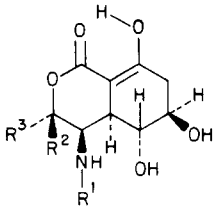
Communications

A Total Synthesis of *N*-Acetylactinobolamine

Summary: Selective osmylation of a 3-azidoglycal in equilibrium with a 1-azidopseudoglycal is used to reach the title system.

Sir: The novel chemical structures and antibiotic properties of bactobolin (**1**)[1a] and actinobolin (**2**)[1b] render them worthy targets for total synthesis.[1c,d] At the outset, our primary focus was on the more complicated structure (**1**). Our subgoal became compound **15** which seemed to have all of the functionality implements and stereochemical relationships necessary to synthesize bactobolin.

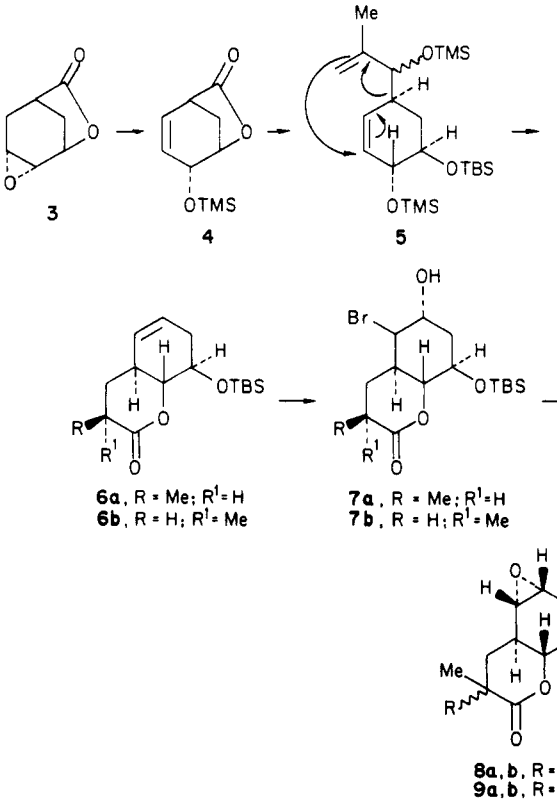
The synthesis of compound **15** was accomplished. The key steps for stereochemical control were siloxy-Cope (**5** → **6**) and allylic azide (**12b** ⇄ **13**) rearrangements. The latter rearrangement was driven by stereospecific osmylation of one of the equilibrium forms (**13** → **14a**). Unfortunately, severe complications have frustrated our efforts to achieve the transformation of compound **15** to bactobolin. However, a route has been devised to convert compound **15** to *N*-acetylactinobolamine (**2a**). The synthesis of compound **15** and its transformation to **2a** is described herein.



1, R^1 = L-alanyl; R^2 = $CHCl_2$, R^3 = Me = bactobolin
2, R^1 = L-alanyl; R^2 = Me; R^3 = H = actinobolin
2a, R^1 = Ac; R^2 = Me; R^3 = H = *N*-acetylactinobolamine

Epoxidation of the readily available[2a] 6-oxabicyclo[3.2.1]oct-3-en-7-one with MCPBA gave a 78% yield of **3**[2b] (mp 111–112 °C). A Noyori-type transformation[3] provided (75%) the siloxy compound **4** (mp 59–61 °C).[2b] This compound was treated successively with: (i) DIBAH/toluene; 78 °C); (ii) isopropenylmagnesium bromide; (iii) *tert*-butyldimethylsilyl triflate/2,6-lutidine; and (iv) trimethylsilyl triflate/2,6-lutidine leading to the differentially protected **5** as a 1:1 mixture of stereoisomers in 59% yield from **4**.

Pyrolysis of this mixture at 310 °C for 1 h accomplished the required siloxy-Cope rearrangement.[4] Selective cleavage of the TMS enol ether and TMS ether functions was accomplished with 0.01 N HCl. The lactol anomers thus produced (45% from **5**) were oxidized (PDC)[5] to afford a 3:1 mixture of lactones **6a** and **6b** in 79% and 84%



6a, R = Me; R^1 = H
6b, R = H; R^1 = Me
7a, R = Me; R^1 = H
7b, R = H; R^1 = Me
8a,b, R = H
9a,b, R = SePh

yields, respectively. These compounds were converted to their respective bromohydrins **7a** (mp 193–194 °C)[2b] and **7b** (mp 164–165 °C)[2b] by stereospecific oxidation with aqueous *N*-bromosuccinimide. Treatment of each bromohydrin with potassium *tert*-butoxide/*tert*-butyl alcohol afforded the epoxide epimers **8** (80% from **6**).

Selenenylation of epimers **8** in the usual way[6] afforded a 93% yield of a 1.4:1 ratio of **9a,b**. The major isomer, mp 135–137 °C,[2b] underwent oxidative elimination (MCPBA) to afford a 92% yield of **10**. Similar treatment of the minor isomer afforded a 1:1.4 mixture of **10**: exocyclic α-methylene lactone isomer. Reduction of **10** (DIBAL; 86%) followed by acetal formation (BF_3–MeOH) afforded an

(1) (a) Kondo, S.; Horiuchi, Y.; Hamada, M.; Takeuchi, T.; Umezawa, H. *J. Antibiot.* **1979**, *32*, 1069. (b) Antosz, F. J.; Nelson, D. B.; Herald, D. L.; Munk, M. E. *J. Am. Chem. Soc.* **1970**, *92*, 4933. For the only synthesis of actinobolin, see: (c) Yoshioka, M.; Nakai, H.; Ohno, M. *J. Am. Chem. Soc.* **1984**, *106*, 1133. For a synthesis of the simpler related natural product ramulosin, see: (d) Cordova, R.; Snider, B. B. *Tetrahedron Lett.* **1984**, 25, 2945.

(2) (a) Kato, M.; Kageyama, M.; Tanaka, R.; Kuwahara, K.; Yoshikoski, A. *J. Org. Chem.* **1975**, *40*, 1932. (b) All compounds were characterized by NMR, IR, MS, and also elemental analysis and/or high resolution mass spectroscopy.

(3) Murata, S.; Suzuki, M.; Noyori, R. *J. Am. Chem. Soc.* **1979**, *101*, 2738.

(4) Thies, R. W.; Wills, M. T.; Chin, A. W.; Schick, L. E.; Walton, E. S. *J. Am. Chem. Soc.* **1973**, *95*, 5281. Attempts to pyrolyze the partially protected diol obtained directly from the propenyllithium addition led to decomposition.

(5) Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, 399.

(6) Reich, H. J.; Renga, J. M.; Reich, I. L. *J. Am. Chem. Soc.* **1975**, *97*, 5434.

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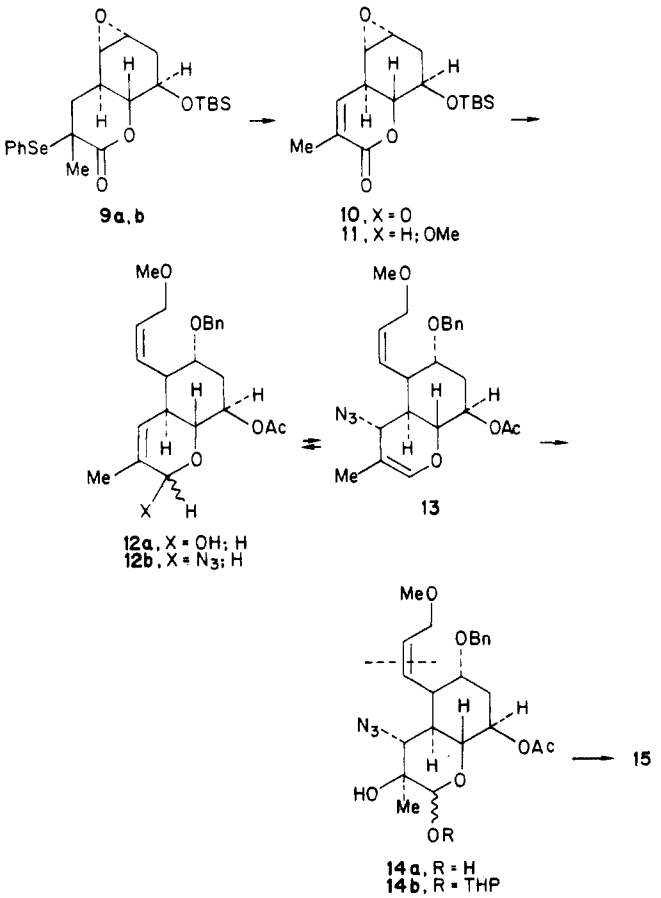
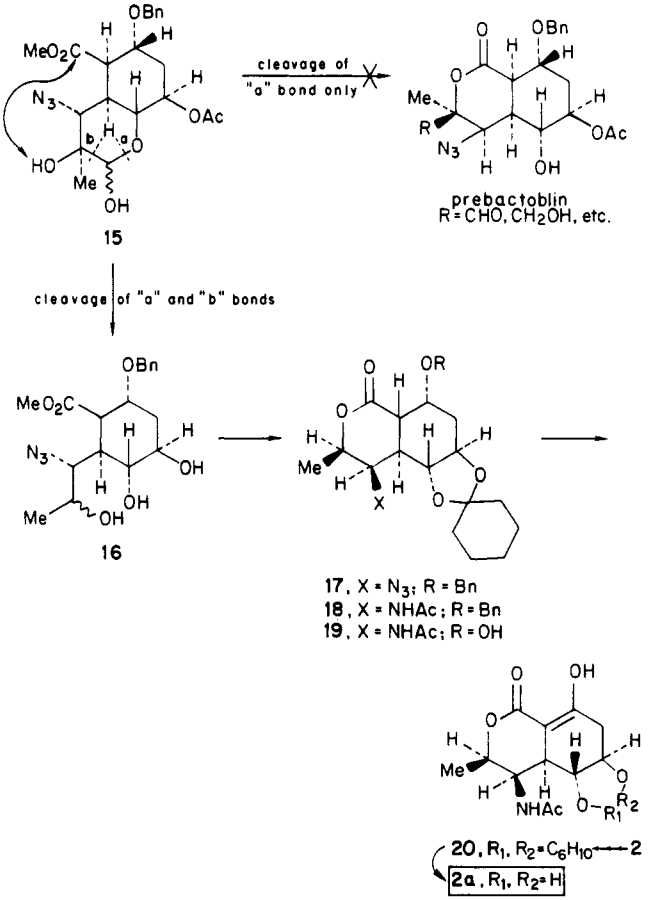
85% yield of **11**. The epoxide was opened (96%) in a Yamaguchi-like reaction, using the lithium acetylide derived from methoxypropyne in the presence of BF_3.[7] Benzylation of the resultant hydroxyl group, followed by Lindlar type reduction of the acetylene,[8] acid-catalyzed cleavage of the methoxy and OTBS groups, acetylation of the hydroxyl groups (Ac_2O–DMAP), and hydrolysis of the anomeric acetate afforded a 74% overall yield of compound **12a**.

Activation of **12a** (MsCl–Et_3N–DMAP–methylene chloride, −40 °C)[9] was followed by reaction with tetra-*n*-butylammonium azide at −40 °C in the same solvent. TLC and spectral examination at this stage indicated the material to consist of an equilibrating mixture of azides **12b** and **13**.[10] *The greater nucleophilicity of the double bond of the glycal-like structure **13** was fully exploited.*[11] *Thus, treatment of the **12b**–**13** equilibrating mixture with catalytic osmium tetraoxide afforded a 71% yield (overall from **12**) of anomers **14a**, wherein osmylation had occurred anti to the azido function, thus solving all of the stereochemical issues associated with the synthesis of intermediate **15**.* The anomeric hydroxyl function was protected as its OTHP derivative **14b**. Degradation ((i) O_3–MeOH–CH_2Cl_2–DMS; (ii) RuO_4–MeCN–CCl_4–H_2O,[12] (iii) CH_2N_2 of the vinylic side chain followed by exposure (HCl) of the hemiacetal indeed gave rise to **15** in 65% overall yield from **14a**.



Unfortunately, a variety of efforts to achieve the seemingly feasible transformation of **15** to a prebactobolin type of intermediate by cleavage of the "a" bond and lactonization of the tertiary hydroxyl group were frustrated. *In envisioning such a scenario, the extraordinary stability of the hemiacetal (a bond) linkage had not been anticipated.*

The conversion of **15** to **2a** (cleavage of a and b bonds) started with oxidation ($NaIO_4$) of the vicinal diol. The resultant ketone was reduced with sodium borohydride–methanol to afford a 1.3:1 mixture of alcohols **16** (61% from **15**). Lactonization of epimers **16** was smoothly achieved with *p*-TsOH–benzene (93%) and the resultant trans diol was protected as its cyclohexylidene derivative. There was thus obtained the properly configured, protected lactone **17**.[13] Lindlar reduction of the azide,[14a] followed by acetylation of the resultant amine, afforded an 81% yield of **18**. Cleavage of the benzyl ether with Pearlman's catalyst[14b] gave a 98% yield of alcohol **19**. Collins' oxidation[14c] of **19** cleanly afforded **20**. The infrared, NMR (250 MHz), and TLC mobility of racemic **20** were identical with an authentic sample prepared from actinobolamine via N-acetylation and protection of the diol with cyclohexanone. Release of the diol and formation of **2a** was easily accomplished by treatment of **20** with 0.1 N HCl in dioxane. A fully synthetic route to *N*-acetylactinobolamine had been accomplished.



(7) Yamaguchi, M.; Hirao, I. *Tetrahedron Lett.* **1983**, *24*, 391.
(8) Nicolaou, K. C.; Petasis, N. A.; Zipkin, R. E.; Uenishi, J. *J. Am. Chem. Soc.* **1982**, *104*, 5555.
(9) The exact species which undergoes attack by azide ion (glycosyl chloride or mesylate) has not been determined.
(10) (a) Gagneux, A.; Winstein, S.; Young, W. G. *J. Am. Chem. Soc.* **1960**, *82*, 5956. (b) Ferrier, R. J.; Vethaviyaser, N. *J. Chem. Soc. C* **1971**, 1907.
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(12) Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936.
(13) The undesired (minor) hydroxyl isomer derived from ketone reduction underwent lactonization to the cis-fused ring system. The desired (major) hydroxyl isomer underwent lactonization with epimerization to the trans-fused ring system, possibly due to a nonbonded 1,3-diaxial interaction with the methyl group and the ring residue in the cis-lactone.
(14) (a) Vollmar, A.; Dunn, M. S. *J. Org. Chem.* **1960**, *25*, 387. (b) Hiskey, R. G.; Northrop, R. C. *J. Am. Chem. Soc.* **1961**, *83*, 4798. (c) Ratcliffe, R.; Rodehorst, R. *J. Org. Chem.* **1970**, *35*, 4000.

Note Added in Proof. A preliminary communication of a synthesis of *N*-acetylactinobolamine has appeared: Rahman, M. A.; Frasier-Reid, B. *J. Am. Chem. Soc.* **1985**, *107*, 5576.

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Registry No. (±)-**2a**, 98903-70-9; (±)-**3**, 93000-77-2; (±)-**4**, 98903-43-6; (±)-**5** (isomer 1), 98903-44-7; (±)-**5** (isomer 2), 98921-20-1; (±)-**6a**, 98903-45-8; (±)-**6b**, 98903-46-9; (±)-**7a**, 98903-47-0; (±)-**7b**, 98903-48-1; (±)-**8** (isomer 1), 98903-49-2; (±)-**8** (isomer 2), 98974-82-4; (±)-**9** (isomer 1), 98903-50-5; (±)-**9** (isomer 2), 98974-83-5; (±)-**10**, 98903-51-6; (±)-**10** (methylene isomer), 98903-52-7; **11**, 98903-53-8; **12a**, 98903-54-9; **12b**, 98903-55-0; (±)-**13**, 98903-56-1; (±)-**14a** (isomer 1), 98903-57-2; (±)-**14a** (isomer 2), 98903-58-3; (±)-**14b** (isomer 1), 98903-59-4; (±)-**14b** (isomer 2), 98903-60-7; (±)-**15** (isomer 1), 98903-61-8; (±)-**15** (isomer 2), 98903-62-9; (±)-**16** (isomer 1), 98903-63-0; (±)-**16** (isomer 2), 98974-84-6; (±)-**16** (lactone), 98903-64-1; (±)-**17**, 98903-65-2; (±)-**17** (X = NH_2), 98903-66-3; (±)-**18**, 98903-67-4; (±)-**19**, 98903-68-5; (±)-**20**, 98903-69-6; (±)-6-oxabicyclo[3.2.1]oct-3-en-7-one, 68217-48-1; methoxypropyne lithium acetylide, 73390-08-6.

Supplementary Material Available: Copies of NMR spectra of advanced synthetic intermediates (6 pages). Ordering information is given on any current masthead page.

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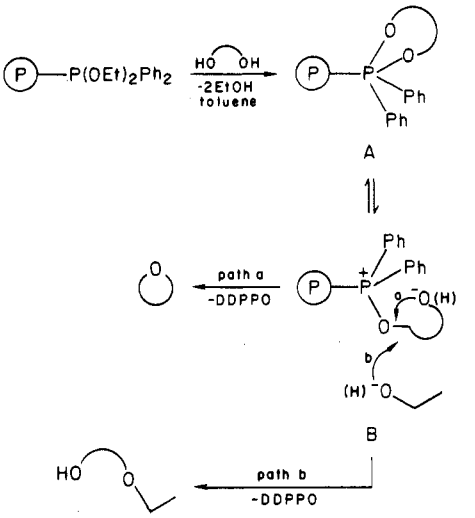
Diethoxydiphenylpolystyrylphosphorane: A New Polymeric Reagent for the Efficient Cyclodehydration of Simple Diols

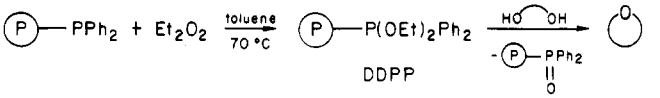
Summary: Diethoxydiphenylpolystyrylphosphorane, prepared by oxidative addition of diphenylpolystyrylphosphine with diethyl peroxide, is a heterogeneous, effectively neutral cyclodehydrating reagent which readily converts diols to cyclic ethers in excellent yields and allows for rapid and efficient product isolation.

Sir: Quite recently, we completed a comprehensive evaluation detailing the synthetic utility of diethoxytriphenylphosphorane, $Ph_3P(OEt)_2$ (DTPP), an effective reagent for promoting the cyclodehydration[1] and rearrangement[2] of an array of diols. On the basis of the current success of solid-phase methodology,[3] we envisioned that a cross-linked, polymer-supported dioxyphosphorane (i.e., diethoxydiphenylpolystyrylphosphorane; DDPP) might possibly allow for expeditious product isolation while simultaneously incorporating the characteristically mild cyclodehydration properties of DTPP. As a bonus, it seemed reasonable to expect the steric bulk and rigidity of the polymeric backbone to favorably influence regioselective phosphoranylation and subsequent cyclodehydration of unsymmetrical diols. In this preliminary account, we describe the preparation of DDPP and its successful application in the conversion of selected diols to cyclic ethers.

Scheme I. Phosphoranylation and Cyclodehydration of Diols with Diethoxydiphenylpolystyrylphosphorane (DDPP)



A typical experimental procedure involves the addition (via an airtight syringe) of diethyl peroxide (0.307 mL, 2.75 mmol)[4] to 2% divinylbenzene cross-linked diphenylpolystyrylphosphine (1.19 g, 4.5 mmol)[5] in anhydrous toluene



solvent (5.0 mL) under nitrogen or argon. This mixture was heated (70 °C) with magnetic stirring for 48 h prior to addition of anhydrous 1,4-butanediol (1) (0.221 mL, 2.5 mmol). After being heated for 24 h (70 °C), the reaction mixture was filtered through a glass wool plug. ^{13}C NMR analysis of the resulting solution revealed >99% tetrahydrofuran (2). Confirmation of sample composition was accomplished by GLC analysis.[6]

^{31}P NMR analysis[7] of the reaction between diphenylpolystyrylphosphine (DDP; 595 mg) and diethyl peroxide (1.37 mmol) [3:1 toluene/benzene-d_6] after 48 h indicated resonances at δ 24.4 (10%), −6.5 (45%), and −55.3 (45%) for diethoxydiphenylpolystyrylphosphine oxide (DDPPO), DDP, and DDPP, respectively. The resonance at δ −55.3 is similar to that observed for DTPP (δ −55.0)[1] where the trigonal bipyramidal conformer having both ethoxy groups in the apical array is preferred.

(1) Robinson, P. L.; Barry, C. N.; Kelly, J. W.; Evans, S. A., Jr. *J. Am. Chem. Soc.* **1985**, *107*, 5210–5219.
(2) Robinson, P. L; Evans, S. A., Jr. *J. Org. Chem.* **1985**, *50*, 3860–3863.
(3) (a) Hodge, P., Sherrington, D. C., Eds. "Polymer Supported Reactions"; Wiley: London, 1980. (b) Mathur, N. K.; Narang, C. K.; Williams, R. E. "Polymers as Aids in Organic Chemistry"; Academic Press: New York, 1980. (c) Frechet, J. M. *Tetrahedron* **1981**, *37*, 663–683. (d) Lieto, J.; Milstein, D.; Albrilght, R. L.; Minkiewicz, J. V.; Gates, B. C. *CHEMTECH* **1983**, 46–53. (e) Balakrishnan, T.; Ford, W. T. *J. Appl. Polym. Sci.* **1982**, *27*, 133–138.

(4) *Diethoxy peroxide*: See ref 1 for full experimental details on the preparation and purification of diethyl peroxide. After crude diethyl peroxide has been prepared, *we recommend that purification by distillation should be done at temperatures of 25–28 °C and pressures between 70–80 torr.* It is best to store diethyl peroxide over 4-Å molecular sieves at −20 °C. Under these conditions it is stable indefinitely. We have consistently avoided the use of ground glass syringes in our transfers of homogeneous diethyl peroxide. See also for early preparative information: Chang, B. C.; Conrad, W. E.; Denney, D. B.; Denney, D. Z.; Edelman, R.; Powell, R. L.; White, D. W. *J. Am. Chem. Soc.* **1971**, *93*, 4004.
(5) Amos, R. A.; Emblidge, R. W.; Havens, N. *J. Org. Chem.* **1983**, *48*, 3598–3600. Also available from Aldrich Chemical Co. (24.3 mmol of phosphine/gram assuming complete reaction with a specified quantity of EtOOEt after 48 h at 70 °C.
(6) The ethereal products were identified in the reaction mixture by comparing their ^{13}C NMR spectral properties with those obtained from authentic materials. Their presence and relative composition was obtained by GLC analysis. Gas chromatographic analyses were obtained with a stainless steel column (0.125 in. i.d. × 10 ft packed with 20% Carbowax 20 M on Chromosorb W-HP-AW-DMCS, 100–200 mesh).
(7) Ford, W. T.; Mohanraj, S.; Periyasamy, M. *Br. Polym. J.* **1984**, *16*, 179–187.

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