-2.75 (m, 2H), 2.64 (dd, 1H, J 9.1 Hz, 14.9 Hz), 2.38 (broad t, 1H, J 12.1 Hz), 1.17 (t, 3H). HRMS (FAB) calcd. for $C_{35}H_{40}O_7Na$ 595.2672, found: m/z 581.2668. α_D = -54 ° (c 1.2, $CHCl_3$).

Trans-5,6-bicyclic ether **20a**: colorless syrup. ^{13}C NMR: 169.8, 147.0, 138.6, 138.0, 128.2-127.2, 104.0, 100.5, 82.2, 79.7, 79.1, 78.1, 74.8, 73.9, 71.4, 60.4, 55.3, 41.2, 14.0. ^{1}H-NMR: 7.41-7.27 (m, 10H), 5.05 (t, 1H, *J* 1.5 Hz), 5.00 (dd, 1H, *J* 1.9 Hz; 2.9 Hz), 4.96-4.91 (m, 1H), 4.90-4.65 (m, 4H), 4.64 (d, 1H, *J* 3.7 Hz), 4.29 (dq, 1H, *J* 10.2 Hz; 2.3 Hz), 4.18 (q, 2H, *J* 7.1 Hz), 4.01 (t, 1H, *J* 9.2 Hz), 3.50 (dd, 1H), 3.41 (s, 3H), 3.37 (t, 1H), 2.76-2.58 (2× dd, 2H, *J* 7.0 Hz; 15.5 Hz), 1.28 (t, 3H). HRMS (FAB) calcd. for $C_{27}H_{32}O_7Na$ 491.2046, found: m/z 491.2051. α_D = +56.2 ° (c 1, $CHCl_3$).

Trans-6,6-bicyclic ether **20b**: white solid. ^{13}C NMR: 170.9, 142.8, 138.9, 138.2, 128.3-127.3, 110.1, 98.8, 82.8, 78.9, 78.7, 75.2, 74.9, 73.6, 67.1, 60.5, 55.1, 38.6, 37.4, 14.1. ^{1}H NMR: 7.41-7.23 (m, 10H), 4.93-4.53 (m, 6H), 4.54 (d, 1H, *J* 3.7 Hz), 4.30 (broad dd, 1H, *J* 4.7 Hz, 8.7 Hz), 4.08 (q, 2H, *J* 7.1 Hz), 3.84 (t, 1H, *J* 9.2 Hz), 3.57-3.47 (m, 2H), 3.37

(s, 3H), 3.31 (t, 1H, *J* 9.3 Hz), 2.79 (dd, 1H, *J* 4.8 Hz, 15.0 Hz), 2.69-2.60 (m, 2H), 2.78 (broad t, 1H, *J* 12.2 Hz), 1.18 (t, 3H). HRMS (FAB) calcd. for $C_{28}H_{34}O_7Na$ 505.2202, found: m/z 505.2207. α_D = +32.6 ° (*c* 1, $CHCl_3$).

Trans-7,6-bicyclic ether **20c**: colorless oil. ^{13}C-NMR: 170.4, 150.9, 138.9, 138.2, 128.2-127.4, 113.3, 97.9, 81.4, 80.2, 80.0, 78.7, 75.7, 73.3, 69.8, 60.4, 55.0, 41.9, 35.5, 26.7, 14.1. ^{1}H-NMR: 7.45-7.26 (m, 10H), 4.99 (bs, 1H), 4.94 (bs, 1H), 4.88-4.61 (m, 4H), 4.48 (d, 1H, *J* 3.7 Hz), 4.12-4.05 (m, 2H), 3.82 (t, 1H, *J* 8.8 Hz), 3.58 (m, 1H), 3.41 (s, 3H), 3.20 (t, 1H), 2.62 (dd, 1H, *J* 7.6 Hz; 13.9 Hz), 2.41-2.10 (m, 3H), 1.22 (t, 3H, *J* 7.1Hz). HRMS (FAB) calcd. for $C_{29}H_{36}O_7Na$ 519.2359, found: m/z 519.2357. α_D = +57.4 ° (*c* 1, $CHCl_3$).

Trans-8,6-bicyclic ether **20d**: colorless oil. ^{13}C-NMR: 170.3, 146.0, 138.8, 138.2, 128.3, 127.5, 120.1, 98.0, 82.5, 81.2, 79.8, 79.0, 75.8, 73.3, 69.7, 60.4, 54.9, 39.5, 32.7, 30.7, 21.5, 14.1. ^{1}H-NMR: 7.42-7.27 (m, 10H), 5.11 (bs, 1H), 5.06 (d, 1H, *J* 1.7 Hz), 4.82-4.59 (m, 5H), 4.44 (d, 1H, *J* 3.7 Hz), 4.17-4.02 (m, 2H), 3.80 (t, 1H, *J* 9.2 Hz), 3.50 (ddd, 1H, *J* 4.2 Hz; 9.9 Hz; 13.8 Hz), 3.43-3.34 (m, 4H), 2.70 (dd, 1H, *J* 7.1 Hz; 14.1 Hz), 2.57-2.46 (m, 2H), 2.13 (m, 1H), 2.05-1.82 (m, 2H), 1.76-1.68 (m, 1H), 1.49-1.39 (m, 1H), 1.21 (t, 3H, *J* 7.1 Hz). HRMS (FAB) calcd. for $C_{30}H_{38}O_7Na$ 533.2626, found: m/z 533.2632. α_D = +80.6 ° (*c* 1, $CHCl_3$).

Tricyclic ether **26**: white solid. ^{13}C NMR: 170.0, 145.3, 138.0, 137.2, 127.4-126.4, 109.0, 97.8, 81.1, 78.2 (2×), 77.5, 75.8, 74.4, 74.2, 72.6, 64.4, 59.6, 54.2, 38.1, 36.2, 33.9, 13.2. ^{1}H NMR (600 MHz): 7.41-7.26 (m, 10H), 4.94 (broad s, 1H), 4.89-4.65 (m, 5H), 4.53 (d, 1H, *J* 3.7 Hz), 4.27 (dd, 1H, *J* 5.3 Hz, 7.9 Hz), 4.17 (q, 2H, *J* 7.1 Hz), 3.83 (t, 1H, *J* 9.3 Hz), 3.57 (ddd, 1H, *J* 4.2 Hz, 9.8 Hz, 13.8 Hz), 3.49 (dd, 1H, *J* 3.7 Hz, 9.4 Hz), 3.37 (s, 3H), 3.28 (ddd, 1H, *J* 4.3 Hz, 9.2 Hz, 13.2 Hz), 3.12 (t, 1H, *J* 9.4 Hz), 3.08 (ddd, 1H, *J* 4.7 Hz, 9.2 Hz, 13.8 Hz), 2.77-2.73 (m, 2H), 2.62 (dd, 1H, *J* 8.4 Hz, 15.3 Hz), 2.30 (broad t, 1H, *J* 12.2 Hz), 2.25 (dt, 1H, *J* 4.4 Hz, 11.2 Hz), 1.49 (q, 1H, *J* 11.4 Hz), 1.26 (t, 3H, *J* 7.1 Hz). HRMS (FAB) calcd. for $C_{31}H_{38}O_8Na$ 561.2464, found: m/z 561.2468. α_D = +47.2 ° (*c* 1, $CHCl_3$).