Rapid Construction of the Roflamycoin System

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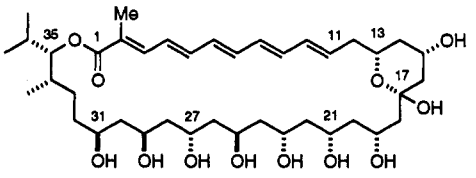
Of the over 200 known polyene macrolide antibiotics,[2] roflamycoin is one of the few that has been shown to form sterol-dependent ion channels.[3] Amphotericin B, a polyene macrolide antibiotic widely used in the treatment of systemic fungal infections, also forms sterol-dependent ion channels that are responsible for its antifungal activity.[4] These molecules are structurally complex and have become challenging targets for organic synthesis.[5] Unfortunately, the same complexity has made it difficult to prepare structurally meaningful analogs to test models for ion channel formation and biological activity. We wish to report a rapid and highly convergent synthesis of a spiroacetal based on the proposed roflamycoin structure **1**.[6] The synthesis is well suited to the preparation of structural and stereoisomers and sheds light on the stereochemistry of natural roflamycoin.

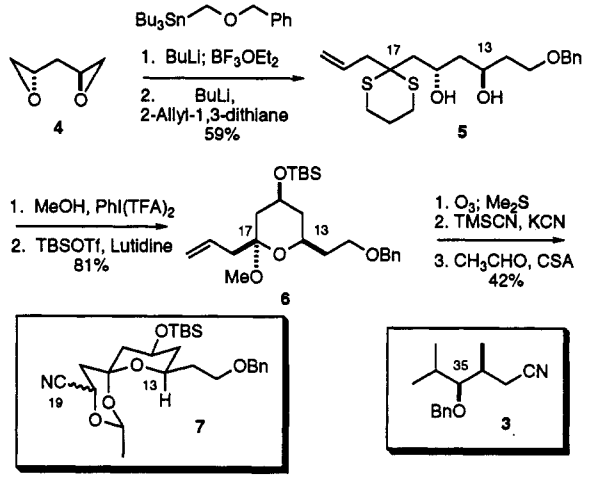


Roflamycoin Synthetic Target (1)

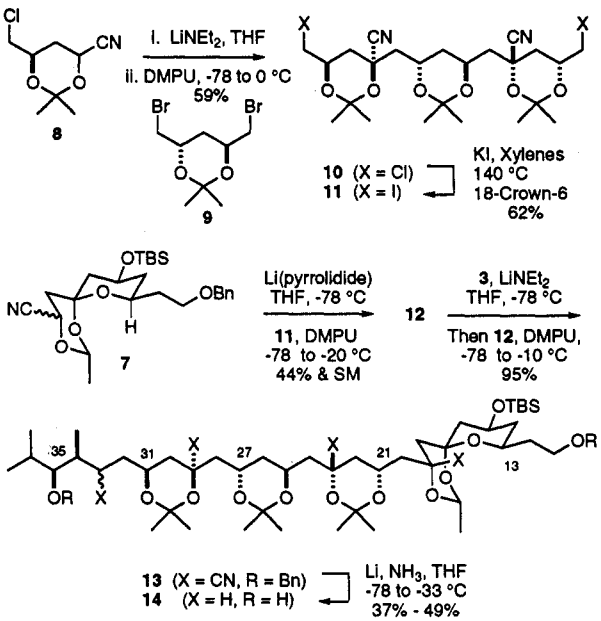
Our approach to roflamycoin[7] is based on our previously developed alkylation and stereoselective reductive decyanation of cyanohydrin acetonides.[8] The initial synthetic target **1** is shown above. It adopts the planar structure proposed by Schlegel[9] and incorporates the C19–C35 stereochemical assignment proposed by Maehr,[6] with the C13 and C15 stereogenic centers being chosen for convenience.

The left-hand nitrile **3** was prepared by standard methods.[10] The right-hand cyanohydrin spiroacetal **7**[11] was prepared by stepwise addition of nucleophiles to (2*S*,4*S*)-1,2:4,5-diepoxypentane (**4**) as shown in Scheme 1.[12] Addition of (benzyloxy)methyllithium with $BF_3{\cdot}OEt_2$ catalysis gave an epoxy alcohol which was deprotonated with *n*-BuLi and alkylated with 2-lithio-2-allyl-1,3-dithiane to give **5** in 59% overall yield. The dithiane was removed using $PhI(TFA)_2$ in $CH_2Cl_2/MeOH$,[13] and the remaining alcohol was protected to give TBS ether **6** in 81% yield. Ozonolysis generated the aldehyde, TMSCN with KCN and 18-crown-6 gave the corresponding cyanohydrin, and treatment with acetaldehyde and CSA gave the protected spiroacetal **7** in 42% yield. The C13 stereogenic center dominates the conformation of the spiroacetal ring and will ultimately control the stereochemistry at C19.[14]

Scheme 1



Scheme 2



Construction of the roflamycoin polyol proceeds by alkylation of dibromide **9**,[12] Scheme 2. Dibromide **9** was alkylated with 2.6 equiv of the lithium anion from cyanohydrin **8**[8b] in the presence of DMPU to give the crystalline dichloride **10** in 59% yield.[15] To activate **10** for further coupling, the chlorides were displaced by

(1) Camille and Henry Dreyfus Teacher-Scholar, 1990–1995. Alfred P. Sloan Research Fellow 1992–1994.

(2) For a general review of macrolide antibiotics, see: *Macrolide Antibiotics: Chemistry, Biology and Practice*; Omura, S. Ed.; Academic Press: New York, 1984.

(3) (a) Schlegel, R.; Grigorjev, P. A.; Thrum, H. *Stud. Biophys.* **1982**, *92*, 135–140. (b) Grigorjev, P.; Schlegel, R.; Thrum, H.; Ermishkin, L. *Biochim. Biophys. Acta* **1985**, *821*, 297–304.

(4) (a) Bolard, J. *Biochim. Biophys. Acta* **1986**, *864*, 257–304. (b) Hartsel, S. C.; Hatch, C.; Ayenew, W. *J. Liposome Res.* **1993**, *3*, 377–408.

(5) (a) Amphotericin B, see: Nicolaou, K. C.; Daines, R. A.; Ogawa, Y.; Chackraborty, T. K.; *J. Am. Chem. Soc.* **1988**, *110*, 4696–4705 and references cited therein. (b) Dehydroamphoteronolide B, see: Kennedy, R. M.; Abiko, A.; Takenasa, T.; Okumoto, H.; Masamune, S. *Tetrahedron Lett.* **1988**, *29*, 451–454. (c) Methyl primarolide: Duplantier, A. J.; Masamune, S. *J. Am. Chem. Soc.* **1990**, *112*, 7079–7081. (d) Mycoticin A: Poss, C. S.; Rychnovsky, S. D.; Schreiber, S. L. *J. Am. Chem. Soc.* **1993**, *115*, 3360–3361.

(6) Maehr, H.; Yang, R.; Hong, L.-N.; Liu, C.-M.; Hatada, M. H.; Todaro, L. J. *J. Org. Chem.* **1989**, *54*, 3816–3819.

(7) For synthetic work on *all-syn* roflamycoin, see: (a) Lipshutz, B. H.; Moretti, R.; Crow, R. *Tetrahedron Lett.* **1989**, *30*, 15–18. (b) Lipschutz, B. H.; Kotsuki, H.; Lew, W. *Tetrahedron Lett.* **1986**, *27*, 4825–4828.

(8) (a) Rychnovsky, S. D.; Zeller, S.; Skalitzky, D. J.; Griesgraber, G. *J. Org. Chem.* **1990**, *55*, 5550–5551. (b) Rychnovsky, S. D.; Griesgraber, G. *J. Org. Chem.* **1992**, *57*, 1559–1563.

(9) Schlegel, R.; Thrum, H.; Zielinski, J.; Borowski, E. *J. Antibiot.* **1981**, *34*, 122–123.

(10) The left-hand fragment **3** was prepared by an enantioselective aldol condensation (Evans), followed by the sequence: (i) $BnOC(NH)CCl_3$, TfOH; (ii), $LiBH_4$; (iii) TsCl, pyridine; and (iv) NaCN, DMSO. For the aldol reaction, see: Gage, J. R.; Evans, D. A. *Org. Synth.* **1989**, *68*, 83–90 and references cited therein.

(11) All new compounds were characterized by ^1H and ^{13}C NMR and either elemental analysis or HRMS.

(12) Rychnovsky, S. D.; Griesgraber, G.; Zeller, S.; Skalitzky, D. J. *J. Org. Chem.* **1991**, *56*, 5161–5169.

(13) Stork, G.; Zhao, K. *Tetrahedron Lett.* **1989**, *30*, 287–290.

(14) Rychnovsky, S. D.; Griesgraber, G. *J. Chem. Soc., Chem. Commun.* **1993**, 291–292.

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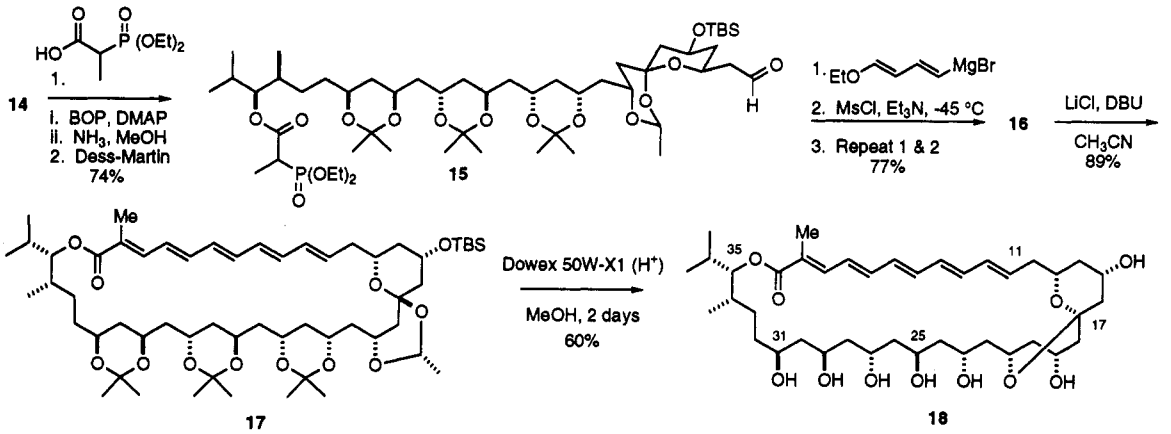
Scheme 3



treatment with KI in refluxing xylenes to give diiodide **11** in 62% yield. The remaining material was partially substituted and could be recycled. The final assembly began with the alkylation of **7** using 2.2 equiv of **11** to give monoalkylated product **12** in 44% yield (77% based on recovered nitrile). Excess **11** was used to limit overalkylation and was recovered. Subsequent dialkylation of **12** with 3.6 equiv of the lithium anion of **3** gave **13** in 95% yield. Reductive decyanation of **13** with Li in liquid ammonia and THF resulted in stereoselective axial protonation at C19, C23, and C29 as well as decyanation at C31 and debenzylation of the C11 and C35 ethers. The completely reduced product **14** was isolated in 37–49% yield, which represents an 89% yield for the reduction of each functional group. Compound **14** incorporates the complete stereochemical backbone of the roflamycoin target and is available in only 10 steps from diepoxypentane **4**.

It remained to introduce the polyene and to form the macrocycle, Scheme 3. Diethyl 2-phosphonopropionate was coupled with **14** using BOP and DMAP. The crude reaction mixture was directly treated with NH_3-saturated MeOH to remove the less-hindered primary ester. Dess–Martin oxidation gave aldehyde **15** in 74% overall yield. The polyene was introduced using Wollenberg's method.[16] The first iteration gave the dienal, and the second application gave the desired tetraenal **16** in 77% overall yield. Horner–Emmons macrocyclization using the Roush–Masamune conditions[17] gave the 36-membered lactone **17** in a remarkable 89% yield. The protecting groups in **16** apparently reinforce a conformation favorable for cyclization. Deprotection of **17** with Dowex 50W-X1 (H^+) in MeOH rapidly removed the acetonides and the TBS ether to give ethylidine acetal-protected roflamycoin in quantitative yield. Prolonged exposure led to loss of the ethylidine acetal and cyclization of the C21 hydroxyl to give the roflamycoin spiroacetal **18** in 60% yield.[18] The spiroacetal of natural roflamycoin was prepared under the same conditions from a sample of the natural product supplied by Dr. Rolf Schlegel. The NMR spectra of the two acetals are similar but not identical, so the stereochemistry of natural roflamycoin differs from that of our synthetic target. We have since determined the structure of natural roflamycoin.[19]

We have developed a rapid synthesis of the roflamycoin system: spiroacetal **18** was prepared in only 18 steps from diepoxypentane **4**. The stereochemical configurations derive from simple chiral precursors, and mixing and matching of these precursors should make a wide variety of stereoisomers available. This versatile synthetic approach lays the groundwork for determining the role of stereochemistry in ion channel formation.

Acknowledgment. We thank Dr. Rolf Schlegel for providing a sample of roflamycoin. Support has been provided by the National Institutes of Health (GM43854) and the National Science Foundation Presidential Young Investigator Program. Additional support was provided by Eli Lilly & Co., American Cyanamid, Hoffman-La Roche, and Pfizer Inc. G.G. thanks the National Science Foundation and the University of Minnesoata for Fellowship support.

Supplementary Material Available: Characterization of compounds **5–7**, **10**, **13**, **14**, **15**, **17**, **18** and natural roflamycoin spiroacetal, and an illustration of the X-ray structure of **10** (10 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(15) The absolute and relative stereochemistry of dichloride **10** (mp = 124–126 °C) were confirmed by X-ray crystallography. See the supplementary material for an illustration.

(16) Wollenberg, R. H. *Tetrahedron Lett.* **1978**, 717–720.

(17) Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183–2186.

(18) Spiroacetal formation might be avoided by protecting the C_{21} hydroxyl before final removal of the acetal. We have focused on elucidating the stereochemistry of natural roflamycoin rather than pursuing this possibility.

(19) Rychnovsky, S. D.; Griesgraber, G.; Schlegel, R. *J. Am. Chem. Soc.*, following paper in this issue.