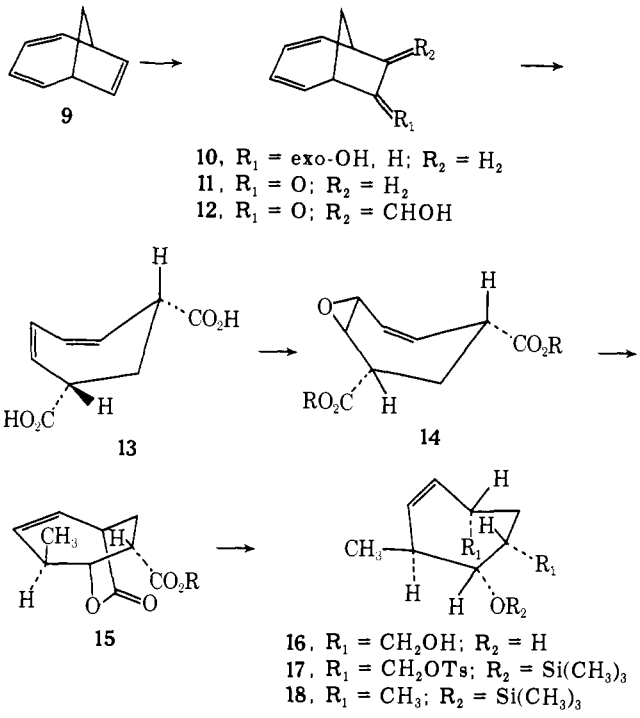
of the homoallylic tosyl group), and the resulting trimethyl(trimethylsilyoxy)cycloheptene (**18**) was subjected to the



Lemieux–Rudloff oxidation ($KMnO_4$–$NaIO_4$)[20] to lead directly to (±)-Prelog–Djerassi lactone **8**, mp 119–120°, as confirmed in the standard manner. The overall yield from **15** to **8** was ca. 70%; This nearly triples the yield obtained through a more conventional route, originally adopted in the investigation.[21,22]

Both segments A and B were thus abundantly available and have successfully been linked together in the proper manner to prepare methynolide and, subsequently, methymycin. This conversion constitutes the subject of the accompanying communication.

Acknowledgment. The authors are extremely grateful to Drs. H. Davis and P. A. Rossy, and Mr. H. Ona for their preparations of several intermediates used in this work and Professors V. Prelog and C. Djerassi for their generous donations of compound **8.** This work has been supported by the National Research Council of Canada and Hoffmann-La Roche, Inc.

References and Notes

(1) This work was presented at the 9th IUPAC Symposium on Chemistry Natural Products, June 24, 1974, Ottawa, Canada (Abstract 1G), and at the Gordon Conference, July 30, 1974, New Hampton, and subsequently at several universities and institutes.
(2) The general names were proposed by R. B. Woodward, *Angew. Chem.*, **69**, 50 (1957).
(3) Representative reviews are: (a) W. Keller-Schierlein, *Fortschr. Chem. Org. Naturst.*, **30**, 313–460 (1973); (b) W. D. Celmer, *Pure Appl. Chem.*, **28**, 413 (1971); (c) M. Berry, *Q. Rev., Chem. Soc.*, , 343 (1963).
(4) See for instance: R. Morin and M. Gorman in "K -Othmer Encyclopedia of Chemical Technology", Vol. 12, 2nd ed, Wiley, New York, N.Y. 1967, p 632.
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(7) As originally defined (ref 2) and distinguished from polyenemacrolides (e.g., amphoterin), pseudomacrolides (e.g., nonactin) and other natural products which do not possess the structural features described in the text.
(8) The gross structure of this antibiotic was elucidated by: C. Djerassi and J. A. Zderic, *J. Am. Chem. Soc.*, **78**, 6390 (1956), and its stereochemical studies were completed by R. W. Rickards and R. M. Smith, *Tetrahedron Lett.*, 1025 (1970); D. G. Manwaring, R. W. Rickards, and R. M. Smith, *ibid.*, 1029 (1970).
(9) For the lactonization of zearalenone seco-acid (14-membered), see S. Masamune, S. Kamata, and W. Schilling, *J. Amer. Chem. Soc.*, **97**, 3515 (1975).
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(12) L. D. Bergel'son, E. V. Dyatlovitskaya, M. Tichy, and V. V. Voronkova, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 1612 (1962).
(13) An examination of the optical purity of this ester, using tris[3-(heptafluoropropylhydroxymethylene)-*d*-camphorato]europium(III), revealed no signals due to the (−)-enantiomer.
(14) R. Anliker, D. Dvornik, K. Gubler, H. Heusser, and V. Prelog, *Helv. Chim. Acta*, **39**, 1785 (1956).
(15) L. G. Cannell, *Tetrahedron Lett.*, 5967 (1966).
(16) H. Kono and J. Hooz, *Org. Synth.*, **53**, 77 (1973); G. Zweifel and H. C. Brown, *Org. React.*, **13**, 1 (1963).
(17) Cyclohepta-1(7),3,5-triene-1,3-dicarboxylic acid (E. Vogel, R. Feldmann, and H. Düwel, *Tetrahedron Lett.*, 1941 (1970); R. Darms, T. Threlfell, M. Pesaro, and A. Eschenmoser, *Helv. Chim. Acta*, **46**, 2893 (1963)) was converted into **13** with sodium amalgam and used in our earlier works.
(18) Reaction of 1,3-cycloheptadiene monoepoxide with this reagent results exclusively in the 1,2-ring opening (unpublished results from this laboratory). Cf. J. Staroscik and B. Rickborn, *J. Am. Chem. Soc.*, **93**, 3046 (1971); D. M. Wieland and C. R. Johnson, *ibid.*, **93**, 3047 (1971).
(19) S. Masamune, P. A. Rossy, and G. S. Bates, *J. Am. Chem. Soc.*, **95**, 6452 (1973); S. Masamune, G. S. Bates, and P. E. Georghiou, *ibid.*, **96**, 3686 (1974); E. C. Ashby, T. F. Korenowski, and R. D. Schwartz, *J. Chem. Soc., Chem. Commun.*, 157 (1974).
(20) R. U. Lemieux and E. von Rudloff, *Can. J. Chem.*, **33**, 1701, 1710 (1955); E. Von Rudloff, *ibid.*, **34**, 1413 (1956).
(21) A reaction sequence consisted of ditosylation of **16**, acetylation, conversion of the tosylate to the diiodide, $NaB(CN)H_3$[22] reduction, $KMnO_4$ + $NaIO_4$, $NaOCH_3$, and finally acidification.
(22) R. O. Hutchins, B. E. Maryanoff, and C. A. Milewski, *Chem. Commun.*, 1097 (1971).

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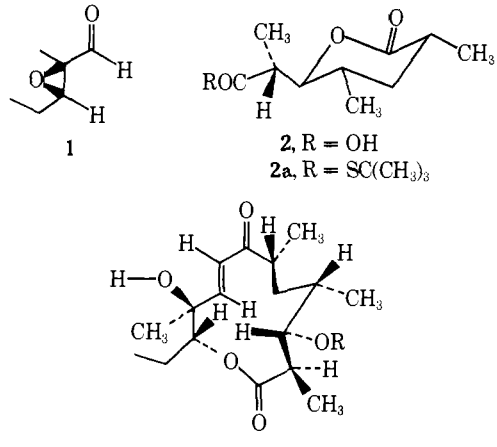
Syntheses of Macrolide Antibiotics. II. Methymycin[1]

Sir:

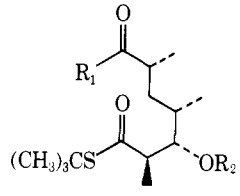
In the preceding note[2] we have outlined the preparations of two segments, **1** and **2,** that constitute the aglycone of the antibiotic, methynolide (**3**). We wish to describe herein that



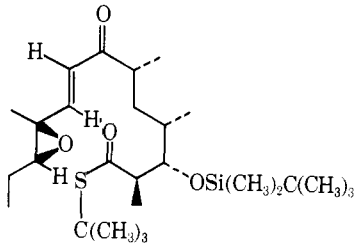
these segments have been combined via a modified Wittig reaction under essentially neutral conditions and that the resulting seco-acid has successfully been lactonized. To effect the latter reaction, the *S-tert*-butyl thioate (thiol ester) group has been chosen, and its utility as a protecting group and subsequent carboxyl activation are delineated in an accompanying paper.[3] The final glycosylation, that involves the delicate selection of reaction media, completes the synthesis of methymycin.

Since (±)-lactonic acid **2** was more readily available and since there was a definite indication that a diastereoisomeric mixture, resulting from the condensation of (+)-**1** and (±)-**2**, would be separable at the lactonization stage, we decided to utilize (+)-**1** as a resolving agent of (±)-acid-**2**.

Treatment of thallous 2-methylpropane-2-thiolate[3] with the acid chloride derived from **2** provided a quantitative yield of the thioate[3,4] which very rapidly consumed 0.95 equiv of potassium hydroxide at 20° to form an amorphous solid (**4**) after removal of all the solvents. Conversion of **4** into its disilyl derivative was effected with 4 equiv of *tert*-butyldimethylsilylimidazole in dimethylformamide[5,6] and subsequent partial hydrolysis (0.95 equiv of potassium hydroxide) led to the formation of silyloxycarboxylic acid (**5**). The overall yield from **2** to **5** is 90%.



4, $R_1 = OK$; $R_2 = H$
5, $R_1 = OH$; $R_2 = Si(CH_3)_2C(CH_3)_3$
6, $R_1 = C_3H_3N_2$;
$R_2 = Si(CH_3)_2C(CH_3)_3$
7, $R_1 = (C_6H_5)_3P{=}CH$;
$R_2 = Si(CH_3)_2C(CH_3)_3$



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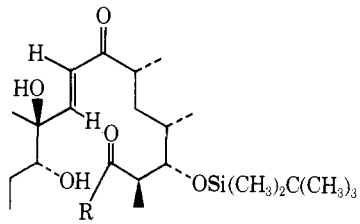
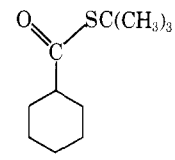


9, $R = SC(CH_3)_3$
11, $R = OH$

Since **5** was relatively sensitive toward acid and base, transformation of **5** to the corresponding acylmethylenephosphorane requires careful selections of reaction conditions. Application of *N,N'*-carbonyldiimidazole to **5** and subsequent treatment of the resulting imidazolide **6**[7] with 1 equiv of salt-free triphenylmethylenephosphorane in benzene[8,9] led to the desired Wittig reagent **7** (95% overall). Use of 2 equiv of the phosphorane as originally recommended[8] should be avoided in this case, because an elimination reaction proceeds readily to form the α,β-unsaturated ester. Refluxing a toluene solution of 2 equiv of (+)-aldehyde **1** and 1 equiv of (±)-Wittig reagent **7** for 2 days brought about the successful condensation to yield a diastereoisomeric (presumably 1:1) mixture of epoxy thioates **8** (60%), which was converted (in 80% yield) to the desired methynolide seco-acid derivative (**9**) on mild acid treatment.

Model studies for the *oxidative* activation of thioates to effect direct conversion of *S-tert*-butyl cyclohexylmethanethioate (**10**) into its esters and acid were encouraging.[10]



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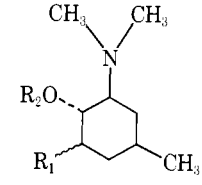
However, because of the van der Waals interactions expected in methynolide,[11] attempts to directly lactonize **9** led extensively to the formation of what appears to be a mixture of the anhydride of **11** and the mixed anhydride of **11** and 3-chlorobenzoic acid. Therefore, the seco-acid (**11**), obtained upon oxidative hydrolysis in wet tetrahydrofuran,[10] was treated with 1.2 equiv of trifluoroacetic acid anhydride (0.02 *M*) in benzene first at 7° for 18 hr, then 25° for 7 hr, and finally at 40° for 10 hr. This operation afforded, after recrystallization from ether–hexane, lactone 3 in up to 25% yield.[12] The identity of the synthetic **3** with methynolide derived from natural methymycin[13] was evident through the usual means of characterization, including circular dichroism (95% optical activity).

Because of the fluctuation in yield and difficulties encountered in optimizing the condition of the above reaction, we have sought for a more reliable and direct lactonization of **9** instead of **11**. Thus, use of 2 equiv of mercuric trifluoroacetate to activate the thio function of **9** (0.01 *M* in acetonitrile) brought about the following remarkable result:[3] within 1 hr at room temperature, the reaction was complete, to furnish the *tert*-butyldimethylsilyl derivative (**12**) of **3** which, without purification, was hydrolyzed with aqueous acid (0.1 *N* CF_3CO_2H in aqueous 10% tetrahydrofuran at 50°) to afford **3** consistently in 20–30% overall yield. An even further improvement is very likely.

The final stage of the synthesis involves glycosylation of **3** with desosamine (**13**). Treatment of 1-β-,2-diacetyldesosamine hydrochloride[14] with a 5:1 mixture of acetic acid and acetic anhydride containing 20–25% hydrogen bromide at room temperature for 1 hr, provided unstable, crystalline 1-α-bromo-2-acetyldesosamine hydrobromide,[15] 3 equiv of which was treated with 1 equiv of **3** in chloroform in the presence of lutidine at 50° for 18 hr.[16,17] The products obtained in 50% yield consisted mainly of the β-glycoside and, after removal of the acetyl group, using methanol containing triethylamine, provided a 5:1 mixture of the β- and α-glycosides. Separation of these products by preparative thin layer chromatography has completed the synthesis of methymycin (β-glycoside).[18,19]



13, $R_1 = \beta\text{-OH}$; $R_2 = H$
14, $R_1 = \beta\text{-OCOCH}_3$; $R_2 = COCH_3$
15, $R_1 = \alpha\text{-Br}$; $R_2 = COCH_3$

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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(3) S. Masamune, S. Kamata, and W. Schilling, *J. Am. Chem. Soc.*, **97**, 3515 (1975).
(4) Heating the lactonic acid chloride of **2** with 2-methylpropane-2-thiol at 40° caused epimerization of **2** presumably at the α-carbon to the carboxyl group. Use of triethylamine for trapping HCl liberated in this reaction resulted in only 40–60% yields of the product. For details, see ref 3.
(5) E. J. Corey and A. Venkateswarlu, *J. Am. Chem. Soc.*, **94**, 6190 (1972).
(6) Treatment of **4** with phenacyl bromide, under the usual conditions, reverts it into the thioate of **2**.
(7) H. A. Staab and H. Bräunling, *Justus Liebigs Ann. Chem.*, **654**, 119 (1962).
(8) H. J. Bestman, N. Sommer, and H. A. Staab, *Angew. Chem., Int. Ed. Engl.*, **1**, 270 (1962).
(9) M. Schlosser and K. F. Christmann, *Justus Liebigs Ann. Chem.*, **708**, 1 (1967).
(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).
(11) Footnote 11 of ref 2.
(12) This yield is based on the amount of the desired diastereoisomer estimated to be 50% rich in **9**. The fate of the other isomer has not been defined but appears to be uncyclized under the conditions employed for the lactonization.
(13) C. Djerassi and J. A. Zderic, *J. Am. Chem. Soc.*, **78**, 6390 (1956).
(14) R. K. Clark, Jr., *Antibiot. Chemother. (Washington, D.C.)*, **3**, 663 (1953); H. Brockmann, H. B. König, and R. Oster, *Chem. Ber.*, **87**, 856 (1954); E. H. Flynn, M. V. Sigal, Jr., P. F. Wiley, and K. Gerzon, *J. Am. Chem. Soc.*, **76**, 3121 (1954).
(15) A. R. Morgan, Ph.D. Thesis, University of Alberta, 1964.
(16) Cf. R. U. Lemieux and A. R. Morgan, *Can. J. Chem.*, **43**, 2199 (1965).
(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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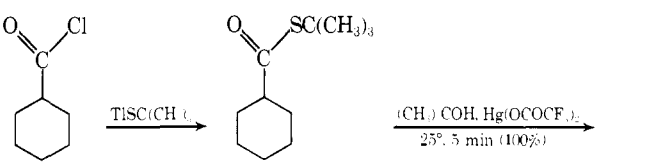
Syntheses of Macrolide Antibiotics. III. Direct Ester and Lactone Synthesis from *S-tert*-Butyl Thioate (Thiol Ester)

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



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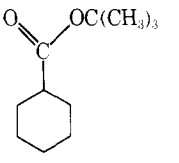

2

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