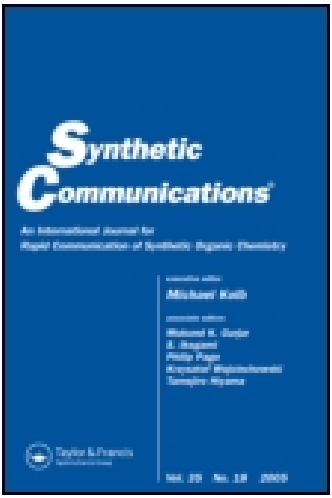


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

FACILE SYNTHESIS OF SATURATED EIGHT-MEMBERED RING LACTONES

Keith R. Buszek [a], Youngmee Jeong [a], Nagaaki Sato [a], Peter C. Still [a], Pedro L. Muiño [a] & Indranath Ghosh [a]

[a] Department of Chemistry, Kansas State University, Manhattan, KS, 66506-3701, U.S.A.

Published online: 09 Nov 2006.

To cite this article: Keith R. Buszek, Youngmee Jeong, Nagaaki Sato, Peter C. Still, Pedro L. Muiño & Indranath Ghosh (2001) FACILE SYNTHESIS OF SATURATED EIGHT-MEMBERED RING LACTONES, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 31:11, 1781-1791, DOI: 10.1081/SCC-100104408

To link to this article: http://dx.doi.org/10.1081/SCC-100104408

SYNTHETIC COMMUNICATIONS, 31(11), 1781–1791 (2001)

FACILE SYNTHESIS OF SATURATED EIGHT-MEMBERED RING LACTONES

Keith R. Buszek,* Youngmee Jeong, Nagaaki Sato, Peter C. Still, Pedro L. Muiño, and Indranath Ghosh

Department of Chemistry, Kansas State University, Manhattan, KS 66506-3701

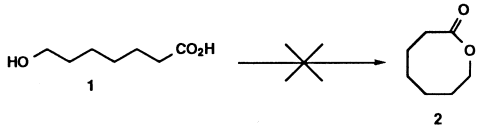
ABSTRACT

The synthesis of functionalized saturated eight-membered ring lactones from their corresponding seco acids is a very facile process using conventional macrolactonization protocols. This heretofore unrecognized and overlooked strategy is illustrated for several examples. A possible explanation for the success of this approach is also presented.

The synthesis of medium-sized rings is an important problem in organic chemistry and represents a fantastic challenge. Such rings are considered among the most challenging and difficult systems to construct presumably due to a combination of unfavorable entropic and enthalpic factors, and the lack of general methods for their preparation.[1] A certain lore has developed that saturated eight-membered ring lactones, in particular, are difficult or impossible to access via their corresponding seco acids. Indeed, the literature is replete with admonitions regarding such attempts. For example, Lee recently stated: ''It is well-known that eight-membered-ring lactones are the least accessible ones via traditional lactone-forming

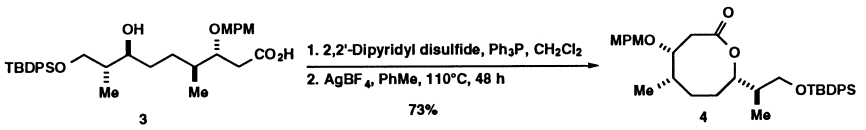
* Corresponding author.

reactions starting from ω-halo and ω-hydroxy-carboxylic acids."[2] Cane also noted that "the chemical synthesis of functionalized eight-membered ring lactones (2-oxocanones) is extremely challenging, and virtually no functionalized eight-membered ring lactones are known among natural products."[3] Funk further observed that eight-membered lactones "are difficult, if not impossible, to prepare from the corresponding hydroxy acids."[4] Despite preliminary evidence published by us to the contrary,[5–7] there persists a nearly universal belief that saturated monocyclic eight-membered lactones in particular cannot be prepared directly from their corresponding seco acids. These views, however, are almost certainly based on the singular observation that 7-hydroxyheptanoic acid 1 does not lactonize under the Corey-Nicolaou,[8] Keck-Boden,[9] Yamaguchi,[10] Mukaiyama,[11] or other macrolactonization protocols (Scheme 1). In fact, in virtually every description of these lactonization protocols, the eight-membered entry is conspicuously absent. As a consequence, an enormous investment has been directed toward developing alternative chemical and enzymatic[3] strategies to circumvent this perceived obstacle, despite the fact that the most straightforward retrosynthetic disconnection often involves the acyl-oxygen bond. Approaches to saturated lactones based on this strategy would yield enormous synthetic simplification. This paper dispels the entrenched misconceptions regarding the synthesis of eight-membered ring lactones in the manner described and reports a simple and expeditious strategy using conventional macrolactonization protocols for effecting this change with a range of variously substituted seco acid precursors.



Scheme 1.

During the course of the first total synthesis of the powerful antitumor agent octalactin A,[5] we observed an unusually efficient ring closure of the saturated hydroxy acid **3** using the Corey-Nicolaou double-activation lactonization method (Scheme 2).[8] It was subsequently found that *this discovery represents a general phenomenon for substituted saturated hydroxy carboxylic acid precursors.* Several representative examples were chosen to document generality and are shown in Table 1. Reaction yields range from good to excellent and reaction times are usually 24 h or less. In the octalactin series (entries 1–3) it was found that removing the substituent at C-7 resulted in even faster ring

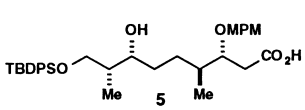
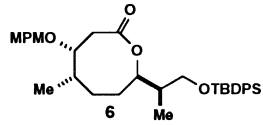
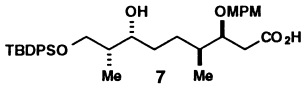
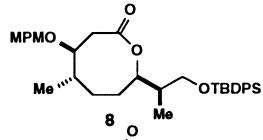
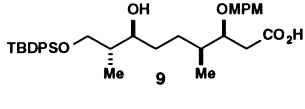
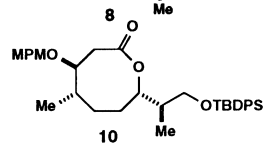
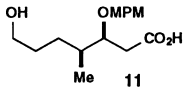
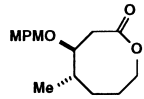
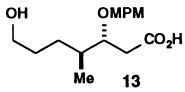
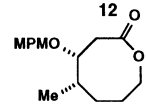
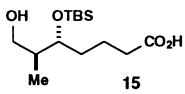
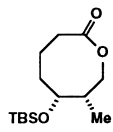
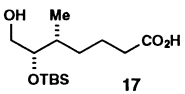
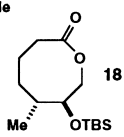
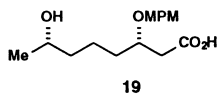
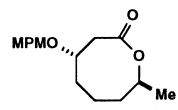
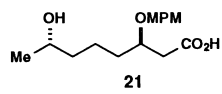
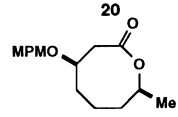


Scheme 2.

closure with the anti-stereoisomer requiring much shorter reaction times (entries 4 and 5). It was also found that the size of the protecting groups had little effect on the reaction times or yields. It is significant to note that a pair of vicinal stereocenters is not required for lactonization (entries 8 and 9). In no case was diolide product formation observed, as evidenced by high resolution mass spectral analysis, under the reaction conditions employed. A kinetic study (Table 2) of three other members of the octalactin series (entries 1–3) revealed that there is a modest dependence of the first-order rate of lactonization on the stereochemical configuration of the seco acid, i.e., at C-3 and C-7. Not surprisingly, the calculated enthalpy of activation correlated with the total steric energy of the lactone as determined by MM2 calculations.[12] In the case of the C-3 epimer this strain was compensated for by a less negative entropy of activation.

The basic idea that substitution in an acyclic chain can facilitate ring closure is certainly known.[13] The Thorpe-Ingold,[14] gem-dialkyl[15] and gem-dialkoxy[16] effects have been widely cited and investigated along with related conformational effects on ring closure. It is surprising then that the current idea has never been applied to the synthesis of medium rings. Substitution limits rotational degrees of freedom and therefore makes the reaction entropically less unfavorable. However, substitution in some cases may be enthalpically advantageous as well, based on changes in bond angle distortion from the seco acid to the lactone. The conformational effect of quatenary centers in controlling torsional angles, for example, has been reported.[17] We compared the minimized bond angles in the seco acid **1** and the corresponding methyl ethers (OMe vs. OMPM) of compounds **19** and **21** to those in their lactones using molecular mechanics computational methods (including Monte Carlo sampling of all conformational space) with the AMBER force field.[18] It is interesting to note that in our study, there is a significantly smaller cumulative bond angle change and smaller change for nearly every individual angle in the substituted lactones compared to the unsubstituted case. Although a complete explanation for the facility of substituted medium-ring lactonization is not yet available, these calculations nevertheless have some predictive value and suggest, for example, that a single substituent at C-3 is more beneficial than one at C-7.[19]

Table 1. Representative Examples of Eight-Membered Ring Lactonization

Entry	Seco Acid	Lactone	Time (h)	Yield (%)[a]
1	 5	 6	48	88
2	 7	 8	48	84
3	 9	 10	96	72
4	 11	 12	04	91
5	 13	 14	24	80
6	 15	 16	15	75
7	 17	 18	24	76
8	 19	 20	12	83
9	 21	 22	12	81

[a]Isolated yields; Corey-Nicolaou method (reference 8) was used for lactonization.

Table 2. Kinetic Data for Lactonization of Selected Epimers in the Octalactin Series

Epimer	$\Delta H^{\neq}$(kcal/mol)	$\Delta S^{\neq}$(kcal/mol·K)	k (sec^{-1}, 115°C)	MM2 (kcal/mol)
C.7	21.4	−0.027	1.33×10^{-5}	2.5
C.3, C.7	20.4	−0.030	1.48×10^{-5}	0.0
C.3	28.2	−0.011	7.52×10^{-6}	9.5

In conclusion, we have identified a general strategy for the facile construction of functionalized, saturated eight-membered lactones, and by extension, their corresponding ethers.[20] The elucidation of the differential contributions of the various groups based on position and stereochemistry and the correlation with the reactive conformations as calculated by molecular mechanics would be a valuable contribution and is under investigation. Application of this approach to the synthesis of other saturated lactone- and ether-containing natural products is also in progress and will be reported as developments merit.

EXPERIMENTAL

General

^{1}H NMR spectra were recorded on a Varian Unity Plus 400-MHz spectrometer operating at 399.886 MHz for ^{1}H and 100.560 MHz for ^{13}C, in the indicated solvents. Infrared (IR) spectra were obtained using a Perkin-Elmer Model 1310 infrared spectrophotometer or a Mattson Sirius 100 FT-IR with 25-mm KBr plates. Mass spectra were recorded at the Mass Spectrometry Laboratory at the University of Kansas using the fast atom bombardment (FAB) technique and employing a matrix of either glycerol or *m*-nitrobenzyl alcohol. Optical rotations were performed on a Perkin-Elmer 241 polarimeter using a 1-cm^3 capacity quartz cell (1-dm path length) in the indicated solvent system at the recorded concentration. Thin layer chromatography (TLC) was performed using E. Merck silica gel (60 F 254) plates of 0.25 mm thickness. Visualization was accomplished with short wavelength ultraviolet light, and anisaldehyde dip reagent. Hydrocarbon and chlorinated solvents were distilled from calcium hydride. All other solvents were performed under a positive atmosphere of dry nitrogen or argon.

Representive Procedure

To a stirred solution of the hydroxy carboxylic acid **21** (125 mg, 0.422 mmol) in 15 mL of dry CH_2Cl_2 was added triphenylphosphine (125 mg, 0.48 mmol) followed by 2,2′-dipyridyl disulfide (105 mg, 0.48 mmol) and the mixture stirred until TLC (40% ethyl acetate in hexanes) showed complete loss of starting material (usually 0.5 h–2 h). The mixture was concentrated *in vacuo* and dissolved in 150 mL of dry toluene. To the solution was added 1.2 mL of a 0.006 M solution of $AgBF_4$ in dry toluene and the mixture heated under reflux for 12 h. The mixture was cooled and solvents removed *in vacuo*. The residue was purified by flash chromatography (0.5% acetone in CH_2Cl_2) to afford 95 mg (81%) of the lactone **22**. High resolution FAB mass spectral analysis revealed the $[M+H]^+$ ion for **22** and thus confirmed the presence of the eight-membered lactone.[21] The structure was further and unequivocally established by oxidative hydrolysis of the MPM ether (DDQ, CH_2Cl_2, H_20) to furnish (+)-cephalosporolide D which exhibited the same physical and spectroscopic data as that reported for the authentic sample, except for the optical rotation, which was opposite in direction.[22]

[4*R*-[4α,5α,8α(*R)]]-8-[2-[[(1,1-Dimethylethyl)diphenylsily1]oxy]-1-methylethyl]-4-[(4-methoxyphenyl)methoxy]-5-methyl-2-oxocanone (4).** ^{1}H NMR ($CDCl_3$) δ 7.61 (4 H, m), 7.39 (6 H, m), 7.29 (2 H, d, $J = 8.4$ Hz), 6.85 (2 H, d, $J = 8.4$ Hz), 4.84 (1 H, d, $J = 12.0$ Hz), 4.56 (1 H, m), 4.36 (1 H, d, $J = 12.0$ Hz), 3.85 (1 H, dd, $J = 10.0$, 4.0 Hz), 3.78 (3 H, s), 3.58 (1 H, d, $J = 6.2$ Hz), 3.51 (1 H, dd, $J = 10.0$, 4.4 Hz), 2.98 (1 H, dd, $J = 13.2$, 6.2 Hz), 2.46 (1 H, d, $J = 13.2$ Hz), 1.93 (2 H, m), 1.63 (3 H, m), 1.16 (1 H, m), 1.04 (12 H, s), 0.96 (3 H, d, $J = 6.8$ Hz); ^{13}C NMR ($CDCl_3$) δ 171.7, 159.1, 135.5, 135.4, 133.4, 133.3, 130.4, 129.7, 129.5, 127.7, 127.6, 113.6, 78.0, 77.8, 70.3, 65.0, 55.2, 40.3, 37.8, 34.8, 31.3, 29.6, 26.9, 23.9, 21.5, 19.3, 13.2; IR (neat) 2920, 2960, 2860, 1720, 1605, 1505, 1455, 1425, 1245, 1175, 1105, 1080, 1035, 820, 740, 700; FAB HRMS, *m/z* 575.3189, M+H calcd for $C_{35}H_{47}O_5Si$ 575.3194; Anal. Calcd for $C_{35}H_{46}O_5Si$: C, 73.13; H, 8.07. Found: C, 73.28; H, 7.99; $[\alpha]^{20}$D: −65.4 (c 1.3, $CHCl_3$).

[4*R*-[4α,5α,8β(*R)]]-8-[2-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]-1-methylethyl]-4-[(4-methoxyphenyl)methoxy]-5-methyl-2-oxocanone (6).** ^{1}H NMR ($CDCl_3$) δ 7.61 (4 H, m), 7.40 (6 H, m), 7.30 (2 H, d, $J = 8.4$ Hz), 6.86 (2 H, d, $J = 8.4$ Hz), 4.80 (1 H, d, $J = 11.5$ Hz), 4.67 (1 H, m), 4.38 (1 H, d, $J = 11.5$ Hz), 3.85 (1 H, dd, $J = 10.1$, 4.0 Hz), 3.78 (3 H, s), 3.62 (1 H, m), 3.51 (1 H, dd, $J = 10.1$, 3.8 Hz), 2.95 (1 H, dd, $J = 13.0$, 6.2 Hz), 2.56 (1 H, d, $J = 13.0$ Hz), 1.88 (2 H, m), 1.65 (3 H, m), 1.18 (1 H, m), 1.04 (9 H, s), 1.02 (3 H, d, $J = 6.8$ Hz), 0.94 (3 H, d, $J = 7.0$ Hz); ^{13}C NMR ($CDCl_3$) δ 172.3, 159.1,

135.5, 135.4, 133.3, 130.1, 129.7, 129.5, 127.9, 127.6, 127.5, 113.7, 78.4, 77.9, 70.6, 65.0, 55.2, 40.2, 37.9, 35.6, 31.4, 29.5, 26.9, 21.3, 19.3, 13.2; IR (neat) 3065, 2920, 1715, 1505, 1460, 1240, 1100, 1090, 1035; FAB HRMS, *m/z* 575.3195, M+H calcd for $C_{35}H_{47}O_5Si$ 575.3194; Anal. Calcd for $C_{35}H_{46}O_5Si$: C, 73.13; H, 8.07. Found: C, 73.35; H, 8.20. $[\alpha]^{20}_D$: −37.0 (c 1.4, $CHCl_3$).

[4*S*-[4*β*,5*α*,8*β*(*R)]]-8-[2-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]-1-methylethyl]-4-[(4-methoxyphenyl)methoxy]-5-methyl-2-oxocanone (8).** ^{1}H NMR ($CDCl_3$) δ 7.64 (4 H, m), 7.41 (6 H, m), 7.31 (2 H, d, $J = 8.6$ Hz), 6.89 (2 H, d, $J = 8.6$ Hz), 4.83 (1 H, br d, $J = 12.3$ Hz), 4.77 (1 H, d, $J = 11.3$ Hz), 4.39 (1 H, d, $J = 11.3$ Hz), 3.80 (3 H, s), 3.63 (1 H, dd, $J = 10.1$, 8.7 Hz), 3.52 (1 H, dd, $J = 10.1$, 5.2 Hz), 3.36 (1 H, m), 2.93 (1 H, dd, $J = 12.8$, 6.5 Hz), 2.75, (1 H, dd, $J = 12.8$, 5.2 Hz), 1.82 (3 H, m), 1.65 (2 H, m), 1.43 (1 H, m), 1.04 (9 H, s), 1.03 (3 H, d, $J = 6.0$ Hz), 0.89 (3 H, d, $J = 7.0$ Hz); ^{13}C NMR ($CDCl_3$) δ 172.0, 159.2, 135.5, 135.4, 133.4, 133.1, 129.8, 129.5, 129.4, 127.9, 127.5, 113.6, 80.1, 77.8, 70.1, 65.1, 55.2, 40.2, 38.5, 35.4, 31.7, 29.4, 26.8, 21.4, 19.3, 13.3; IR (neat) 3070, 2960, 2920, 1715, 1505, 1450, 1250, 1110, 1090, 1035, 820, 740, 705 cm^{-1}; FAB HRMS, *m/z* 575.3189, M + H calcd for $C_{35}H_{47}O_5Si$ 575.3194; Anal, Calcd for $C_{35}H_{46}O_5Si$: C, 73.13; H, 8.07. Found: C, 72.92; H, 7.98. $[\alpha]^{20}_D$: −15.6 (c 0.85, $CHCl_3$).

[4*S*-[4*β*,5*α*,8*α*(*R)]]-8-[2-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]-1-methylethyl]-4-[(4-methoxyphenyl)methoxy]-5-methyl-2-oxocanone (10).** ^{1}H NMR ($CDCl_3$) δ 7.61 (4 H, m), 7.40 (6 H, m), 7.25 (2 H, d, $J = 8.6$ Hz), 6.88 (2 H, d, J = 8.6 Hz), 4.63 (1 H, m), 4.58 (1 H, d, $J = 10.9$ Hz), 4.39 (1 H, d, $J = 10.9$ Hz), 3.84 (1 H, dd, $J = 10.1$, 4.2 Hz), 3.80 (3 H, s), 3.53 (1 H, dd, $J = 10.1$, 3.8 Hz), 3.22 (1 H, td, $J = 10.4$, 3.7 Hz), 2.89 (1 H, dd, $J = 11.6$, 3.8 Hz), 2.72 (1 H, t, $J = 11.6$), 1.91, (1 H, m), 1.67 (3 H, m), 1.45 (1 H, br d, $J = 12.9$ Hz), 1.20 (1 H, m), 1.08 (1 H, d, $J = 6.7$ Hz), 1.04 (9 H, s), 0.99 (3 H, d, $J = 6.9$ Hz); ^{13}C NMR ($CDCl_3$) δ 172.7, 159.3, 135.6, 135.4, 133.4, 133.3, 130.0, 129.7, 129.5, 128.6, 127.7, 127.6, 113.8, 82.6, 78.1, 71.5, 64.9, 55.2, 40.2, 39.0, 36.6, 32.3, 28.0, 26.9, 21.2, 19.3, 13.3; IR (neat) 3070, 2960, 2920, 1715, 1505, 1450, 1250, 1110, 1090, 1035, 820, 740, 705 cm^{-1}; FAB HRMS, *m/z* 575.3190, M+H calcd for $C_{35}H_{47}O_5Si$ 575.3194; Anal. Calcd for: C, 73.13; H, 8.07. Found: C, 73.39; H, 8.01; $[\alpha]^{20}_D$: −9.0 (c 0.77, $CHCl_3$).

[4*S*-(4*β*,5*α*)]-4-[(4-methoxyphenyl)methoxy]-5-methyl-2-oxocanone (12) ^{1}H NMR ($CDCl_3$) δ 7.25 (2 H, d, $J = 8.6$ Hz), 6.88 (2 H, d, $J = 8.6$ Hz), 4.54 (1 H, d, $J = 10.6$ Hz), 4.51 (2 H, m), 4.36 (1 H, d, $J = 10.6$ Hz), 3.77 (3 H, s), 3.72 (1 H, m), 2.92 (1 H, dd, $J = 12.4$, 4.0 Hz), 2.72 (1 H, apparent t, $J = 12.4$ Hz), 1.61–1.88 (5 H, m), 1.05 (3 H, d, $J = 6.8$ Hz); ^{13}C NMR ($CDCl_3$) δ 172.1, 159.3, 130.1, 129.5, 113.8, 79.6, 78.1, 68.9, 55.2, 40.2, 38.1, 31.4, 29.5, 21.4; IR (neat) 3055, 2990, 1705, 1421, 1265, 1090 cm^{-1}; FAB HRMS, *m/z* 279.1593, M+H calcd for $C_{16}H_{23}O_4$ 279.1597; Anal.

Calcd for $C_{16}H_{22}O_4$; C, 69.04; H, 7.97. Found: C, 68.94; H, 8.16; $[\alpha]^{20}_D$: −48.1 (c 2.2, $CHCl_3$).

[4*R*-(4α,5α)]-4-[(4-methoxyphenyl)methoxy]-5-methyl-2-oxocanone (14) ^{1}H NMR ($CDCl_3$) δ 7.27 (2 H, d, $J = 8.8$ Hz), 6.83 (2 H, d, $J = 8.8$ Hz), 4.71 (1 H, d, $J = 11.6$ Hz), 4.60 (2 H, m), 4.38 (1 H, d, $J = 11.6$ Hz), 3.81 (3 H, s), 3.75 (1 H, m), 2.94 (1 H, dd, $J = 12.6$, 6.8 Hz), 2.71 (1 H, dd, $J = 12.6$, 2.6 Hz), 1.66–1.75 (3 H, m), 1.81–1.90 (2 H, m), 1.04 (3 H, d, $J = 6.8$ Hz); ^{13}C NMR ($CDCl_3$) δ 172.6, 159.3, 130.3, 129.5, 113.8, 79.0 77.7, 70.6, 55.2, 38.3, 37.6, 31.9, 20.6, 19.3; IR (neat) 3045, 2990, 1700, 1422, 1240, 1090 cm^{-1}; FAB HRMS, *m*/*z* 279.1595, M+H calcd for $C_{16}H_{23}O_4$ 279.1597; Anal. Calcd for $C_{16}H_{22}O_4$: C, 69.04; H, 7.97. Found: C, 68.87; H, 7.99; $[\alpha]^{20}_D$: −21.4 (c 2.5, $CHCl_3$).

[6*R*-(6α,7α)]-6-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-7-methyl-2-oxocanone (16). ^{1}H NMR ($CDCl_3$) δ 4.69–4.72 (2 H, m), 3.48 (1 H, m), 2.71–2.93 (2 H, m), 1.59–1.87 (5 H, m), 1.01 (3 H, d, $J = 6.4$ Hz), 0.91 (9 H, s), 0.17 (3 H, s), 0.12 (3 H, s); ^{13}C NMR ($CDCl_3$) δ 171.6, 74.4, 70.2, 38.3, 37.7, 32.2, 25.6, 21.9, 19.3, 19.0, −4.2, −5.2; IR (neat) 2955, 1710, 1265, 1095; FAB HRMS, *m*/*z* 273.1893, M+H calcd for $C_{14}H_{29}O_3Si$ 273.1887; Anal. Calcd for $C_{14}H_{28}O_3Si$: C, 61.72; H, 10.36. Found: C, 61.56; H, 10.18; $[\alpha]^{20}_D$:+16.7 (c 1.7, $CHCl_3$).

[6*R*-(6α,7β)]-7-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-6-methyl-2-oxocanone (18) ^{1}H NMR ($CDCl_3$) δ 4.71–4.76 (2 H, m), 3.54 (1 H, m), 2.63–2.85 (2 H, m), 1.64–1.94 (5 H, m), 0.98 (3 H, d, $J = 6.4$ Hz), 0.89 (9 H, s), 0.15 (3 H, s) 0.08 (3 H, s); ^{13}C NMR ($CDCl_3$) δ 172.5, 75.1, 69.6, 39.0, 37.5, 31.0, 25.6, 22.1. 19.7, 19.2,−4.2, −4.8; IR (neat) 2955, 1705, 1250, 1090; FAB HRMS, *m*/*z* 273.1883, M+H calcd for $C_{14}H_{29}O_3Si$ 273.1887; Anal. Calcd for $C_{14}H_{28}O_3Si$: C, 61.72; H, 10.36. Found: C, 61.37; H, 10.04; $[\alpha]^{20}_D$:+12.4 (c 1.5, $CHCl_3$).

[4*R*-(4α,8β)]-4-[(4-methoxyphenyl)methoxy]-8-methyl-2-oxocanone (20). ^{1}H NMR ($CDCl_3$) δ 7.24 (2 H, d, $J = 8.8$ Hz), 6.87 (2 H, d, $J = 8.8$ Hz), 4.71 (1 H, m), 4.50 (1 H, d, $J = 11.6$ Hz), 4.46 (1 H, d, $J = 11.6$ Hz), 3.88 (3 H, s), 3.75 (1 H, m), 2.89 (1 H, dd, $J = 12.9$, 6.2 Hz), 2.71 (1 H, dd, $J = 12.9$, 3.8 Hz), 1.64–1.96 (6 H, m), 1.35 (3 H, d, $J = 6.0$ Hz); ^{13}C NMR ($CDCl_3$) δ 184.2, 159.5, 130.3, 129.4, 114.1, 77.5, 75.6, 70.7, 55.5, 38.3, 37.7, 32.2, 21.9, 19.0; IR (neat) 3054, 2987, 1702, 1422, 1266, 1092 cm^{-1}; FAB HRMS, *m*/*z* 279.1602, M+H calcd for $C_{16}H_{23}O_4$ 279.1597; Anal. Calcd for $C_{16}H_{22}O_4$: C, 69.04; H, 7.97. Found: C, 69.15; H, 8.21; $[\alpha]^{20}_D = -26.0$ (c 1.2, $CHCl_3$).

[4*S*-(4β,8β)]-4-[(4-methoxyphenyl)methoxy]-8-methyl-2-oxocanone (22). ^{1}H NMR ($CDCl_3$) δ 7.27 (2 H, d, $J = 8.8$ Hz), 6.86 (2 H, d, $J = 8.8$ Hz), 4.77 (1 H, m), 4.61 (1 H, d, $J = 11.2$ Hz), 4.45 (1 H, d, $J = 11.2$ Hz), 3.79 (3 H, s), 3.75 (1 H, m), 2.68–2.76 (2 H, m), 1.81–1.87 (3 H, m), 1.60–1.67 (3 H, m), 1.33 (3 H, d, $J = 6.4$ Hz); ^{13}C NMR ($CDCl_3$) δ 172.8, 159.4, 130.5, 129.5,

114.0, 94.6, 75.7, 70.1, 55.5, 38.7, 38.2, 33.3, 21.6, 19.4; IR (neat) 3054, 2990, 1698, 1436, 1258, 1092 cm^{-1}; FAB HRMS, *m/z* 279.1596, M+H calcd for $C_{16}H_{23}O_4$ 279.1597; Anal. Calcd for $C_{16}H_{22}O_4$: C, 69.04; H, 7.97. Found: C, 69.31; H, 7.80; $[\alpha]^{20}{}_D = +18.6$ (c 1.4, $CHCl_3$).

ACKNOWLEDGMENT

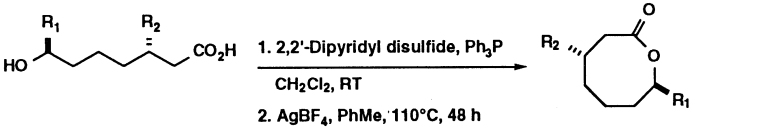
This work was generously supported by the American Cancer Society and the NSF-EPSCoR program. Acknowledgment is also made to the Donors of the Petroleum research Fund, administered by the American Chemical Society, for additional support of this research.

REFERENCES

1. Illuminati, G.; Mandolini, L. Acc. Chem. Res. **1981**, *14*, 95.
2. Lee, E.; Yoon, C.H.; Lee, T.H.; Kim, S.Y.; Ha, T.J.; Sung, Y.-S.; Park, S.-H.; Lee, S. J. Am. Chem. Soc. **1998**, *120*, 7469, and references cited therein.
3. Kao, C.M.; McPherson, M.; McDaniel, R.N.; Fu, H.; Cane, D.E.; Khosla, C. J. Am. Chem. Soc. **1997**, *119*, 11339. In fact, there at least 40 natural products that feature as the main topology an eight-membered ring, of which no fewer than six possess saturated lactone rings: Rosseau, G. Tetrahedron **1995**, *51*, 2777 and references cited therein.
4. Funk, R.L.; Abelman, M.M. J. Org. Chem. **1986**, *51*, 3247.
5. Buszek, K.R.; Sato, N.; Jeong, Y. J. Am. Chem. Soc. **1994**, *116*, 5511.
6. Buszek, K.R.; Jeong, Y. Tetrahedron Lett. **1995**, *36*, 7189.
7. Perchellet. J.-P.; Perchellet, E.M.; Newell, S.W.; Freeman, J. A.; Ladesich, J.B.; Jeong, Y.; Sato, N.; Buszek, K.R. *Anticancer Research* **1998**, *18*, 97.
8. Corey, E.J.; Nicolaou, K.C. J. Am. Chem. Soc. **1974**, *96*, 5614.
9. Boden, P.B.; Keck, G.E. J. Org. Chem. **1985**, *50*, 2394.
10. Inanaga, J.; Hirata, K.; Saeki, H.; Kastuki, T.; Yamaguchi, M. Bull. Chem. Soc. Jpn. **1979**, *52*, 1989.
11. Mukaiyama, T.; Usui, K.; Saigo, K. *Chem. Lett*. **1976**, 49.
12. Allinger, N. Pure Appl. Chem. **1982**, *54*, 2512.
13. The most often cited example involves the Woodward erythronolide A lactone system: Woodward, R. B.; Logusch, E.; Nambiar, K.P.; Sakan, K.; Ward, D.E; Au-Yeng, B.-W.; Balaram, P.; Browne, L.J.; Card, P.J.; Chen, C.H.; Chenevert, R.B.; Fliri, A.; Frobel, K.; Gais, H.-J.;

Garratt, D.G.; Hayakawa, K.; Heggie, W.; Hesson, D.P.; Hoppe, D.; Hoppe, I.; Hyatt, J.A.; Ikeda, D.; Jacobi, P.A.; Kim, K,S.; Kobuke, Y.; Kojima, K.; Krowicki, K.; Lee, V.J.; Leutert, T.; Malchenko, S.; Martens, J.; Matthews, R.S.; Ong, B.S.; Press, J.B.; Rajan Babu, T.V.; Rousseau, G.; Sauter, H.M.; Suzuki, M.; Tatsuta, K.; Tolbert, L.M.; Truesdale, E.A.; Uchida, I.; Ueda, Y.; Uyehara, T.; Vasella, A.T.; Vladuchick, W.C.; Wade, P.A.; Williams, R.M.; Wong, H.N.-C. J. Am. Chem. Soc. **1981**, *103*, 3213. The cyclic ketals employed presumably facilitated the lactonization.

14. Beesley, R.M.; Ingold, C.K.; Thorpe, J.F. J. Chem. Soc. **1915**, *107*, 1080.
15. Jung, M.E.; Gervay, J. Tetrahedron Lett. **1988**, *29*, 2429.
16. Jung, M.E.; Marquez, R. Tetrahedron Lett. **1997**, *38*, 6521.
17. Alder, R.W.; Maunder, C.M.; Orpen, A.G.R. Tetrahedron Lett. **1990**, *31*, 6717.
18. Cornwell, W.D.; Cieplak, P.; Bayley, C.I.; Gould, I.R.; Merz, K.M., Jr.; Ferguson, D.M.; Spellmeyer, D.C.; Fox, R.; Caldwell, J.W.; Kollman, P.A. J. Am. Chem. Soc. **1995**, *117*, 5179.
19. Indeed, we observed that monosubstituted seco acids also lactonize, albeit in lower yields. In these cases, a single substituent at C-3 is apparently more important than one at C-7:



23: R_1 = Me; R_2 = H
25: R_1 = H; R_2 = OMPM

24: R_1 = Me; R_2 = H (18%)
26: R_1 = H; R_2 = OMPM (34%)

Geminal dimethyl substitution at C-7 failed to induce lactonization. The complete results from these calculations will be described elsewhere.

20. Nicolaou, K.C.; McGarry, D.G.; Somers, P.K.; Kim, B.H.; Ogilvie, W.W.; Yiannikouros, G.; Prasad, C.V.C.; Veale, C.A.; Hark, R.R. *J. Am. Chem. Soc.* **1990**, *112*, 6263.
21. For an example of diolide formation, see Fox, C.M.J; Ley, S.V.; Slawin. A.M.Z.; Williams, D.J. *J. Chem Soc., Chem. Commun.* **1985**, 1805.
22. Total synthesis of (+)- and (−)-cephalosporolide D: Buszek, K.R.; Ghosh, I.; Jeong, Y., manuscript in preparation. The specific rotation for (+)-cephalosporolide D, $[\alpha]^{20}_D = +47.5^\circ$ (c 0.20, $CHCl_3$), was nearly opposite than that reported for the natural compound: Ackland, J.J.;

Hanson, J.R.; Hitchcock, P.B.; Ratcliffe, A.H. J. Chem. Soc., Perkin Trans. 1 **1985**, 843.

Received in the USA May 26, 2000