Cyclization to Stereoisomeric Hexahydro-3,6-pentaleno[1,6-*cd*]pyran-1(3*H*)-ones. A Model Study Explains the Preference for Trans Products

Stephane Borrelly[1] and Leo A. Paquette*

Evans Chemical Laboratories, The Ohio State University, Columbus, Ohio 43210

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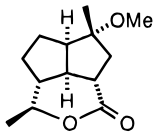
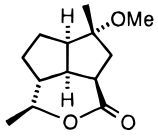
Our studies directed toward a total synthesis of kalmanol[2] have centered around an ability to elaborate the entire carbocyclic framework of the target by sequential Tebbe olefination and Claisen rearrangement of lactones typified by **3** (Scheme 1).[3] Arrival at these lactones occurs *spontaneously* following treatment of enantiopure keto esters **1** (or their endocyclic olefin equivalents) with the lithium derivative of scalemic cyclopentenyl bromide **2**.[4] Although the remarkably high levels of π-facial stereoselectivity accompanying the nucleophilic 1,2-additions to **1** were a welcomed synthetic development, our attention was also drawn to the readiness with which ring closure occurred despite the fact that the lactone ring in **3** spans the diquinane core in trans fashion. When molecular mechanics (MM2) calculations[5] on the simpler structural models **5** and **6** indicated the latter to be approximately 8 kcal/mol *more stable* than the cis-bridged



5

E_{total} 51.34 kcal/mol



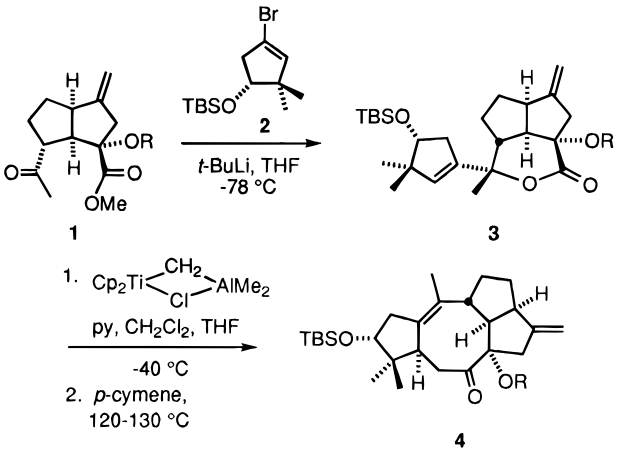
6

43.23 kcal/mol

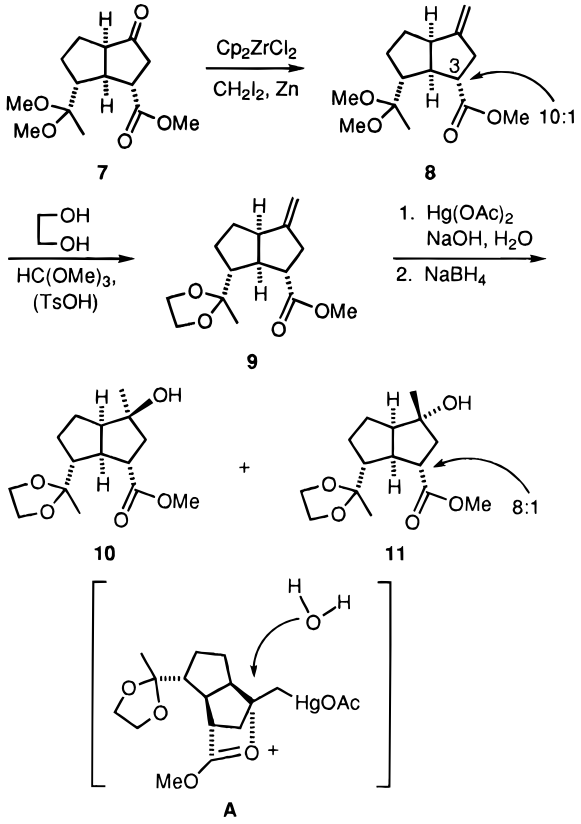
option, we were led to question whether this significant difference in strain energy would impact adversely on lactonization rates in the cis series. The present investigation was undertaken to resolve this issue.

The available keto ester **7** was not amenable to conventional one-carbon homologation by means of the Wittig and Peterson reactions. However, smooth methylenation did take place following exposure to the zirconocene dichloride−diiodomethane couple in the presence of an excess of zinc.[6] During this process, the stereochemical integrity at C-3 was somewhat compromised in that a 10:1 mixture of the α- and β-diastereomers of **8** was produced (Scheme 2). Installation of the tertiary hydroxyl group at C-1 via oxymercuration required that the dimethyl acetal first be replaced by a dioxolane ring as in **9**. In sharp contrast to the highly exo-stereoselective response to electrophilic attack exhibited in general by diquinanes,[7] treatment of **9** with mercuric acetate under basic conditions[8] provided **10** and **11** in a ratio of 1:2. Furthermore, the rate of consumption of **9** was rather slow, more than 12 h being required to achieve complete conversion. Relevantly, **10** was found to be a single diastereomer (α) at C-3, whereas **11** was isolated as an 8:1 (α/β) mixture. In a control experiment, treatment of **9** containing a higher proportion of the 3β-isomer[9] (now 2.3:1 α/β) afforded **10** and **11** in a 1:4.4 ratio. Once again, **10** was found to be only the α isomer. These results are consistent only with neighboring-group participation on the part of the carbomethoxy substituent

Scheme 1



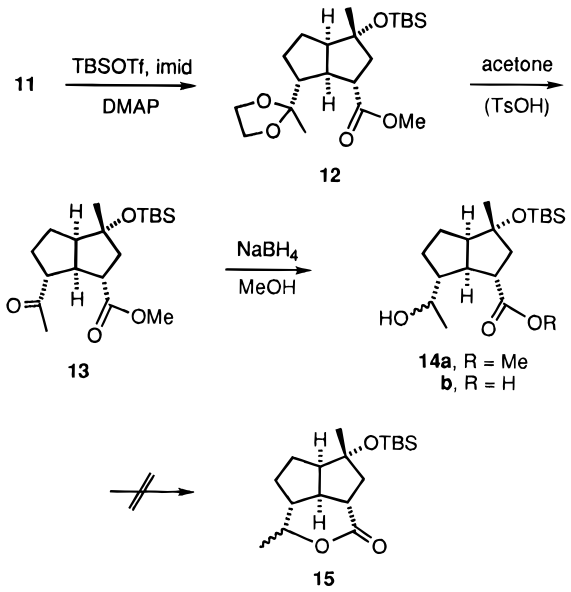
Scheme 2



(1) The Ohio State University Presidential Fellow, 1994.
(2) Burke, J. W.; Doskotch, R. W.; Ni, C.-Z.; Clardy, J. *J. Am. Chem. Soc.* **1989**, *111*, 5831.
(3) Borrelly, S.; Paquette, L. A. *J. Am. Chem. Soc.* **1996**, *118*, 727.
(4) Borrelly, S.; Paquette, L. A. *J. Org. Chem.* **1993**, *58*, 2714.
(5) Allinger, N. L. *J. Am. Chem. Soc.* **1977**, *99*, 8127. Burkett, U.; Allinger, N. L. *Molecular Mechanics*; American Chemical Society: Washington, D. C., 1982, Monograph 177, MODEL version KS 2.96, provided to us by K. Steliou, was the actual program used.
(6) Tour, J. M.; Badworth, P. V.; Wu, R. *Tetrahedron Lett.* **1989**, *30*, 3927.
(7) (a) Brown, H. C.; Hammar, W. J. *J. Am. Chem. Soc.* **1967**, *89*, 1522. (b) Brown, H. C.; Kawakami, J. H.; Ikegami, S. *J. Am. Chem. Soc.* **1967**, *89*, 1526.
(8) Brown, H. C.; Hammar, W. J. *Tetrahedron* **1978**, *34*, 3405.
(9) Paquette, L. A.; Borrelly, S. *J. Org. Chem.* **1995**, *60*, 6912.

0022-3263/96/1961-2569$12.00/0

Scheme 3



(see **A**). To the extent that this tricyclic intermediate is formed, exo hydration of the organomercurial is precluded and water is required to approach from the endo surface. This observation holds interest because the only other recorded case of carbonyl involvement in an oxymercuration reaction known to us has involved an acetyl group.[10]

Once the tertiary hydroxyl group in **11** was silylated and deketalization effected (Scheme 3), the stage was set for the reduction of **13** to **14a** with sodium borohydride as a prelude to lactonization studies. No evidence for the direct conversion of **14a** to **15** could be garnered under a variety of conditions, including KH in THF and KO*tert*-Bu in DMF. All attempts to bring about the ring closure of hydroxy acid **14b**, including the mixed anhydride, DCC-promoted,[11] and Mukaiyama conditions,[12] were equally unsuccessful. Similar difficulties do not plague ring closure when the two interactive groups are trans oriented as in **1**.[3] In view of these successes, no attempts were made to epimerize **14a**.

Examination of molecular models of **14** revealed that the necessarily interactive centers are held rather distal to each other when two side chains are appended to the diquinane in a cis manner. This is not the case when a trans relationship is adopted. It would appear therefore that the strain necessarily associated with the formation of **15** is a powerful deterrent to lactonization and contrasts strikingly with the relative ease with which **3** and its congeners are produced.

Experimental Section[13]

Methyl (1*S*,3a*R*,6*R*,6a*R*)-6-(1,1-Dimethoxyethyl)-octahydro-3-methylene-1-pentalenecarboxylate (8). To a nitrogen-blanketed solution of **7**[3] (300 mg, 1.11 mmol), zirconocene dichloride (422 mg, 1.3 equiv), and zinc metal (800 mg, 11 equiv) in dry THF (40 mL) was added diiodomethane (0.25 mL, 2.7 equiv) dropwise. The resulting heterogeneous solution was stirred for 45 min at rt, diluted with ether (30 mL), and washed with saturated $NaHCO_3$ solution (20 mL). The organic phase was dried and concentrated to leave a residue which was purified by silica gel chromatography (elution with 3:1 hexanes−ether) to give 238 mg (80%) of **8** as a 10:1 (α/β) mixture of diastereomers: IR (neat, cm^{-1}) 1735, 1650, 1435, 1380, 1250, 1160, 1120, 1050, 860; ^1H NMR (300 MHz, C_6D_6) δ 4.89 (br s, 1 H), 3.45 (s, 3 H), 3.05 (s, 3 H), 3.02 (s, 3 H), 3.01−2.58 (m, 5 H), 2.23 (m, 1 H), 1.87−1.69 (m, 2 H), 1.54−1.33 (m, 2 H), 1.16 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 175.5, 155.4, 105.8, 103.7, 51.2, 51.1, 51.0, 49.9, 49.2, 48.0, 47.6, 39.2, 32.6, 29.7, 17.7; HRMS *m/z* [$M^+ - CH_3$] calcd 253.1439, obsd 253.1436.

Methyl (1*S*,3*R*,3a*R*,6*R*,6a*R*)-Octahydro-6-(2-methyl-1,3-dioxolan-2-yl)-3-methylene-1-pentalenecarboxylate (9). Ester **8** (500 mg, 1.86 mmol) was stirred at rt for 2 h with a 1:1 mixture of trimethyl orthoformate and ethylene glycol (6 mL total) in the presence of a catalytic amount of *p*-toluenesulfonic acid. The reaction mixture was diluted with ether and washed with water (2 × 10 mL). Filtration through a small plug of silica gel followed by concentration to dryness gave a 10:1 (α/β) diastereomeric mixture of **9** (491 mg, 99%) as a colorless oil: IR (neat, cm^{-1}) 1720, 1650, 1430, 1355, 1150, 860; ^1H NMR (300 MHz, C_6D_6) δ 4.87 (br s, 1 H), 4.78 (br s, 1 H), 3.61−3.41 (m, 4 H), 3.40 (s, 3 H), 2.99 (m, 2 H), 2.74 (m, 2 H), 2.59 (m, 1 H), 2.06 (m, 1 H), 1.89 (m, 1 H), 1.74−1.63 (m, 2 H), 1.19 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 175.6, 155.3, 111.2, 105.8, 64.9, 64.5, 55.0, 51.1, 50.4, 50.2, 49.3, 39.2, 33.2, 30.6, 22.9; HRMS *m/z* [M^+] calcd 266.1518, obsd 266.1516. Anal. Calcd for $C_{15}H_{22}O_4$: C, 67.65; H, 8.33. Found: C, 67.84; H, 8.38.

Methyl (1*S*,3*S*,3a*R*,6*R*,6a*R*)-Octahydro-3-hydroxy-3-methyl-6-(2-methyl-1,3-dioxolan-2-yl)-1-pentalenecarboxylate (10) and Methyl (1*S*,3*R*,3a*R*,6*R*,6a*R*)-Octahydro-3-hydroxy-3-methyl-6-(2-methyl-1,3-dioxolan-2-yl)-1-pentalenecarboxylate (11). To a nitrogen-blanketed solution of **9** (400 mg, 1.5 mmol) in a 1:1 mixture of aqueous 10^{-6} N NaOH (10 mL) and THF (10 mL) was added mercuric acetate (1.21 g, 2.5 equiv) in one portion, and the resulting bright yellow solution was stirred for 3 h. The reaction mixture was cooled to 0 °C, treated with 0.5 N sodium borohydride solution (45 mL) in 10^{-6} N NaOH, stirred for 0.5 h, diluted with ether (50 mL), and washed with saturated brine (30 mL). The separated aqueous phase was extracted with ethyl acetate (2 × 20 mL), and the combined organic phases were dried and concentrated. The residue was purified by silica gel chromatography (elution with 3:1 hexanes−ether) to give 107 mg (25%) of **10** and 213 mg (50%) of **11**.

For **10**: colorless oil; IR (neat, cm^{-1}) 3600−3200, 1720, 1435, 1470, 1150, 1030; ^1H NMR (300 MHz, C_6D_6) δ 3.72−3.46 (m, 4 H), 3.44 (s, 3 H), 3.08 (m, 2 H), 2.24 (m, 1 H), 1.95−1.51 (m, 6 H), 1.24 (s, 3 H), 0.94 (s, 3 H), 0.71 (br s, 1 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 178.3, 111.0, 80.9, 65.1, 64.8, 58.3, 57.7, 51.6, 51.2, 47.2, 41.7, 30.4, 30.0, 23.4; HRMS *m/z* [M^+] calcd 284.1623, obsd 284.1635; $[\alpha]^{20}_D$ +3.95° (*c* 1.02, CH_2Cl_2).

For **11**: colorless oil; IR (neat, cm^{-1}) 3600−3200, 1720, 1435, 1470, 1150, 1030; ^1H NMR (300 MHz, C_6D_6) δ 3.67−3.53 (m, 4 H), 3.37 (s, 3 H), 3.26 (m, 1 H), 2.86 (br s, 1 H), 2.62 (m, 1 H), 2.38 (br q, J = 8.1 Hz, 1 H), 2.06 (br d, J = 1.7 Hz, 1 H), 1.79−1.41 (m, 5 H), 1.26 (s, 3 H), 1.17 (s, 3 H), 0.73 (m, 1 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 178.3, 111.0, 80.9, 65.1, 64.8, 58.3, 57.7, 51.6, 51.2, 47.2, 41.7, 30.4, 30.0, 23.4; HRMS *m/z* [M^+] calcd 284.1623, obsd 284.1635.

Methyl (1*S*,3*R*,3a*R*,6*R*,6a*R*)-Octahydro-3-(*tert*-butyldimethylsiloxy)-3-methyl-6-(2-methyl-1,3-dioxolan-2-yl)-1-pentalenecarboxylate (12). To a solution of **11** (113 mg, 0.392 mmol), imidazole (57 mg, 2 equiv), and a catalytic amount of 4-(dimethylamino)pyridine in dry DMF (5 mL) was added *tert*-butyldimethylsilyl triflate (190 μL, 2.1 equiv). The mixture was stirred at rt overnight, diluted with ether (10 mL), and washed with saturated brine (2 × 10 mL). The organic layer was dried and concentrated to leave a residue which was purified by silica gel chromatography (elution with 3:1 hexanes−ether). There was obtained a 9:1 (α/β) diastereomeric mixture of **12** (148 mg, 95%) as a colorless oil: IR (neat, cm^{-1}) 1730, 1440, 1370, 1245, 1095; ^1H NMR (300 MHz, C_6D_6) δ 3.77−3.48 (m, 4 H), 3.45 (s, 3 H), 2.55−2.36 (m, 2 H), 2.32 (m, 1 H), 1.82−1.51 (m, 6 H), 1.30 (s, 3 H), 1.14 (s, 3 H), 0.94 (s, 9 H), 0.93 (m, 1 H), 0.16 (s, 3 H), 0.09 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 175.2, 111.1, 83.8, 65.2, 64.8, 57.9, 57.6, 51.2, 51.1, 46.1, 44.3, 30.2, 29.9, 26.1, 24.2, 23.5, 18.2, −2.0, −2.2; HRMS *m/z* [M^+] calcd 398.2488, obsd

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(11) De Tar, D. F.; Silverstein, R. *J. Am. Chem. Soc.* **1966**, *88*, 1013, 1020.
(12) Mukaiyama, T.; Ushui, M.; Shimada, E.; Saigo, K. *Chem. Lett.* **1975**, 1045.
(13) Consult reference 3 for a synopsis of general experimental protocol.

398.2499. Anal. Calcd for $C_{21}H_{38}O_5Si$: C, 63.28; H, 9.61. Found: C, 63.49; H, 9.66.

Methyl (1*S*,3*R*,3a*R*,6*R*,6a*R*)-6-Acetyl-3-(*tert*-butyldimethylsiloxy)-octahydro-3-methyl-1-pentalenecarboxylate (13). A solution of **12** (148 mg, 0.372 mmol) in dry acetone (10 mL) was stirred in the presence of a catalytic amount of *p*-toluenesulfonic acid for 6 h. At this time, a few drops of triethylamine were added, and the reaction mixture was concentrated to leave a residue which was purified by silica gel chromatography (elution with 2:1 hexanes−ether) to give a 9:1 (α/β) diastereomeric mixture of **13** (123 mg, 93%) as a colorless oil; IR (neat, cm^{-1}) 3000−2880, 2850, 1800−1720, 1425, 1360, 1315, 1150, 1100; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.61 (s, 3 H), 3.22 (m, 1 H), 2.63 (m, 1 H), 2.49 (m, 1 H), 2.38 (m, 1 H), 2.21 (dd, J = 8.9, 1.4 Hz, 1 H), 2.15 (s, 3 H), 1.94 (dd, J = 13.4, 9.6 Hz, 1 H), 1.80−1.72 (m, 3 H), 1.23 (s, 3 H), 1.19 (m, 1 H), 0.76 (s, 9 H), 0.19 (s, 3 H), 0.05 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 209.7, 174.9, 83.2, 60.4, 57.7, 56.1, 51.6, 50.3, 48.7, 43.6, 41.4, 29.5, 28.9, 28.7, 25.7, 24.1, 17.8, −2.3, −2.5; HRMS m/z [M^+] calcd 354.2226, obsd 354.2227. Anal. Calcd for $C_{19}H_{34}O_4Si$: C, 64.36; H, 9.66. Found: C, 64.64; H, 9.69.

Methyl (1*S*,3*R*,3a*R*,6*R*,6a*R*)-6-(1-Hydroxyethyl)-3-(*tert*-butyldimethylsiloxy)-octahydro-3-methyl-1-pentalenecarboxylate (14a). A solution of **13** (15 mg, 0.042 mmol) in methanol (5 mL) was treated in one portion with sodium borohydride (1 mg, 2.36 hydride equiv). The reaction mixture was stirred for 5 min at rt, quenched with 10% aqueous acetic acid (1 mL), and diluted with ether (10 mL). The separated organic phase was washed with saturated brine (2 × 5 mL) and concentrated. Purification of the residue by silica gel chromatography (elution with 2:1 ether−hexanes) afforded **14a** (14 mg, 94%) as a 2:1 mixture of diastereomers: IR (neat, cm^{-1}) 3700−3200, 1720, 1440, 1245, 1100, 1050, 1000; ^{1}H NMR (300 MHz, C_6D_6) δ 3.61−3.50 (m, 1 H), 3.42 and 3.37 (s, 3 H), 3.05 (m, 1 H), 2.48−2.22 (m, 4 H), 1.71−1.66 (m, 2 H), 1.51−1.22 (m, 3 H), 1.18 and 1.16 (d, J = 6.21 Hz, 3 H), 1.13 and 1.11 (s, 3 H), 0.94 and 0.92 (s, 9 H), 0.91−0.71 (m, 1 H), 0.13−0.08 (m, 6 H); ^{13}C NMR (75 MHz, C_6D_6) ppm (176.3, 175.3), (83.9, 83.8), (72.9, 70.8), (58.9, 58.6), (58.4, 57.1), (51.6, 51.3), (50.9, 50.0), 47.5, (43.6, 42.9), (31.7, 30.7), (29.9, 29.8), (26.0, 25.9), (24.1, 24.0), (22.1, 21.7), (18.2, 18.1), (-2.05, −2.1); HRMS m/z [M^+] calcd 341.2148, obsd 341.2145.

A solution of **14a** (26 mg) in methanol (2 mL) and THF (2 mL) was stirred with excess 10% KOH at rt for 35 h, cooled to 0 °C, and acidified with 10% HCl. Extraction of the product into CH_2Cl_2, drying, and solvent evaporation left **14b** as a white solid (24 mg).

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Supporting Information Available: Copies of the 300 MHz ^{1}H and 75 MHz ^{13}C NMR spectra of **8**, **10**, **11**, and **14a** (8 pages). This information 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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Additions and Corrections

Vol. 60, 1995

Cynthia L. Revis, Markku Rajamäki, and James C. Fishbein*. Reexamination of the Mechanisms of Decomposition of Simple α-Acetoxynitrosamines in the Physiological pH Range.

Page 7736, Table 2. Units for $\Delta H^{\ddagger}$ are kcal mol^{-1} and units for $\Delta S^{\ddagger}$ are cal deg^{-1} mol^{-1}.

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