Cleavage and Activation of Benzylidene Lactones with *N*-Bromosuccinimide

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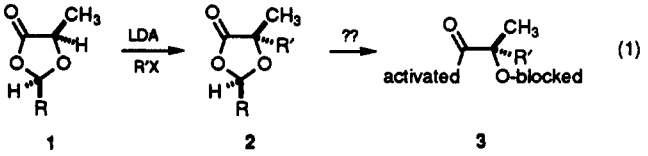
For a synthesis in the angucycline antibiotic series, our group developed a plan which would use C-branched lactic acids with the carboxyl activated and hydroxyl blocked. The preparation of the C-branch was to be via the elegant Seebach chirality transfer method[1] while the activation and blocking procedures were questions to be resolved (eq 1).



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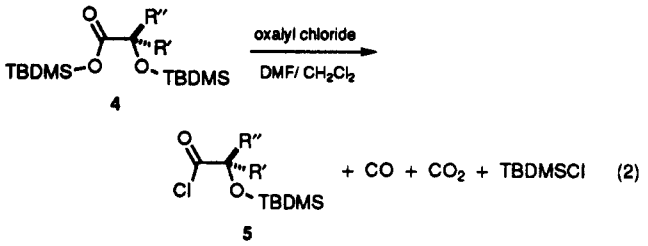
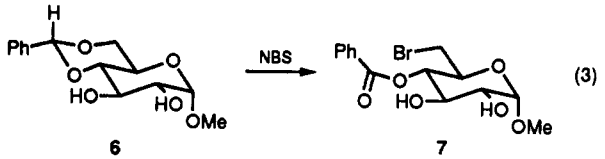
A literature survey suggested that the treatment of a persilylated derivative of the hydroxy acid with oxalyl chloride might serve to produce the activated carboxyl under conditions where acid-sensitive groups in the side chain might survive[2] (eq 2). However, in our hands, acid-



4 5 (2)

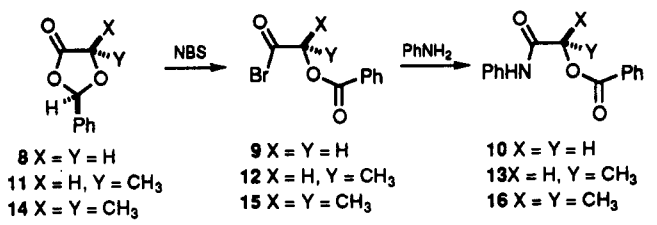
sensitive groups were not immune to degradation when these conditions were applied.

We then turned to the well-known NBS fragmentation of benzylidene acetals in the carbohydrate series (eq 3). Although the so-called Hanessain–Hullar reaction[3] has



6 7 (3)

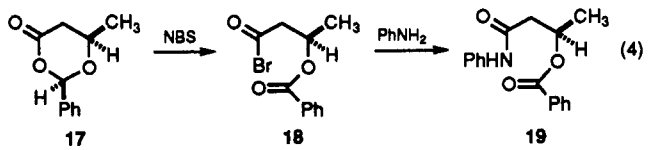
been widely used, we could find no example where a benzylidene lactone had been subjected to the standard Hanessian–Hullar conditions of heating with NBS in an organic solvent. In the event, the four lactones shown all reacted cleanly to form the intermediate acid bromide benzoates which were characterized as their anilide derivatives. It should be noted that the lactones 8, 11, and 17 have hydrogens α to carbonyls. When Zimmerman



8 X = Y = H
11 X = H, Y = CH3
14 X = Y = CH3

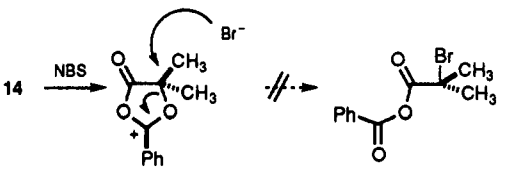
9 X = Y = H
12 X = H, Y = CH3
15 X = Y = CH3

10 X = Y = H
13X = H, Y = CH3
16 X = Y = CH3



17 18 19 (4)

and Seebach[4] performed NBS-AIBN chemistry with the lactones corresponding to structures 11 and 17, but with the acetal group derived from pivalaldehyde, these α-positions were brominated. However, in our series, in the absence of AIBN, no α-bromination was detected. In the case of lactone 14, it might have been argued that the presumed intermediate ion 20 of the Hanessian–Hullar reaction could have decomposed to yield the tertiary bromide–mixed anhydride species 21 rather than the



14 20 21

observed product. However, the anhydride product or a product of its decomposition was not identified. In conclusion, the extension of the NBS cleavage of benzylidene acetals to benzylidene lactones is a simple and efficient method for simultaneous activation of carboxyl and blocking of hydroxyl in the hydroxy acid series.[5]

Experimental Section

Nuclear magnetic resonance spectra were obtained on a GE QE-300 MHz instrument. Infrared spectra were recorded on a Perkin-Elmer 1310 spectrophotometer. The high resolution mass spectra were obtained by the mass spectrometry facility at Penn State U. Optical rotations were determined using a Rudolph Research AUTOPOL III automatic polarimeter. Elemental analyses were performed by the Schwarzkopf Microanalytical Laboratory Inc., Woodside, NY. Melting points were determined on a Fisher-Johns melting point apparatus and were uncorrected. Thin-layer chromatograms were done on precoated TLC sheets of silica gel $60F_{254}$ (E. Merck) and aluminum oxide $60F_{254}$ neutral type E (EM Separations) with the use of (2,4-dinitrophenyl)-hydrazine spray, phosphomolybdic acid, and/or short and long wave ultraviolet light to visualize the spots. Chromatotron (radial chromatography) plates were prepared by using Kieselgel $60PF_{254}$ gipshaltig (E. Merck), and all operations using the chromatotron were done under nitrogen atmosphere.

Materials. α-Hydroxy and β-hydroxy acids were purchased from Aldrich Chemical Co. All solvents used were dried and distilled.

General Procedures. A flame-dried two-necked flask (100 mL) fitted with a reflux condenser was charged with benzylidene lactone (1 mmol), *N*-bromosuccinimide (1.2 mmol), and benzene (7 mL). The mixture was refluxed for 4–5 h under nitrogen. After 1 h the reaction mixture turned from colorless to orange

(1) Seebach, D.; Naef, R.; Calderari, G. *Tetrahedron*, **1984**, *40*, 1313–1324.

(2) (a) Wissner, A.; Grudzinskas *J. Org. Chem.* **1978**, *43*, 3972–3974. (b) For a very recent method using a cyclic carbonate, see Moher, E. D.; Grieco, P. A.; Collins, J. L. *J. Org. Chem.* **1993**, *58*, 3879–3790.

(3) (a) Hanessian, S. *Methods Carbohydr. Chem.* **1972**, *6*, 183–189. (b) Hanessian, S. *Org. Synth.* **1987**, *65*, 243.

(4) Zimmerman, J.; Seebach, D. *Helv. Chim. Acta* **1987**, *70*, 1104–1104.

(5) This research was presented by V.D.R. at the MARM of the American Chemical Society, June 3, 1993; paper no. 178.

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red. After 4–5 h the reaction mixture was cooled to room temperature and filtered through a plug of Celite dropwise into a flask (100 mL) containing aniline (1.2 mmol) in benzene (5 mL) and stirred for 1 h at room temperature. Solvent was removed on a rotary evaporator. The residue thus obtained was dissolved in chloroform and filtered through a plug of Celite to remove salts. The filtrate was removed on a rotary evaporator and the residue was purified by either radial chromatography (silica gel), column chromatography (Florisil), or preparative TLC (neutral alumina) (hexane/ethyl acetate 85:15), yield 60–80%.

The spectral data and melting points of the compounds obtained by using the general procedure described above are as follows.

Anilides of Acid Bromides Generated from the Reactions of Benzylidene Lactones with *N*-Bromosuccinimide. (a) Benzoate of Glycolic Acid Anilide. The benzylidene lactone was synthesized according to a literature method:[6] mp 140–141 °C, IR ($CHCl_3$) 3400 (m), 1670 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.9 (s, 2 H, CH_2), 8.16 (d, 2 H, J = 7.21 Hz, *Ph*CO), 7.96 (s br, ArN*H*), 7.69 (t, 1 H, J = 7.1, *Ph*CO), 7.49–7.60 (m, 4 H, *Ph*CO and *Ph*NH), 7.38 (t, 2 H, J = 7.8 Hz, *Ph*NH), 7.22 (t, 1 H, J = 7.20 Hz, *Ph*NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 64.28, 121.68, 125.64, 129.36, 129.70, 130.42, 132.65, 134.53, 137.29, 165.79, 165.85; HRMS (EI) calcd for $C_{15}H_{13}NO_3$ (M) 255.0896, found 255.0918.

(b) Benzoate of Lactic Acid Anilide. The lactone was synthesized following a literature method:[7] $[\alpha]^{32}_D$ +59.9° (c = 0.49, $CHCl_3$); mp = 124–125 °C; IR ($CHCl_3$) 3410 (m), 1670 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.74 (d, 3 H, J = 6.8 Hz, CH_3), 5.65 (q, 1 H, J = 6.8 Hz, $CHCH_3$), 8.15 (d, 2 H, J = 7.1 Hz, *Ph*CO), 8.07 (s br N*H*), 7.69 (t, 1 H, J = 7.4, *Ph*CO), 7.57 (m, 4 H, *Ph*CO, *Ph*NH), 7.37 (t, 2 H, J = 7.5, *Ph*NH), 7.18 (t, 1 H, J = 7.3, *Ph*NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.28, 71.95, 120.77, 125.42, 129.31, 129.64, 129.87, 130.35, 132.59, 137.63, 165.98, 168.94; HRMS (EI) calcd for $C_{16}H_{15}NO_3$ (M) 269.1052, found 269.1046. Anal. Calcd for $C_{16}H_{15}NO_3$: C, 71.34; H, 5.57; N, 5.20. Found: C, 71.58; H, 5.40; N, 5.22.

(c) Benzoate of 2-Hydroxyisobutyric Acid Anilide. The benzylidene lactone was prepared according to a literature method:[8] mp = 89–90 °C; IR ($CHCl_3$) 3400 (m), 1660 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.91 [s, 6 H, $C(CH_3)_2$], 8.10 (d, 2 H, J = 7.5 Hz, *Ph*CO), 7.97 (s, br, 1 H, N*H*), 7.64 (t, 1 H, J = 7.4 Hz, *Ph*CO), 7.56 (m, 4 H, *Ph*CO), 7.37 (t, 2 H, J = 7.8 Hz, *Ph*NH), 7.18 (t, 1 H, J = 7.3 Hz, *Ph*NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.18, 82.96, 120.90, 125.20, 129.21, 129.60, 130.26, 130.85, 134.04, 138.05, 165.82, 171.61; HRMS (EI) calcd for $C_{17}H_{17}NO_3$ (M) 283.1209, found 283.1204. Anal. Calcd for $C_{17}H_{17}NO_3$: C, 72.05; H, 6.01; N, 4.94. Found: C, 71.98; H, 6.01; N, 4.68.

(d) Benzoate of β-Hydroxybutyric Acid Anilide. The benzylidene lactone was synthesized according to a literature method:[5a] anilide mp = 109–110 °C; IR ($CHCl_3$) 3405 (m), 1660 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.57 (d, 3 H, J = 6.3 Hz, CH_3), 2.76 (dd, 1H, J = 14.63, 5.75 Hz, $COCH_2CH$), 2.88 (dd, 1 H, J = 14.65, 5.92 Hz, $COCH_2CH$), 5.62 (m, 1 H, J = 6.19 Hz, $CHCH_3$), 8.08 (d, 2 H, J = 7.03 Hz, *Ph*CO), 7.74 (s br, PhN*H*), 7.62 (t, 1 H, *Ph*CO), 7.49 (m, 4 H, *Ph*CO, *Ph*NH), 7.35 (t, 2 H, J = 7.67, *Ph*NH), 7.14 (t, 1 H, J = 7.3 Hz, *Ph*NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.81, 44.84, 69.73, 120.92, 124.76, 129.10, 129.82, 130.15, 133.86, 138.23, 138.66, 164.47, 168.32; HRMS (EI) calcd for $C_{17}H_{17}NO_3$ (M) 283.1209, found 283.1208.

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