$COCH_2$), 3.15 and 3.31 (each 3 H, each s, each N-CH_3), 5.30 (2 H, m, $NHCH_2$), 6.90 (1 H, br s, 5-NH, deuterium exchangeable), 9.40 (1 H, br s, 9-NH, deuterium exchangeable).

This method is not only useful as a new method for synthesizing the lumazines as described above but also it is widely applicable as a general method for the synthesis of 7-azalumazines (fervenulins).

Thus, after irradiation of **1** (0.011 M) and formylhydrazine (0.033 M) in THF for 3 h with aeration, the solvent was evaporated therefrom, and the residue was subjected to column chromatography (silica gel–chloroform) to obtain fervenulin (**6a**, R = H), mp 174–175 °C (lit.[9] mp 178 °C), in 55% yield. The structure was identical with an authentic sample prepared according to the procedure reported by Yoneda et al.[10]

Similarly, a mixture of **1** and various acylhydrazines in THF was irradiated to give the corresponding 3-substituted fervenulins (**6b–e**) in high yields (see Table II).

We have also studied a reaction of **1** with amino acid esters, amino ketones, or acylhydrazines with heating but we could not isolate the desired products. This suggests that the formation of these lumazines and fervenulins requires photochemical activation.

References and Notes

(1) S. Senda, K. Hirota, M. Suzuki, T. Asao, and K. Maruhashi, *J. Chem. Soc., Chem. Commun.*, 731 (1976).
(2) (a) D. J. Brown "The Pyrimidines", Vol. XVI in the series "The Chemistry of Heterocyclic Compounds", A Wessberger and E. C. Taylor, Ed., Wiley-Interscience, New York, N.Y., 1962, p 138; (b) D. J. Brown, "The Pyrimidines. Supplement I", in the same series, Wiley-Interscience, New York, N.Y., 1970, p 94; (c) E. C. Taylor and F. Sowinski, *J. Org. Chem.*, **39**, 907 (1974), and references cited therein.
(3) Irradiation was carried out in a flask equipped with a Pyrex-jacketed immersion lamp until disappearance of 1 (monitored by TLC) was complete. The light source was a Riko-UVL 100W high-pressure mercury arc lamp.
(4) Analogous synthesis of 7,8-dihydro-6-hydroxypteridines have been reported: W. R. Boon, W. G. M. Jones, and G. R. Ramage, *J. Chem. Soc.*, 96 (1951).
(5) T. K. Liao and C. C. Cheng, *J. Heterocycl. Chem.*, **1**, 212 (1964).
(6) All new compounds gave satisfactory elemental analyses and spectral properties consistent with the assigned structure.
(7) (a) Irradiation of **9** in the presence of primary or secondary amines gave 6-alkylamino-2,5-diaminopyrimidin-4(3*H*)-ones, which are significant intermediates for pterins,[7b] in one step and good yields.[7c] (b) W. Pfleiderer, *Angew. Chem. Int. Ed. Engl.*, **3**, 194 (1964). (c) S. Senda, unpublished results.
(8) Cyclization to the pterins is now under investigation.
(9) E. C. Taylor and F. Sowinski, *J. Org. Chem.*, **40**, 2321 (1975).
(10) F. Yoneda, M. Kanahori, K. Ogiwara, and S. Nishigaki. *J. Heterocycl. Chem.*, **7**, 1443 (1970).

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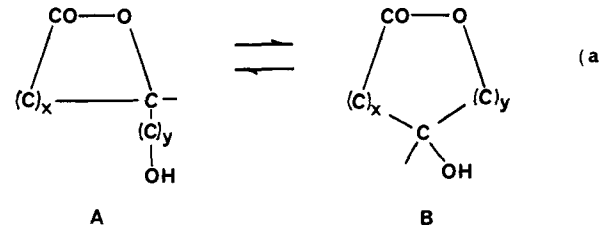
A Translactonization Route to Macrocyclic Lactones

Sir:

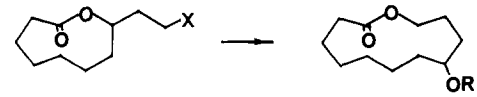
The invention of new synthetic methodology is one of the more crucial métiers for the development of effective syntheses for complex biologically active macrocyclic lactones and lactams.[1] In this communication we demonstrate that internal translactonization (i.e., internal transesterification) represents a useful new approach to the generation of macrocyclic lactones. The reversibility of the translactonization reaction, under either acid or base catalysis, implies that this process normally will lead to thermodynamically controlled products. Thus, it can also be expected to provide quite precise information concerning the relative stabilities of isomeric lactones of different ring size. The general type of translactonization which is described herein can be summarized by eq a.



(a)

There are a number of aspects of this reversible change which can be anticipated on general structural and mechanistic grounds. For example, if $x = 2$ the γ-lactone A can be expected to be considerably more stable than the larger cycle B; thus the observed transformation in this series will be ring contraction (B → A) and not ring expansion. Also the rate of the interconversion can be expected to drop as y increases from 1 to 2 to 3 to 4 (≡ transition state bridge ring sizes 5, 6, 7, 8, respectively).

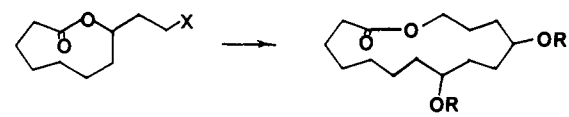
The lactone acid **1**,[2] mp 66–67 °C, IR max 1711 and 1726 cm^{-1} (film),[3] was reduced to the corresponding primary alcohol (**2**, oil) by reaction with 1.1 equiv each of triethylamine and ethyl chloroformate in THF to form the mixed anhydride and treatment with 4 equiv of sodium borohydride at 0 °C for 15 min (83% overall yield). Exposure of the 9-membered lactone **2** to 1 mol % p-toluenesulfonic acid in methylene chloride at 23–25 °C for 2 h effected internal translactonization to form the 12-membered hydroxy lactone **3** in 97% yield (IR max in $CHCl_3$ at 1723 cm^{-1}), also characterized as its acetate (**4**, 2 equiv of acetyl chloride–pyridine in methylene chloride at 25 °C for 2 h, 97% yield). The transformation of **2** into **3** could



1, X = COOH
2, X = CH_2OH
3, R = H
4, R = CH_3CO

also be effected (more slowly and somewhat less efficiently) by heating with 2 equiv of 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) in dimethylformamide (DMF) at 120 °C for 25 h.[4] The ring expansion of **2** by three members to form **3** is obviously driven mainly by the relative instability of the 9-membered cyclic system.[5]

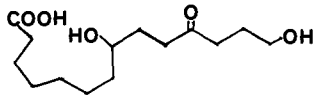
The acid **1** also served as a starting point for the generation of a 15-membered lactone by a *six*-carbon ring expansion. Conversion of **1** to the 2-pyridinethiol ester[6] followed by reaction in THF with the Grignard reagent from 3-*tert*-butyldimethylsilyloxy-1-bromopropane[7] (excess magnesium turnings in THF at 23 °C under argon) afforded[6c] the keto lactone **5** in 84% yield. Reduction of **5** with sodium borohydride in ethanol at 0 °C followed by desilylation with 3 equiv of tetra-n-butylammonium fluoride in THF at 23 °C gave the dihydroxy lactone **6** (90%). Ring expansion of **6** was effected by treatment with a catalytic amount of p-toluenesulfonic acid



5, X = $CO(CH_2)_3OSiMe_2tBu$
6, X = $CH(OH)(CH_2)_3OH$
7, R = H
8, R = CH_3CO

in methylene chloride at 23 °C for 36 h to give the 15-membered lactone **7**[8] in 90% yield as a mixture of cis and trans isomers (ratio ~1:1). The cis and trans diol lactones **7** were separated by chromatography on silica gel (2:1 methylene chloride–acetone). Each of the pure isomers was converted to the corresponding diacetate **8** in >95% yield using acetyl chloride in pyridine at 23 °C. The same lactone diols **7** were

independently synthesized from the dihydroxy keto acid **9** by the following sequence: (1) lactonization of the 1-isopropyl-4-*tert*-butyl-2-thiolimidazole[9] ester using the double activation method[5a] to give **10** in 78% yield and (2) reduction by sodium borohydride in ethanol at 0 °C.[10]



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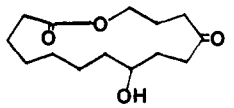

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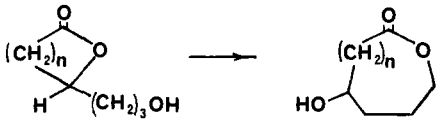
A number of other informative experiments on translactonization have been performed which can be summarized briefly (items I–IV below).

I. The 8-membered hydroxy lactone **11**,[11a] the lower homologue of **2**, undergoes ring expansion (3 mol % *p*-toluenesulfonic acid in methylene chloride, 24 h, 0 °C) somewhat more slowly and less efficiently[12] than **2**, to form the 11-membered lactone **12** in 69% yield.

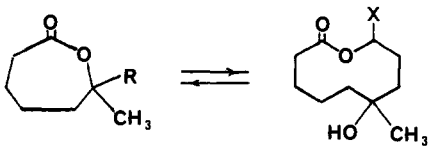


11, n = 5
13, n = 4

12, n = 5
14, n = 4

II. The 7-membered hydroxy lactone **13**[11b] does not undergo observable ring expansion to the 10-membered lactone **14** (3 mol % *p*-toluenesulfonic acid in methylene chloride, 6 h, 25 °C) and is converted (65%) only to polar materials.[12] In this case it is probable that the 7-membered lactone **13** is more stable than the 10-membered isomer **14**.

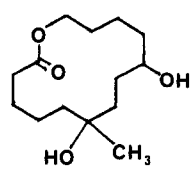
III. The 7-membered lactone **15**[13] is converted by storage at 23 °C either neat or in chloroform solution for 3 days into an equilibrium mixture of **15** and **16** (ratio 35:65). The same mixture is generated rapidly (<1 h) at 0 °C with 1 mol % *p*-toluenesulfonic acid in methylene chloride.



15, R = $(CH_2)_3OH$
17, R = $(CH_2)_2CH(CH_2)_4OH$ (OH)

16, X = H
18, X = $(CH_2)_4OH$

IV. The 7-membered lactone **17** undergoes translactonization to form an equilibrium mixture of **17** and the 10-membered isomer **18** (ratio 1:1). However, under either basic or acidic equilibration conditions none of the 14-membered lactone **19** which is to be expected from further translactonization



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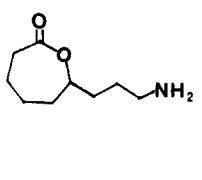

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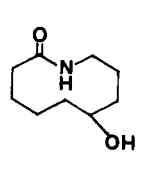

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can be detected, clearly because of an unfavorable rate rather than unfavorable equilibrium.[5] The ring expansion **18** → **19** (by four members) necessitates an 8-membered cyclic transition state which is evidently much more difficulty attained than the 7-membered cyclic structure involved in the other translactonization processes outlined above. It seems likely that the general translactonization scheme indicated by eq a is generally workable only for $y = 1$, 2, or 3 and not $y = 4$.

Based on relative stabilities of various lactone ring sizes[5] and the constraint that $y = 1$, 2, or 3 in eq a, the following ring expansions can be expected to be most favorable (in terms of lactone ring size):

$$8 \rightarrow 11 \rightarrow 13 \text{ or } 14$$

$$9 \rightarrow 12 \rightarrow 14 \text{ or } 15$$

$$10 \rightarrow 13$$

In these instances ring expansion may also be facilitated by the presence of one or more substituents which can be accommodated more readily on the larger ring. Finally it seems likely that the basic approach outlined here will also serve for the synthesis of macrocyclic lactams, e.g., **20** → **21**. This and other extensions of our work are being pursued.[14]

References and Notes

(1) For a recent review, see K. C. Nicolaou, *Tetrahedron*, **33**, 683 (1977).
(2) Synthesized from the pyrrolidine enamine of cyclooctanone by the sequence (1) reaction with ethyl acrylate in dioxane at reflux for 1 h and aqueous cleavage of the enamine adduct so obtained, (2) ester saponification using 2 N sodium hydroxide in aqueous methanol at reflux for 6 h, (3) Baeyer–Villiger reaction with excess 20% peracetic acid in ethyl acetate at 50–60 °C.
(3) Satisfactory infrared, proton magnetic resonance, and mass spectral data were obtained for each compound described herein using a purified and chromatographically homogeneous sample.
(4) This result is quite general in our experience; i.e., translactonization proceeds more rapidly under catalysis by *p*-toluenesulfonic acid than by DBN.
(5) This instability is indicated by the generally low rates of formation of 9-membered lactones:[5a-c] (a) E. J. Corey and K. C. Nicolaou, *J. Am. Chem. Soc.*, **96**, 5614 (1974); (b) C. Galli, G. Illuminati, L. Mandolini, and P. Tamborra, *ibid.*, **99**, 2591 (1977); (c) E. J. Corey, D. J. Brunelle, and P. J. Stork, *Tetrahedron Lett.*, 3405 (1976); as well as by thermodynamic data for cycloparaffins:[5d] (d) V. Prelog, *Bull. Soc. Chim. Fr.*, 1255 (1960).
(6) See (a) T. Mukaiyama, R. Matsueda, and M. Suzuki, *Tetrahedron Lett.*, 1901 (1970); (b) T. Mukaiyama, R. Matsueda, and H. Marayama, *Bull. Chem. Soc. Jpn.*, **43**, 1271 (1970); (c) K. Lloyd and G. T. Young, *J. Chem. Soc. C*, 2890 (1971); (d) T. Mukaiyama, M. Araki, and H. Takei, *J. Am. Chem. Soc.*, **95**, 4763 (1973).
(7) Prepared by reaction of 3-bromopropanol with 1.2 equiv of *tert*-butyldimethylsilyl chloride and 2 equiv of imidazole in DMF at 0 °C for 6 h followed by aqueous workup and distillation.
(8) The ^1H NMR spectrum clearly indicates that this product corresponds to structure **7** rather than the isomeric 9-membered lactone, which obviously is a reaction intermediate.
(9) E. J. Corey and D. J. Brunelle, *Tetrahedron Lett.*, 3409 (1976).
(10) The keto acid **9** was prepared from **5** by hydrolysis with 2 N sodium hydroxide in aqueous methanol at reflux for 24 h.
(11) Synthesized from (a) cycloheptanone or (b) cyclohexanone by a sequence paralleling that used for **2**.
(12) Very polar by-products, quite possibly linear polyesters, were also formed.
(13) Synthesized from 10-methyl-4-octal-3-one (C. H. Heathercock and J. E. Ellis, *Tetrahedron Lett.*, 4995 (1971)) by (1) oxidation with permanganate–periodate, (2) Baeyer–Villiger reaction, and (3) reduction of carboxyl to CH_2OH as for **2**.

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Homoenolate Anion Precursor. Reaction of Ester Homoenol Silyl Ether with Carbonyl Compounds

Sir:

Recognition of homoenolization[1] is a much newer event compared with that of enolization, and synthetic chemists have not paid any significant attention to this phenomenon (formation of **1** or **2**) until quite recently.[2]

However, the concept of homoenolate anion **2** has become one of the major subjects with respect to polarity inversion[3] (or