Aluminum-Mediated 1,2-Alkyl Migration Resulting from Hydrocyanation of an α-Epoxy Ketone

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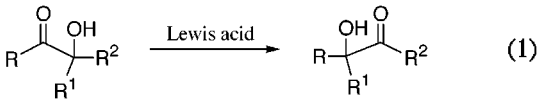
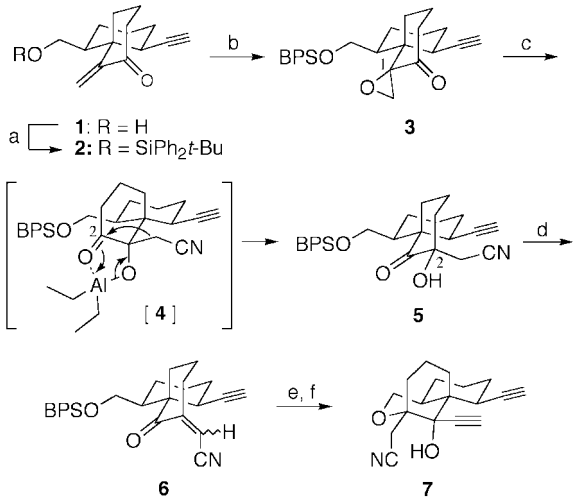
Treatment of α-hydroxy ketones with Lewis acid is known to result in 1,2-anionotropic rearrangement of either alkyl or hydride to afford the transposed ketone (eq 1).[1] The first example of this reaction is the Lobry de Bruyn−Alberda van Ekenstein transformation, the classic isomerization of an aldose to a ketose.[2] The synthetic utility of the α-ketol rearrangement is exemplified in the ring expansion approaches used to construct the taxane ring system[1a,c,3] and in ring contractions.[4] The rearrangements proceed to deliver the more stable α-hydroxy ketone.



(1)

Whereas the α-ketol rearrangement generally proceeds by direct treatment of an α-hydroxy ketone with Lewis acid, the in situ generation of an α-hydroxy ketone in the presence of Lewis acid might also result in the isomerization. Indeed, we have observed a facile 1,2-alkyl migration from an α-epoxy ketone after forming a transient α-oxy ketone. In the event, an epoxide opening with subsequent 1,2-alkyl migration proceeds to transform an α-epoxy ketone directly to a corresponding transposed ketone.

Scheme 1[a]



[a] (a) TBDPSCl, Et_3N, DMAP, CH_2Cl_2, 100%; (b) *t*-BuOOH, Triton B, C_6H_6, 84% (49% for depicted isomer); (c) Et_2AlCN, toluene, 45 °C, 74%; (d) $SOCl_2$, pyridine, 68%; (e) HCCLi, $CeCl_3$, THF, −78 °C; (f) TBAF, THF, two-step 55%.

Protection of the hydroxyl group in **1**[5] (Scheme 1) as its corresponding *tert*-butyldiphenylsilyl (BPS) ether, followed by treatment with basic *tert*-butyl hydroperoxide, provides α-epoxy ketone **3** as a 1.4:1 mixture of C(1) diastereomers (major isomer shown).[6] Hydrocyanation of **3** using the method of Nagata[7] results in regioselective ring opening of the epoxide and subsequent 1,2-cyanomethyl migration to yield transposed α-hydroxy ketone **5**. We postulate that the epoxide addition product readily assumes chelate structure [**4**] wherein the axial cyanomethyl group is favorably aligned for 1,2-migration. The minor diastereomer from epoxidation of **2** also undergoes the tandem Nagata-Lobry de Bruyn−Alberda van Ekenstein transformation to give the C(2) epimer of **5**, although in lower yield.[8] Thus, the rearrangement occurs via syn-facial migration and is dependent on epoxide stereochemistry. Apparently, the **3** → **5** transformation is assisted by the relief of steric congestion resulting from the adjacent vicinal quaternary centers in [**4**]. Although the relief of internal ring strain has been shown to control 1,2-anionotropic rearrangements, the alleviation of steric strain has not been previously shown to direct the migration.

The carbonyl transposition was unequivocally confirmed by X-ray analysis of a derivative. Treatment of **5** with thionyl chloride in pyridine provides the corresponding vinylogous acyl nitrile **6** as a 3:1 (*Z*:*E*) mixture of diastereomers. The assignment of alkene stereochemistry is based on ^{1}H NMR chemical shift analysis of the olefinic proton according to the method of Fry.[9] Regi-

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(1) (a) Zeng, Q.; Bailey, S.; Wang, T.-Z.; Paquette, L. A. *J. Org. Chem.* **1998**, *63*, 137. (b) White, J. D.; Cutshall, N. S.; Kim, T.-S.; Shin, H. *J. Am. Chem. Soc.* **1995**, *117*, 9780. (c) Holton, R. A.; Williams, A. D. *J. Org. Chem.* **1988**, *53*, 5983. (d) Palmisano, G.; Danieli, B.; Lesma, G.; Mauro, M. *J. Chem. Soc. Chem. Commun.* **1986**, 1564. (e) Stevens, C. L.; Glenn, F. E.; Pillai, P. M. *J. Am. Chem. Soc.* **1973**, *95*, 6301.

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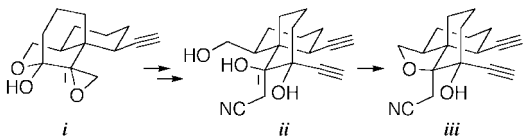
(3) Paquette, L. A.; Elmore, S. W.; Combrink, K. D.; Hickey, E. R.; Rogers, R. D. *Helv. Chim. Acta* **1992**, *75*, 1755.

(4) (a) Nagahama, S.; Tazaki, M. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 4175. (b) Bach, R. D.; Tubergen, M. W.; Klix, R. C. *Tetrahedron Lett.* **1986**, *27*, 3565.

(5) (a) Spence, J. D.; Lowrie, L. E.; Nantz, M. H. *Tetrahedron Lett.* **1995**, *36*, 5499. (b) Spence, J. D.; Wyatt, J. K.; Bender, D. M.; Moss, D. K.; Nantz, M. H. *J. Org. Chem.* **1996**, *61*, 4014.

(6) The epoxide stereochemistry was determined by correlation with the major epoxide ***i*** that results from treatment of enone **1** with basic *t*-BuOOH (see: Nantz, M. H.; Moss, D. K.; Spence, J. D.; Olmstead, M. M. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 470). Silylation of ***i*** gave epoxide **3**. The stereochemistry was confirmed when epoxide opening and subsequent transformations on ***i*** gave ***ii***, which when treated with PPh_3 and diethyl azodicarboxylate gave tetrahydrofuran ***iii*** (Moss, D. K.; Nantz, M. H. unpublished results).



i *ii* *iii*

(7) Nagata, W.; Yoshioka, M. *Tetrahedron Lett.* **1966**, 1913.

(8) The C(2) epimer of **5** is formed in 48% yield from the C(1) epoxide epimer of **3**.

(9) The β-proton of an (*S*)-cis,(*Z*)-substituted enone resonates upfield relative to the corresponding (*E*)-substituted enone; see: Faulk, D. D.; Fry, A. *J. Org Chem.* **1970**, *35*, 364.

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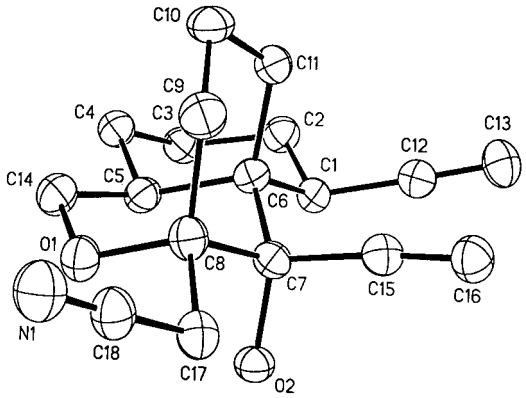

Figure 1. Molecular structure of compound **7**.

oselective 1,2-addition of cerium acetylide[10] to the (*Z*)-isomer of **6** followed by desilylation provides **7**. The hydroxyl group deprotection effected a spontaneous Michael addition to the resident vinyl nitrile. Figure 1 shows the X-ray structure of **7**.[11] The newly formed pyranyl ring supports the assigned structure of **5**.

In summary, we have observed a tandem epoxide cleavage−1,2-anionotropic rearrangement to directly provide a transposed α-ketol from an α-epoxy ketone. While this reaction may point toward a limitation of the Nagata reaction on α-epoxy ketones, the reaction may prove to be a useful entry to functionalized α-hydroxy ketones. In the present example, a cyanomethyl group migrates to relieve steric congestion.

Experimental Section

General. All reactions were carried out under an atmosphere of nitrogen. CH_2Cl_2 was distilled from calcium hydride immediately prior to use. THF and Et_2O were distilled from sodium benzophenone ketyl immediately prior to use, and benzene and toluene were distilled from sodium. All amine reagents were distilled from CaH_2. Column chromatography was carried out using 230−400 mesh silica gel, slurry packed in glass columns, eluting with the solvents indicated. Yields were calculated for material judged to be homogeneous by TLC and NMR. TLC was performed on kieselgel 60 F_{254} plates, staining with an ethanolic solution of *p*-anisaldehyde containing 5% concentrated H_2SO_4.

^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) were recorded in $CDCl_3$. High-resolution mass spectrometry was performed by Mass Spectrometry Service Lab, Minneapolis, MN. Infrared (IR) data were obtained on neat samples.

11-{[(*tert*-Butyldiphenylsilyl)oxy]methyl}-7-ethynyl-1-methylidene-spiro[5.5]undecan-2-one (2). To a solution of **1** (462 mg, 1.99 mmol) in CH_2Cl_2 (20 mL) at 0 °C were added 4-(dimethylamino)pyridine (123 mg, 1.00 mmol), triethylamine (0.840 mL, 6.00 mmol), and *tert*-butylchlorodiphenylsilane (0.570 mL, 2.19 mmol). The reaction was stirred for 16 h while being warmed to room temperature. The reaction mixture was then diluted with $CHCl_3$ and washed successively with saturated aqueous $NaHCO_3$ and brine. The aqueous phase was extracted with $CHCl_3$, and the combined organic fraction was dried (Na_2SO_4). The solvents were removed by rotary evaporation to provide a crude oil that was purified by flash chromatography (1:1:8 EtOAc:$CHCl_3$:hexane) to afford 935 mg (100%) of **2** as a clear waxy solid: IR 3305, 3072, 3014, 2112, 1693, 1591 cm^{-1}; ^{1}H NMR δ 7.63 (m, 4H), 7.42 (m, 6H), 6.22 (s, 1H), 5.31 (s, 1H), 3.69 (dd, J = 9.7, 3.3 Hz, 1H), 3.41 (dd, J = 9.3, 9.3 Hz, 1H), 2.30 (overlapping m, 4H), 1.97 (d, J = 2.4 Hz, 1H), 1.83 (m, 5H), 1.57 (m, 1H), 1.38 (m, 4H), 1.08 (s, 9H); ^{13}C NMR δ 201.2, 150.7, 135.4, 135.3, 133.4, 133.3, 129.6, 129.5, 127.6, 122.7, 86.0, 71.1, 64.4, 49.4, 45.6, 43.7, 38.6, 28.8, 26.8, 25.0, 24.7, 24.3, 19.9, 19.1; exact mass calcd for $C_{31}H_{39}O_2Si$ $(M + H)^+$ 471.2719, found 471.2709.

11-{[(*tert*-Butyldiphenylsilyl)oxy]methyl}-7-ethynyl-1,2′-oxiranespiro[5.5]undecan-2-one (3). To a solution of **2** (318 mg, 0.677 mmol) in benzene (7 mL) at room temperature was added *t*-BuOOH (0.26 mL of a 70% solution in H_2O, 2.7 mmol). The reaction was cooled to 0 °C, and Triton B (0.12 mL of a 40% solution in methanol, 0.68 mmol) was added. The reaction was stirred at room temperature for 15 h. The reaction mixture was then diluted in Et_2O and washed with saturated aqueous $NaHCO_3$ and brine. The aqueous layer was extracted with Et_2O, and the combined organic fraction was dried (Na_2SO_4). The solvents were removed by rotary evaporation to provide a crude product that was purified by flash chromatography (gradient 1:9 EtOAc:hexane to 1:4 EtOAc:hexane) to afford 275 mg (84%) of a 1.4:1 mixture of epoxide diastereomers. Spectral data for the major isomer (**3**): IR 3306, 3072, 3013, 2132, 1721, 1605 cm^{-1}; ^{1}H NMR δ 7.61 (m, 4H), 7.40 (m, 6H), 3.72 (dd, J = 10.4, 3.6 Hz, 1H), 3.60 (dd, J = 10.4, 6.6 Hz, 1H), 3.37 (ABd, J = 5.2 Hz, 1H), 2.80 (ABd, J = 5.5 Hz, 1H), 2.41 (m, 2H), 2.10 (overlapping m, 4H), 1.70 (m, 5H), 1.29 (m, 4H), 1.09 (s, 9H); ^{13}C NMR δ 208.2, 135.7, 135.5, 133.6, 133.3, 129.6, 129.5, 127.6, 86.6, 71.1, 64.7, 64.1, 55.2, 45.4, 41.9, 39.7, 36.0, 29.2, 27.0, 25.9, 24.4, 19.7, 19.3; exact mass calcd for $C_{31}H_{38}O_3Si$ 486.2590, found 486.2590.

11-{[(*tert*-Butyldiphenylsilyl)oxy]methyl}-2-(cyano)methyl-7-ethynyl-2-hydroxy-spiro[5.5]undecan-1-one (5). To a solution of **3** (54 mg, 0.11 mmol) in toluene (0.7 mL) at room temperature was added Et_2AlCN (0.55 mL of a 1.0 M solution in toluene, 0.55 mmol). The reaction was stirred at 45 °C for 3 h. The reaction was cooled to room temperature and diluted with Et_2O and an aqueous solution of Rochelle's salt (saturated potassium sodium tartrate). The biphasic mixture was vigorously stirred for 30 min whereupon the organic layer was separated and washed with brine. The aqueous layer was extracted with Et_2O, and the combined organic fraction was dried (Na_2SO_4). The solvent was removed by rotary evaporation to provide a crude product that was purified by flash chromatography (3:7 EtOAc:hexane) to provide 42 mg (74%) of **5** as a clear oil: IR 3400 (br), 3300, 3072, 3051, 2252, 2112, 1722 cm^{-1}; ^{1}H NMR δ 7.61 (m, 4H), 7.42 (m, 6H), 3.55 (dd, J = 10.6, 4.7 Hz, 1H), 3.34 (dd, J = 10.5, 7.3 Hz, 1H), 2.81 (ABd, J = 17.0 Hz, 1H), 2.64 (s, 1H), 2.58 (ABd, J = 17.0 Hz, 1H), 2.08 (d, J = 2.7 Hz, 1H), 1.92 (m, 4H), 1.68 (m, 6H), 1.33 (m, 4H),

(10) (a) Imamoto, I.; Sugiura, Y.; Takiyama, N. *Tetrahedron Lett.* **1984**, *25*, 4233. (b) For an experimental procedure to prepare anhydrous cerium chloride, see: Imamoto, T. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol.1, Chapter 1.8, p 231.

(11) Crystal data: colorless, monoclinic, $P2_1/n$, a = 8.160(2), b = 14.790(4), and c = 12.572(3) Å, β = 105.06(2)°, V = 1465.1(7) Å^3, Z = 4, D_{calcd} = 1.285 mg/m^3, T = 130(2) K, full matrix refinement on F^2 (Siemens P4, SHELXTL 5, 1930 independent reflections, 1444 with $I > 2\sigma(I)$), $R_1(F)$ = 7.62%, $R_2(wF^2)$ = 15.7%, GOF(F^2) = 1.042.

1.09 (s, 9H); ^{13}C NMR δ 214.6, 135.7, 135.6, 133.1, 133.0, 129.8, 127.8, 127.7, 116.9, 86.2, 72.3, 71.3, 66.0, 52.9, 48.8, 40.4, 32.9, 28.1, 27.5, 26.8, 24.5, 24.4, 23.6, 19.1, 18.1; exact mass calcd for $C_{32}H_{40}NO_3Si$ $(M + H)^+$ 514.2777, found 514.2760.

11-{[(*tert*-Butyldiphenylsilyl)oxy]methyl}-2-(cyano)methylidene-7-ethynylspiro[5.5]undecan-1-one (6). To a solution of alcohol **5** (16 mg, 0.032 mmol) in pyridine (0.35 mL) at 0 °C was added $SOCl_2$ (5 μL, 0.064 mmol). The reaction was stirred at 0 °C for 2 h, warmed to room temperature, and stirred for an additional 2 h. After the reaction was quenched with H_2O, the mixture was diluted with $CHCl_3$ and washed with saturated aqueous NH_4Cl and brine. The aqueous layer was extracted with $CHCl_3$, and the combined organic fraction was dried (Na_2SO_4). The solvent was removed by rotary evaporation to provide a crude product that was purified by flash chromatography (1:4:20 EtOAc:$CHCl_3$:hexane) and followed by preparative thin-layer chromatography to provide 11 mg (68%) of **6** as a 3:1 mixture of *Z*/*E* isomers. **(*E*)-isomer:** IR 3306, 3071, 3051, 3018, 2257, 2113, 1664, 1598 cm^{-1}; ^{1}H NMR δ 7.56 (m, 4H), 7.39 (m, 6H), 7.04 (m, 1H), 3.42 (m, 2H), 3.22 (ABd, J = 19.5 Hz, 1H), 3.06 (ABd, J = 19.8 Hz, 1H), 2.77 (m, 1H), 2.59 (m, 1H), 2.23 (m, 2H), 2.03 (m, 1H), 1.97 (d, J = 2.4 Hz, 1H), 1.76 (m, 2H), 1.56 (m, 2 H), 1.46−1.12 (overlapping m, 3H), 1.09 (s, 9H); ^{13}C NMR δ 199.8, 146.0, 135.6, 135.5, 133.3, 133.1, 130.4, 129.8, 127.7, 127.6, 117.6, 104.6, 85.1, 71.0, 65.6, 49.9, 46.6, 39.3, 27.8, 26.8, 24.6, 23.6, 23.5, 21.5, 19.1, 18.7; exact mass calcd for $C_{32}H_{38}NO_2Si$ $(M + H)^+$ 496.2671, found 496.2661.

(*Z*)-isomer: IR 3302, 3089, 3069, 3051, 2218, 2113, 1686, 1599 cm^{-1}; ^{1}H NMR δ 7.59 (m, 4H), 7.38 (m, 6H), 6.10 (dd, J = 2.8, 1.5 Hz, 1H), 3.35 (m, 2H), 2.95 (m, 1H), 2.79 (m, 1H), 2.67 (m, 1H), 2.39 (m, 1H), 2.03 (d, J = 2.4 Hz, 1H), 1.96 (m, 2H), 1.65 (m, 2H), 1.61−1.15 (overlapping m, 6H), 0.96 (s, 9H); ^{13}C NMR δ 201.5, 154.9, 138.2, 135.5, 133.1, 133.0, 129.8, 127.8, 127.7, 116.4, 103.7, 85.2, 71.3, 65.6, 51.2, 47.0, 40.6, 29.8, 27.9, 26.7, 24.4, 24.3, 23.1, 20.1, 19.0; exact mass calcd for $C_{32}H_{38}NO_2Si$ $(M + H)^+$ 496.2671, found 496.2673.

2-(2,13-Diethynyl-13-hydroxy-8-oxatricyclo[7.3.1.0^{1,6}]tridec-9-yl)ethanenitrile (7). To a suspension of $CeCl_3$[10] (205 mg, 0.83 mmol) in THF (0.3 mL) at −78 °C was added a solution of lithium acetylide (0.41 mmol, prepared according to the method of Midland[12]) in THF. The reaction was stirred at −78 °C for 1.5 h, and then a cooled solution of **6** (20 mg, 41 μmol) in THF (0.3 mL) was added via cannula. The reaction was stirred at −78 °C for 1 h and quenched by addition to a separatory funnel containing 5% aqueous HCl and Et_2O. The organic layer was separated and successively washed with 5% HCl, saturated aqueous $NaHCO_3$, and brine. The combined aqueous phase was extracted with Et_2O. The organic fractions were combined and dried (Na_2SO_4). The solvents were removed by rotary evaporation. Purification of the crude product by flash chromatography (gradient: 1:9 EtOAc:hexane to 1:1 EtOAc:hexane) provided 11 mg of unreacted **6** and 7 mg (72%, based on recovered starting material) of the corresponding 1,2-addition product as a clear oil; ^{1}H NMR δ 7.72 (m, 4H), 7.48 (m, 6H), 6.11 (m, 1H), 3.87 (dd, J = 11.3, 7.6 Hz, 1H), 3.43 (dd, J = 7.4, 3.1 Hz, 1H), 2.83 (s, 1H), 2.77 (m, 2H), 2.15 (d, J = 2.6 Hz, 1H), 1.98 (m, 2H), 1.78−1.50 (overlapping m, 6H), 1.28 (m, 5H), 1.06 (s, 9H).

To the 1,2-addition product (9.0 mg, 17 μmol) in THF (0.2 mL) at room temperature was added TBAF (40 μL of a 1.0 M solution in THF, 40 μmol). The resultant dark brown reaction was stirred at room temperature for 6 h. The reaction was quenched by the addition of H_2O. After dilution with $CHCl_3$, the organic layer was separated and washed with brine. The aqueous layer was extracted with $CHCl_3$, and the combined organic fraction was dried (Na_2SO_4). After solvent removal by rotary evaporation, the crude was purified by flash chromatography (gradient, 1:9 EtOAc:hexane to 1:1 EtOAc:hexane) to provide 4 mg (77%) of **7**: IR 3684, 3305, 2934, 2861, 2247, 2112 cm^{-1}; ^{1}H NMR δ 3.97 (t, J = 12.4 Hz, 1H), 3.62 (dd, J = 12.1, 7.1 Hz, 1H), 2.89 (ABq, J = 16.8 Hz, 2H), 2.80 (m, 1H), 2.62 (s, 1H), 2.60 (m, 1H), 2.52−2.09 (overlapping m, 4H), 2.07 (d, J = 2.2 Hz, 1H), 2.01−1.42 (overlapping m, 9H); ^{13}C NMR δ 117.8, 85.7, 82.3, 80.6, 77.7, 77.2, 73.6, 67.8, 41.8, 37.0, 34.2, 32.2, 30.8, 27.1, 25.3, 23.6, 22.8, 20.1; exact mass calcd for $C_{18}H_{21}NO_2$ 283.1572, found 283.1563.

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Supporting Information Available: ^{13}C NMR spectra of compounds **2**−**6** and X-ray crystallographic data for compound **7** (12 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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