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Preparation of Macrocyclic Lactones by Ring Closure of Cesium Carboxylates

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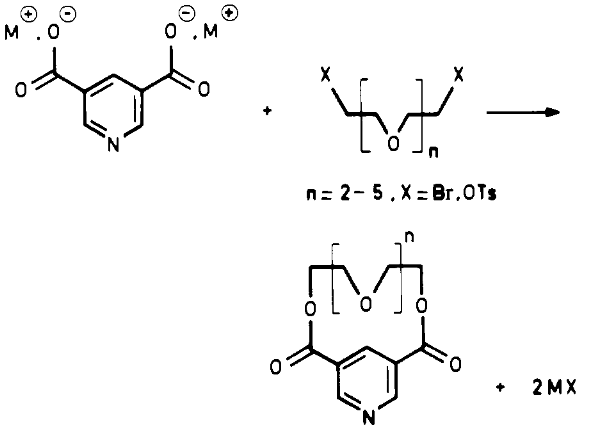
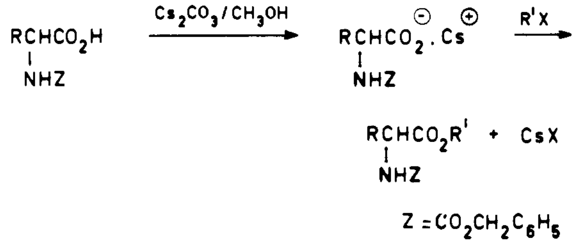
Abstract: A series of ω-halo fatty acids, the longest being 16-iodohexadecanoic acid, was prepared by oxidation of the corresponding ketones with *m*-chloroperbenzoic acid in boiling chloroform, followed by ring opening usually with hydrogen iodide in acetic acid at 100 °C. Solutions of these acids in dimethylformamide (DMF) at concentrations of 5×10^{-3}–5×10^{-2} M were treated with an equivalent amount of dry Cs_2CO_3. The solutions were stirred at 40 °C overnight. Workup of the reaction mixture produced a mixture of (macro)cyclic lactone (macrolide) and its dimer (dilide). For the case of 16-iodohexanoic acid the lactone was isolated in 85% yield. Yields for other large ring macrolides were also excellent. It was demonstrated that substitution by carboxylate on a secondary halide also goes well to afford the corresponding macrolide with no detectable amount of elimination. The effects of ring size, concentration, and solvent on the ring closure of the cesium carboxylates formed in situ were investigated. DMF is the best solvent of those investigated for the ring closure. Cesium carboxylates also undergo more readily ring closure and in far better yield than the carboxylates of lithium, sodium, potassium, rubidium, silver, thallium, magnesium, strontium, or barium. The *S*-lactone of ricinelaidic acid was prepared optically pure in 80% yield from optically pure mesylate of *R*-ricinelaidic acid, which was treated with cesium carbonate in dry DMF. This demonstrates that the ring closure proceeds with the anticipated S_N2 inversion at the hydroxyl-bearing carbon atom. With the same approach optically pure *S*-zearalenone was protected and subjected to ring opening, and the hydroxyl group was activated as mesylate. Some racemization was found to occur in the ring-opening step. On treatment of this material with dry cesium carbonate in DMF, the desired ring closure took place in 80% yield to provide an excess of the protected *R* enantiomer of zearalenone. On the basis of these results, some speculations are made concerning the action of cesium in promoting ring closure to macrocyclic lactones.

A general problem encountered in the synthesis of macrocycles[1] is the ring closure of alicyclic precursors. In recent years, however, it has become apparent that this particular synthetic problem can be solved if methods are developed that circumvent the unfavorable entropy effects involved in forming a macrocyclic system.[2]

Our interest in macrocyclic compounds started with attempts to prepare 3,5-bridged pyridines by a Williamson-like synthetic approach (eq 1).[3] Such bridged pyridines after alkylation and reduction afford *N*-alkyl-3,5-bridged-1,4-hydropyridines that serve as useful mimics for NAD(P)H.[4] Initial attempts to bring about the reaction of eq 1 were not satisfying owing chiefly to insufficient reactivity of the metal (K^+, Na^+) carboxylates. We decided to try to solve this problem by using cesium as the counterion on the basis of extrapolation of a report by Gisin and co-workers concerning the alkylation of the cesium salts of N-protected amino acids in dimethylformamide (DMF) under very mild conditions (eq 2).[5] Indeed, with cesium carboxylates the synthesis of eq 1 could be brought about in yields up to 90% (*n* = 4).



(1)



$$\underset{\mathrm{NHZ}}{\mathrm{RCHCO_2H}} \xrightarrow{\mathrm{Cs_2CO_3/CH_3OH}} \underset{\mathrm{NHZ}}{\mathrm{RCHCO_2^{\ominus}\cdot Cs^{\oplus}}} \xrightarrow{\mathrm{R'X}} \underset{\mathrm{NHZ}}{\mathrm{RCHCO_2R'}} + \mathrm{CsX} \qquad (2)$$

$$Z = CO_2CH_2C_6H_5$$

This synthetic approach was subsequently extended with considerable success to the preparation of a large number of other crown ether like systems.[6] In such syntheses the chains being closed contain heteroatoms capable of complexing, at least in principle, to the cesium atom, allowing it to act as a template.[2b,c] This possibility is eliminated for long polymethylene chains. To see whether cesium would nevertheless still have a positive effect on ring closure in such cases, we attempted the cyclization of some long-chain ω-halo aliphatic acids. These results are reported here together with further applications of this methodology in the preparation of some naturally occurring macrolides.[7] We also

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(1) See for example: (a) Cram, D. J. In "Techniques of Chemistry", Vol. 10; Jones, J. B.; Sih, C. J.; Perlman, D., Eds.; Wiley-Interscience: New York, 1976; p 815; (b) Lehn, J-M. *Structure Bonding* (*Berlin*) **1973**, *16*, 1; (c) Simon, W.; Morf, W. E.; Meier, P. C. *Ibid.* **1973**, *16*, 113; Stoddart, J. F. *Chem. Soc. Rev.* **1979**, *8*, 85.

(2) For reviews of some of the more common approaches, see (a) Prelog, V. *J. Chem. Soc.* **1950**, 420; (b) Busch, D. H. *Rec. Chem. Progr.* **1964**, *25*, 107; (c) Eschenmoser, A. *Pure Appl. Chem.* **1969**, *20*, 1; (d) Nicolaou, K. C. *Tetrahedron* **1977**, *23*, 683; (e) Masamune, S., Bates, G. S., Corcoran, J. W. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 585; (f) Back, T. G. *Tetrahedron* **1977**, *33*, 3041; (g) Newkome, G. R.; Sauer, J. D.; Roper, J. M.; Hager, D. C. *Chem. Rev.* **1977**, *77*, 513; (h) Vögtle, F.; Neumann, P., *Chem.-Ztg.* **1973**, *97*, 600.

(3) See, for example: (a) Piepers, O.; Kellogg, R. M. *J. C. S., Chem. Commun.* **1978**, 383; (b) Kellogg, R. M.; van Bergen, T. J.; van Doren, H.; Hedstrand, D.; Kooi, J.; Kruizinga, W. H.; Troostwijk, C. B. *J. Org. Chem.* **1980**, *45*, 2854.

(4) (a) de Vries, J. G.; Kellogg, R. M. *J. Am. Chem. Soc.* **1979**, *101*, 2759; (b) Jouin, P.; Troostwijk, C. B.; Kellogg, R. M. *Ibid.* **1981**, *103*, 2091.

(5) (a) Gisin, B. F. *Helv. Chim. Acta* **1973**, *56*, 1476; (b) Wang, S.-S.; Gisin, B. F.; Winter, D. P.; Makofske, R.; Kulesha, I. D.; Tzougraki, C.; Meienhofer, J. *J. Org. Chem.* **1977**, *42*, 1286.

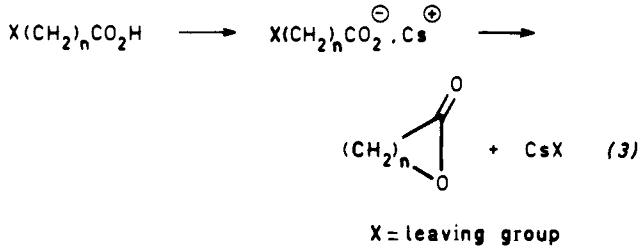
(6) (a) van Keulen, B. J.; Kellogg, R. M.; Piepers, O. *J. Chem. Soc., Chem. Commun.* **1979**, 285; (b) Buter, J.; Kellogg, R. M. *Ibid.*, **1980**, 466; (c) Vriesema, B.; Kellogg, R. M., unpublished results.

(7) A portion of the results reported here appeared as a preliminary communication: Kruizinga, W. H.; Kellogg, R. M. *J. Chem. Soc., Chem. Commun.* **1979**, 286.

make some suggestions concerning the mechanism of ring closure promoted by cesium ions.

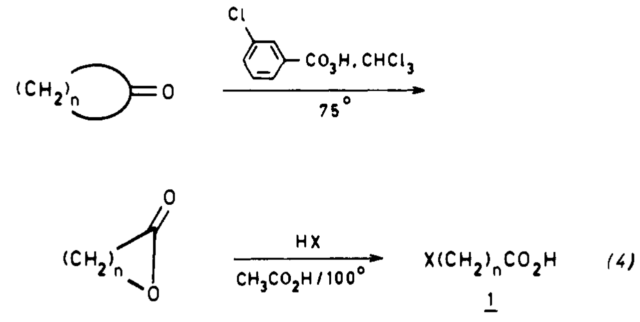
Results

An approach to macrocyclic lactones by ring closure of cesium carboxylates requires that the substrate be a long-chain acid with a good leaving group at the site at which ring closure must occur (eq 3). Equation 3 contains, of course, the basic chemical tenets of the Hunsdiecker[8] approach to macrocyclic lactones. Such reactions often proceed in excellent yields but only under conditions of very high dilution and slow addition. We wanted to work under simpler experimental conditions and, moreover, to avoid high dilution. The most direct approach is in situ formation in DMF of the carboxylate anion by deprotonation of the acid with dry Cs_2CO_3. In this way the chance of oligomerization or polymerization during preparation and isolation of salts is minimized.



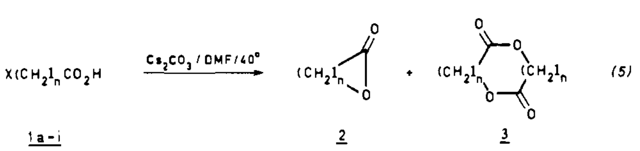
(3)

To assess the method a series of ω-iodo acids were prepared as shown in eq 4. Smaller ring lactones are opened readily by HBr in acetic acid, but for the larger rings the more reactive reagent HI/CH_3CO_2H is required.[9] Cyclizations (eq 5) were carried out at 40 °C with 5×10^{-3}–5×10^{-2} M solutions of the ω-haloacid in distilled DMF to which an equivalent amount of dry Cs_2CO_3 was added. During the course of the reaction the Cs_2CO_3 slowly went into solution and cesium halide began to precipitate. The cesium carboxylates themselves are usually reasonably soluble in DMF.



(4)

a) n = 4, X = I ; b) n = 5, X = Br
c) n = 8, X = Br ; d) n = 9, X = I
e) n = 10, X = I ; f) n = 11, X = I
g) n = 12, X = I ; h) n = 13, X = I
i) n = 14, X = I ; j) n = 15, X = I



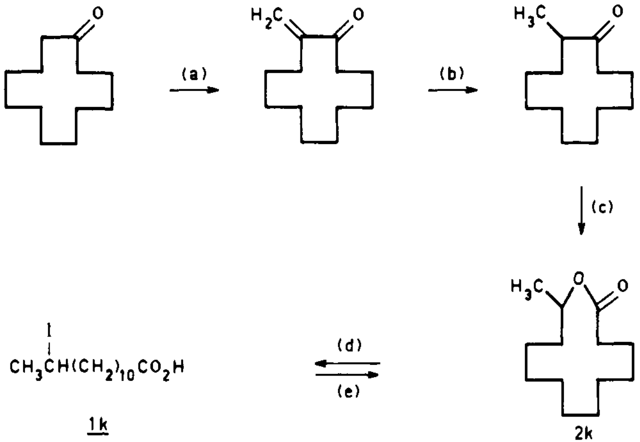
(5)

Table I. Yields of Macrolides and Dilides from ω-Halogeno Aliphatic Acids and Cs_2CO_3 in DMF

aliphatic acid	yield, %[a] 2	yield, %[a] 3
1a	70	4
1b	*a* (87)[d]	88 (7)[d]
1c	*c*	95
1d	23	55
1e	33 (64)[d]	54 (30)[d]
1f	62 (76)[d]	30 (7)[d]
1g	77 (79)[d]	18 (6)[d]
1h	72	13
1i	83	17
1j	85 (88)[d]	15 (5)[d]
1k	76	7

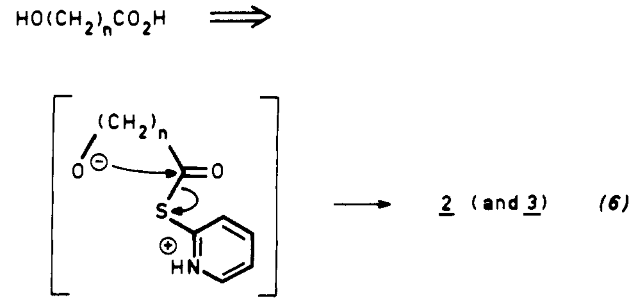
[a] Yields determined by combined ^1H NMR/GLC method; accuracy is estimated to be ±5%. [b] Yield of dimer = ([**3**]/[**1**])2. [c] No monomer detected. [d] Maximum reported yields from cyclization of ω-hydroxy 2-pyridine thiolesters (from ref 10a).

Scheme I. Syntheses of **1k**[a]



[a] (a) $C_6H_5NH_2C_2H_5^+$, $^-O_2CCF_3$, paraformaldehyde; (b) H_2/Pd/C 10%; (c) *m*-chloroperbenzoic acid (excess), $CHCl_3$, 70 °C; (d) HI, CH_3CO_2H, 100 °C; (e) Cs_2CO_3, DMF, 40 °C.

Workup of the reaction mixture afforded the crude cyclized materials, which were identified by a combination of gas–liquid chromatography (GLC) mass spectral measurements and by isolation by preparative layer chromatography. The yields of monomers (macrolides, **2**) and dimers (dilides, **3**) formed are given in Table I. All these materials are known compounds. Evidence in some cases for small amounts of trilides and tetralides was obtained from the mass spectra. For comparison purposes the yields reported by Corey and Nicolaou,[10a] using the elegant method of lactonization by carbonyl–oxygen bond formation (eq 6), are given in parentheses in Table I.



(6)

Particularly for the larger rings, the yields from the cesium salt method compared favorably with the pyridinethiol cyclization

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(8) (a) Hunsdiecker, H.; Erlbach, H. *Chem. Ber.* **1947**, *80*, 129; (b) Galli, C.; Illuminati, G.; Mandolini, L.; Tamborra, P. *J. Am. Chem. Soc.* **1977**, *99*, 2591.

(9) Method taken from Zapesochnaya, G. G.; Sarycheva, I. K.; Preobrazhenkii, N. A. *Zh. Obshch. Khim.* **1963**, *33*, 2552; *Chem. Abstr.* **1964**, *60*, 2745b.

(10) (a) Corey, E. J.; Nicolaou, K. C. *J. Am. Chem. Soc.* **1974**, *96*, 5614. For some other approaches, see ref 2d–f; (b) Stork, G.; Nakamura, E. *J. Org. Chem.* **1979**, *44*, 4010; (c) Nicolaou, K. C.; Seitz, S. P.; Pavia, M. R.; Petasis, N. A. *Ibid* **1979**, *44*, 4011; (d) Rastetter, W. H.; Phillion, D. P. *Tetrahedron Lett.* **1979**, 1469; (e) Trost, B. M.; Verhoeven, T. R. *J. Am. Chem. Soc.* **1980**, *102*, 4743.

Table II. Yields of Macrolide and Dilide from **1i**, Using Different Alkali Metal Carbonates in DMF

metal carbonate[b]	yields, %[a] 2i	3i[b]
Li_2CO_3	*d*	*d*
Na_2CO_3	54	10
K_2CO_3	67	9
Rb_2CO_3	68	12
Cs_2CO_3	80	12
Ag_2CO_3	53	6
Tl_2CO_3	64	8
$MgCO_3$	*e*	*e*
$SrCO_3$	*e*	*e*
$BaCO_3$	*e*	*e*

[a] Yields determined by GLC using internal standards; only for Cs_2CO_3 reaction were the products isolated. [b] All the metal carbonates are virtually insoluble in DMF. [c] Yields are ([3]/[1])2. [d] No lactones detected. [e] The iodides were for the greater part recovered; neither **2i** nor **3i** could be detected in the reaction mixtures.

method (eq 6).[10] The latter method is better, however, for preparation of the smaller ring compounds. The simplicity of the present method (the method of eq 6 requires slow addition by syringe pump of the reagents to xylene at reflux) recommends it for further applications. The next critical test was to see if substitution at a secondary carbon is also possible. Fortunately this reaction proceeds well also as seen with **1k**, prepared as shown in Scheme I.[11] The macrolide **2k** is reported to be a natural product.[12]

In order to assess the effect of cesium ions relative to other ions, we carried out similar cyclizations with a series of alkali metal carbonates, using 15-iodopentadecanoic acid (**1i**), which was available in reasonable quantities from cyclopentadecanone, which is one of the cheaper macrocyclic ketones. The cyclizations reported in Table II were carried out with **1i** (5×10^{-2} M) and an equivalent of Cs_2CO_3 in DMF. A clear trend of increasing yield of **2i** is seen progressing from Li_2CO_3 to Cs_2CO_3. Reaction with the latter was also by far the cleanest with only minor amounts of side products. Although both Ag_2CO_3 and Tl_2CO_3 give reasonable yields of **2i**, the conversions of iodide were not complete nor are the reaction mixtures especially clean. In our experience the reactions with cesium carboxylates as well as the cesium salts of other acidic compounds are normally very clean, conversions of starting material are complete, and the reactions are easy to work up, which is often not true of the reactions of other metal carboxylate salts.

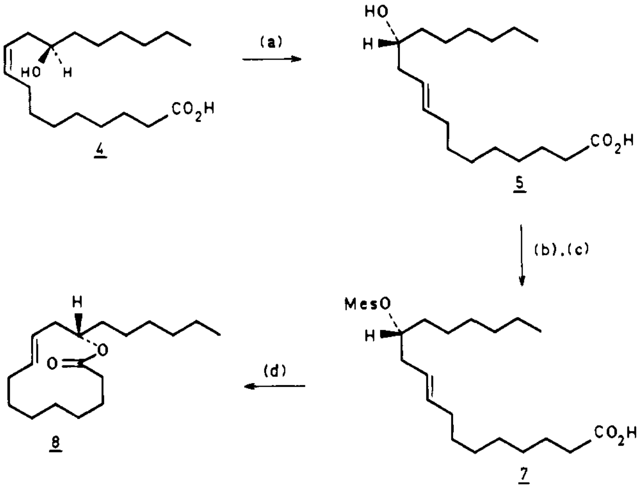
To assess cation effects better, we carried out the following experiments. Small alkali metal cations can be changed from charged spheres with a high charge/surface ratio to very large complexes with a hydrophobic outer layer and *low* charge/surface ratio by complexation with a "cryptate".[1b] The cyclization of **1i** in DMF with K_2CO_3 (the potassium ion complexes better than the larger cesium ion with smaller cryptates) and 5 mol % of [2.2.2]cryptate yielded 66% monomer, which represents no improvement. However, complexation of K_2CO_3 with a *stoichiometric* amount of [2.2.2] cryptate in methanol followed by removal of methanol and addition of DMF resulted in a *soluble* complex, whereas noncomplexed K_2CO_3 in DMF is insoluble. Addition of an equivalent amount of **1i** led to a smooth reaction. The macrolide was obtained in 79% yield and the dilide in 9% yield. The significance of these observations will be discussed in the following section.

Table III. Cyclization of the Cesium Carboxylate of 15-Iodopentadecanoic Acid (**1i**) in Various Solvents

solvent[a]	yield, % 2i	3i[b]
DMF	72	18
1,2-dimethoxyethane (DME)[c]	47	28
tetrahydrofuran (THF)[c]	30	8
dimethyl sulfoxide (Me_2SO)	35	40
N-methylpyrrolidone[c]	29	15
hexamethylphosphorustriamide (HMPTA)[c]	11	2

[a] Concentration 0.5 mmol **1i** in 10 mL of solvent to which 1 equiv of dry Cs_2CO_3 is added; reaction temperature 40 °C; reaction time, 24 h. [b] Yield = ([3]/[1])2. [c] In none of these cases was **1i** entirely consumed owing probably to the low solubility of Cs_2CO_3 as well as the cesium carboxylates in these solvents.

Scheme II. Synthesis of Ricinelaidic Acid Lactone[a]



[a] (a) $(C_6H_5S)_2$, $h\nu$, C_6H_{12}; (b) CH_3SO_2Cl, $(C_2H_5)_3N$, $(C_2H_5)_2O$, CH_2Cl_2; (c) Na_2CO_3, H_2O; (d) Cs_2CO_3, DMF, 40 °C, 24 h.

DMF seems to be a superior solvent for these reactions. Several other potential solvents were investigated for the cyclization of **1i** and the results shown in Table III were obtained. Note that the experiments reported in Table III were carried out at a 10 times higher concentration than those of Table II (5×10^{-2} compared to 5×10^{-3} M). The cesium carboxylates still react cleanly and give a good, although slightly lower, yield of monomer.

In view of the encouraging results with the ring closures of ω-halo cesium carboxylates in DMF,we decided to examine the effectiveness of the method for the synthesis of some naturally occurring macrolides. In addition to the general question of whether ring closure will occur, there is also an important stereochemical point. Most macrolides are closed at a secondary hydroxyl group. The experiment with **2k** (Table I) was encouraging because of the good yield of macrolide and the absence of any significant amount of olefinic material formed from E2 elimination. However, since racemic material was used there is no way of judging whether the ring closure occurred with the anticipated inversion of configuration (S_N2 displacement).[13]

The lactone of ricinelaidic acid was chosen as an initial target because of the ready availability of materials and the known absolute configuration of starting material as well as maximum rotation of the product.[14] The hydroxyl group was activated by mesylation. The overall synthesis starting from commercially available ricinoleic acid was carried out as shown in Scheme II.

The ring-closure step (10^{-2} M in DMF with 2 equiv of dry Cs_2CO_3) proceeded in 80% isolated yield and the product **8**, $[\alpha]_D$ $-43°$, can be compared with (R)-**8**, known to be optically pure, which has a rotation of $[\alpha]^{20}_D$ $+42°$.[14] Clearly S_N2 inversion occurs during the ring-closure step. The rest of the synthesis proceeded routinely except for the mesylation step. When the

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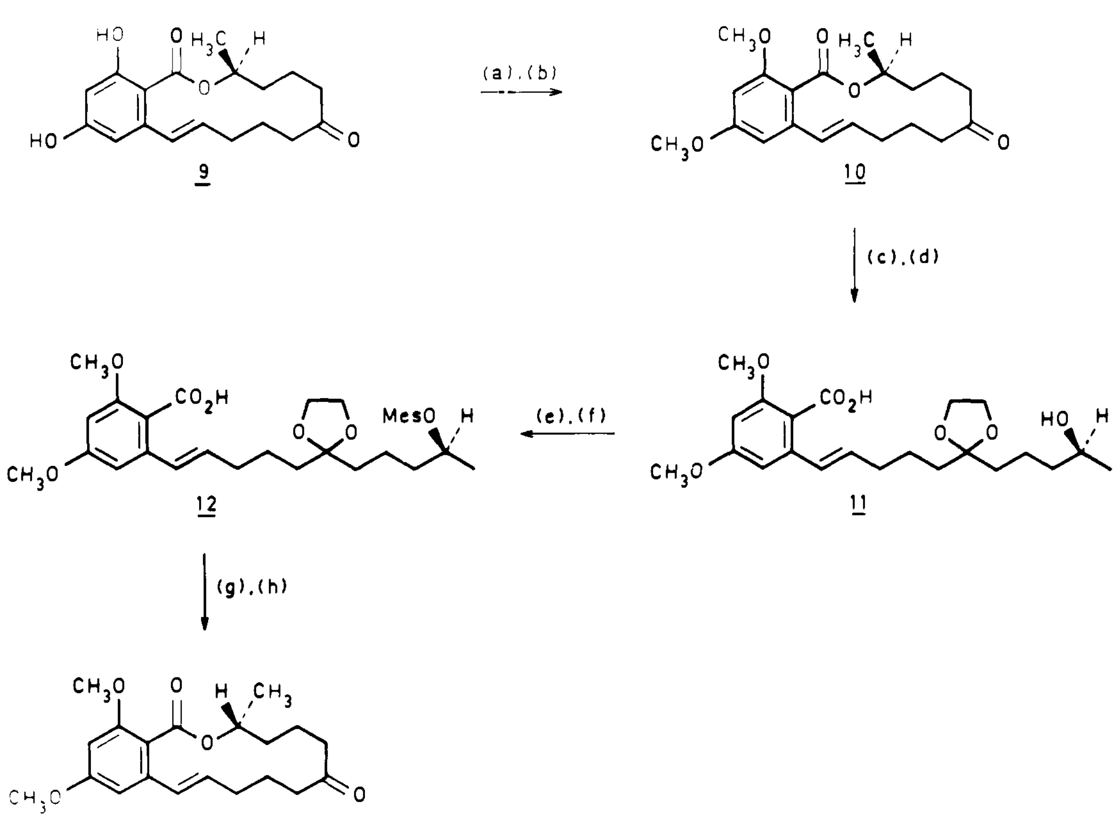
(11) The α-methenylation is carried out by the method of J. L. Graz (*Tetrahedron Lett.* **1978**, 2111, 2955).

(12) Kaiser, R.; Lamparsky, D. *Helv. Chem. Acta* **1978**, *61*, 2671.

(13) The problem of change of configuration of the secondary hydroxyl group during ring closure does not occur, of course, in methods of macrolide synthesis similar to that shown in eq 6.

(14) We are grateful to Professor H. Gerlach for providing us with a preprint of the method for transforming rinoleic to ricinelaidic acid: Thalmann, A.; Oertle, K.; Gerlach, H. *Org. Synth.* **1977**, *57*, procedure 2010.

Scheme III. Synthesis of (−)-*R*-Zearalenone[a]

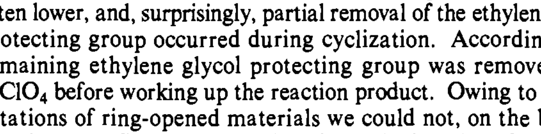


[a] (a) Cs_2CO_3, CH_3OH; (b) CH_3I, DMF; (c) $HOCH_2CH_2OH$, TsOH, $C_6H_5CH_3$; (d) NaOH, Me_2SO, H_2O; 100 °C; (e) CH_3SO_2Cl, $(C_2H_5)_3N$, $(C_2H_5)_2O$, CH_2Cl_2; (f) NaOH, H_2O; (g) Cs_2CO_3, DMF; (h) $HClO_4$, THF.

free acid (**5**) was used with an excess of methanesulfonyl chloride, the mesylated anhydride (**6**, not shown) was formed. This was identified by its characteristic IR absorption at 1810 cm^{-1} and lack of solubility in base. It was directly hydrolyzed to the desired mesylated acid (**7**) without further purification.[15]

The ring closure of **7** was also carried out by using 100% excesses of K_2CO_3 and Rb_2CO_3; the isolated yields after Kugelrohr distillation of **8** were 28% and 54%, respectively, compared to 80% for Cs_2CO_3. Owing to the fact that these products were not entirely pure, the optical rotations were not determined.

The cesium salt approach was also used for the ring closure of a protected derivative of the macrolide zearalenone.[16] The required protected derivative **12** was obtained from natural zearalenone following roughly the procedure described by Taub et al.[16c] for protection of the phenolic groups and ketone function, with the important exception that the former were methylated by conversion to the bis(cesium phenolate) and treatment with methyl iodide in DMF (Scheme III). This reaction proceeds in far better yield than the described procedure using dimethyl sulfate. We also found the hydrolysis step from fully protected **10** to **11** using NaOH/Me_2SO (the carbonyl group is strongly deactivated) to be very capricious. The chief problem was partial to complete deprotection of the ethylene glycol group during hydrolysis. This results in partially racemized product, racemization probably occurring by the mechanism suggested by Taub et al. (eq 7).[17]


(7)

After mesylation to form **12** via the anhydride, hydrolysis of which was more troublesome in this case, ring closure using cesium carbonate was carried out in 80% yield. The highest enantiomeric excess obtained in any run, however, was 80% of the *R* enantiomer expected from a S_N2 inversion mechanism. Optical purities were often lower, and, surprisingly, partial removal of the ethylene glycol protecting group occurred during cyclization. Accordingly the remaining ethylene glycol protecting group was removed with $HClO_4$ before working up the reaction product. Owing to the low rotations of ring-opened materials we could not, on the basis of rotations, confidently determine the optical purity of **12**. This led to serious concern that racemization might be occurring in the cyclization step. For checking of this point, a sample of **11** known to have been racemized partially during hydrolysis was converted by deprotection to **14**, which was esterified with *R*-3,3,3-trifluoro-2-methoxy-2-phenylpropionyl chloride (**15**) (Scheme IV).[18] From the ^{19}F NMR spectrum it was determined that the *S* enantiomer of **14** was present in 26% enantiomeric excess. A portion of the same sample of **14** was mesylated (ketone protection is not needed at this stage) and ring closed following the procedure of Scheme III. The sample of **13** obtained had a 24.5% enantiomeric excess of the *R*-zearalenone derivative, thereby estab-

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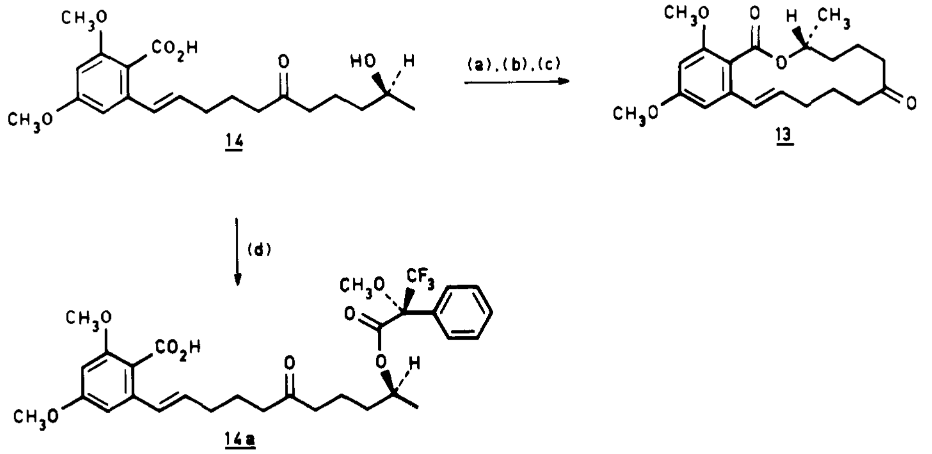
(15) The mesylation probably involves a sulfene intermediate; it has been reported (and should be expected) that sulfenes should dehydrate acids, probably by forming first a mixed anhydride. Review of sulfene chemistry: King, J. F. *Acc. Chem. Res.* **1975**, *8*, 10. The methyl ester of **5** can be mesylated smoothly, but we were unable to saponify the ester without destroying the mesylate. LiOH in 1:1 CH_3OH/H_2O was used following the procedure described by Corey, E. J.; Nicolaou, K.; Machida, Y.; Malmston, C. L.; Samuelsson, B. *Proc. Natl. Acad. Sci. U.S.A.* **1975**, *72*, 3355.

(16) (a) Isolation: Stob, M.; Baldwin, R. S.; Tuite, J.; Andrews, F. N.; Gillette, K. G. *Nature (London)* **1962**, *196*, 1318; (b) structural elucidation: Urry, W. H.; Whermeister, H. L.; Hodge, E. B.; Hidy, P. H. *Tetrahedron Lett.* **1966**, 3109; (c) first total synthesis: Taub, D.; Girotra, N. N.; Hoffsommer, R. D.; Kuo, C. H.; Slates, H. L.; Weber, S.; Wendler, N. L. *Tetrahedron* **1968**, *24*, 2443; (d) review: Shipchandler, M. T. *Heterocycles* **1975**, *3*, 471.

(17) This mechanism was suggested to explain the complete racemization that occurs on hydrolysis of **10** in which the ketone group has not been protected as the ketal.[16c] We found also that during saponification in NaOH/Me_2SO that zearalenone with the ketone protected as the thioketal of ethane-1,2-dithiol was also completely racemized; the thioketal protecting group was removed rapidly and completely during hydrolysis.

(18) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.

Scheme IV. Determination of Optical Purity of **14**[a]



[a] (a) CH_3SO_2Cl, $(C_2H_5)_3N$, $(C_2H_5)_2O$, CH_2Cl_2; (b) NaOH, H_2O; (c) Cs_2CO_3, DMF, 40 °C; (d) *R*-$C_6H_5C(OCH_3)H(CF_3)COCl$, pyridine.

lishing that the racemization step or steps *do not* occur at the cyclization stage. We made no further effort to study the mechanism of the deprotection and racemization that occur during hydrolysis.

Discussion

The ability of cesium ions to promote intramolecular cyclizations is by no means restricted to lactone formation. We have found similar effects with phenolates,[6a] thiolates,[6b] and tosylamides.[6c] Moreover, we have found that cesium carboxylates as well as other anionic nucleophiles with cesium as counterion in DMF give in general unusually clean S_N2 substitutions with relatively little elimination.[19]

The information now available is insufficient to allow us to pinpoint all the reasons for this effect of cesium ions. We can, however, offer some comments that provide guidance for design of future experiments. First, the properties of the cesium ion should be considered. The ion is very large (ionic diameter, 3.3 Å), and it has a low charge/surface area ratio (0.03 Z/Å^2) compared to smaller cations such as Na^+ (ionic diameter, 1.96 Å; surface charge density, 0.085 Z/Å^2) or Li (ionic diameter, 1.56 Å; surface charge density, 0.13 Z/Å^2).[1b] Cesium is the most polarizable of the alkaline earth cations (2.9 Å^3 for Cs^+, 1.9 Å^3 for Rb^+, 1.1 Å^3 for K^+, 0.3 Å^3 for Na^+, and 0.03 Å^3 for Li^+) and with the exception of thallium (4.3 Å^3), the most polarizable of the common monovalent cations.[20]

Because of these properties the cesium ion is not as well solvated as smaller ions even in good coordinating solvents such as THF. Likewise in DMF the solvent sheath is also much less than, for example, that of the much smaller Li^+ cation.[21,22] These solvation effects affect the reactivity of the ions and the kind of ion pairing that occurs. The explanation for the ability of Cs^+ cations to promote intramolecular cyclizations is in turn probably to be found in ion pairing phenomena. The consequence that one expects from poor solvation of the cation is the predominant occurrence of contact ion pairs. This line of thinking is used to rationalize the fact that, for example, the well-delocalized fluorenyl anion with Cs^+ as counterion is a contact ion pair in THF, whereas with Li^+ as counterion in THF, solvent-separated ion pairs are formed.[23] THF solvates Li^+ better than it solvates Cs^+. However, for more strongly basic and harder anions such as $(CH_3)_3CO^-$, exactly the opposite trend is observed owing probably in this case to better solvation of the anion.[24a,b] The situation for less basic carboxylates such as dealt with in this work probably lies somewhere between these two extremes. Extrapolating from Bordwell's results in Me_2SO for potassium benzoate, which is ion paired to a moderate degree ($K_{assoc} = 48$), to less polar DMF (dielectric constant 37 compared to 47 for Me_2SO) and the much larger Cs^+ ion, one can anticipate that cesium carboxylates in DMF will chiefly be in the form of contact ion pairs.

If the foregoing conclusion is true, one must next consider the tendency of cesium salts to form triple ions, X^-–Cs^+–X^-. This behavior is well documented for benzyl cesium formed during anionic polymerization of styrene ("living polymer")[25] and has been studied in detail with the so-called "bolaform" electrolytes, derived from bis-9-fluorenyls, connected through the 9-positions by a polymethylene chain.[26] For such systems, which admittedly contain a highly delocalized anion, there is a pronounced tendency to form "sandwiched" triple ions. There appears to be little or no information whether cesium carboxylates have similar tendencies to form triple ions. Such behavior, especially at the fairly high concentrations used in our work (5×10^{-3}–5×10^{-2} M) would however, not be too surprising.

The following point to consider is that, in general, free ions are much more reactive than tight ion pairs of the small alkali metal cations such as Li^+, Na^+, and K^+.[27] Reactivity differences between the free ions and ion pairs, for the cases that have been measured quantitatively, usually are several orders of magnitude. Such reactivity effects lie behind the explanations of enhanced reactivity of "naked anions" generated by phase transfer catalysis or by the use of crown ethers or cryptates. The reactivity of a tight ion pair should increase, however, with increasing size of the cation.

How then does cesium work to promote intramolecular cyclizations? A possible answer may lie in the observations (Results section) of the reaction of the *fully cryptated K^+ salt* of **1i** in DMF. This reaction proceeded as cleanly and in as good a yield as that of the corresponding cesium carboxylate. The cryptated K^+ ion (diameter roughly 9.8 Å for [2.2.2]cryptate) may, as pointed out by Lehn,[28] be viewed as a "super" alkali metal cation with an abnormally low charge/surface ratio. This complexation of the cation by a cryptate will result in increased reactivity of the anion, in this case carboxylate. However, something of a paradox arises

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[22] Such effects are, however, certainly not sufficiently strong to prevent cesium ions from being complexed by sufficiently large crown ethers or cryptates. The same type of ion–dipole interactions involved in solvation stabilize the crown ether and cryptate complexes. See, for example: Poonia, N. S.; Bajaj, A. V. *Chem. Rev.* **1979**, *79*, 389.

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[27] (a) Solovyanov, A. A.; Beletskaya, I. P. *Russ. Chem. Rev.* **1978**, *47*, 425; an interesting example is provided by the anionic oxy-Cope rearrangement; see (b) Steigerwald, M. T.; Goddard, W. A., III; Evans, D. A. *J. Am. Chem. Soc.* **1979**, *101*, 1994; (c) Evans, D. A.; Nelson, J. V. *Ibid.* **1980**, *102*, 774.

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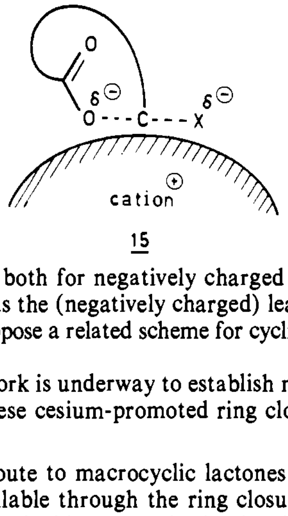
for solvents of fairly low dielectric constant, for the cryptated cation and its counterion are still present chiefly, if not entirely, as tight ion pairs.[29] This is especially true for the case of carboxylates as the counterion.[29b]

That cryptated carboxylates are highly reactive in S_N2 substitutions carried out in benzene (and incidentally give little E2 elimination) has already been demonstrated by others.[30] Although the following analysis is undoubtedly oversimplified, especially in view of the maddening complexity of ion pairing phenomena, we draw an analogy between a cryptated cation and cesium, as the largest of the alkali earth cations, and assume that similar factors govern the reactivity of an associated carboxylate anion. These factors will probably be more pronounced for the cryptated cation because of its lower charge/surface ratio and much greater size.

First and foremost the reactivity of the carboxylate counterion will be enhanced even though it is associated as an ion pair with its cation. Several factors must operate now to enhance ring closure. Those reactive carboxylates have a lesser tendency to undergo *intermolecular* than *intra*molecular reaction; i.e., the ion pairs do not react rapidly with each other. To understand this one may envisage that the reactive carboxylate stays fairly tightly associated with its counterion rather than coming free and attacking an electrically neutral ion pair. On the other hand the reactive carboxylate does have a good change of finding its own tail. If the nucleophilic substitution occurs now in the ion pair, one can speculate that the positive polarizable surface of a large cation might be ideal for promotion of an S_N2 substitution as illustrated schematically in **15**. The positive surface can act as coordinating site both for negatively charged nucleophilic carboxylate as well as the (negatively charged) leaving group. One can, of course, propose a related scheme for cyclization in a "triple ion".[26,27]



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Mechanistic work is underway to establish more precisely the mechanism of these cesium-promoted ring closures.

Summary

An effective route to macrocyclic lactones (and other compounds)[3,4] is available through the ring closure of cesium carboxylates. The method is extremely simple, yields are generally excellent, and high dilution conditions are not necessary. Although the results with K^+ cryptates are promising, the need for stoichiometric amounts of expensive [2.2.2]cryptate and a difficult workup procedure make this method less attrative. Cesium salts, especially the carbonate used in this work, are not excessively expensive. Recycling could be carried out for reactions on a larger scale because the cesium halides have only a low solubility in DMF.

We believe that the use of cesium salts deserves serious consideration as a method for the synthesis of macrocyclic lactones.

Experimental Section

General. Melting points were recorded on a Mettler automatic FP-2 apparatus. UV spectra were taken with a Zeiss PMQ II apparatus and optical rotations were measured on a Perkin-Elmer 241 polarimeter. ^1H NMR spectra (Me_4Si internal standard) were recorded on 60-MHz Varian or JEOL instruments or on a Varian XL-100, ^{13}C NMR spectra (Me_4Si internal standard) were also recorded on the latter instrument. Mass spectra were measured on a MS-9 instrument. Elemental analyses were carried out in the analytical division of these laboratories. Compounds cited without reference were either in stock or were prepared by standard laboratory procedures. Macrocyclic ketones were obtained pure from Fluka Chemical Co. or from K & K Chemicals. Cs_2CO_3 was purchased from Fluka Chemical Co.

General Procedure for the Preparation of ω-Iodo Acids Illustrated by the Preparation of 12-Iodododecanoic Acid (1f). Cyclododecanone (2.0 g, 11 mmol) was added to *m*-chloroperbenzoic acid (4.2 g, 21 mmol) in 25 mL of dry $CHCl_3$. The reaction mixture was heated at reflux for 48 h after which time a starch–iodine test for peroxide was negative. After the mixture was cooled in ice water, the precipitated *m*-chlorobenzoic acid was removed by filtration and the $CHCl_3$-soluble material was evaporated to dryness. The residue was taken up in 60 mL of diethyl ether, washed 3 times with 20-mL portions of aqueous K_2CO_3 and 1 time with brine solution. After drying and removal of the solvent there remained crude dodecanolide (1.9 g, 9.6 mmol, 87% yield), which was used without further purification.

The above dodecanolide (1.9 g, 9.6 mmol) was added to a mixture of 67% HI (5 g, 24 mmol) and glacial acetic acid (3 g). The reaction mixture was held for 2 h at 100 °C and after cooling was poured out into 50 mL of a cold 10% aqueous solution of $Na_2S_2O_3$. The reaction mixture was extracted 3 times with 25-mL portions of $CHCl_3$. After the mixture was dried over $MgSO_4$, the solvent was removed to leave crude 12-iodododecanoic acid (**1f**), which after recrystallization from diethyl ether/light petroleum (40–60 °C) was obtained in 93% yield (2.95 g, 9.0 mmol), mp 61–62.5 °C (lit.[31] mp 62.5 °C).

Analogous procedures were followed for the preparation of **1d**, **1e**, **1g**, **1h**, **1i**, and **1j**, which were obtained in similar yields.

General Procedure for Ring Closure Illustrated by the Reaction of 16-Iodohexadecanoic Acid (1j). To **1j** (190 mg, 0.5 mmol) dissolved in 50 mL of dry DMF and held in a single-necked flask containing a magnetic stirring bar was added Cs_2CO_3 (180 mg, 1.1 equiv). The reaction mixture was stirred magnetically at 40 °C for 24 h during which time all the solid Cs_2CO_3 went into solution. A precipitate of cesium halide usually formed slowly during the course of the reactions. The DMF was removed under vacuum (2–3 Torr) on a rotary evaporator. A saturated aqueous NaCl solution was added to the residue and extraction with diethyl ether was carried out (3 times). There was obtained a mixture of **2j** and **3j** (127 mg, 0.5 mmol in total), which by GLC using an internal standard was shown to consist for at least 99% of **2j** and **3j**, present in yields of 85% and 15%, respectively. In a reaction carried out with 1 mmol of **1j**, the cyclization products were isolated by preparative layer chromatography on silica gel, using a 9:1 light petroleum (40–60 °C)/ether eluant. Macrolide **2j** was isolated pure in 68% yield and dilide **3j** in 4% yield. Both were identified from the mass spectra and comparison with authentic materials.

Other cyclizations were carried out in a similar fashion but only on a 0.5-mmol scale owing to expense. Yields were determined from a combination of ^1H NMR and GLC, using internal standards to calibrate the latter.

***N*-Methylanilinium trifluoroacetate** was prepared following the method of Graz.[11] Trifluoroacetic acid (40 g, 0.38 mol) in 100 mL of diethyl ether was added dropwise to a solution of *N*-methylaniline (40 g, 0.36 mol) in 200 mL of diethyl ether held at 0 °C. The solution was stirred for another 1 h at 0 °C and then filtered through a P3 glass filter and the precipitate was washed 3 times with portions of $(C_2H_5)_2O$. There was obtained 60.4 g (0.33 mol, 91% yield) of *N*-methylanilinium trifluoroacetate, mp 64–65 °C (lit.[11] mp 66.5 °C).

Synthesis of 2-Methylenecyclodecanone. The general method of Graz[11] was followed but with some modifications. A solution of *N*-methylanilinium trifluoroacetate (15 g, 72 mmol), paraformaldehyde (6 g, 200 mmol)8 and cyclododecanone (7.8 g, 45 mmol) was made in 30 mL of dioxane. This mixture was warmed for 4 h to 100 °C. After the mixture was cooled, 100 mL of diethyl ether was added, and the reaction mixture was washed 4 times with 50-mL portions of H_2O. After the mixture was dried over $MgSO_4$ and the solvent removed, there was left pure 2-methylenecyclododecanone (8.9 g, 46 mmol, 100% yield): IR 1670 (C=O) and 1630 cm^{-1} (C=C); ^1H NMR ($CDCl_3$) δ 1.0–2.0 (complex m, 16 H), 2.1–2.5 (br t, 2 H), 2.5–2.9 (br t, 2 H), 5.6 (s, 1 H), 5.8 (s, 1 H).

In some runs there was some residual ketone in the product; this can be removed by chromatography over silica gel, eluting with CH_2Cl_2. In our hands the use of trioxan as formaldehyde source, as described in the literature,[11] was unsatisfactory and led to low yield of products.

2-Methylcyclododecanone was prepared by the hydrogenation of 2-methylenecyclododecanone (8.9 g, 46 mmol) in 100 mL of absolute C_2H_5OH over 0.7 g of Pd/C catalyst under 2 atm of H_2 pressure for 3

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(32) Bollinger, G.; Tamm, C. *Helv. Chim. Acta* **1972**, *55*, 3030.

h. After workup the residue was distilled to give 6.3 g (32 mmol, 71% yield) of 2-methylcyclododecanone: IR (neat) 2950, 1710, 1480, 1430, and 1380 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 0.9 (d, J = 7 Hz, 3 H), 0.9–2.20 (complex m, 18 H), 2.25–3.0 (complex m, 3 H).

12-Iodotridecanoic acid (1k) was prepared following the general experimental descriptions already given. Baeyer–Villiger oxidation of 2-methylcyclododecanone with *m*-chloroperbenzoic acid gave in 91% yield 12-hydroxytridecanoic acid lactone: ir (neat) 2940, 1720, 1470, 1380, 1340, 1250, and 1230 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 1.17 (d, J = 7 Hz, 3 H), 1.10–2.20 (complex m, 18 H), 2.20–2.60 (complex m, 2 H), 4.60–5.30 (m, 1, tertiary H).

Ring opening of the lactone with HI/CH$_3$CO$_2$H gave in 65% yield 12-iodotridecanoic acid in 65% yield: ^{1}H NMR (CDCl$_3$) δ 0.8–2.1 (complex m, 18 H), 1.89 (d, J = 7 Hz, 3 H), 2.10–2.55 (complex m, 2 H), 3.80–4.40 (m, 1, tertiary H).

Preparation of (+)-*S*-*trans*-12-Hydroxy-9-octadecenoic Acid Lactone (8). Starting from commercial ricinoleic acid (4) the trans isomer (5) was prepared following the procedure described by Gerlach.[14] This material (mp 51–51.5 °C), had $[\alpha]^{20}{}_D$ +6.6° (c 1, C$_2$H$_5$OH). To a sample of 5 (1 g, 3.3 mmol) with (C$_2$H$_5$)$_3$N (1 g, 10 mmol) in 25 mL of a 9:1 (C$_2$H$_5$)$_2$O/CH$_2$Cl$_2$ mixture well-stirred at 0 °C was added CH$_3$SO$_2$Cl (850 mg, 7.5 mmol). After 2 h the reaction mixture was filtered and the filtrate was washed 2 times with 25-mL portions of H$_2$O. The organic layer was dried over MgSO$_4$ and then evaporated. The residue, which was not soluble in base, was clearly the anhydride (6) as revealed by strong IR absorptions at 1810 cm^{-1}. The crude reaction product was taken up in a saturated aqueous Na$_2$CO$_3$ solution (20 mL) and held at 20 °C for 3 h after which time the reaction mixture was acidified with dilute HCl and extracted 3 times with 25-mL portions of (C$_2$H$_5$)$_2$O. After the mixture was dried and the solvent removed, there was obtained 7 (900 mg, 2.4 mmol, 73% yield) as a colorless oil: IR (neat) 3500, 2900, 1720, 1480, 1360, and 1180 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 0.8–2.5 (complex m, 29, aliphatic H) 3.10 (s, 3, CH$_3$), 4.72 (complex m, 1, tertiary H), and 5.56 (complex m, 2, vinyl H).

To 7 (300 mg, 0.8 mmol) dissolved in 80 mL of dry DMF was added dry Cs$_2$CO$_3$ (390 mg, 1.2 mmol). The reaction mixture was stirred at 40 °C for 24 h after which time the DMF was removed under vacuum. Brine solution was added and extraction was carried out with 25-mL portions of ether. After the mixture was dried over MgSO$_4$, the solvent was removed and the crude product was subjected to Kugelrohr distillation (0.01 Torr, 120 °C) to yield 8 (180 mg, 0.642 mmol, 80% yield): IR (neat) 2950, 1730, 1470, 1245, 1180, 970, and 720 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 0.6–2.6 (complex, 29, aliphatic H), 4.95 (m, 1, tertiary H), and 5.40 (complex m, 2, vinyl H). The material gave a single spot on TLC (pentane/ether) $[\alpha]^{20}{}_D$ −43° (c 1, CHCl$_3$) [lit.[14] $[\alpha]^{20}{}_D$ +42° (c 1, CHCl$_3$) for optically pure *R*-8]. It is therefore concluded that complete inversion of configuration occurs during ring closure.

Preparation of *S*-Zearalenone Dimethyl Ether (10). The methylation of zearalenone (9) was carried out by treating 9 (1 g, 3.15 mmol) dissolved in 50 mL of dry CH$_3$OH with dry Cs$_2$CO$_3$ (1.96 g, 6 mmol). After the Cs$_2$CO$_3$ had dissolved, the solvent was removed under vacuum and the residue held under N$_2$ atmosphere was put in 50 mL of dry DMF. This DMF together with traces of methanol was distilled off under vacuum and then 100 mL of dry DMF was added followed by methyl iodide (4.2, 8.6 mmol, excess). After the mixture was stirred overnight at room temperature, the DMF was removed under vacuum and the residue was taken up in 60 mL of H$_2$O and extracted 2 times with 25-mL portions of diethyl ether. The combined organic layers were washed successively with 10% NaOH solution (twice, 40-mL portions) and brine (twice, 25-mL portions). After the mixture was dried over MgSO$_4$ and the solvent removed, there remained 10 (1.01 g, 2.90 mmol, 92% yield): mp 106–110 °C (lit.[16c] mp 107–110 °C); $[\alpha]^{20}{}_D$ +24.7° (c 1, CH$_3$OH) [lit.[16c] $[\alpha^{20}{}_D$ +25° (c 1, CH$_3$OH)].

Preparation of 1-(3,5-Dimethoxy-6-carboxyphenyl)-10-methylsulfonate-1-undecene 6-Ethylene Ketal (12). Formation of the ethylene ketal from 10 and subsequent saponification to 11 were carried out exactly as described in the literature (but note the comments on racemization below). A portion of 11 (320 mg, 0.88 mmol) in a well-stirred solution of 40 mL of CH$_2$Cl$_2$ containing (C$_2$H$_5$)$_3$N (1.8 g, 18 mmol) at 0 °C was treated dropwise with mesyl chloride (400 mg, 3.5 mmol). After 2-h reaction time, the solvent was removed and the residue was taken up in 50 mL of diethyl ether/CH$_2$Cl$_2$ mixture (9:1). After the mixture was washed twice with 25-mL portions of H$_2$O and once with brine, the organic layer was dried over MgSO$_4$. Evaporation of the solvent left the anhydride as residue (IR 1785 cm^{-1}), which was not purified or studied further. The anhydride was taken up in 20 mL of a mixture of water/dioxane (1:1), and NaOH pellets (2 g, 50 mmol) were added, and the mixture was stirred for 3 h. Acidification with dilute HCl and extraction with three 25-mL portions of a 9:1 diethyl ether/CH$_2$Cl$_2$ mixture gave after drying over MgSO$_4$ and evaporation of the solvent 12 (280 mg, 0.6 mmol, 67% yield) as an oil: IR (neat) 3000, 2900, 1720, 1600, 1360, and 1160 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 0.8–2.4 (m, 12, aliphatic H), 1.40 (d, J = 7 Hz, 3, CH$_3$), 2.95 (s, 3, CH$_3$SO$_2$), 4.80 (s, 6, OCH$_3$), 4.85 (s, 4, OCH$_2$CH$_2$O), 4.6 (m, 1, tertiary H), 5.6–6.8 (complex, 4, vinyl H and aromatic H).

Cyclization of 12 to Zearalenone Dimethyl Ether (13). To the mesylate 12 (120 mg, 0.25 mmol) in 80 mL of dry DMF was added 0.25 mmol of dry Cs$_2$CO$_3$ and the stirred mixture was held at 40 °C for 24 h. The DMF was removed by vacuum distillation and the residue was taken up in brine solution. This was extracted 3 times with 25-mL portions of diethyl ether, and the organic layers were washed with brine and dried over MgSO$_4$. There was obtained 90 mg of a crude product that had only half the expected integration for the ethylene glycol bridge as established by ^{1}H NMR spectroscopy. The entire reaction mixture was treated with HClO$_4$ solution, following the described procedure for deblocking the ethylene glycol bridge.[16c] There was obtained 13 (70 mg, 0.20 mmol, 80% yield) having IR and ^{1}H NMR spectra identical with those for pure *R*-9. The material (13) had $[\alpha]^{20}{}_D$ −40° (η, 1 CHCl$_3$) [lit.[32] for *S*-10, $[\alpha]^{24}{}_D$ +49.8° (c, 1 CHCl$_3$). A batch of 11, which had consistently given low enantiomeric excesses, was deblocked to 14. The material was divided in two batches and one batch was mesylated and subjected to ring closure as described above for 11. The cyclized product 13 was obtained in 80% yield and had after purification $[\alpha]^{20}{}_D$ −13.7° (c, 1, CHCl$_3$), corresponding to an enantiomeric excess of 27.5% of *R*-13.

The other batch of 14 (46 mg, 0.126 mmol) was dissolved in 5 drops of CCl$_4$ and 5 drops of pyridine. (*R*)-3,3,3-Trifluoro-2-methoxy-2-phenylpropanoic chloride (60 mg, 0.24 mmol) was added. A white precipitate formed immediately. The solution was allowed to stand for 12 h in a closed tube, whereupon 1 mL of H$_2$O was added. The material was taken up in 20 mL of diethyl ether and was extracted once with 1 N HCl, once with saturated Na$_2$CO$_3$ solution, and one with H$_2$O. The ether layer was dried over MgSO$_4$, the ether was removed, and the residue (72 mg) was taken up in CDCl$_3$. No purification was carried out. In the ^{1}H NMR there were seen absorptions at δ 3.62 (*RS* diastereomer, first letter is the configuration of Mosher reagent, second is the configuration of carbon in the aliphatic chain) and 3.50 (*RR*), identified by their relative heights (δ 3.62 is largest peak). It was not possible to obtain a reliable integration of these peaks. In the ^{19}F NMR spectrum (CDCl$_3$) the CF$_3$ absorptions were observed separately at −71.828 and −71.976 ppm in the ratio of 37:63 for *RR*:*RS*, corresponding to an enantiomeric excess of 26% *S*-14.

Experiments with [2.2.2]Cryptofix. To 30 mL of CH$_3$OH were added [2.2.2]cryptofix (680 mg, 1.8 mmol) and K$_2$CO$_3$ (105 mg, 0.75 mmol). The solution was stirred 20 min. The CH$_3$OH was removed under vacuum, 50 mL of dry DMF was added, this was removed under vacuum together with traces of CH$_3$OH, and the residue was dissolved in 200 mL of dry DMF to which 15-iodopentadecanoic acid (1i, 368 mg, 1 mmol) was added. This was allowed to react 24 h at 40 °C. The DMF was removed under vacuum, the residue was taken up in 60 mL of brine solution, and this was extracted 3 times with diethyl ether. Difficulty was encountered in the separation of the layers. The combined ether layers were extracted with brine solution and then dried over MgSO$_4$. After removal of the solvent there remained 240 mg of material that consisted, as determined by ^{1}H NMR and GLC, of 79% monomer (2i) and 9% dimer (3i), the molecular ratio of monomer/dimer being 17.5.

With use of the same amounts as above, a similar experiment was carried out, but in this case the [2.2.2]cryptate, K$_2$CO$_3$, and 1i were added directly to DMF. The yields of 2i and 3i were identical, indicating that the direct addition procedure may safely be followed.

An experiment was carried out with the same amounts of DMF, K$_2$CO$_3$, and 1i as above in the presence of a catalytic amount (5 mol %) of [2.2.2]cryptate. The reaction mixture was not clean. By ^{1}H NMr and GLC the presence of monomer (2i) and dimer (3i) could be determined in yields of 66% and 4.3%, respectively.

An experiments was carried out with the same amounts of DMF, 1i, and [2.2.2]cryptofix as described in the first paragraph (all mixed directly in DMF) but with 1 equiv of Cs$_2$CO$_3$ (245 mg, 0.75 mmol). There was obtained after workup 2i and 3i in 87% and 9.6% yields, respectively, with a molecular ratio of 18.5.

Acknowledgment. We are indebted to International Minerals and Chemical Corporation, Terre Haute, IN, for a gift of *S*-zearalenone. Professor J. Smid, State University of New York, kindly provided useful comments. Helpful discussions with Mr. O. Piepers of this laboratory are appreciated.