Preparation of Medium-Ring Lactones and Lactams by Electrophilic Cyclizations

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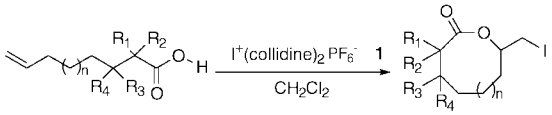
Preparation of medium-ring compounds is still a challenge in organic synthesis even if some interesting results have been reported in recent years.[1] Our interest in this research field led us to examine the preparation of medium-ring lactones[2] and ethers[3] by electrophilic heteroatom cyclizations of linear precursors. The difficulty of closure inherent in these ring sizes[4] led us to study the structural parameters and the reagents that should favor it. In our previous work, we have shown that bis(collidine)iodine(I) hexafluorophostate (**1**) is an interesting reagent to carry out such reactions, even though, in some cases, yields were modest. The search for a more efficient reagent is probably not the unique answer to the problems raised by these medium-ring closures. Substrate modifications should also bring beneficial results. For example, we found that substitution of one of the carbons of the chain by an oxygen atom[2a] or the introduction of a *gem*-dimethyl group[2b] on one of these carbon atom favored these cyclizations.

We report here our results concerning the influence of the introduction of a geometrical constraint imposed to one or two carbon atoms of the chain. At first, we decided to carry out a study on the influence of a conformational constraint brought by a dioxolane or dithiolane in the β position, or an *exo*-carbon−carbon double bond in α position, of the acid function. The desired acids **2**−**4** were prepared by standard procedures. Their iodolactonizations were carried out at room temperature in methylene chloride in the presence of 1.3 equiv of bis(collidine)-iodine(I) hexafluorophosphate (**1**).[2] Our results are reported in Table 1. No reaction was observed with the 7-octanoic acids **2a** and **3**. Only acids **2b** and **4** led in low yields to the desired iodo lactones **5** and **6**, whose structures were easily established from their ^{1}H and ^{13}C NMR spectra. We suggest that the low reactivity of the acids **2a**,**b** and **3** is due in part to the presence of a hydrogen bond that induces an unfavorable conformation of the chain during the cyclization (Chart 1). The influence of a one-carbon conformational constraint is thus insufficient to allow the formation of medium-ring lactones in our reaction conditions.

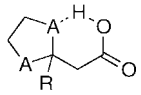
These results led us to examine the influence of a conformational constraint brought by two carbon atoms

Table 1. Influence of One-Carbon Conformational Constraint on the Formation of Mediolides

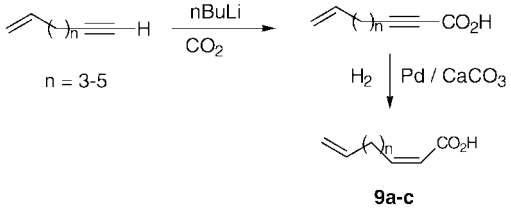


2a	R_1, R_2 = H; R_3, R_4 = $(OCH_2)_2$	n = 1		NR
2b	R_1, R_2 = H; R_3, R_4 = $(OCH_2)_2$	n = 2	**5**	11 %
3	R_1, R_2 = H; R_3, R_4 = $(SCH_2)_2$	n = 1		NR
4	R_1, R_2 = CH_2; R_3, R_4 = H	n = 1	**6**	20 %

Chart 1



Scheme 1



9a-c

(sp^3 and sp^2 carbons). The acids used were prepared by standard methods and required no special comments, except for acids **9a**−**c**. The latter were obtained in three steps from the corresponding 1-bromoalkenes **2b**−**d** by reaction with the lithium acetylide−ethylenediamine complex, followed by carboxylation and subsequent cis hydrogenation (Scheme 1). We found that the cis hydrogenation could be achieved in the presence of the Lindlar catalyst desactivated by quinoleine. However, it was difficult to avoid a partial reduction (≤10% from VPC and ^{1}H NMR) of the terminal carbon−carbon double bond. Reaction of these acids in methylene chloride in the presence of 1.3 equiv of bis(collidine)iodine(I) hexafluorophosphate **1** led to the formation of iodo lactones. Our results are reported in Table 2. These lactones were mainly characterized from their ^{1}H and ^{13}C NMR spectra. Comparison of the results reported in Table 2 with those reported in Table 1 shows that introduction of a two-carbon conformational restriction in the chain has a positive effect. Eight-membered-ring lactones **10a**, **16a**, **19a**, and **21a** were obtained in exceptionally high yields. The only exception was the cyclization of acid **7**, which led to two diastereoisomeric lactones **8** in moderate yields. Comparison of this latter result with that observed in the cyclization of acid **20a** shows that the rigidity introduced by a cyclohexane is apparently not enough to give a satisfactory reaction. Conformationally more rigid cyclopentane or cyclobutane rings should give better results. The relative stereochemistry at the C7 in the two diastereoisomers **8** was not determined. However, it was possible to measure by NMR the coupling constants between the two hydrogens fixed at the cycle junction (J = 6.5, 7.5 Hz). These values means that we probably have a cis cycle junction, since higher values would be expected for a trans cycle junction (this determination was not possible on the starting acid **7**).

(1) For reviews see: (a) Petasis, N. A.; Patane, M. A. *Tetrahedron* **1992**, *48*, 5757. (b) Roxburgh, C. J. *Tetrahedron* **1993**, *49*, 10749. (c) Evans, P. A.; Holmes, A. B. *Tetrahedron* **1991**, *47*, 9131. (d) Rousseau, G. *Tetrahedron* **1995**, *51*, 2777. (e) Moody, C. J.; Davies, M. J. In *Studies in Natural Products Chemistry*; Attar-ur-Rahman, Ed.; Elsevier Science Publishers: New York, 1992; Vol. 10, p 201. (f) Rousseau, G.; Homsi, F. *Chem. Soc. Rev*. **1997**, *26*, 453.

(2) (a) Simonot, B.; Rousseau, G. *J. Org. Chem*. **1994**, *59*, 5912. (b) Simonot, B.; Rousseau, G. *Tetrahedron Lett*. **1993**, *34*, 4527.

(3) Brunel, Y.; Rousseau, G. *J. Org. Chem*. **1996**, *61*, 5793.

(4) Illuminati, G.; Mandolini, L. *Acc. Chem. Res.* **1981**, *14*, 95.

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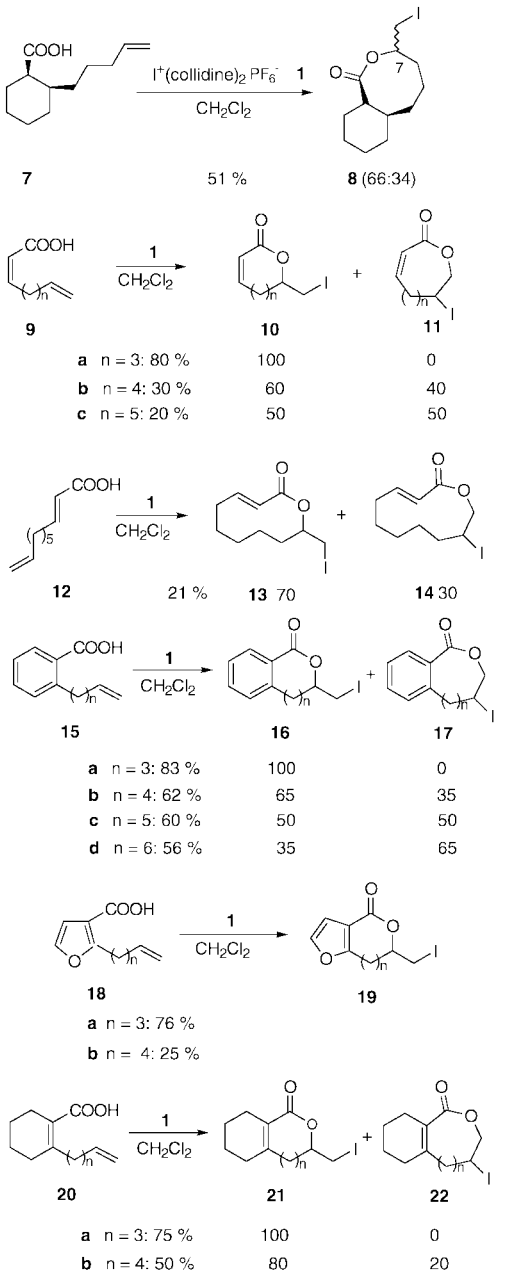
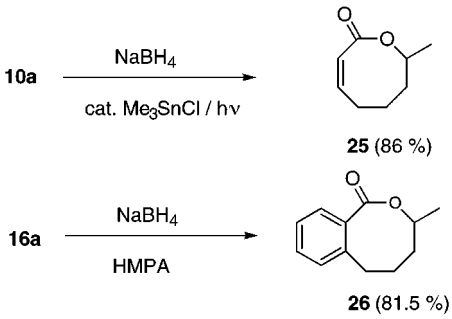
Table 2. Preparation of Iodo Lactones



We confirmed this assumption by molecular calculations.[5] From our experience with this kind of cyclizations, we think that the trans acid should give a lower yield of lactone. For higher ring-size lactones, the results were less conclusive. Indeed, if satisfactory yields were observed in the cyclization of benzoic acids **15b**−**d**, it was not the case with unsaturated acids **9b**−**c**, **12**, and **18b**. We can explain this difference in yield by the fact that with the unsubstituted α,β-ethylenic acids **9b**−**c** and **12** we probably had a competitive addition of the iodonium on the conjugated double bond, which led to nonidentified polymeric materials. This assumption was confirmed when 2-octenoic acid reacted with iodonium reagent **1** to give polymeric materials.[6] This competitive polymerization was not observed with the acid **9a**, due probably to the easier cyclization into eight-membered lactone **10b**. The low yield observed in the formation of lactone **19b** appeared to be due to the competitive addition of the iodonium salt **1** on the furan ring, which led to nonidentified polar products. It is interesting to not that the *Z*-acid **9c** and *E*-acid **12** led to iodo lactones with the same global yields, though the *Z*-lactones were reported to be thermodynamically less stable than the *E*-lactones.[7] Such a result means, as we previously reported,[2] that these electrophilic cyclizations occur under kinetic control. In both cases, the decrease in entropy appeared to be enough to allow the ring closure. For lactones with nine-membered ring size and higher, we observed in general[8] a competition between the exo- and endo-mode cyclizations. Apparently, as the ring size of lactone increases, the endo−exo ratio increases.

Scheme 2



We tested the reduction of the iodine atom. Unsatisfactory results were observed using the standard tributyltin hydride procedure. However, reduction of lactone **10a** was efficently carried out using sodium borohydride in the presence of a catalytic amount of trimethyltin chloride.[9] However, this method was unsuccessful with the benzo lactone **16a** for which only tar material was obtained. In this latter case, we found that the reduction could be carried out with sodium borohydride in DMSO or HMPA[10] (Scheme 2).

Nothing seems to be known concerning the obtention of medium-ring lactams[1c,f] by electrophilic cyclizations. We decided to investigate this possibility using sulfonamides. The desired amide **23** was obtained by reaction of the acid chloride prepared from the acid **15a** with the lithium salt of toluenesulfonamide (25% yield). When the reaction was carried out in the presence of bis(collidine)-iodine(I) hexafluorophosphate (**1**), we isolated the corresponding lactam **24a** in 44% yield. This cyclization was also observed with the corresponding bromo reagent, with lower yields (Scheme 3). These results open the possibility to obtain medium-ring lactams by electrophilic cyclizations.

In conclusion, we have reported in this paper that medium-ring heterocycles (lactones and lactams) could be obtained by electrophilic cyclizations if two conditions could be fulfilled:

(5) Molecular calculations were made using MAD (2.3 version) program.

(6) A hypothesis to explain these polymerizations may be the intermediate formation of α-lactones (by 3-exo cyclization), which are known to be only low-temperature stable species. See: Wierlacher, S.; Sander, W.; Liu, M. T. H. *J. Org. Chem.* **1992**, *57*, 1051 and references cited therein.

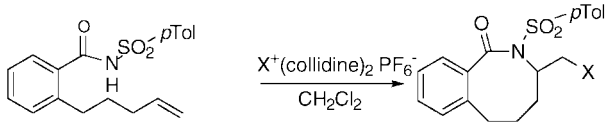
(7) Fouque, E.; Rousseau, G.; Seyden-Penne, J. *J. Org. Chem.* **1990**, *55*, 4817.

(8) We cannot exclude that the absence of *endo*-lactone in the cyclization of the furanoic acid **18b** was due to its degradation during the workup of the reaction mixture.

(9) Corey, E. J.; Suggs, J. W. *J. Org. Chem.* **1975**, *40*, 2555.

(10) Hutchins, R. O.; Kandasamy, D.; Dux, F., III; Maryanoff, C. A.; Rotstein, D.; Goldsmith, B.; Burgogne, W.; Cistone, F.; Dalessandro, J.; Puglis, J. *J. Org. Chem.* **1978**, *43*, 2259.

Scheme 3



23 X = I 44 % **24a**
X = Br 33 % **24b**

(1) A conformational constraint must be introduced in the chain. From our results it appears that the conformational restriction must be introduced to at least two vicinal atoms to obtain satisfactory yields.[11]

(2) The reagent must be highly electrophilic with an unreactive counteranion.

Experimental Section

General Remarks. All NMR spectra were measured in $CDCl_3$, and chemical shifts are expressed in ppm relation to internal $CHCl_3$. All solvents were purified by known standard procedures; in particular, methylene chloride was distilled from CaH_2. The iodolactonizations were conducted in the dark. After the reactions, the iodo lactones could be handled for a short time wihout special care and stored at −20 °C in the dark. ^{1}H NMR spectra were measured in $CDCl_3$ at 200 or 250 MHz. Bis(collidine)iodine(I) hexafluorophosphate (**1**) and bis(collidine)bromine(I) hexafluorophosphate (**25**) were prepared using the same procedure as previously reported.[2a,12]

General Procedure for the Iodolactonization. To a solution of bis(collidine)iodine(I) hexafluorophosphate (0.36 g, 0.7 mmol) in dry methylene chloride (70 mL) was added by a push syringe over 10 h 0.54 mmol of the desired acid in methylene chloride (10 mL). Subsequently, 1 g of silica gel was added to the reaction mixture, and the solvent was removed. The solid was put on the top of a flash silica gel column and a mixture pentane−ethyl acetate or pentane−ether used for the elution.

9-(Iodomethyl)-1,4,8-trioxaspiro[4.3]tridecan-7-one (5): oil; ^{1}H NMR δ 1.40−2.00 (m, 8H), 2.52 (d, J = 20 Hz) and 2.75 (d, J = 20 Hz) (AB system), 3.30 (d, J = 7.5 Hz, 2H), 3.90−4.05 (m, 4H), 4.83−5.00 (m, 1H); ^{13}C NMR δ 16.86, 23.77, 25.56, 30.38,36.65, 43.82, 49.65, 61.17, 67.12, 71.07, 166.70. Anal. Calcd for $C_{11}H_{17}O_4I$: C, 38.84; H, 5.04. Found: C, 39.03; H, 5.23.

9-(Iodomethyl)-3-methyleneoxocane-2-one (6): oil; ^{1}H NMR δ 1.30−1.60 (m, 4H), 1.70−2.00 (m, 4H), 2.40−2.50 (m, 2H), 3.20−3.35 (m, 2H), 4.65−4.80 (m, 1H), 5.30 (m, 2H). Anal. Calcd for $C_9H_{13}O_2I$: C, 38.59; H, 4.68. Found: C, 38.47; H, 4.81.

(2*R*,3*S*)-7-(Iodomethyl)-6-oxa-decahydrobenzocycloocten-5-one (8). The two diastereoisomers were separated by liquid chromatography over silica gel (ether−pentane 5:95). Less polar isomer (34%): oil; ^{1}H NMR δ 1.25−2.05 (m, 14H), 2.25−2.40 (m, 1H), 2.60−2.70 (m, 1H), 3.30 (d, J = 6 Hz, 2H), 4.85−5.00 (m, 1H); ^{13}C NMR δ 6.74, 21.06, 23.17, 24.41, 32.21, 35.88, 35.96, 40.08, 43.62, 76.71, 178.55. Anal. Calcd for $C_{12}H_{19}O_2I$: C, 44.74; H, 5.94. Found: C, 44.95; H, 6.06. More polar isomer (76%): solid; mp 88−89 °C; ^{1}H NMR δ 1.10−1.85 (m, 11H), 1.85−2.10 (m, 4H), 2.62−2.75 (m, 1H), 3.30 (dd, J = 7, 2 Hz, 2H), 4.75−4.85 (m, 1H); ^{13}C NMR δ 7.87, 22.30, 23.68 (2C), 25.26, 31.08, 33.28 (2C), 37.35, 43.24, 78.15, 177.13. Anal. Calcd for $C_{12}H_{19}O_2I$: C, 44.74; H, 5.94. Found: C, 44.81; H, 6.01.

(*Z*)-7-(Iodomethyl)-2-heptenolide (10a): white crystals; mp 86−88 °C; ^{1}H NMR δ 1.65−2.00 (m, 4H), 2.10−2.30 (m, 1H), 2.30−2.65 (m, 1H), 3.10−3.30 (m, 2H), 4.75 (m, 1H), 5.8 (m, 1H), 6.25 (m, 1H); ^{13}C NMR δ 6.37, 19.77, 31.02, 35.38, 78.11, 117.46, 141.90, 168.56. Anal. Calcd for $C_8H_{11}O_2I$: C, 36.11; H, 4.17. Found: C, 35.91; H,4.07.

(*Z*)-8-(Iodomethyl)-2-octenolide (10b): oil; ^{1}H NMR δ 1.10−1.90 (m, 6H), 1.90−2.20 (m, 2H), 3.40 (m, 2H), 4.85 (m, 1H), 5.90 (dd, J = 11, 2 Hz, 1H), 6.50 (dt, J = 11.0, 6.0 Hz, 1H). Anal. Calcd for $C_9H_{13}O_2I$: C, 38.59; H, 4.68. Found: C, 38.52; H,4.60.

(*Z*)-8-Iodo-2-nonenolide (11b): oil; ^{1}H NMR δ 1.10−2.20 (m, 6H), 2.00−2.50 (m, 2H), 4.20 (m, 2H), 5.15 (m, 1H), 5.90 (d, J = 9 Hz, 1H), 6.35 (dt, J = 9, 7 Hz, 1H). Anal. Calcd for $C_9H_{13}O_2I$: C, 38.59; H, 4.68. Found: C, 38.74; H,4.92.

(*E*)-9-(Iodomethyl)-2-nonenolide (13): oil; ^{1}H NMR δ 1.10−1.80 (m, 8H), 2.12−2.38 (m, 2H), 3.22−3.38 (m, 2H), 4.80−4.95 (m, 1H), 5.70−5.90 (m, 1H), 6.82−7.10 (dt, J = 16, 6 Hz, 1H); ^{13}C NMR δ 7.40, 23.34, 25.28, 25.53, 34.60, 36.46, 72.00, 122.71, 142.63, 170.12. Anal. Calcd for $C_{10}H_{15}O_2I$: C, 40.84; H, 5.14. Found: C, 41.02; H, 5.08.

(*E*)-10-Iodo-2-decenolide (14): oil; ^{1}H NMR δ 1.10−1.80 (m, 8H); 2.12−2.38 (m, 2H), 4.10−4.40 (m, 2H), 4.50−4.70 (m, 1H), 5.70−5.90 (m, 1H), 6.82−7.10 (dt, J = 16, 6 Hz, 1H); ^{13}C NMR δ 7.11, 23.24, 25.22, 25.50, 34.55, 36.33, 72.10, 120.7, 149.80, 165.02. Anal. Calcd for $C_{10}H_{15}O_2I$: C, 40.84; H, 5.14. Found: C, 41.11; H, 5.23.

7-(Iodomethyl)-6-oxa-7,8,9,10-tetrahydrobenzocycloocten-5-one (16a): white crystals; mp 86−88 °C; ^{1}H NMR δ 1.90−2.20 (m, 4H), 2.70−2.95 (m, 2H), 3.15−3.40 (m, 2H), 4.25−4.40 (m, 1H), 7.15−7.55 (m, 4H); ^{13}C NMR δ 9.04, 26.16, 32.43, 34.39, 79.72, 126.96, 128.47, 129.79, 130.90, 131.85, 139.22, 170.75. Anal. Calcd for $C_{12}H_{13}O_2I$: C, 45.59; H, 4.14. Found: C, 45.51; H, 4.09.

7-(Iodomethyl)-6-oxa-8,9,10,11-tetrahydro-(7*H*)-benzocyclononen-5-one (16b): oil; ^{1}H NMR δ 1.40−2.10 (m, 6H), 2.65 (ddd, J = 4, 7.5, 12 Hz, 1H), 3.50 (d, J = 5, 2H), 3.30 (m, 1H), 4.10−4.40 (m, 2H), 5.05 (m, 1H), 7.20−7.50 (m, 3H), 7.90 (dd, J = 6, 1 Hz, 1H); ^{13}C NMR δ 7.57, 23.03, 31.18, 32.12, 33.33, 67.94, 126.34, 130.42, 130.83, 131.39, 132.30, 144.81, 169.98. Anal. Calcd for $C_{13}H_{15}O_2I$: C, 47.29; H, 4.58. Found: C, 47.22; H, 4.28.

8-Iodo-6-oxa-7,8,9,10,11,12-hexahydrobenzocyclodecen-5-one (17b): oil; ^{1}H NMR δ 1.15−1.70 (m, 4H), 1.78−1.95 (m, 1H), 2.30−2.60 (m, 2H), 3.25 (m, 1H), 4.15−4.35 (m, 2H), 5.05 (dd, J = 9, 3.5 Hz, 1H), 7.20−7.50 (m, 3H), 7.80 (dd, J = 6, 1 Hz, 1H); ^{13}C NMR δ 23.18,27.60, 29.08, 32.15,36.62, 70.50, 126.31, 130.57, 130.98, 132.05, 143.46, 169.53. Anal. Calcd for $C_{13}H_{15}O_2I$: C, 47.29; H, 4.58. Found: C, 47.10; H, 4.49.

6-(Iodomethyl)-5-oxa-6,7,8,9-tetrahydrofurancycloocten-4-one (19a): white solid; ^{1}H NMR δ 1.85−2.20 (m, 4H), 2.65−2.80 (m, 1H), 3.05−3.20 (m, 1H), 3.23−3.45 (m, 2H), 4.58−4.80 (m, 1H), 6.63 (d, J = 2 Hz, 1H), 7.33 (d, J = 2 Hz, 1H); ^{13}C NMR δ 19.75, 27.89, 34.94, 78.50, 111.78, 112.85, 141.40, 157.50, 165.15. Anal. Calcd for $C_{10}H_{11}O_3I$: C, 39.24; H, 3.62; I, 41.46. Found: C, 38.63; H, 3.77; I, 40.14.

6-(Iodomethyl)-5-oxa-7,8,9,10-tetrahydro-(6*H*)-furancyclononen-4-one (19b): oil; ^{1}H NMR δ 1.55−1.90 (m, 6H), 2.02−2.20 (m, 1H), 2.78−2.95 (m, 1H), 3.30−3.50 (m, 2H), 4.65−4.80 (m, 1H), 6.70 (d, J = 2 Hz, 1H), 7.28 (d, J = 2 Hz, 1H). Anal. Calcd for $C_{11}H_{13}O_3I$: C, 41.27; H, 4.09. Found: C, 41.63; H, 3.85.

7-(Iodomethyl)-6-oxa-1,2,3,4,7,8,9,10-octahydrobenzocycloocten-5-one (21a): white solid; mp 81 °C; ^{1}H NMR δ 1.35−2.65 (m, 12H), 3.15−3.40 (m, 2H), 4.60−4.75 (m, 1H); ^{13}C NMR δ 9.00, 21.14, 21.49, 22.12, 26.34, 29.77, 33.28, 34.64, 79.11, 123.46, 141.40, 172.05. Anal. Calcd for $C_{12}H_{17}O_2I$: C, 45.02; H, 5.35. Found: C, 45.28; H, 5.48.

7-(Iodomethyl)-6-oxa-1,2,3,4,7,8,9,10-octahydro-(7*H*)-benzocyclononen-5-one (21b): oil; ^{1}H NMR δ 1.35−1.85 (m, 10H), 1.95−2.23 (m, 5H), 2.36−2.55 (m, 1H), 3.18−3.33 (m, 1H), 3.35 (dd, J = 6, 1 Hz, 2H), 4.87−4.90 (m, 1H); ^{13}C NMR δ 8.52, 21.96, 22.65 (2C), 25.92, 29.76, 33.10, 33.52, 34.20, 75.52, 125.63, 152.33, 171.12. Anal. Calcd for $C_{13}H_{19}O_2I$: C, 46.72; H, 5.73. Found: C, 46.98; H, 5.91.

8-Iodo-6-oxa-1,2,3,4,7,8,9,10,11,12-decahydrobenzocyclodecen-5-one (22b): oil; ^{1}H NMR δ 1.30−2.40 (m, 15H), 2.60−2.80 (m, 1H), 4.15−4.28 (m, 1H), 4.85 (t, J = 10 Hz, 1H), 4.85 (dd, J = 5, 10 Hz, 1H); ^{13}C NMR δ 21.88, 22.47, 24.80, 25.91, 26.58, 27.18, 31.75, 31.93, 36.57, 70.07, 126.02, 147.09, 169.31. Anal. Calcd for $C_{13}H_{19}O_2I$: C, 46.72; H, 5.73. Found: C, 47.11; H, 5.82.

(*Z*)-9-Methyl-2-heptenolide (25). To the iodo lactone **10a** (0.5 g, 1.88 mmol) and trimethyltin chloride (0.15 g, 0.75 mmol) in air-free ethanol (40 mL) cooled to 15 °C, was rapidly added

(11) We recently found that oxocanes could be also formed in excellent yields if a conformational constraint was introduced in the chain. Renard, S. Unpublished results.

(12) Homsi, F.; Robin, S.; Rousseau, G. *Organic Syntheses*, submitted for publication.

with a syringe sodium borohydride (0.09 g) dissolved in ethanol (10 mL). The reaction mixture was irradiated with a 200-W mercury lamp for 30 min. Then oxalic acid dihydrate (0.015 g) was added followed 5 min later by methylene chloride (200 mL). The resulting solution was washed once with saturated $NaHCO_3$ and dried over $MgSO_4$ and the solvent removed under reduced pressure. The product was purified by chromatography over silica gel (elution: 70% hexane−30% ethyl acetate) to give 0.20 g (86%) of lactone **25**: ^{1}H NMR δ 1.30 (d, J = 5.5 Hz, 3H), 1.50−2.20 (m, 4H), 2.45 (m, 2H), 4.80 (m, 1H), 5.70 (dt, J = 12, 0.5 Hz, 1H), 6.20 (dt, J = 4, 12 Hz, 1H); ^{13}C NMR δ 19.53, 21.41, 31.13, 37.47, 74.62, 117.48, 141.40, 169.89. Anal. Calcd for $C_8H_{12}O_2$: C, 68.55; H, 8.63. Found: C, 58.71; H, 8.90.

3-(Iodomethyl)-2-(toluene-4-sulfonyl)-3,4,5,6-tetrahydro-(2*H*)-benzo[*c*]azocin-1-one (24a). The iodolactamization was conducted following the general procedure used for the iodolactonization. A white solid that decomposed at 163−165 °C was isolated by chromatography over silica gel: ^{1}H NMR δ 1.45−2.20 (m, 4H), 2.37−2.50 (s, 3H), 2.50−2.65 (m, 1H), 2.80−2.93 (m, 1H), 3.18−3.28 (m, 1H), 3.28−3.40 (m, 1H), 4.20−4.40 (m, 1H), 7.13−7.42 (m, 4H), 7.42−7.55 (m, 2H), 7.78−8.00 (m, 2H); ^{13}C NMR δ 6.90, 21.47, 25.90, 32.16, 33.48, 66.94, 83.50, 126.89, 127.39 (2C), 129.11 (2C), 130.03, 132.64, 138.76, 141.34, 143.22, 168.43. Anal. Calcd for $C_{19}H_{20}INO_3S$: C, 48.62; H, 4.30. Found: C, 48.81; H, 4.22.

7-Methyl-6-oxa-7,8,9,10-tetrahydrobenzocycloocten-5-one (26). To a 500 mL round-bottomed flask were added the iodo lactone **16a** (0.52 g, 1.6 mmol), dry HMPA (80 mL), and $NaBH_4$ (0.12 g, 3.2 mmol). The reaction mixture was stirred for 6 min at room temperature. Subsequently, water (200 mL) was added and the aqueous solution extracted with ether (3 × 40 mL). The organic layers were combined, washed ounce with water, and dried over $MgSO_4$, and the solvent was removed on a rotary evaporator. The residue was purified by chromatography over silica gel (80% hexane−20% ethyl acetate) to give 0.24 g (82%) of lactone **26**: ^{1}H NMR δ 1.25−1.35 (d, J = 7.5 Hz, 3H), 1.50−2.20 (m, 4H), 2.70−2.90 (m, 2H), 4.35−4.45 (m, 1H), 7.15−7.35 (m, 3H), 7.35−7.50 (m, 1H); ^{13}C NMR δ 23.40, 26.52, 32.85, 36.35, 77.16, 126.72, 128.30, 129.71, 131.48, 131.63, 140.30, 171.84. Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.93; H, 7.66.

Supporting Information Available: Preparations and spectral data for the acids **2**−**4**, **7**, **9**, **12**, **15**, **18**, and **20** and the amide **23**. ^{1}H and ^{13}C spectral data for the lactones **11c**, **16c**,**d**, **17c**,**d**, and the amide **24b** (9 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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