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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Rudolf Sandmeier,[20c] Stephen Clark[20d]
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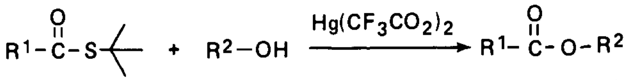
Received January 29, 1976

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

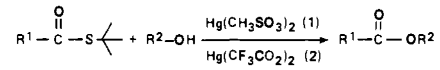
Sir:

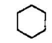
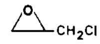
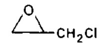
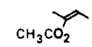
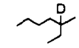
Activation of a 2-methylpropane-2-thiol ester with $Hg^{II}(CF_3CO_2)_2$ in the presence of an alcohol leads to the efficient formation of the corresponding ester or lactone (S → O ester conversion) (reaction 1),[1] and has recently been utilized in the synthesis of methymycin.[2] Although this reaction 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 $AgCF_3CO_2$) 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.



(1)

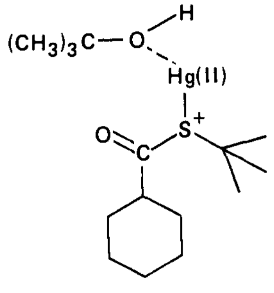
Table I. Selected Examples of Reaction 1



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.

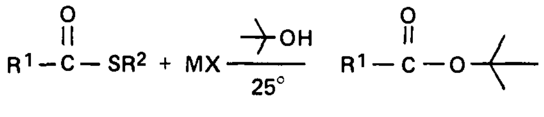
General Features of the S → O Ester Conversion. With Hg(II) (as well as other soft metal cations) the reaction has now been found to be more versatile than previously reported.[1] As summarized in Table I, bulky substituents or double bonds located near the reaction centers, both the hydroxy and acyl 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.

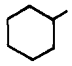
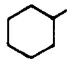
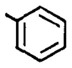
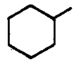
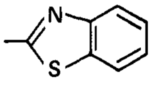
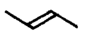
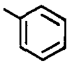
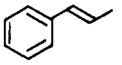
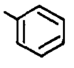
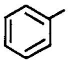
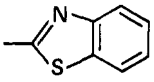
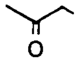
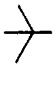
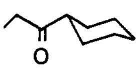
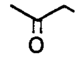
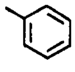


I

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

Table II. Reactions of Ag(I), Cu(I), and Cu(II) with Thiol Esters



Entry	R^1	R^2	MX	Solvent	Time	Yield (%)
1			$AgCF_3CO_2$ $AgCF_3SO_3$	THF THF	18 hr 18 hr	0 0
2			$CuCF_3SO_3$	C_6H_6/THF	10 min	95
3			$AgCF_3CO_2$	C_6H_6	10 min	100
4			$CuCF_3SO_3$	C_6H_6/THF	5 hr	80
5			$Cu(CF_3SO_3)_2$ $AgCF_3CO_2$ $AgBF_4$ $AgCF_3SO_3$	CH_3CN $C_6H_6(\Delta)$ $C_6H_6(\Delta)$ $C_6H_6(\Delta)$	1.5 hr 1.5 hr 1 hr 1 hr	24 100 <5 <5
6			$AgCF_3CO_2$ $CuCF_3SO_3$ $Cu(CF_3SO_3)_2$	$C_6H_6(\Delta)$ C_6H_6/THF CH_3CN	1.5 hr 5 hr 0.5 hr	100 90 100
7[a]			$Hg(CF_3CO_2)_2$ $AgCF_3CO_2$ $CuCF_3SO_3$	CH_3CN THF C_6H_6	0.5 hr 18 hr 2 hr	0 recovered 100
8[a]			$CuCF_3CO_2$	CH_2Cl_2	2 hr	100
9[a]			$Hg(CF_3CO_2)_2$ $AgCF_3CO_2$	CH_3CN THF	0.5 hr 2 hr	0 95

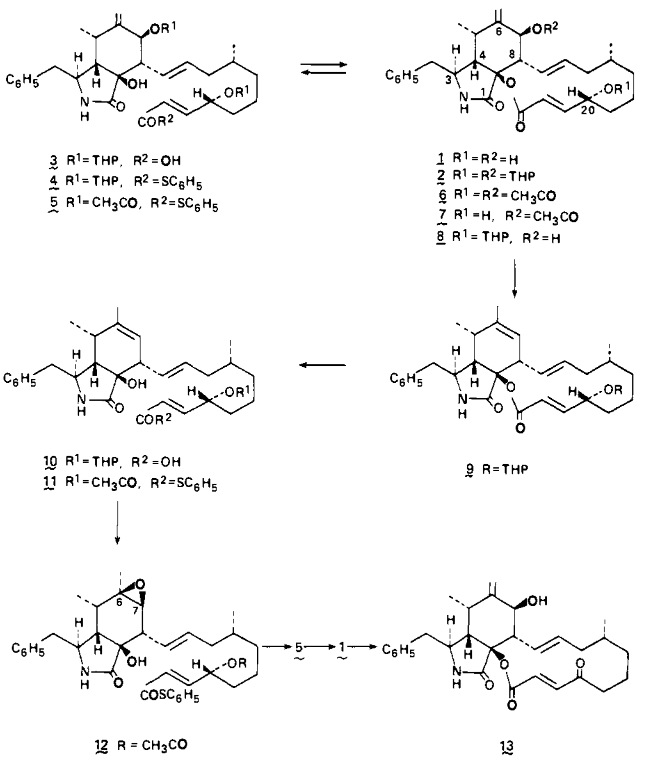
[a] Cyclohexanol was used in place of *tert*-butyl alcohol.

Ag(I), Cu(I), and Cu(II), and their reactions with a variety of R^1COSR^2 compounds in the presence of *tert*-butyl alcohol have been examined and are summarized in Table II. Some trends are evident. The more acidic the reacting thiol is, the less thiophilic metal cation is suitable for effecting the reaction (cf. entries 1 and 3). In many cases Cu(I), Cu(II), and Ag(I) are even superior to Hg(II) and a remarkable difference in reactivity between $Ag^{I}CF_3CO_2$ and $Ag^{I}BF_4$ is noted (entry 5). Gerlach's earlier report[7b] that $Ag^{I}ClO_4$ or $Ag^{I}BF_4$ activates 2-pyridinethiol esters appears to comply with all these observations. Entries 7 to 9 constitute model studies for the cyclization of the seco-acid derivatives corresponding to pikromycin (a 14-membered β-ketolactone).

Partial Synthesis of Cytochalasins A and B. If one succeeds in lactonizing the seco acid derivatives related to cytochalasin, the problem associated with the total synthesis of the latter compound will be greatly simplified. The scope of the S → O ester conversion has now been significantly broadened and can be performed without Hg(II). Thus the important transformation of cytochalasin B (**1**) has been achieved as outlined in Scheme I.[9]

Alkaline hydrolysis (1 N ethanolic NaOH, 60 °C, 1 h) of an isomeric mixture of cytochalasin B *cis*-tetrahydropyranyl ethers (**2**) provided the corresponding seco acid (**3**) which was converted into the benzenethiol ester (**4**) with diethyl phosphorochloridate and then thallium benzenethiolate.[10] Acid

Scheme I



treatment (aqueous CH_3CO_2H) of **4** and then acetylation afforded the diacetate-thiol ester (**5**). A stirred mixture of 16 mg of **5** and 27 mg of Na_2HPO_4 and 22 mg of $AgCF_3CO_2$[11] in 8 mL of benzene was heated at reflux for 2 h under an argon atmosphere. Upon the usual workup there was isolated 4.8 mg (36%) of the cyclized product (**6**), which afforded **1** upon mild alkaline hydrolysis. Identification of these products obtained by cyclization was established in the standard fashion.

Partial hydrolysis of **6** proceeded efficiently to afford monoacetate **7** (in >70%), which after the protection (THP) of the liberated hydroxy group was converted into the hydroxy compound (**8**). Treatment of **8** with methanesulfonyl chloride followed by sodium cyanoborohydride effected reductive migration of the double bond, and the resulting Δ^6 compound (**9**) upon alkaline hydrolysis was converted into the corresponding seco acid (**10**). The preparation of the benzenethiol ester of **10** and then conversion of the 20-*O*-THP into the 20-*O*-acetate (**11**) proceeded well in a manner analogous to that described for **5** (vide supra). Treatment of **11** with *tert*-butyl hydroperoxide and vanadyl acetylacetonate (Sharpless' procedure)[12] provided the 6,7-epoxide (**12**) (in 50 ~ 60% based on consumed **11**), which was subsequently transformed into **5** upon acid treatment[13] (2 N HCl in 50% aqueous acetone for 18 h), followed by acetylation. The Ag(I)-assisted lactonization of **5** in the manner described above completes a conversion of **10** into **1**. The latter compound has already been reported to provide cytochalasin A (**13**) upon oxidation with MnO_2.[14,15]

Utility of **10** as a relay compound in the synthesis of **1** and **13** is evident. The stereochemistry of the tetrahydroisoindole moiety of **10** is such that a Diels-Alder reaction of two appropriately functionalized components would directly lead to the construction of the system. In fact, Auerbach and Weinreb have recently demonstrated that the reaction indeed proceeds in this predictable manner.[16] Thus dissection of **10** into three synthetic units now constitutes a rational synthetic scheme.

Acknowledgment. The authors are grateful to Drs. D. C. Aldridge and W. B. Turner for a generous gift of cytochalasin B and their unpublished data, and to the National Research Council of Canada for financial support.

Supplementary Material Available: A listing of spectral data for the cytochalasin derivatives (3 pages). Ordering information is given on any current masthead page.

References and Notes

(1) S. Masamune, S. Kamata, and W. Schilling, *J. Am. Chem. Soc.*, **97**, 3515 (1975).

(2) (a) S. Masamune, C. U. Kim, K. E. Wilson, G. O. Spessard, P. E. Georghiou, and G. S. Bates, *J. Am. Chem. Soc.*, **97**, 3512 (1975); (b) S. Masamune, H. Yamamoto, S. Kamata, and A. Fukuzawa, *ibid.*, **97**, 3513 (1975).

(3) Selenol esters appeared to be a likely choice for a more reactive species than the thiol ester owing to the comparatively weak bonding between carbon and selenium. Accordingly, several alkane- and areneselenol esters of cyclohexanecarboxylic acid, prepared in excellent yields by several methods,[17] were tested. However, *O*-ester formation utilizing metal cations which are inert to the C=C bond (e.g., Ag(I), Cu(I)), were rather discouraging, and we have concluded at this time that selenol esters do not offer any advantages for this purpose over thiol esters, although ample room is still left for further investigation.

(4) For instance, Hg(II) reacts with electron-rich, activated double bonds (oxymercuration) more readily than with a thiol ester, and, if this is the case, another thiophilic metal cation must be used.

(5) The Saville rules (*Angew. Chem., Int. Ed. Engl.*, **6**, 928 (1967)) derived from Pearson's hard-soft acids and bases (HSAB) principle (R. G. Pearson and J. Songstad, *J. Am. Chem. Soc.*, **89**, 1827 (1967)) have been used as a guide in selecting appropriate pairs of reactive species, although the words "hard" and "soft" are interpreted in a sense broader than and modified from that originally defined. Note that intermediate I involves a hard-hard pair (RCO^+ and OH) and a soft-soft pair (SR and Hg(II)). For a review, see T.-L. Ho, *Chem. Rev.*, **75**, 1 (1975). Cf. R. Gompper and H.-U. Wagner, *Angew. Chem., Int. Ed. Engl.*, **15**, 321 (1976).

(6) For a recent review, see M. Binder and Ch. Tamm, *Angew. Chem., Int. Ed. Engl.*, **12**, 370 (1973).

(7) Compound **1** with or without the protection of the hydroxy groups reacts instantaneously with mercury(II) salts. The other lactonization methods tested in our hands without success follow. (a) The "double activation" method: E. J. Corey and K. C. Nicolaou, *J. Am. Chem. Soc.*, **96**, 5614 (1974). (b) A modification of the method in 7a: H. Gerlach and A. Thalmann, *Helv. Chim. Acta*, **57**, 2661 (1974). For the application of Gerlach's method to cytochalasin B, see D. Scherling, I. Csendes, and Ch. Tamm, *ibid.*, **59**, 914 (1976).

(8) Designated as "authentic" macrolides in ref 2a and include the compounds originally defined as macrolides (R. B. Woodward, *Angew. Chem.*, **69**, 50 (1957)). For a classification of this entire family, see S. Masamune, G. S. Bates, and J. W. Corcoran, *Angew. Chem., Int. Ed. Engl.*, in press.

(9) The yield of each step is higher than 90%, unless otherwise specified in the text.

(10) S. Masamune, S. Kamata, J. Daikur, Y. Sugihara, and G. S. Bates, *Can. J. Chem.*, **53**, 3693 (1975). Also see G. S. Bates, J. Diakur, and S. Masamune, *Tetrahedron Lett.*, 4423 (1976).

(11) Neither $AgBF_4$ nor $AgCF_3SO_3$ effected the lactonization.

(12) K. B. Sharpless and R. C. Michaelson, *J. Am. Chem. Soc.*, **95**, 6136 (1973).

(13) D. C. Aldridge, B. F. Burrows, and W. B. Turner, *J. Chem. Soc., Chem. Commun.*, 148 (1972); D. C. Aldridge, D. Greatbanks, and W. B. Turner, *ibid.*, 551 (1973); G. Büchi, Y. Kitaura, S.-S. Yuan, H. E. Wright, J. Clardy, A. L. Demain, T. Glinsukon, N. Hunt, and G. N. Wogan, *J. Am. Chem. Soc.*, **95**, 5423 (1973).

(14) D. C. Aldridge, J. J. Armstrong, R. N. Speake, and W. B. Turner, *J. Chem. Soc. C*, 1667 (1967).

(15) Spectral data of all the compounds described in this note appear in the microfilm edition of the journal and experimental details will be available on request.

(16) J. Auerbach and S. M. Weinreb, *J. Org. Chem.*, **40**, 3311 (1975).

(17) Preparation of alkane- and areneselenol esters: (1) reaction of cyclohexanecarboxylic acid with either benzeneselenenyl chloride or diphenyl diselenide in the presence of tri-*n*-octylphosphine, (2) reaction of cyclohexanecarboxylic acid chloride or imidazolide with the Tl(I) salt of benzeneselenoxide or butaneselenoxide, and (3) reaction of cyclohexanecarboxylic acid diethylphosphoric acid anhydride with the above salt.

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Received May 10, 1977

Bent Bonds in the Bridgehead Triptycyl Radical

Sir:

Magnetic resonance experiments have provided most of the present information of the geometry of reactive free radicals and carbenes.[1] A particularly powerful technique involves determining the hyperfine splitting of the atom with an unshared valence. The isotropic and anisotropic components of