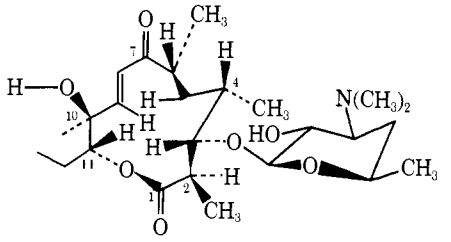
Communications to the Editor

Syntheses of Macrolide Antibiotics. I. Methymycin[1]

Sir:

The macrolide antibiotics[2] are rich in chemistry[3] and striking in biological activities.[4] Structurally characteristic of this group of compounds, now numbering presumably more than a hundred (since Brockmann's first isolation of pikromycin[5]) are: (1) the presence of a 12-, 14-, 16-, or larger-membered lactone ring, (2) an array of substituents uniquely and systematically[3b] attached to the ring system, and (3) the linkage of one or more sugars, very often one of them being nitrogen containing. The fascinating structural features of the antibiotics have, in the past, tempted synthetic organic chemists to explore feasible approaches to syntheses of these compounds. Several model studies are reported.[6] It is with great pleasure that we record herein, the first total synthesis of an authentic[7] macrolide antibiotic, methymycin (**1**).[8] The construction of a 12-membered ring

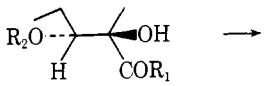


1
1a, aglycone of 1
2, seco-acid of 1

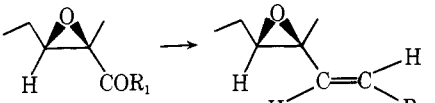
system has created challenging problems, more so than those of the larger (14- and 16-) lactones,[9] and even the successful glycosylation of the amino sugar, desosamine, with a sterically hindered hydroxyl group of a macrolide aglycone by itself, represents an achievement never accomplished previously.

A conformational analysis of **1**, based on its CPK atomic model, and spectral information available from its NMR spectrum, reveals that **1** is a conformationally rigid molecule and further predicts that the corresponding seco-acid (**2**) would retain the rigidity of **1** owing to the uniquely arranged substituents, except for the free rotation along the bond between the C-6 and C-7 carbon atoms. Thus the lactone formation may compete favorably with intermolecular condensations, reactions well-known since Stoll's original work.[10,11] In order to test this encouraging, nonetheless risky prediction, we have designed a synthetic scheme that involves the condensation of segments A (C-9 through C-11) and B (C-1 through C-8) leading to the seco-acid **2**. The preparations of these fragments are described below.

Segment A. After the resolution of (±)-*erythro*-2,3-dihydroxy-2-methylvaleric acid with the aid of L-(+)-*threo*-2-amino-1-(4-nitrophenyl)-1,3-propanediol,[12] the minimum 95% optically pure (+)-acid (**3**), mp 149–151°, $[\alpha]^{25}D$ +13.1° (*c* 3.02%, water), after conversion into its methyl ester, was transformed to the monotosylate (**4**), mp 23°, $[\alpha]^{23}D$ +13.0° (*c* 3.08%, chloroform), and then to the epoxide (**5**), bp 64–64.5° (21 mm), $[\alpha]^{24}D$ −1.3° (*c* 3.13%, chloroform)[13] with triethylamine. Careful reduction of **5** with diisobutylaluminum hydride yielded the corresponding aldehyde (**6**), $[\alpha]^{22}D$ +85° (*c* 2.82%, chloroform), in 75%



3, R_1 = OH; R_2 = H
4, R_1 = OCH_3; R_2 = Ts

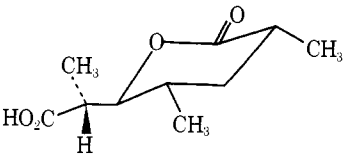


5, R_1 = OCH_3
6, R_1 = H

7, R = CH_3CO

yield. Wittig reaction of **6** with stabilized phosphoranes proceeds unexceptionally; thus with acetylmethylenephosphorane, for example, **6** provides a greater than 80% yield of an (*E*)-α,β-unsaturated ketone (**7**) that undergoes epoxide ring opening under mild acidic conditions to yield the corresponding dihydroxy (*E*)-α,β-unsaturated ketone. This completes, in a straight-forward manner, the synthesis of segment A of **2**.

Segment B. The so-called Prelog–Djerassi lactonic acid (**8**),[8,14] a degradation product of **1**, retains the original



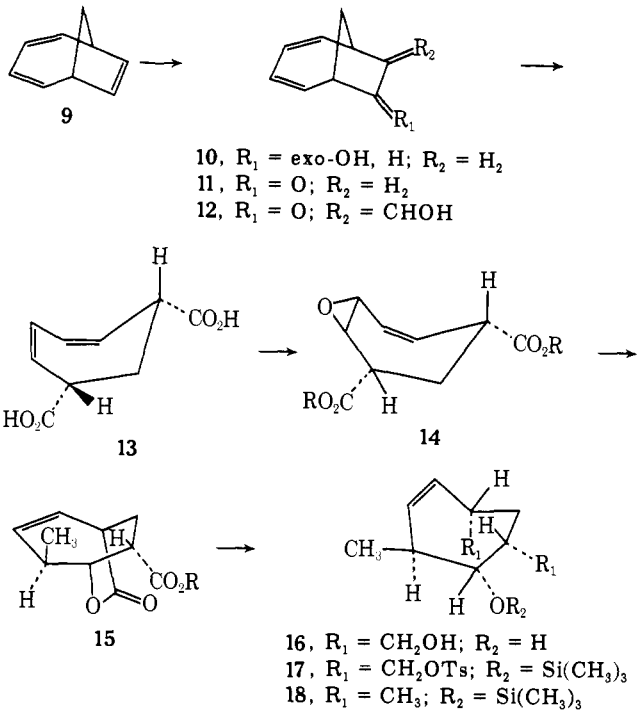
8

stereochemistry of C-1 through C-7 of the aglycone, methynolide (**1a**); thus a synthesis of **8** or its equivalent constitutes the construction of segment B.

Readily available bicyclo[4.2.1.]nona-2,4,7-triene (**9**) obtained by means of pyrolysis of tricyclo[4.2.1.$0^{2,5}$]nona-3,7-diene[15] was hydrated with bis(3-methyl-2-butyl)borane and oxidative work-up[16] to provide in 75–80% yield the exo-hydroxy compound (**10**), bp 78–81° (0.3 mm), which in turn, was converted into the corresponding ketone (**11**), bp 67–68° (0.7 mm), in 75–81% (4-benzoquinone and aluminum tri-*tert*-butoxide) and then formylated to afford compound **12**, mp 112–115°, in 85–90% yield. Treatment of **12** with sodium metaperiodate led to a quantitative formation of *cis*-dicarboxylic acid (**13**),[17] mp 290°. Treatment of **13**, with 3-chloroperbenzoic acid, led to a 7:3 mixture of cis and trans (with respect to the carboxy groups) epoxydicarboxylic acids (**14**) which, without purification, was esterified with diazomethane and then alkylated with lithium dimethylcuprate[18] to give a crystalline lactonic ester (**15**), 65–68°, in 30% overall yield.

Lithium aluminum hydride reduction converted **15** into the corresponding triol (**16**). The two primary hydroxy groups were tosylated, and the secondary one was trimethylsilylated to produce compound **17**. Lithium dihydrocuprate,[19] a reagent recently developed for the present purpose, cleanly removed the tosyl groups (without elimination

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.
(5) H. Brockmann and W. Henkel, *Naturwissenschaften*, **37**, 138 (1950); *Chem. Ber.*, **84**, 284 (1951).
(6) E. J. Corey and H. A. Kirst, *J. Am. Chem. Soc.*, **94**, 667 (1972); I. J. Borowitz, G. J. Williams, L. Gross, H. Beller, D. Kurland, N. Sucui, V. Banducro, and R. D. G. Rigby, *J. Org. Chem.*, **37**, 581 (1972); E. J. Corey and K. C. Nicolaou, *J. Am. Chem. Soc.*, **96**, 5614 (1974), and references cited therein.
(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).
(10) M. Stoll, A. Rouvé, and G. Stoll-Comte, *Helv. Chim. Acta*, **17**, 1289 (1934); M. Stoll and A. Rouvé, *ibid.*, **18**, 1087 (1935); M. Sisido, *Macromolecules*, **4**, 737 (1971).
(11) van der Waal interactions among the three hydrogen atoms attached at C-3, -5, and -9 are not severe, but certainly are not neglible.
(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