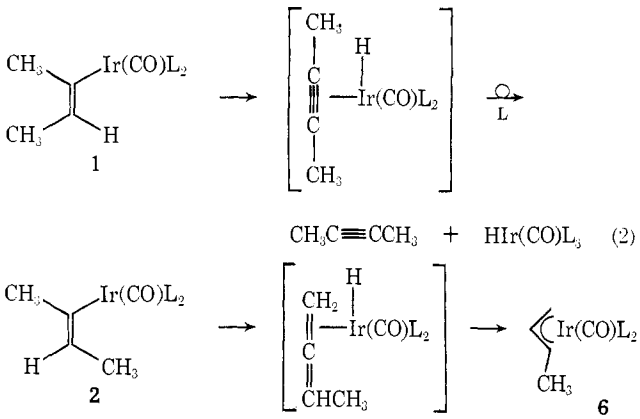

$$CH_3C{\equiv}CCH_3 + HIr(CO)L_3 \quad (2)$$

isolated. Compound **3** (in which no accessible β-H is present) slowly produced propene as the sole organic product when heated to 80° in C_6D_6.

Reactions of Rh(I) vinylic complexes were briefly investigated. Hydride rearrangements in these systems were so rapid, however, that treatment of either $L_2Rh(CO)Cl$ or L_3RhCl with *trans*-2-lithio-2-butene yielded, on immediate work-up, products derived from isomerization to η^3-crotyl complexes[12]; only a small amount of material attributed to **4** was detected by ir.

Stereochemical factors affecting β-H elimination from Pt(II) alkyls have been noted; acyclic alkyls[13] eliminate faster than do metallocyclic ones.[14] We note that elimination from aklyliridium(I) complexes is faster than from vinylic analogs. Stereochemical arguments may play some role in assessing this difference in rates, too. However, such considerations do not appear to account for the large difference in rates observed for cis β-vinylic *H vs.* β-allylic *H* elimination. Bond strength arguments cannot be used to explain the observed order of rates for β-H elimination since they would predict the opposite trend. The relative stability of complexes formed by β-H elimination (η^2-acetylene *vs.* η^2-allene) may dictate the direction of reaction for η^1-vinylic systems, and this phenomenon should be added to the growing list of considerations thus far established for it.

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(12) C. A. Reilly and H. Thyret, *J. Amer. Chem. Soc.*, **89**, 5144 (1967).
(13) G. M. Whitesides, J. F. Gaasch, and E. R. Stedronsky, *J. Amer. Chem. Soc.*, **94**, 5258 (1972).
(14) J. X. McDermott, J. F. White, and G. M. Whitesides, *J. Amer. Chem. Soc.*, **95**, 4451 (1973); J. X. McDermott and G. M. Whitesides, *ibid.*, **96**, 947 (1974).

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An Efficient and Mild Lactonization Method for the Synthesis of Macrolides

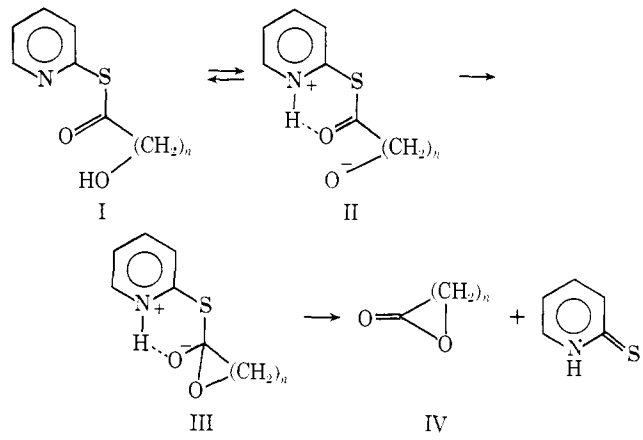
Sir:

The synthesis of naturally occurring large ring lactones, including such important substances as the erythromycins[1a] and cytochalasans,[1b] is rendered all the more formidable by the limited utility of most of the existing cyclization methods.[2-4] We describe here a new method for internal esterification of hydroxy acids to form medium and large ring lactones which appears to be highly effective and yet mild enough to be used with complex and polyfunctional substrates. The development of the method was guided by the following considerations.

(1) Because lactone formation becomes relatively slow in going from common to large ring sizes,[5] undesirably high reaction temperatures or excessively slow addition of the hydroxy acid derivative to the reaction medium would be required (for maintenance of high dilution) unless some means can be found to activate the reacting groups.

(2) One way of simultaneously activating both the carboxyl and hydroxyl groups for mutual reaction would be to utilize a carboxylic derivative which would favor proton transfer from hydroxyl to carboxylic oxygen. This idea is illustrated for the specific case of a 2-pyridinethiol ester of a hydroxy acid (I) in Scheme I.

Scheme I



The proton transfer from hydroxyl to carbonyl in I is clearly more favorable than for simple esters. The dipolar intermediate II (or hydrogen bonded equivalent) generated by internal proton transfer in I, could reasonably be expected to undergo a facile, *electrostatically driven*, cyclization to III which then would yield the

(1) (a) W. Keller-Shierlein, *Fortschr. Chem. Org. Naturst.*, **30**, 313 (1973); (b) M. Binder and C. Tamm, *Angew. Chem., Int. Ed. Engl.*, **12**, 370 (1973).
(2) For methods involving internal esterification see (a) M. Stoll and A. Rouvé, *Helv. Chim. Acta*, **17**, 1283 (1934); **18**, 1087 (1935) [acid catalysis]; (b) D. Taub, N. N. Girotra, R. D. Hoffsommer, C. H. Kuo, H. L. Slates, S. Weber, and N. L. Wendler, *Tetrahedron*, **24**, 2443 (1968) [carboxyl activation *via* $(CF_3CO)_2O$]; (c) E. W. Colvin, T. A. Purcell, and R. A. Raphael, *J. Chem. Soc., Chem. Commun.*, 1031 (1972) [carboxyl activation as imidazolide]; (d) M. Stoll and P. Bolle, *Helv. Chim. Acta*, **31**, 98 (1948) [heterogeneous gas-phase reaction over TiO_2]; and (e) E. W. Spanagel and W. Carothers, *J. Amer. Chem. Soc.*, **58**, 654 (1936) [thermal catalytic depolymerization of polyesters].
(3) For cyclizations generating bonds other than the ester linkage see (a) J. Carduff, G. Eglinton, W. McCrae, and R. A. Raphael, *Chem. Ind. (London)*, 559 (1960) [oxidative coupling of a diacetylene]; (b) E. J. Corey and H. A. Kirst, *J. Amer. Chem. Soc.*, **94**, 667 (1972) [cyclization of a dihalide by $Ni(CO)_4$]; (c) R. N. Hurd and D. H. Shah, *J. Org. Chem.*, **38**, 390 (1973) [Dieckmann cyclization]; and (d) H. Hunsdiecker and H. Erlbach, *Chem. Ber.*, **80**, 129 (1947) [internal nucleophilic displacement by carboxylate].
(4) For macrocycle formation by C=C cleavage of fusion bonds see (a) I. J. Borowitz, V. Bandurco, M. Heyman, R. D. G. Rigby, and S. Ueng, *J. Org. Chem.*, **38**, 1234 (1973), and earlier papers, and (b) J. Falbe and F. Korte, *Chem. Ber.*, **96**, 919 (1963).
(5) See C. Galli, G. Illuminati, and L. Mandolini, *J. Amer. Chem. Soc.*, **95**, 8374 (1973).

lactone IV by elimination of 2-pyridthione. Although a comparable path can be followed by two molecules of I reacting *intermolecularly*, this should be subject to experimental control using high-dilution procedures provided the cyclization I → IV is sufficiently fast under acceptable reaction conditions. In fact, the cyclization of 2-pyridinethiol esters of a series of ω-hydroxy acids has been found to be a useful method.

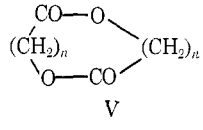
A series of ω-hydroxy acids, $HO(CH_2)_nCOOH$ with n = 5, 7, 10, 11, 12, or 14, was utilized in the cyclization studies. These substances were converted to 2-pyridinethiol esters by reaction in xylene (mixture of isomers) with 2,2′-dipyridyl disulfide according to Mukaiyama, *et al.*[6] The thiol esters so generated were subjected to lactonization without isolation by slow addition to xylene at reflux. The addition was conveniently performed using a mechanically driven syringe. After completion of the reaction the yield of lactone was determined by gas–liquid chromatographic (glc) analysis and the lactone was isolated after removal of xylene under reduced pressure. The identity of each lactone was proved by comparison (infrared, proton magnetic resonance, and thin-layer chromatography) with an authentic sample. As indicated in Table I, good to

Table I. Formation of Lactones and Dilides by Cyclization of 2-Pyridinethiol Esters of ω-Hydroxy Carboxylic Acids I (n = 5, 7, 10, 11, 12, 14)

		Lactone			Diolide	
n	Solvent	Ring size	Glc yield (%)	Isolated yield (%)	Ring size	Isolated yield (%)
5[a]	Benzene	7	87	71	14	7
7[b]	Xylenes	9	25	8	18	41
10[c]		12	64	47	24	30
11[a]		13	76	66	26	7
12[a]		14	79	68	28	6
14[a]		16	88	80	32	5

Slow addition of thioate to refluxing solvent was followed by [a] 10 hr at reflux, [b] 30 hr at reflux, [c] 20 hr at reflux.

excellent yields were obtained with the exception of the highly strained nine-membered ring. In addition to the lactones, IV, dimeric cyclic diesters (dilides) of type V



V

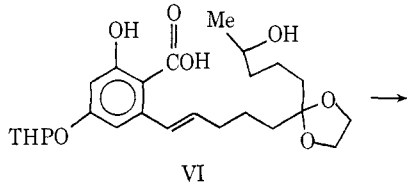
were also produced in varying amount as is also indicated in Table I. The dilides, all of which are crystalline,[7] were identified by infrared, proton magnetic resonance, and mass spectra. In the case of the cyclization of I, n = 14, the 48-membered trilide could be isolated in 1% yield. Although trilides appeared (by tlc analysis) to be formed in small amounts in other cases, no attempts were made to isolate these products.

(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. Jap.*, **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. Amer. Chem. Soc.*, **95**, 4763 (1973). 2-Pyridinethiol esters have been utilized as intermediates in peptide synthesis (a, b, c) and for the synthesis of ketones (d).

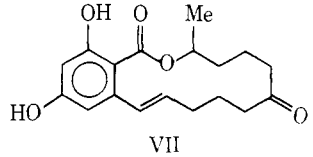
(7) Observed data on melting points (ring size) for the dilides V are: 111–112° (14) [see F. J. Van Natta, J. W. Hill, and W. H. Carothers, *J. Amer. Chem. Soc.*, **56**, 455 (1934)]; 91–92° (18); 73–74° (24); 103–104° (26); 81–82° (28); 90–91° (32).[2a]

The following general procedure was used in the experiments referred to in Table I. The hydroxy acid[8] (0.5 mmol), 2,2′-dipyridyl disulfide[9] (165 mg, 0.75 mmol), and triphenylphosphine (197 mg, 0.75 mmol) were dissolved in dry, oxygen-free xylene under argon and stirred at 25° for 5 hr. The reaction mixture containing the 2-pyridinethiol ester was diluted with 10 ml of dry, oxygen-free xylene and the resulting solution was added slowly from a mechanically driven syringe over 15 hr to 100 ml of dry xylene at reflux under argon. Refluxing was continued for an additional 10 hr (except for n = 7, 30 hr, and n = 10, 20 hr). Quantitative glc analysis was performed directly on the solution of product so obtained (10 ft, 10% silicone SE-30 column) using the next higher homologous lactone as standard. The solvent was removed under reduced pressure and the ether soluble part of the residue was subjected to preparative layer chromatography on silica gel (10% ether in pentane for development) to afford pure lactones (IV) and dilides (V), purified further by recrystallization from hexane.[10]

The use of the 2-pyridinethiol ester method for the lactonization of more complex hydroxy acids may be illustrated by the synthesis of (±)-zearalenone (VII)[11] from the protected (±)-hydroxy acid derivative. (VI).[12,13a] The 2-pyridinethiol ester of VI was prepared in benzene at 25° and subjected to cyclization in benzene at reflux as described above to afford after removal of the protecting groups (acetic acid–water–THF, 3:3:2 at 60° for 5 hr) 75% of pure VII.[13]



VI



VII

In accord with the operation of the scheme shown above for the lactonization of ω-hydroxy-2-pyridinethiol carboxylic esters are several observations made with the hydroxy acid n = 11. Neither added triethyl-

(8) The hydroxy acids used in this study were obtained by saponification of the corresponding lactones which in turn were prepared by Bayer–Villiger oxidation of commercially available cycloalkanones. Purified samples of the intermediate lactones also served as reference materials for comparison with the products of hydroxy acid cyclization.

(9) 2,2′-Dipyridyl disulfide was prepared by treatment of 2-pyridthione with equivalent amounts of sodium hydroxide and potassium triiodide in aqueous solution. W. Marckwald, W. Klemm, and H. Trabert, *Ber.*, **33**, 1556 (1900).

(10) Dimethylformamide and nitromethane were also studied as solvents. Both were satisfactory for thiol ester formation but not for the lactonization step.

(11) W. H. Urry, H. L. Wehrmeister, E. B. Hodge, and P. H. Hidy, *Tetrahedron Lett.*, 3109 (1966).

(12) The (±)-acid VI was prepared from zearalenone monotetrahydropyranyl ether ethylene ketal by basic hydrolysis (NaOH–H_2O–DMSO at 120°).

(13) Previously (±)-zearalenone dimethyl ether has been obtained in poor yields (a) by cyclization of t e corresponding hydroxy acid using trifluoroacetic anhydride in benzene (D. Taub, N. N. Girotra, R. D. Hoffsommer, C. H. Kuo, H. L. Slates, S. Weber, and N. L. Wendler, *Tetrahedron*, **24**, 2443 (1968)] or (b) from the corresponding hydroxy methyl ester using potassium *tert*-amylate in toluene at reflux (I. Vlattas, I. T. Harrison, L. Tökés, J. H. Fried, and A. D. Cross, *J. Org. Chem.*, **33**, 4175 (1968)).

amine (3 equiv) or tributylamine (10 equiv) had an effect on the rate or yield of the cyclization process. Further, use of the benzenethiol ester instead of I, n = 11, in the above procedure, either in the presence of pyridine (10 equiv) or without pyridine, resulted in the formation of only a trace of lactone.[14]

A subsequent publication will describe application of the cyclization method disclosed herein to the total synthesis of complex, naturally occurring macrolide systems.[15]

(14) Although these observations are consistent with the scheme outlined herein, they do not elevate it beyond the level of a reasonable hypothesis. Further work is required before a more definitive view is possible of the mechanism of the reaction I → IV or of the scope of this approach to the formation of macrocyclic carboxylic acid derivatives.

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Succinimidyl Radical as a Chain Carrier. Mechanism of Allylic Bromination

Sir:

Early mechanisms for allylic brominations with *N*-bromosuccinimide involved a succinimidyl chain reaction (the Bloomfield mechanism).[1] Subsequently a variety of evidence indicated a marked similarity between NBS and Br_2 radical-chain reactions in substitutions at benzylic positions and allylic positions of some highly substituted alkenes, resulting in the general acceptance of the bromine atom chain reaction to explain allylic brominations (the Goldfinger mechanism).[2] Although these considerations brought conviction to many, it must remain a negative argument rather than a positive one. Until one knows the behavior of a succinimidyl radical, one can only say that NBS allylic bromination may occur with a bromine atom chain or with some other chain carrier of similar selectivity, possibly the unexamined succinimidyl radical. We report here the characteristic behavior of succinimidyl radicals, which forces one to conclude it is not an intermediate in the Ziegler allylic brominations.

Succinimidyl radical is a radical of low discrimination in hydrogen abstraction reactions, quite different from bromine atoms. The failure to recognize the behavior of this radical unambiguously is attributable to the domination of reaction paths by even small amounts of bromine, such as is inevitably produced early in most NBS-containing systems.[3] Bromine (Br_2) is much more reactive than NBS in capturing radicals, thus perpetuating a bromine atom chain, the NBS serving only as a reservoir for more Br_2 *via* the rapid reaction of NBS with HBr.[4]

(1) D. H. Hey, *Annu. Rep. Chem. Soc.*, 41 184 (1944); G. F. Bloomfield, *J. Chem. Soc.*, 114 (1944).

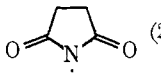
(2) The bromine atom as the chain carrier in NBS allylic bromination was first suggested by Goldfinger in 1953: P. A. Gosselain, J. Adam, and P. Goldfinger, *Bull. Soc. Chim. Belg.*, **65**, 533 (1956). For general reviews of work pertaining to the mechanism(s) of NBS bromination see W. A. Thaler, *Methods Free Radical Chem.*, **2**, 121 (1969); M. L. Poutsma, *Free Radicals*, **2** 211 (1973).

(3) The suggestion that a hydrogen-abstracting species other than the bromine atom might be involved in NBS bromination has previously been presented. See, for example, J. G. Traynham, E. E. Green, Y. Lee, F. Schweinsberg, and C. Low, *J. Amer. Chem. Soc.*, **94**, 6552 (1972).

To minimize bromine atom chains, and perhaps eliminate them entirely, the concentration of NBS is increased, and the bromination reactions are carried out in the presence of an alkene which reacts readily by addition of Br_2 and by addition of Br· (no H abstraction). We have found ethylene or *tert*-butylethylene suitable for this purpose.

Carbon tetrachloride and the Freons are very poor solvents for NBS (0.006 and 0.0005 *M*, respectively) so that even minute concentrations of Br_2 are sufficient to dominate the reactions. The solubility of NBS in methylene chloride (0.25 *M*) and acetonitrile (0.8 *M*) are large enough to make NBS the dominant chain carrier in the presence of a bromine scavenger. In the absence of ethylene (or *tert*-butylethylene), irradiation of NBS, in the presence of most hydrogen-containing substances, produces a yellow color quickly (~0.005 *M* Br_2), and from then on the reaction is Br_2 dominated. In the presence of ethylene, the reaction mixtures remain free of discernible bromine. The major negative result of carrying out reactions in the presence of alkenes is that a portion of the NBS goes to production of 1,2-dibromoethane and β-bromopropionyl isocyanate.[5]

For example, bromination of 1-bromobutane in the presence of ethylene results in formation of 1,1-, 1,3-, and 1,4-dibromobutanes in yields of 7, 44, and 18% respectively; the remainder (31%) is attributed to abstraction at the 2-position, which under these circumstances results in formation of 1,2-dibromobutane and products derived from substitution on 1-butene.[6] These proportions contrast sharply with those obtained in the presence of Br_2: 1,3/1,2 = 0.18 and no 1,4 is obtained. In the absence of Br_2, the succinimidyl radical must be the chain carrier (succinimide is the major product); it shows a hydrogen-abstraction selectivity similar to that of Cl atoms.

Abstracting agent	CH_3—CH_2—	—CH_2—	—CH_2Br
Br· (60°)[7]	0	14	85	1
 (25°)	18	44	31	7
Cl· (60°)[7]	23	50	22	5

Bromination of cyclohexene by the Ziegler procedure, in CCl_4, has been reexamined; the only monobromide is 3-bromocyclohexene, without even traces of the 4-bromocyclohexene. Photobromination of cyclohexene with NBS in acetonitrile solvent produces both 3- and 4-bromocyclohexene in 5.6 ratio. In acetonitrile the concentration of NBS is much larger than in

(4) P. S. Skell, D. L. Tuleen, and P. D. Readio, *J. Amer. Chem. Soc.*, **85**, 2850 (1963); K. J. Shea, D. C. Lewis, and P. S. Skell, *ibid.*, **95**, 7770 (1973).

(5) The rearrangement of NBS to β-bromopropionyl isocyanate is enhanced in the presence of olefin. H. W. Johnson, Jr., and D. E. Bublitz, *J. Amer. Chem. Soc.*, **80**, 3150 (1958); J. C. Martin and P. D. Bartlett, *ibid.*, **79**, 2533 (1957); C. Walling, A. L. Rieger, and D. D. Tanner, *ibid.*, **85**, 3129 (1963); R. E. Pearson and J. C. Martin, *ibid.*, **85**, 3142 (1963).

(6) A typical reaction: 17 mmol of 1-bromobutane, 4.3 mmol of NBS, and 2.5 mmol of ethylene in 7 ml of CH_2Cl_2 is irradiated with a medium-pressure mercury vapor lamp, through Pyrex, at 25° for 30–60 min, producing 15–25% C_4 dibromides. The products are separated and identified with the aid of gc procedures. Substitution at C_2 is complicated in the absence of Br_2 by decomposition of the 1-bromo-2-butyl radical to 1-butene (small amounts detected) and ultimately formation of crotyl bromide and 1,4-dibromo-2-butene, in addition to 1,2-dibromobutane. Main product composition does not vary with time or change to CH_3CN solvent.

(7) W. A. Thaler, *J. Amer. Chem. Soc.*, **85**, 2607 (1963).