spectively. Compound **3a** whose structure was evident from the analytical and spectral data was methylated (CH_3I, acetone, K_2CO_3) to give 5-benzyl-2,4-dimethylthiopyrimidine (**4a**, oil).[5] Oxidation of the latter by H_2O_2 in acetic acid followed by acid hydrolysis of the resulting 2,4-dimethylsulfonylpyrimidine gave 5-benzyluracil (**5a**).[7]

The thioglycoside **2b** (mp 81–82 °C)[8] was prepared by treating **1** with either 1,2,3,5-tetra-*O*-acetyl-D-ribofuranose (BF_3·Et_2O, dichloroethane, 0 °C) or 2,3,5-tri-*O*-acetyl-D-ribofuranosyl bromide (acetone, K_2CO_3). The β configuration of this *S*-nucleoside was anticipated because of its method of synthesis.[9] Compound **2a** and **2b** displayed a closely related photochemical behavior. Irradiation[6] of **2b** gave a mixture which, after methylation, was separated by silica gel column chromatography affording 2,4-dimethylthiopyrimidine (**6**) and **4b** (oil, 15% yield).[8] Compound **4b** is a pseudonucleoside as shown by comparison of the NMR spectra of **2b** and **4b.** In the spectrum of **4b** the H-6 signal appears as a singlet at 8.31 ppm, whereas the H-1′[10] signal is observed at higher field as expected for a *C*-nucleoside. Comparison of the signals exhibited by the ribose carbons in the ^{13}C NMR spectra of **2b** and **4b** shows only minor differences for C-2′, C-3′, C-4′, and C-5′. However, the signal due to C-1′ is found at 78.01 ppm in **4b** instead of 84.10 ppm in **2b.** This upfield shift is compatible with the replacement of a C–S bond by a C–C bond at C-1′.

NMR spectroscopy and TLC indicated that compound **4b** was anomerically pure; the configuration at C-1′ was assigned on the basis of the observed difference of the chemical shift values between the methyl resonances in the isopropylidene derivative **4d.**[11] Deacetylation ($NaOCH_3/CH_3OH$) of **4b** afforded a *C*-nucleoside which was treated with 2,2-dimethoxypropane to yield **4d** (oil).[8] For this compound $\Delta\delta_{CH_3}$ was 0.264 ppm suggesting the β configuration. Hence, there is retention of chirality at C-1′ during the photorearrangement; as previously demonstrated in the case of 4-benzylthiopyrimidin-2-ones,[4] it might be inferred that this rearrangement was also *intra*molecular.

Confirmation of structure **4b** was achieved by transformation of this substance into β-pseudouridine (**5b**). Thus, overnight oxidation of **4b** with *m*-chloroperbenzoic acid in CH_2Cl_2 gave the corresponding 2,4-dimethylsulfonyl derivative which upon treatment in water at 90 °C followed by deacetylation ($NaOCH_3/CH_3OH$) afforded β-pseudouridine.[12]

The 4-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyl)-thio-2-methylthiopyrimidine (**2c,** mp 147–149 °C)[13] was quantitatively prepared by treating **1** with 2,3,4,6-tetra-*O*-acetylglucopyranosyl bromide (acetone, K_2CO_3). The coupling constant $J_{H\text{-}1',H\text{-}2'}$ = 10 Hz indicates that this new glycosylthiopyrimidine has the β configuration. It was irradiated[6] to give a mixture of photoproducts which after methylation (CH_3I, acetone, K_2CO_3) afforded the three pyrimidine derivatives **6, 4c,** (oil, yield 8%),[13] and **7** (mp 162–164 °C, yield 7%).[13]

Structures **4c** and **7** are based on spectral evidences. The presence of a thiocarbonyl in **7** is confirmed by UV. Its NMR spectrum displays an AB pattern (J = 6 Hz) attributed to H-5 and H-6; the lowest field signal at 7.95 ppm is due to the anomeric H-1′. The deshielding of this signal results from the anisotropy of the thiocarbonyl;[14] consequently the glycosyl moiety in **7** is at N-3. The value of the coupling constant $J_{H\text{-}1',H\text{-}2'}$ = 9.7 Hz suggests that this nucleoside has retained the β configuration of the starting material.

Compound **4c** is a 2,4-dimethylthiopyrimidine with a glycosyl residue at C-5. In its NMR spectrum the H-6 signal appears as a singlet at 8.46 ppm and the H-1′ signal is part of the multiplet due to H-2′, H-3′, and H-4′.

We have firmly established that thionueoside **2a** and **2c** undergo a photorearrangement to provide stereospecifically the corresponding C-5 pseudonucleosides. These results demonstrate the potential utility of this reaction with pentose derivatives. In the case of **2c** migration of the hexopyranosyl residue occurred unselectively toward C-5 as well as N-3 in poor yield. The extension of this rearrangement to other systems through modification of the heterocyclic and carbohydrate moieties is underway in this laboratory.

Acknowledgment. We are very grateful to Dr. J. Polonsky for her encouragement and support throughout this work.

References and Notes

(1) R. J. Suhadolnik, "Nucleoside Antibiotics", Wiley-Interscience, New York, N.Y., 1970; K. Gerzon, D. C. De Long, and J. C. Kline, *Pure Appl. Chem.*, **28,** 489 (1971).
(2) S. Hanessian and A. G. Pernet, *Adv. Carbohydr. Chem.*, **33,** 111 (1976).
(3) L. Kalvoda, *Collect. Czech. Commun.*, **38,** 1679 (1973); H. Ohrul, H. Kuzuhara, and S. Emoto, *Agr. Biol Chem. (Tokyo)*, **36,** 1651 (1972).
(4) J. L. Fourrey and P. Jouin, *Tetrahedron Lett.*, 3201 (1976).
(5) **2a:** M^+· 248; UV (EtOH) λ_{max} 257 and 303 nm; NMR ($CDCl_3$) δ 8.12 (1 H, d, J = 5 Hz, H-6), 6.77 (1 H, d, J = 5 Hz, H-5), 4.47 (2 H, s, CH_2), and 2.55 (3 H, s, SCH_3). **3a:** M^+· 248; UV (EtOH) λ_{max} 241, 285, and 353 nm; NMR ($CDCl_3$) δ 7.56 (1 H, s, H-6), 4.05 (2 H, s, CH_2), and 2.57 (3 H, s, SCH_3). **4a:** M^+· 262; UV (EtOH) λ_{max} 256 and 305 nm; NMR ($CDCl_3$) δ 7.83 (1 H, s, H-6), 3.80 (2 H, s, CH_2), and 2.55 (6 H, s, SCH_3).
(6) A 5.10^{-3} M *t*-BuOH solution of the benzylthio- or glycosylthiopyrimidine was irradiated under nitrogen with 254-nm light until 75% of the starting material had disappeared. All new compounds gave satisfactory analytical data and/or correct composition by mass spectrometry.
(7) T. B. Johnson and J. C. Ambelang, *J. Am. Chem. Soc.*, **60,** 2941 (1938); B. R. Baker and J. L. Kelley, *J. Med. Chem.*, **11,** 686 (1968).
(8) **2b:** M^+· 416; UV (EtOH) λ_{max} 253 and 303 nm; NMR ($CDCl_3$) δ 8.17 (1 H, d, J = 5 Hz, H-6), 6.83 (1 H, d, J = 5 Hz, H-5), 6.25 (1 H, d, J = 3 Hz, H-1′), and 2.52 (3 H, s, SCH_3). **4b:** M^+· 430; UV (EtOH) λ_{max} 257 and 303 nm; NMR ($CDCl_3$) δ 8.31 (1 H, s, H-6), 5.07 (1 H, d, J = 5 Hz, H-1′), and 2.58 (6 H, s, SCH_3). **4d:** M^+· 344; UV (EtOH) λ_{max} 256 and 304 nm; NMR ($CDCl_3$) δ 8.24 (1 H, s, H-6), 4.78 (1 H, d, J = 3 Hz, H-1′) and 2.58 (6 H, s, SCH_3).
(9) D. A. Shuman, A. Bloch, R. K. Robins, and M. J. Robins, *J. Med. Chem.*, **12,** 653 (1969).
(10) Although nucleoside numbering should not be applied to *C*-glycosyl derivatives, we use it here for the sake of clarity and convenience.
(11) J. L. Imbach, *Ann. N.Y., Acad. Sci.*, 225, 177 (1975).
(12) It was found identical with an authentic sample obtained after purification of commercially available pseudouridine (Sigma Chemical Co.).
(13) **2c:** M^+· 488; UV (EtOH) λ_{max} 259 and 299 nm; NMR ($CDCl_3$) δ 8.20 (1 H, d, J = 4.5 Hz, H-6), 6.81 (1 H, d, J = 4.5 Hz, H-5), 5.85 (1 H, d, J = 10.25 Hz, H-1′), and 2.57 (3 H, s, SCH_3). **4c:** M^+· 502; UV (EtOH* λ_{max} 257 and 302 nm; NMR ($CDCl_3$) δ 8.46 (1 H, s, H-6), ~5.30 (H-1′), and 2.58 (6 H, s, SCH_3). **7:** M^+· 488; UV (EtOH) λ_{max} 245, 293, and 369 nm; NMR ($CDCl_3$) δ 7.42 (1 H, d, J = 6 Hz, H-6), 7.11 (1 H, d, J = 6 Hz, H-5), 7.95 (1 H, d, J = 9.7 Hz, H-1′), and 2.61 (3 H, s, SCH_3).
(14) H. Vorbruggen, P. Strehlke, and G. Schulz, *Angew. Chem., Int. Ed. Engl.*, **8,** 976 (1969).

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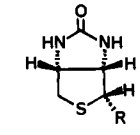
A Stereospecific Total Synthesis of (±)-Biotin[1]

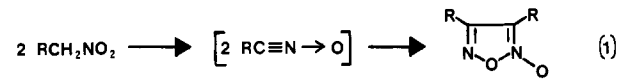
Sir:

Biotin, a member of the B vitamin complex, plays an essential nutritional role in various CO_2 fixation reactions.[2] Recognition of biotin's important function as a growth factor in poultry, coupled with its relative unavailability from natural sources, spurred interest in synthetic approaches, and a stereoselective commercial synthesis has been developed.[3] We now wish to disclose a stereospecific total synthesis of (±)-biotin which differs fundamentally from previous approaches.[4]



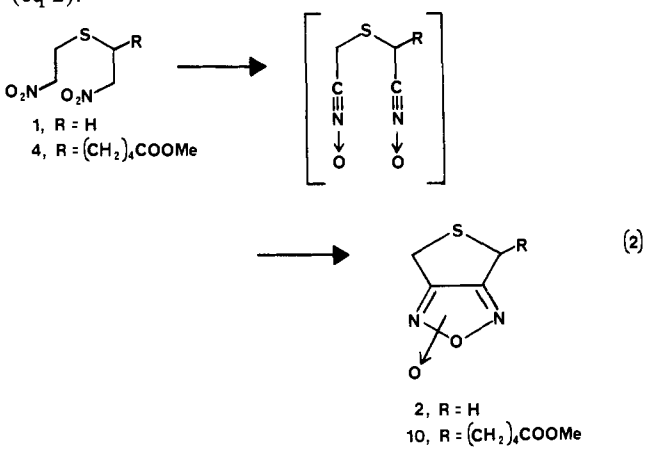
Biotin, R = $(CH_2)_4COOH$
3, R = H

Our synthetic strategy focused on formation of the novel thienofuroxan ring system, e.g., **10,** and its subsequent reduction, as a means of introducing and controlling the stereochemistry of the functionalities around the thiophane ring of biotin. The formation of furoxans from 2 molecules of a nitroparaffin under dehydrating conditions, presumably through the intermediacy of nitrile oxides, has been reported by Mukaiyama (eq 1).[5] We became intrigued with the possibility of



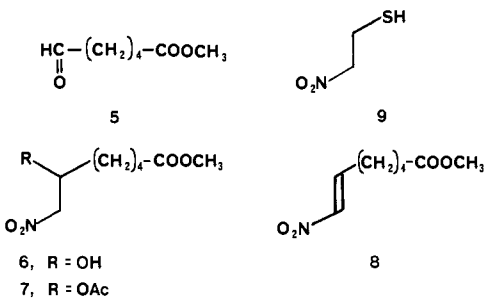
(1)

effecting an (hitherto unreported) intramolecular nitrile oxide "dimerization". In principle, such an intramolecular cyclization could furnish, *in a single step from an acyclic precursor,* a bicyclic intermediate incorporating the thiophene ring as well as all of the necessary functionality for elaboration to biotin (eq 2).



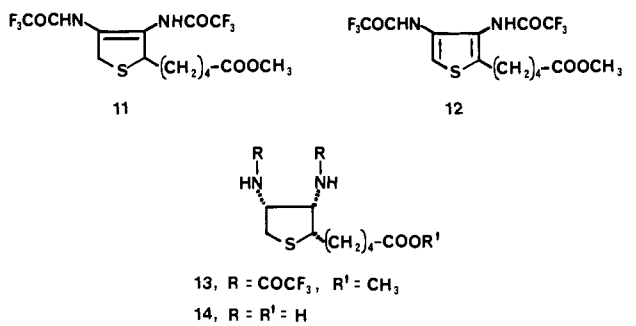
(2)

In a model reaction, bis(2-nitroethyl) sulfide[6] (**1**) was treated in $CHCl_3$ solution with $POCl_3$ and triethylamine (TEA).[7] From the tarry reaction mixture there was obtained in ~10% yield, after silica gel chromatography, the new heterocycle 4*H*,6*H*-thieno[3,4-*d*]furoxan (**2**), mp 58 °C.[8] Somewhat encouraged by this result, we turned our attention to the synthesis of the potential biotin precursor **4.** Condensation of adipaldehydic ester **5**[9] with CH_3NO_2 (MeOH,



NaOH, 0 °C–room temperature) furnished nitro alcohol **6,** which was converted via the corresponding (not purified) nitro acetate **7,**[10] to the oily methyl 7-nitrohept-6-enoate (**8**)[8,11] ((1) Ac_2O, H_2SO_4, room temperature, (2) $NaHCO_3$, CH_3COOEt/H_2O, 50 °C) in 38% overall yield.

The conceptually trivial synthesis of 2-nitroethanethiol (**9**), which was to furnish the remaining fragment required to complete the skeletal framework of key intermediate dinitro ester **4,** proved unexpectedly difficult. The best reported procedure for the synthesis of **9** proceeds in <10% overall yield from 2-nitroethanol.[6] We were thus stimulated to develop a new synthesis of nitroethanethiol involving reaction of the excellent sulfur nucleophile trisodium phosphorothioate[12] with 2-nitroethyl acetate (H_2O, 20 °C, 16 h) followed by in situ acid hydrolysis (1 N HCl, 40 °C 1 h) of the intermediate phosphorothioic ester[13] to furnish **9,** bp 37–39 °C (0.3 mm), in 30% overall yield. Conjugate addition of **9** to nitro olefin **8** then proceeded smoothly (MeOH, 20 °C, 2 h, 80%) to give the bis(nitroethyl) sulfide ester **4.**[8] When ester **4** (0.01 mol) in 200 ml of dry $CHCl_3$ was added (20 °C) during 18 h to a solution of $POCl_3$ (0.08 mol) and TEA (0.2 mol, freshly distilled from $LiAlH_4$) in 400 mL of the same solvent there was obtained, in markedly favorable contrast to the model reaction, an 81% yield of furoxan **10** (mixture of isomers by ^{13}C NMR) after silica gel chromatography (2:1 Et_2O–hexane): oil;[8] UV (MeOH) 234, 265 nm (ϵ 1750, 5130); IR 1735, 1645 (C=N), 1455 (O—N(=)→O), 980 cm^{-1}; mass spectrum (70 eV) *m/e* 242 ($M^+ - O$), 227 ($M^+ - OCH_3$). On treatment with Zn/Ag couple[14] (dimethoxyethane–$(CF_3CO)_2O$, 5 °C, 1.5 h, 40%) **10** underwent an unusual reduction[15] to afford the acylated enediamine **11**—mp 84–85 °C;[8] IR 3250, 1735, 1710, 1170,



880 cm^{-1}; NMR ($CDCl_3$) δ 3.83, 4.10 (m (ABX), J_{AB} = 15 Hz, J_{AX} = 2 Hz, 2 H), 4.3–4.6 (m, 1 H); mass spectrum *m/e* 422 (M^+)—along with a smaller amount of the corresponding thiophene **12.** Catalytic hydrogenation of **10** followed by acylation led, unexpectedly,[15] to the same spectrum of products but with a higher proportion of the undesired **12.** Dihydrothiophene **11** proved remarkably refractory toward further reduction.[16] However, hydrogenation over a 20% Pd-$(OH)_2$/charcoal catalyst[18] (MeOH, 60 psi H_2, 20 °C, 24 h) furnished tetrahydrothiophene ester **13,** GLC examination of which disclosed the presence of some low molecular weight (presumably desulfurized) impurities but not of any other stereoisomers.

The stereochemistry of **13,** which tended to decompose in the course of purification efforts, was established by subjecting the crude material first to simultaneous ester hydrolysis–deacylation ($K_2CO_3/MeOH/H_2O$, room temperature) followed by in situ treatment of the resulting acid **14** with $COCl_2$ (benzene, 0 °C–room temperature) to furnish in 77% overall yield from **11** after silica gel chromatography (5% HOAc/EtOAc), crystalline (±)-biotin: mp 224 °C; mp 228–230 °C after recrystallization (reported mp 232,[4a] 226–228 °C[4d]); NMR (^1H and ^{13}C) and mass spectra identical with those of authentic (+)-biotin. A sample resolved via the L-(+)-arginine salt[19] gave (+)-biotin, mp 228–229 °C, undepressed on admixture with an authentic sample, and displaying the full activity of (+)-biotin in microbiological assays.

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References and Notes

(1) Contribution No. 498 from the Institute of Organic Chemistry.
(2) S. P. Mistry and K. Dakshinamurti, *Vitam. Horm. (N.Y.),* **22,** 1 (1964), and references therein.
(3) M. W. Goldberg and L. H. Sternbach, U.S. Patents 2 489 232, 289 235, and 2 489 238 (1949).
(4) For other biotin syntheses, see (a) S. A. Harris et al., *J. Am. Chem. Soc.,* **66,** 1756 (1944); (b) S. A. Harris et al., *ibid.,* **87,** 2096 (1945); (c) A. Grussner, J. P. Bourquin, and O. Schnider, *Helv. Chim. Acta,* **28,** 517 (1945); (d) B. R. Baker et al., *J. Org. Chem.,* **12,** 186 (1946); (e) S. Bory, M. J. Luche, B. Moreau, S. Lavielle, and A. Marquet, *Tetrahedron Lett.,* 827 (1975); (f)

S. I. Zav'yalov et al., *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1643 (1975); (g) P. N. Confalone, G. Pizzolato, and M. R. Uskokovic, *Helv. Chim. Acta*, **59**, 1005 (1976). Since the completion of the work described herein, two noteworthy syntheses of optically active biotin have been disclosed; H. Ohrui and S. Emoto, *Tetrahedron Lett.*, 2765 (1975); P. N. Confalone, G. Pizzolato, E. G. Baggiolini, D. Lollar, and M. R. Uskokovic, *J. Am. Chem. Soc.*, **97**, 5938 (1975).
(5) T. Mukaiyama and T. Hoshino, *J. Am. Chem. Soc.*, **82**, 5339 (1960).
(6) R. L. Heath and A. Lambert, *J. Chem. Soc.*, 1477 (1947). We found that bis(2-nitroethyl) sulfide could be prepared simply and in essentially quantitative yield by treatment of 2-nitroethyl acetate with methanolic potassium sulfide.
(7) G. B. Bachman and L. E. Strom, *J. Org. Chem.*, **28**, 1150 (1963); R. V. Stevens, C. G. Christensen, W. L. Edmonson, M. Kaplan, E. B. Reid, and M. P. Wentland, *J. Am. Chem. Soc.*, **93**, 6629 (1971).
(8) Satisfactory combustion analysis was obtained on this compound. All isolated intermediates gave infrared, NMR, and mass spectral data in accord with their assigned structures.
(9) K. Alder and H. von Brachel, *Justus Liebigs Ann. Chem.*, **651**, 141 (1962).
(10) C. A. Grob and H. von Sprecher, *Helv. Chim. Acta*, **35**, 885 (1952).
(11) The dehydration procedure is based on that of E. J. Corey, N. H. Andersen, R. M. Carlson, J. Paust, E. Vedejs, I. Vlattas, and R. K. Winter, *J. Am. Chem. Soc.*, **90**, 3245 (1968).
(12) J. R. Piper and T. P. Johnston, *J. Org. Chem.*, **32**, 1261 (1969).
(13) In all likelihood the reaction proceeds by conjugate addition to in situ generated nitroethylene. We expect to report further in due course on this new and potentially useful reaction mode for the phosphorothioate ion.
(14) M. Denis, C. Girard, and J. M. Conia, *Synthesis*, 549 (1972). The use of conventionally activated Zn results in inferior yields, as does replacement of $(CF_3CO)_2O$ by $(CH_3CO)_2O$ to give the di-*N*-acetyl derivative corresponding to **11**.
(15) Unusual in that the normal reduction products of furoxans, either with Zn/AcOH or by catalytic hydrogenation, are the corresponding glyoximes; cf., inter alia, A. R. Katritzky and J. M. Lagowski, "Chemistry of the Heterocyclic N-Oxides", Academic Press, New York, N.Y., 1971.
(16) In a model reaction sequence, the acylated enediamine obtained from reduction of unsubstituted thienofuroxan **2** was cleanly hydrogenated at moderate H_2 pressures employing Pd/C catalyst and converted to the imidazolone **3** (previously described).[17]
(17) B. R. Baker et al., *J. Org. Chem.*, **12**, 174 (1946).
(18) M. Pearlman, *Tetrahedron Lett.*, 1663 (1967). Use of this catalyst, which was brought to our attention by Dr. J. M. Muchowski of this institute, proved crucial to the successful synthesis of biotin. Conventional Pd catalysts failed to effect reduction of **11** at moderate H_2 pressures, while hydrogenation at 1500 psi led in high yield to a single tetrahydrothiophene stereoisomeric with **13**, which was converted by means of the reaction sequence described for **13** to (±)-epibiotin.
(19) D. E. Wolf, R. Mozingo, S. A. Harris, R. C. Anderson, and K. Folkers, *J. Am. Chem. Soc.*, **67**, 2100 (1945).
(20) Syntex Postdoctoral Fellow: (a) 1974–1975; (b) 1971–1972; (c) 1973–1974; (d) 1972–1973.

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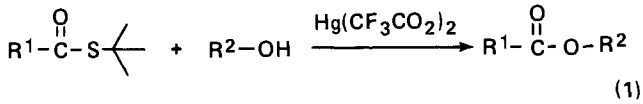
Activation of Thiol Esters. Partial Synthesis of Cytochalasins A and B

Sir:

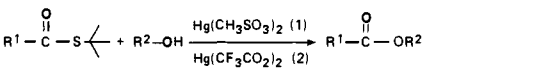
Activation of a 2-methylpropane-2-thiol ester with $Hg^{II}(CF_3CO_2)_2$ in the presence of an alcohol leads to the efficient formation of the corresponding ester or lactone (S → O ester conversion) (reaction 1),[1] and has recently been utilized

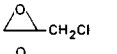
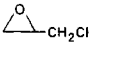


(1)

in the synthesis of methymycin.[2] Although this reaction in this original form is widely applicable (vide infra), the structures of R^1 and R^2 in some cases demand modification of the four variables (represented by S,[3] *tert*-butyl, Hg(II), and CF_3CO_2) in this reaction system in order to meet the restriction arising in each individual case.[4] The modification invariably requires that the reactivities of the above variables be properly "matched" [5] to bring about the efficient S → O conversion. We have examined numerous combinations to this end and have significantly widened the scope of this type of reaction. For instance, a modification (use of benzenethiol and $Ag-CF_3CO_2$) has led to the successful cyclization of the seco acid derived from cytochalasin B (1),[6] a task that has never been achieved by any other known methods.[7] This communication summarizes these developments.

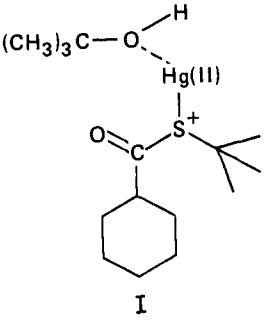
Table I. Selected Examples of Reaction 1



Entry	R^1	R^2	Reagent	Buffer	Yield (%)
1			1 or 2	Na_2HPO_4 (or none)	100[a]
2			1		90
3			1 or 2		85
4			1	Na_2HPO_4	90
5			1	Na_2HPO_4	100 (No deuterium loss)

[a] Taken from ref 1.

General Features of the S → O Ester Conversion. With Hg(II) (as well as other soft metal cations) the reaction has now been found to be more versatile than previously reported.[1] As summarized in Table I, bulky substituents or double bonds located near the reaction centers, both the hydroxy and acyl groups, did not impede the reaction even at room temperature. Thus, *tert*-butyl pivalate and *tert*-butyl crotonate were prepared in excellent yields (entries 2 and 3). In the absence of alcohols, *S-tert*-butyl cyclohexanemethanethioate reacted with $Hg(CF_3CO_2)_2$ to form cyclohexanecarboxylic trifluoroacetic anhydride.[1] However, the reaction of this mixed anhydride with *tert*-butyl alcohol to give *tert*-butyl cyclohexanecarboxylate proceeded ~10 times more slowly than the above, direct S → O conversion. Thus this anhydride is not involved in the major course of the latter reaction. The full retention of the deuterium content shown in entry 5 as well as the formation of *tert*-butyl pivalate eliminates the possibility that the corresponding ketene is an intermediate. These new pieces of evidence are in full accord with the involvement of intermediate I proposed earlier,[1] and ensure the retention of stereochemistry at the carbon α to the carboxy group.



I

Use of Thiophilic Metal Cations Other Than Hg(II). The above procedure can be applied successfully in most cases since Hg(II) reacts with sulfur significantly more rapidly than with ordinary or electron-deficient (C=C–C=O) double bonds (e.g., those in most "polyoxo" macrolides[8]). However, the nondiscriminating reactivity of Hg(II) toward electron-rich centers occasionally presents serious problems. Indeed, cytochalasins are such a case and have been found not to survive Hg(II) treatment. Other thiophilic (soft) cations include