Acknowledgment. The authors are deeply grateful to Mr. R. W. Rickards of the Australian National University, Dr. F. L. Weisenborn of the Squibb Institute for Medical Research, and Dr. M. Suzuki of the Tanabe Seiyaku Co., Japan, for their generous donations of methymycin. This work has been supported by the National Research Council of Canada and Hoffman-La Roche, Inc.

Supplementary Material Available. A listing of NMR and ir spectra will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D.C. 20036. Remit check or money order for $4.00 for photocopy or $2.50 for microfiche, referring to code number JACS-75-3513.

References and Notes

(1) A major portion of this work has already been presented publicly. See ref 1 of the preceding communication.
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(6) Treatment of **4** with phenacyl bromide, under the usual conditions, reverts it into the thioate of **2**.
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(10) Addition of 3 equiv of 3-chloroperbenzoic acid to a 1:3 mixture of **10** and an alcohol (concn 0.1 *M*) in CH_2Cl_2 at −70° and subsequent warming to room temperature over a 2-hr period provided the corresponding ester in excellent yield (75–95%). Alcohols used are cyclohexylmethanol, cyclohexanol, 2,4-dimethylpentan-5-ol, and 4-methyloct-5-ene-2-one-3,4-diol (see ref 2). For hydrolysis, THF was used as a solvent. It appears that the formation of α-carbonyl sulfone proceeds even at −30°, and the direct attack of the hydroxy group, as well as 3-chlorobenzoic acid, at the carbonyl function is possible. It is, however, very likely that the α-carbonyl sulfone rearranges to the carboxylic 2-methylpropane-2-sulfinic anhydride at higher temperatures that undergoes a complicated series of reactions. See J. S. Showell, J. R. Russell, and D. Swern, *J. Org. Chem.*, **27**, 2853 (1962); M. Kobayashi and A. Yamamoto, *Bull. Chem. Soc. Jpn.*, **39**, 961 (1966); M. Kobayashi, *ibid.*, **39**, 967 and 1296 (1966); M. Kobayashi and R. Kiritani, *ibid.*, **39**, 1782 (1966).
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(17) For review on glycosylation, see G. Wulff and G. Röhle, *Angew. Chem., Int. Ed. Engl.*, **13**, 157 (1974). Retaining 1 mol of hydrobromide as the salt of the dimethylamino group during the reaction is essential for the success of the glycoside formation. Desosamine has been attached in this way to cholesterol (72%) and 2,4-dimethylpentan-3-ol (67%). Use of Ag and Hg salts and bases stronger than lutidine led to the complete destruction of the sugar moiety.
(18) All the intermediates reported herein are chromatographically (TLC) pure, and their spectral data are summarized in a table which will accompany the microfilm edition of this volume of the journal.
(19) NOTE ADDED IN PROOF. Drs. D. W. Westlake and L. Bryan have kindly determined the antimicrobial activity of the synthetic methymycin and its anomer (α-glycoside) against streptococcus pyogenes group A, type 5. These compounds exhibited 100% and ca. 20% activity, as compared with the antibiotic obtained from the natural source.

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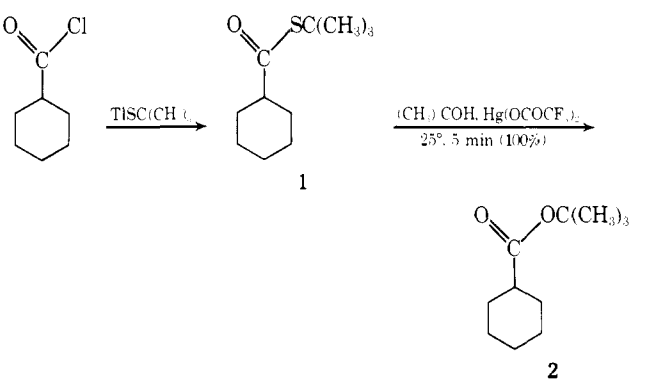
Syntheses of Macrolide Antibiotics. III. Direct Ester and Lactone Synthesis from *S-tert*-Butyl Thioate (Thiol Ester)

Sir:

The electrophilicity of Hg(II),[1] in particular toward bivalent sulfur[2] as exemplified by the oxidative cleavage of thioketals, is well documented.[2b] It is rather surprising, therefore, that reactions of Hg(II) and the isoelectronic Tl(III)[3] with thioates have received virtually no attention in the past except for presumably only two reports which appeared in the 1920's. Sachs describes that Hg(II) cleaves *S*-ethyl ethanethioate, with extreme ease, to form S-containing mercuric salts.[4] Problems associated with the synthesis of methymycin[5] necessitated us to explore this aspect of sulfur chemistry, and we describe in this communication the superb properties of the *tert*-butyl thioate group for the protection of carboxylic acids and subsequent direct ester (and lactone) formation.

Preparation of *S-tert*-Butyl Thioates. Although conventional ways to prepare thioates proceed in only fair to good yields with 2-methylpropane-2-thiol, thallous 2-methylpropane-2-thiolate,[6-8] on the other hand, has been found to react with acid chlorides readily and quantitatively. This method is used for all the thioates described in this note.[9]

Preparation of Esters. Using *S-tert*-butyl cyclohexylmethanethioate (**1**), we have examined ester formation with respect to reagent, solvent, and the kind of alcohols to be condensed. The results are summarized in Table I. For secondary, tertiary, and hindered primary alcohols, the reaction proceeds very efficiently at room temperature by the use of mercuric trifluoroacetate (I) (entries 1–7); for methyl and ethyl esters, the combination of mercuric chloride and cadmium carbonate is the preferred choice (entries 8–11). Mercuric acetate and thallic trifluoroacetate were found to be inefficient. The preparation of *tert*-butyl cyclohexanecarboxylate (**2**) is representative, and was carried



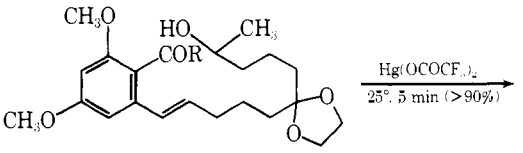
out in the following manner. To a solution of 1.00 g (5 mmol) of **1** and 0.74 g (10 mmol) of *tert*-butyl alcohol in 50 ml of acetonitrile was added 4.27 g (10 mmol) of I at room temperature, and the reaction mixture was stirred for 30 min. The reaction was complete within 5 min to yield **2** quantitatively (GLPC). After processing the mixture in the usual manner, **2** was isolated in 90% yield by distillation.[10]

Preparation of Lactones. Aside from several compounds modeled after natural compounds, the cyclization of (+)-dimethylzearalenone seco-acid ketal (**3**)[11] probably best illustrates the present method. Thus, a 0.01 *M* solution of the *S-tert*-butyl thioate (**4**) in acetonitrile at room temperature, underwent immediate cyclization (within 5 min) upon addition of 2 equiv of I to give a quantitative yield of zearalenone dimethyl ether (**5**) (90% of pure material after recrystallization). The efficiency of this technique is evident, even if compared with the recently reported pyridinethiol

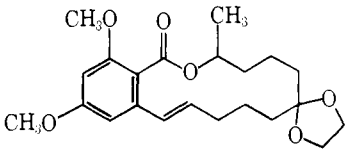
Table I. Reaction of Hg (II) and Tl(III) with *S-tert*-Butyl Cyclohexylmethanethioate (1) and Alcohols

Entry	Alcohol	Reagent	Base	Solvent	Reaction time	Yield (%)
1	$(CH_3)_2CHOH$	$Hg(OCOCF)_2$	----	Acetonitrile	rt, 5 min	75[a]
2	c-$C_6H_{11}CH_2OH$	$Hg(OCOCF_3)_2$	----	Acetonitrile	rt, 5 min	88[a]
3	$[(CH_3)_2CH]_2CHOH$	$Hg(OCOCF_3)_2$	----	Acetonitrile	rt, 5 min	95[a]
4	c-$C_6H_{11}OH$	$Hg(OCOCF_3)_2$	----	Acetonitrile	rt, 5 min	96[a]
5	$(CH_3)_3COH$	$Hg(OCOCF_3)_2$	----	Acetonitrile	rt, 5 min	100[a] 90[b]
6	$(CH_3)_3COH$	$Hg(OCOCF_3)_2$	----	Dichloromethane	rt, 5 hr	82[a]
7	$(CH_3)_3COH$	$Hg(OCOCF_3)_2$	----	Benzene	rt, 3 hr	73[a]
8	CH_3OH	$HgCl_2$	$CdCO_3$	Acetonitrile	Reflux, 3 hr	98[a]
9	C_2H_5OH	$HgCl_2$	$CdCO_3$	Acetonitrile	Reflux, 3 hr	90[a]
10	c-$C_6H_{11}OH$	$HgCl_2$	$CdCO_3$	Acetonitrile	Reflux, 3 hr	97[a]
11	$(CH_3)_3COH$	$HgCl_2$	$CdCO_3$	Acetonitrile	Reflux, 3 hr	76[a]
12	c-$C_6H_{11}OH$	$Hg(OCOCH_3)_2$	$CdCO_3$	Acetonitrile	Reflux, 15 hr	41[a]
13	$(CH_3)_3COH$	$Hg(OCOCH_3)_2$	$CdCO_3$	Acetonitrile	Reflux, 15 hr	22[a]
14	CH_3OH	$Tl(OCOCF_3)_3$	----	Acetonitrile	rt, 5 min	44[a]
15	c-$C_6H_{11}OH$	$Tl(OCOCF_3)_3$	----	Acetonitrile	rt, 5 min	55[a]
16	$(CH_3)_3COH$	$Tl(OCOCF_3)_3$	----	Acetonitrile	rt, 5 min	45[a]

[a] The yield of the product was determined by gas–liquid chromatographic analysis (corrected for the sensitivity relative to a standard). [b] Isolated yield. [c] rt = room temperature.



3, R = OH
4, R = $SC(CH_3)_3$



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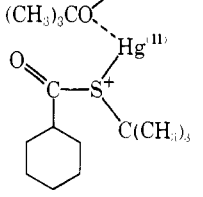
ester method that requires refluxing a benzene (or xylene) solution for a prolonged period of time.[12]

In the absence of alcohols, a mixture of **1** and reagent I forms cyclohexanecarboxylic trifluoroacetic anhydride as confirmed by infrared spectroscopy. However, preliminary control experiments appear to indicate that the efficient ester (and lactone) formation with sterically hindered alcohols such as *tert*-butyl alcohol proceeds, at least partially, through coordination of the alcohol with a possible intermediate as shown in **6**, and then collapses into **2** and mercuric



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salts. To what extent this process competes with the conventional mixed anhydride pathway seems to depend largely on the structures of the alcohols used.

The *S-tert*-butyl thioate group is relatively stable and survives under mild acidic and alkaline conditions as demonstrated in the synthesis of methymycin.[5] Conversion into the carboxylic acid obviously presents no problem by use of wet organic solvents. More importantly, of course, the successful direct lactonization as utilized in the construction of medium ring systems clearly demonstrates that the present method will be widely applicable to numerous natural products broadly classified as macrolides.[13-16] The quantitative formation of *tert*-butyl ester even suggests its possible utilization for the synthesis of the cytochalasans.[17,18]

Acknowledgment. The authors are grateful to Dr. D. Taub for his generous gift of zearalenone and to the National Research Council of Canada and Hoffmann-La Roche, Inc., for financial support.

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(6) This salt was prepared in the following manner. To a stirred solution of 5.00 g (20 mmol) of thallous ethoxide in 20 ml of benzene under nitrogen, was dropwise added 1.98 g (22 mmol) of 2-methylpropane-2-thiol within 3 min. After an additional 15 min stirring, the precipitate was filtered under nitrogen and washed with three portions of dry pentane to give 5.56 g (95%) of thallous 2-methylpropane-2-thiolate as bright yellow crystals, mp 170–175° dec.
(7) See footnote 4 of ref 5b.
(8) For reviews of thallium chemistry, see A. G. Lee, *Q. Rev., Chem. Soc.*, **24**, 310 (1970); E. C. Taylor and A. McKillop, *Acc. Chem. Res.*, **3**, 338 (1970). However, see J. Hooz and J. Smith, *J. Org. Chem.*, **37**, 4200 (1972).
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(10) Small amounts of by-products that appeared to have formed from the solvent and I were noticed and were readily removed from **2** by passing it through a short column of basic alumina.
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(18) NOTE ADDED IN PROOF. "Thioate" may not be the correct group name of "thiol ester," but is used herein for simplicity and clarity.

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