where F is the fraction of reaction (0.51–0.79 in the present experiments), R is the molar activity of recovered, and R_0 is the molar activity of the original reactant.

Registry No. ^{14}C, 14762-75-5; ^{34}S, 13965-97-4; (2-phenylethyl)dimethylsulfonium ion, 16315-48-3.

Proton-Transfer Steps in Steglich Esterification: A Very Practical New Method for Macrolactonization

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The development of synthetic methodology for the preparation of large ring lactones from the corresponding ω-hydroxy acids has, perhaps more than any other single development of recent years, dramatically impacted the field of natural products total synthesis. Practitioners of this art may now attack complex macrolide antibiotics secure in the knowledge that a variety of methods such as those due to Corey,[1] Mukaiyama,[2] Masamune,[3] and Mitsunobu[4] are available for formation of the large ring as the penultimate step in the synthesis and thus focus their creative efforts on the stereochemical challenges associated with such materials. In fact, it is probably not overstating the impact of macrolactonization methodology to trace the current explosion of methodology for "acyclic stereochemical control" to the availability of reliable macrolactonization procedures.

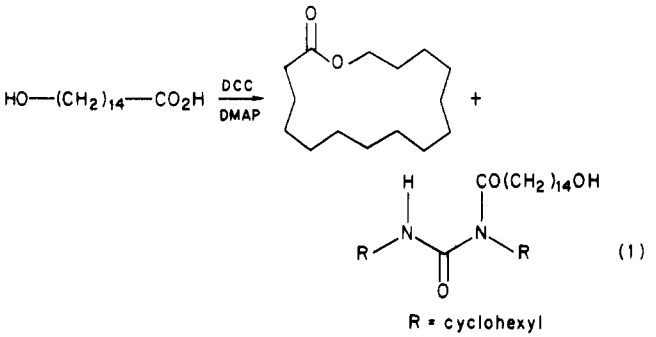
Despite the impressive advances in this area, some problems still remain, and our investigations on the macrocyclic bis-lactone colletodiol[5] have encouraged us not only to closely examine the available literature in this area but also to consider the characteristics of an "idealized" lactonization procedure. For example, in situ generation of an active ester is preferable to the formation of a discrete intermediate which is then subjected to macrolactonization conditions.[6] Moreover, activation of the carboxyl function should be accomplished in such a way as to allow for the regeneration of the active ester if the intermediate is destroyed by adventitious moisture. Finally, since these reactions are generally performed on rather small scale, reagents should be usable in excess without complicating conventional (e.g., TLC) chromatographic monitoring or product isolation.[7]

Consideration of these and other criteria has led us to examine Steglich[8] esterification, a very successful method for bimolecular esterification even with tertiary alcohols, as a method for macrolactonization. In this context it should be explicitly noted that the only chromatographically mobile (in common solvent systems) component derived from the reagents employed is dicyclohexylcarbodiimide (DCC), which can be converted, prior to isolation, to a urea which is generally easily removed by conventional techniques involving precipitation and chromatography.

Unfortunately, in our hands, all attempts at macrolactonization using this procedure, including those with excess reagents and very slow (syringe pump) addition of hydroxy acid, fail. For example, the VPC yield of the hexadecanolide from 15-hydroxypentadecanoic acid is only 4%, and the major isolable product is *N*-acylurea. (eq 1).

Table I. Isolated Yields of Lactones from ω-Hydroxy Acids

acid	lactone ring size	lactone yield, %	diolide yield, %
$HO(CH_2)_{11}CO_2H$	13	32	32
$HO(CH_2)_{12}CO_2H$	14	77	11
$HO(CH_2)_{14}CO_2H$	16	95	trace
$HO(CH_2)_{15}CO_2H$	17	96	



These results prompted us to critically examine the accepted mechanism for such esterifications, *including* proton transfer steps, with the conclusion that the failure might conceivably arise from low effective concentrations of alcohol and acid (both proton sources) under conditions appropriate for macrolactonization.[9] Therefore this approach to macrolactonization was reexamined in the presence of additives (specifically various amine hydrochlorides) to mediate such proton-transfer steps. Best results were obtained in media where such salts were totally soluble, and the use of DMAP·HCl as the amine hydrochloride proved most efficient and convenient. The optimal protocol is detailed below (vide infra), however, *for the present it is sufficient to note the isolated yield of crystalline hexadecanolide using this simple variation is 95%.*

Bimolecular esterification experiments verify the crucial role of such proton-transfer agents in preserving "active ester" species under conditions of high dilution. For example, exposure of cinnamic acid to DCC and 4-(di-

† Fellow of the Alfred P. Sloan Foundation, 1981–1985.

(1) (a) Corey, E. J.; Nicolaou, K. C. *J. Am. Chem. Soc.* **1974**, *96*, 5614–5616. (b) Corey, E. J.; Nicolaou, K. C.; Melvin, L. S., Jr. *Ibid.* **1975**, *97*, 653–654, 654–655. (c) Corey, E. J.; Nicolaou, K. C.; Toru, T. *Ibid.* **1975**, *97*, 2287–2288. (d) Corey, E. J.; Brunelle, D. J. *Tetrahedron Lett.* **1976**, 3409–3412.

(2) (a) Mukaiyama, T.; Usui, M.; Saigo, K. *Chem. Lett.* **1976**, 49–50. (b) Mukaiyama, T. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 707–721.

(3) (a) Masamune, S.; Kamata, S.; Schilling, W. *J. Am. Chem. Soc.* **1975**, *97*, 3515–3516. (b) Masamune, S.; Hayase, Y.; Schilling, W.; Chan, W. K.; Bates, G. S. *J. Am. Chem. Soc.* **1977**, *99*, 6756–6758. (c) Masamune, S. *Aldrichimica Acta* **1978**, *11*, 23–32.

(4) (a) Kurihara, T.; Nakajima, Y.; Mitsunobu, O. *Tetrahedron Lett.* **1976**, 2455–2458. (b) Mitsunobu, O. *Synthesis* **1981**, 1–28. (c) Tsutsui, H.; Mitsunobu, O. *Tetrahedron Lett.* **1984**, *25*, 2163–2166.

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(6) What appears to be the state-of-the-art procedure requires delivery of a (preformed) active ester to the reaction flask via a cryocooled syringe to preclude biomolecular reactions.[1d]

(7) Difficulties due to the numerous byproducts produced in some thiol ester procedures have been explicitly noted: (a) Corey, E. J.; Clark, D. A. *Tetrahedron Lett.* **1979**, 2875–2878. (b) Schmidt, U.; Dietsche, M. *Angew Chem., Int. Ed. Engl.* **1981**, *20*, 771–772.

(8) Neises, B.; Steglich, W. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 522–524.

(9) (a) The original Steglich procedure is 1.0 M in acid and ≥1.0 M in alcohol. (b) The process described herein may be mechanistically related to the method of Fujisawa,[9c] although other roles for the amine hydrochloride can be envisioned in precluding *N*-acylurca formation. (c) Fujisawa, T.; Mori, T.; Fukumoto, K.; Sato, T. *Chem. Lett.* **1982**, 1891–1894.

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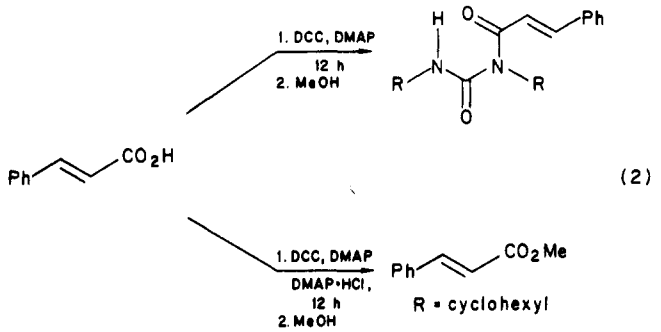
methylamino)pyridine (DMAP) under conditions of high dilution (1 mg/12 mL) for 12 h results in essentially quantitative formation of *N*-acylurea, and addition of large excesses of methanol after 12 h does not result in the formation of detectable quantities of methyl cinnamate. However, in the presence of 4-(dimethylamino)pyridine hydrochloride (DMAP·HCl) *N*-acylurea is produced in only minor amounts, and methyl cinnamate is now the major product. We therefore expect that this simple protocol will prove useful for bimolecular esterifications which must, of necessity, be conducted at rather high dilutions, such as those involving radiolabelled compounds or small amounts of biologically derived materials (eq 2).



(2)

Although the generality of this method for macrolactonization using complex substrates has yet to be demonstrated, *isolated* yields obtained with the usual collection of simple ω-hydroxy acids of various chain lengths (Table I) suggest that this simple procedure may prove competitive with more elaborate methods as an approach to macrolactonization, particularly for the ring sizes commonly encountered in natural products. In this context, we note that all reagents are commercially available except for DMAP·HCl, which is trivially prepared from DMAP and anhydrous HCl in THF. Additionally, the procedure detailed below (which affords a *95%* isolated yield of hexadecanolide on a 200-mg scale) uses only 30 mL of solvent, and the only expensive apparatus employed is a Sage syringe pump, an item common to most laboratories where macrolactonization reactions are performed. Finally, this method has been employed in one reasonably complex example in a synthetic approach to (−)-colletodiol,[10] a system where lactonization has proven quite difficult.[11]

Experimental Section

General Methods. 12-Hydroxydodecanoic acid, cyclododecanone, cyclotridecanone, cyclopentadecanone, and 16-hydroxyhexadecanoic acid were purchased from Aldrich Chemical Company. Oxidation of cyclododecanone, cyclotridecanone, and cyclopentadecanone, using MCPBA in methylene chloride as previously described,[1a] furnished authentic samples of tridecanolide, tetradecanolide, and hexadecanolide, respectively. Hydrolysis with KOH in methanol afforded 12-hydroxydodecanoic acid, 13-hydroxytridecanoic acid, and 15-hydroxyhexadecanoic acid, respectively. Structures assigned to lactonization products from these acids rest on spectral and chromatographic comparisons with authentic samples obtained as described above; the structure of the lactone obtained from 16-hydroxyhexadecanoic acid was assigned from spectral (NMR, IR, MS) data alone.

All lactonizations were performed by using the same general procedure detailed below for the preparation of hexadecanolide.

Hexadecanolide from 15-Hydroxypentadecanoic Acid. A flame-dried 50-mL round-bottomed flask, equipped with stirring bar, reflux condenser with serum cap, argon inlet (through serum cap), and syringe pump inlet (vide infra, through serum cap), was charged with 25 mL of ethanol-free[12] chloroform, 0.343 g (1.66 mmol) of DCC, 0.305 g (2.50 mmol) of 4-(dimethylamino)pyridine, and 0.263 g (1.66 mmol) of 4-(dimethylamino)pyridine hydrochloride. The resulting solution was brought to reflux, and a solution of 0.215 g (0.832 mmol) of 15-hydroxypentadecanoic acid in 5.0 mL of THF[13] was infused via syringe pump over 16 h. (A Glenco gas tight syringe with a Teflon seal and Teflon tubing was utilized, and the inlet of the Teflon tubing was positioned in the condensate formed at the tip of the reflux condenser.) After addition was completed, the syringe apparatus was removed and the reaction mixture was cooled to room temperature. The residual contents of the syringe and Teflon tubing were rinsed into a tared flask and concentrated to afford 11.5 mg of starting hydroxy acid. Methanol (1.0 mL) and acetic acid (0.19 mL, 4.0 equiv) were added to the reaction flask and stirring was continued for 30 min, at which time no DCC was detected by TLC analysis (10% EtOAc–hexanes). Further TLC analysis in two solvent systems revealed the formation of the desired lactone (R_f 0.34 in 10% EtOAc–hexanes), *N*-acylurea (independently prepared, R_f 0.32 in 35% THF–hexanes) was not detected. The mixture was concentrated to 5 mL, diluted with 25 mL of ether, filtered, and concentrated. The residue was taken up in a minimal amount of chloroform and applied to a 24 × 1.5 cm column of silica gel (Davisil 60–200 mesh) slurry packed in hexanes. Elution was with 20 mL of hexanes and then with 3% THF–hexanes; 6-mL fractions were collected. Concentration of fractions 11–13 gave 0.180 g (95%, based on hydroxy acid delivered to the reaction vessel) of hexadecanolide, identical in all respects with an authentic sample.

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Registry No. $HO(CH_2)_{11}CO_2H$, 505-95-3; $HO(CH_2)_{12}CO_2H$, 7735-38-8; $HO(CH_2)_{14}CO_2H$, 4617-33-8; $HO(CH_2)_{15}CO_2H$, 506-13-8; tridecanolide, 1725-04-8; tetradecanolide, 3537-83-5; hexadecanolide, 109-29-5; heptadecanolide, 5637-97-8.

(10) Our efforts in this area will be reported separately.
(11) Schnurrenberger, P.; Hungerbühler, E.; Seebach, D. *Tetrahedron Lett.* **1984**, *25*, 2209–2212.
(12) Chloroform utilized in this procedure was purified as described in "Purification of Laboratory Chemicals." Perrin, D. D., Armarego, W. L.; F., Perrin, D. R., Eds.; Permagon Press: Oxford, 1966. Without such purification, significant amounts of ethyl esters are formed in small-scale experiments.
(13) Tetrahydrofuran (THF) was utilized only due to the low solubility of this particular hydroxy acid in chloroform; chloroform is preferable as solvent (if possible) since the use of THF as the sole solvent affords very low yields of lactones. The major products formed in THF are *N*-acylureas, most probably because DMAP·HCl is very insoluble in THF, even at reflux temperature.

Isolation and Purification of Benzene-1,2,4,5-tetrathiol

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The title compound has been reported in the literature in the past.[1] Yields were reported to be good to very good but we have had difficulty obtaining these results with reliable frequency. We needed to be able to prepare large amounts of the tetrathiol in a straightforward fashion since we wanted to use it, among other projects,[2] as a monomer.[3]

(1) (a) Maiolo, F.; Testaferri, L.; Tiecco, M.; Tingoli, M. *J. Org. Chem.* **1981**, *46*, 3070. (b) Testaferri, L.; Tingoli, M.; Tiecco, M. *J. Org. Chem.* **1980**, *45*, 4376. (c) Reifschneider, W. *Chem. Abstr.* **1968**, *69*, 106244.
(2) Cox, S. D.; Dirk, C. W.; Wellman, D. E.; Wudl, F. *J. Am. Chem. Soc.* **1984**, *106*, 7131.

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