Use of a Conformational Radical Clock for Evaluating Alkyllithium-Mediated Cyclization Reactions

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SUPPORTING INFORMATION

General Experimental: IR spectra were recorded on a MIDAC Prospect FT-IR spectrometer. ^{1}H NMR were recorded at 500 and 400 MHz and ^{13}C NMR spectra were recorded at 125 and 75 MHz on Bruker instruments. Chemical shifts of the ^{1}H NMR spectra were referenced to residual chloroform at 7.26 ppm. Chemical shifts of the ^{13}C spectra were referenced to $CDCl_3$ at 77.0 ppm. Capillary chiral GC analysis was performed on a Hewlett Packard 5890 instrument using a CHIRALDEX γ-cyclodextrin trifluoroacetyl (G-TA) column (20 m × 0.25 mm) or a CHIRALDEX β-cyclodextrin permethylated hydroxylpropyl (B-PH) column (20 m × 0.25 mm). A flame ionization detector and a Hewlett Packard computer interfaced integrator were employed for analysis. Optical rotations were determined on a JASCO DIP-370 digital polarimeter. Combustion analyses were performed by M–H–W laboratories, Phoenix, Arizona. Mass spectra were determined on an AE2–MS 30, a PG 7070E–HF, a CG Analytical 7070E, or a Fisions autospec spectrometer. Tetrahydrofuran (THF), Et_2O, and CH_2Cl_2 were dried by filtration through alumina according to the procedure described by Grubbs.[1] Liquid chromatography was performed using forced flow (flash chromatography) of the indicated solvent system on E. Merck reagent silica gel 60 (230–400 mesh). Moisture sensitive reactions were carried out under atmosphere of N_2 or argon using oven or flame dried glassware and standard syringe/septa techniques.

2-Carboethoxy-tetrahydro-pyran (9). Tetrahydropyran-2-methanol (**5**) (15.63 g, 135 mmol) was dissolved in CH_2Cl_2 (200 mL), and TEMPO (250 mg) was added. The mixture was cooled to 0 °C, and Aliquat® 336 (2.80 g) was added, followed by 0.5 M KBr (27 mL). With vigorous stirring, a pH 8.6 solution of NaOCl (prepared by dissolving 57.6 g $NaHCO_3$ in 480 mL commercial bleach and 480 mL water) was added dropwise via addition funnel to the reaction. The biphasic reaction was allowed to warm to room temperature overnight, then was basified by the addition of solid NaOH (15 g). The aqueous layer was extracted with CH_2Cl_2 (100 mL × 2), and was then acidified *carefully* with conc. HCl (150 mL). The crude acid was extracted with EtOAc (250 mL × 8), dried ($MgSO_4$), and concentrated under high vacuum to afford a yellow oil. Ethanol (100 mL) was added, followed by acetyl chloride (ca. 10 mL), and the mixture was refluxed for 2 h. The mixture was cooled to room temperature, and poured into an ice-cold solution of saturated $NaHCO_3$ (250 mL). Filter through Celite, extract with Et_2O (× 6), and dry

[1] Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K. Timmers, F. J. *Organometallics*, **1996**, *15*, 1518-1520.

($MgSO_4$). Distill product under house vacuum (117-120 °C) to yield a colorless oil (15.71 g, 99.3 mmol, 71% for 2 steps). IR (neat) 2941, 2857, 1756, 1736, 1193, 1175, 1098 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.22 (q, *J* = 7.1 Hz, 2 H), 4.11–4.08 (m, 1 H), 3.97 (dd, *J* = 10.4, 2.6 Hz, 1 H), 3.49 (td, *J* = 11.3, 2.3 Hz, 1 H), 1.96–1.93 (m, 1 H), 1.89–1.86 (m, 1 H), 1.66–1.52 (m, 4 H), 1.28 (t, *J* = 7.1 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.7, 76.3, 68.2, 61.0, 28.9, 25.3, 22.9, 14.2. Anal. Calcd. for $C_8H_{14}O_3$: C, 60.74; H, 8.92. Found: C, 60.46; H, 9.09.

2-Carboethoxy-2-(4-pentenyl)tetrahydropyran (6). THF (150 mL), was cooled to 0 °C and diisopropylamine (8.8 mL**,** 62.8 mmol) was added. A solution of *n*-BuLi (25 mL, 2.2 M in hexanes) was added at once and after 15 min, the yellow solution was cooled to –78 °C. A solution of **6** (8.26 g, 52.3 mmol) was added via cannula as a solution in THF (20 mL). After 10 min at –78 °C, the reaction was warmed to –20 °C for 10 min, then cooled back down to –78 °C. The iodide[2] (12.3 g, 62.8 mmol) was added via cannula and the solution was allowed to warm slowly to room temperature overnight. After 20 h, the reaction mixture was quenched by the addition of saturated NH_4Cl, and water was added to the mixture to dissolve the precipitated salts. The mixture was extracted with Et_2O (2 x 75 mL) and dried ($MgSO_4$). Chromatography (10% EtOAc/hexanes) afforded the product (8.55 g, 38 mmol, 72%) as pale yellow oil: IR (neat) 2942, 2865, 1741, 1728, 1641, 1444, 1177, 1095, 909 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.76 (dddd, *J* = 17.0, 10.3, 6.6, 6.6 Hz, 1 H), 4.98 (dd, *J* = 17.1, 1.6 Hz, 1 H), 4.93 (dd, *J* = 10.2, 1.1 Hz, 1 H), 4.24 (q, *J*= 7.1 Hz, 2 H), 3.85–3.82 (m, 1 H), 3.69 (td, *J*= 11.7, 3.0 Hz, 1 H), 2.17-1.14 (m, 1 H), 2.04-1.99 (m, 2 H), 1.73-1.69 (m, 1 H), 1.66 (dd, *J* = 9.5, 7.4 Hz, 2 H), 1.55-1.38 (m, 6 H), 1.30 (t, *J* = 7.1 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.8, 138.3, 114.7, 79.8, 64.7, 60.7, 39.7, 33.8, 32.8, 25.3, 22.4, 20.7, 14.4. Anal. Calcd. for $C_{13}H_{22}O_3$: C, 68.99; H, 9.80. Found: C, 69.13; H, 10.03.

Diastereomeric amides *(R,R)*-7 and *(S,R)*-7'. A mixture of amide diastereomers was prepared in quantitative yield from **6** using the same procedure that was use to prepare compound **11** in ref 3.[3] The diastereomers were separated by MPLC (20% EtOAc/hexanes) and isolated as pale yellow oils.

More polar diastereomer 7 (absolute configuration at quaternary carbon undetermined). Data for **7**: R_f = 0.39 in 30% EtOAc/hexanes; $[\alpha]^{24}_D$ = 37.5 *(c* 1.04, $CHCl_3$); IR (neat) 3417, 3334, 3064, 3030, 2938, 2866, 1667, 1510, 1453, 1376, 1212, 1083, 1044, 909, 762, 700 cm^{-1}; ^1H NMR (500 MHz, $CDCI_3$) δ 7.34-7.30 (m, 4 H), 7.25-7.23 (m, 1 H), 6.90 (d, *J* = 8.0 Hz, 1 H), 5.67 (dddd, *J* = 17.0, 10.3, 6.7, 6.7 Hz, 1 H), 5.15-5.09 (app quintet, 1 H), 4.93-4.89 (m, 2 H), 3.69-3.67 (m, 2 H), 1.97-1.90 (m, 3 H), 1.82-1.76 (app td, 1 H), 1.72-1.67(m, 1 H), 1.64-1.57 (m, 3H), 1.55-1.53 (m, 2 H), 1.52 (d, *J* = 6.9 Hz, 3 H), 1.27-1.22 (m, 1 H), 1.19-1.13 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.3, 143.4, 138.5, 128.5, 127.2, 126.2, 114.5, 79.3, 63.2, 48.2, 35.0, 33.7, 31.8, 25.4, 22.3, 21.9, 19.6. Anal. Calcd. for $C_{19}H_{27}NO_2$: C, 75.71; H, 9.03; N, 4.65. Found: C, 75.80; H, 8.98; N, 4.65.

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[2] The iodide was synthesize from 4-penten-1-ol by tosylation (TsCl, pyr) and Finkelstein displacement (NaI, acetone) in an overall yield of 66%.

[3] Buckmelter, A. J.; Kim, A. I.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2000**, *122*, 9386-9390.

2-(4-Pentenyl)tetrahydropyran-2-carboxamide (8). Prepared in 95% yield from optically pure **7** following the identical procedure as for the preparation of **12** in ref 3. After chromatography, the product was isolated as a white solid: mp 94-95 °C; IR (neat) 3436, 3214, 2939, 2868, 1628, 1042 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.57 (br s, 1 H), 5.78 (dddd, *J* = 17.0, 10.3, 6.7, 6.7 Hz, 1 H), 5.36 (br s, 1 H), 5.03-4.93 (m, 2 H), 3.71-3.69 (app t, 2 H), 2.07-1.95 (m, 2 H), 1.89-1.81 (m, 1 H), 1.72-1.51 (m, 7 H), 1.44-1.33 (m, 2 H); ^{13}C NMR (125 MHz, $CDC1_3$) δ 177.2, 138.5, 114.7, 79.6, 63.5, 35.1, 33.8, 31.6, 25.3, 22.4, 19.7. Anal. Calcd. for $C_{11}H_{19}NO_2$: C, 66.97; H, 9.71; N, 7.10. Found: C, 67.12; H, 9.93; N, 7.35.

(–)-2-Cyano-2-(4-Pentenyl)tetrahydropyran (9). Prepared from **7** following the identical procedure as for the preparation of **4** in ref. 3. After chromatography, the product was isolated as a pale yellow oil (86% yield). Resolution of enantiomers by chiral GC: enantiomers elute at 42.87 min & 43.64 min; conditions: B-PH column, initial temperature = 50 °C for 5 min, then gradient of 2.0 °C/min until 150 °C is reached. Data for **9**: $[\alpha]_D^{24} = -63.4$ *(c* 1.90, $CHCl_3$); IR (neat) 2946, 2865, 1641, 1441, 1092, 1046 cm^{-1}; ^1H NMR (500 MHz, $CDCI_3$) δ 5.79 (dddd, *J* = 17.0, 10.2, 6.7, 6.7 Hz, 1 H), 5.03 (dd, *J* = 17.1, 1.2 Hz, 1 H), 4.98 (dd, *I*= 10.2, 1.0 Hz, 1 H), 3.96-3.92 (m, 1 H), 3.83-3.78 (app td, 1 H), 2.12-2.09 (m, 2 H), 1.89-1.80 (m, 3 H), 1.79-1.68 (m, 3 H), 1.64-1.51 (m, 4 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.8, 119.1, 115.2, 75.2, 65.7, 40.0, 34.8, 33.3, 24.8, 22.8, 20.3. Anal. Calcd. for $C_{11}H_{17}NO$: C, 73.70; H, 9.56; N, 7.81. Found: C, 73.47; H, 9.80; N, 7.74.

General procedure for the LiDBB-mediated reductive lithiation of 40, cyclization, and trapping with CO_2.

Spiro acid (precursor to ester 11). Di-*tert*-butylbiphenyl (3.0 g, 11.3 mmol) was dissolved in THE (20 mL) and a crystal of 1,10-phenanthroline was added. The mixture was cooled to 0 °C and was titrated to a brown endpoint with *n*-BuLi. Lithium wire (536 mg, 77.2 mmol) was cut into the solution, forming a deep malachite green solution within 10 min. The solution was stirred at 0 °C for 5 h, forming a *ca.* 0.57 M LiDBB solution. In a separate flask, cyanohydrin **9** (486 mg, 2.7 mmol) was azeotroped with benzene (3x) to remove residual moisture, and was dissolved in THF (5.0 mL). The LiDBB solution was cooled to –78 °C, and the cyanohydrin solution was added into the reaction mixture via cannula. After 10 min, dry CO_2 (g) was bubbled through the reaction mixture for 1 h, gradually turning the solution orange as the CO_2 was consumed. The solution was warmed to room temperature, 1 N NaOH (10 mL) was added, and the organic layers were extracted with CH_2Cl_2 (2x). The basic layer was acidified with 6 N HCl, back-extracted with CH_2C1_2 (3x), and dried (Na_2SO_4). Chromatography (50% EtOAc/hexanes) afforded the product as a yellow oil (384 mg, 1.94 mmol, 71%) which solidified under high vacuum: mp 60-62 °C; IR (neat) 2936, 2863, 1704, 1295, 1087 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.73 (br d, *J* 11.3 Hz, 1 H), 3.61-3.56 (m, 1 H), 2.62 (dd, *J* = 15.9, 4.9 Hz, 1 H), 2.41 (dd, *J* = 15.9, 6.8 Hz, 1 H), 2.07-2.02 (m, 1 H), 1.96-1.88 (m, 2 H), 1.75-1.70 (m, 2 H), 1.65-1.45 (m, 7 H), 1.36-1.33 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.2, 83.3, 62.4, 46.0, 34.3, 33.8, 32.7, 29.9, 25.9, 21.8, 20.9. HIRMS (CI) *m/z* calcd for $C_{11}H_{18}O_3$ (M^+) 198.1256, found 198.1256. Anal. Calcd. for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.81; H, 9.23.

Methyl ester 11. An analytical sample was prepared (92% yield) by treatment of the acid described above with CH_2N_2. Resolution of enantiomers by chiral GC: enantiomers elute at 30.37 min & 31.00 min; conditions: G-TA column, initial temperature = 120 °C for 5 min, then gradient of 0.5 °C/min until 150 °C is reached. Data for **11**: IR (neat) 2937, 2857, 1738, 1437, 1087 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.66 (s, 3 H), 3.66-3.62 (m, 1 H), 3.56-3.51 (m, 1 H), 2.55 (dd, *J* = *15.8,* 4.0 Hz, 1 H), 2.25 (dd, *J* = 15.8, 9.9 Hz, 1 H), 2.10-2.05 (m, 1 H), 1.95 (dddd, *J* = 9.5, 9.5, 7.6, 4.0 Hz, 1 H), 1.90-1.84 (m, 1 H), 1.73-1.64 (m, 2 H), 1.61-1.39 (m, 7 H), 1.33-1.28 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.9, 82.5, 62.0, 51.4, 46.1, 33.6, 33.5, 32.5, 30.1, 26.2, 21.5, 21.1. HIRMS (CI) *m/z* calcd for $C_{12}H_{20}O_3$ (M^+) 212.1412, found 212.1404.

2-(4-Pentenyl)tetrahydropyran (12). Obtained in 76% yield from reductive decyanation of **9** using Li/NH_3. Data for **12**: IR (neat) 3077, 2935, 2841, 1641, 1441, 1092, 1049 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.80 (dddd, *J* = 17.0, 10.3, 6.7, 6.7 Hz, 1 H), 4.99 (dd, *J* = 17.1, 1.6 Hz, 1 H), 4.93 (dd, *J* = 10.2, 1.1 Hz, 1 H), 3.98-3.94 (m, 1 H), 3.40 (td, *J* = 11.5, 2.4 Hz, 1 H), 3.25-3.20 (m, 1 H), 2.05 (q, *J* = 6.9 Hz, 2 H), 1.82-1.80 (m, 1 H), 1.60-1.35 (m, 8 H), 1.25-1.20 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.9, 114.4, 77.7, 68.5, 36.1, 33.8, 31.9, 26.2, 24.8, 23.6.

Spiro ether 13. The same procedure for the preparation of spiro acid of **11** was used, except that the reaction was quenched with methanol. Dichloromethane and water were added, and the layers were separated. The aqueous phase was extracted with CH_2C1_2 (2x) and dried (Na_2SO_4). A check of the crude GC showed 2 peaks corresponding to **13** (10.07 min) and uncyclized **12** (10.03 min) in a *ca.* 10:1 ratio. The product was purified by column chromatography (20% CH_2Cl_2/hexanes then 5% EtOAc/hexanes) but must be concentrated carefully due to its volatile nature. Data for **13**: ^1H NMR (500 MHz, $CDCl_3$) δ 3.69-3.65 (m**,** 1 H), 3.60-3.55 (m, 1 H), 2.10 (ddd, *J* = 13.5, 8.7, 5.0 Hz, 1 H), 1.75 (dddd, *J* = 11.9, 7.9, 7.9, 4.0 Hz, 1 H), 1.70-1.44 (m, 8 H), 1.42-1.35 (m, 2 H), 1.25-1.23 (m, 1 H), 0.93 (d, *J* = 6.9 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$, DEPT) δ *C* 82.7, *C*H 43.9, *C*H_2 62.1, 33.5, 32.5, 31.9, 26.4, 21.2 (one CH_2 is superimposed), *C*H_3 12.7.

Spiro lactone 14.[4] The desired lactone was isolated in 78% yield from spiro ether **13** following a literature precedent for anomeric oxidations.[5] Data for compound **14**: IR (neat) 2958, 2875, 1727, 1254, 1019 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.61-2.55 (m, 1 H), 2.45-2.38 (m, 1 H), 2.03 (ddd, *J* = 13.3, 8.6, 4.5 Hz, 1 H), 1.93-1.53 (m, 10 H), 0.99 (d, *J* = 6.6 Hz, 3 H); ^{13}C NMR (125 MHz, $CDC1_3$) δ 171.6, 93.2, 44.2, 39.3, 31.8, 30.4, 29.8, 21.0, 17.8, 12.7. LRMS (El) *m/z* calcd for $C_{10}H_{16}O_2Na$ ($M+Na^+$) 191.11, found 191.07.

[4] Canonne, P.; Boulanger, R.; Bernatchez, M. *Tetrahedron* **1989**, *45*, 2525-40.
[5] Tenaglia, A.; Terranova, E.; Waegell, B. *J. Org. Chem.* **1992**, *57*, 5523-5528.

Calculated using B3LYP/3-21G(X, 6-31G*)//MM3
Correction = shift*(-1.168) + 230.2
Forsyth, D. A.; Sebag, A. B. *J. Am. Chem. Soc.* **1997**, *119*, 9485-9494..

cis_spiro_MM3.log

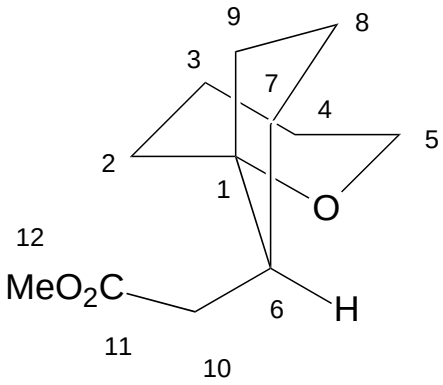
Atom Label	Calc. Shifts	delta-calc	C#
A	47.0	175.3	11
B	127.0	81.9	1
C	144.9	61.0	5
D	153.5	50.9	12
E	156.2	47.8	6
F	166.8	35.4	10
G	169.7	32.0	2
H	169.7	32.0	7
I	169.8	31.9	9
J	174.4	26.5	4
K	177.4	23.0	8
L	178.0	22.3	3

trans_spiro_MM3.log

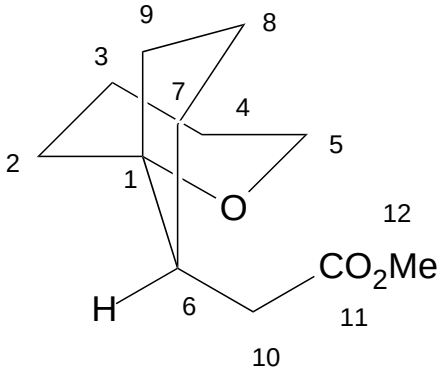
Atom Label	Calc. Shifts	delta-calc	C#
A	47.7	174.5	11
B	127.4	81.4	1
C	142.4	63.9	5
D	153.5	50.9	12
E	157.1	46.7	6
F	166.3	36.0	10
G	168.3	33.6	9
H	171.3	30.1	7
I	174.4	26.5	4
J	175.2	25.6	2
K	178.8	21.4	8
L	179.2	20.9	3

C#	Cis-Pred.	C#	Trans-Pred.	**Exptl**
1	81.9	1	81.4	**82.5**
2	*32.0*	*2*	*25.6*	***33.6*** key shift
3	22.3	3	20.9	**21.5**
4	26.5	4	26.5	**26.5**
5	61.0	5	63.9	**61.8**
6	47.8	6	46.7	**46.7**
7	32.0	7	30.1	**30.7**
8	23.0	8	21.4	**21.9**
9	31.9	9	33.6	**32.5**
10	35.4	10	36.0	**33.9**
11	175.3	11	174.5	**174.1**
12	50.9	12	50.9	**50.9**

Chi Test with exptl	0.999999	0.993068



trans isomer



cis isomer