

SYNTHESIS OF EXTENDED 1,3-POLYOLS USING FOUR-CARBON UNITS: AN APPROACH TO THE CONSTRUCTION OF THE POLYOL FRAGMENT OF ROXATICIN

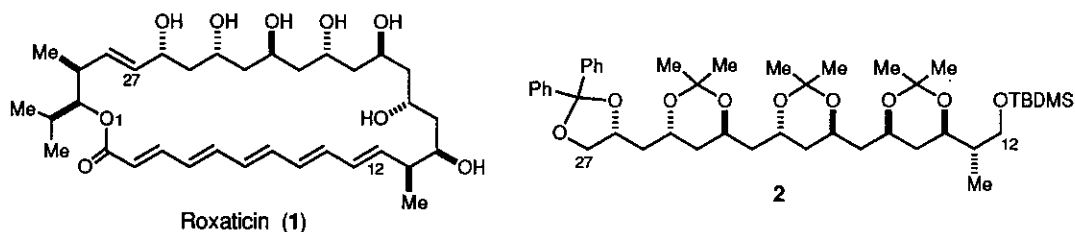
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Abstract - The polyol fragment of roxaticin containing eight chiral centers has been prepared in a reiterative manner using coupling reactions of chiral dithianes with epoxides followed by stereoselective reduction.

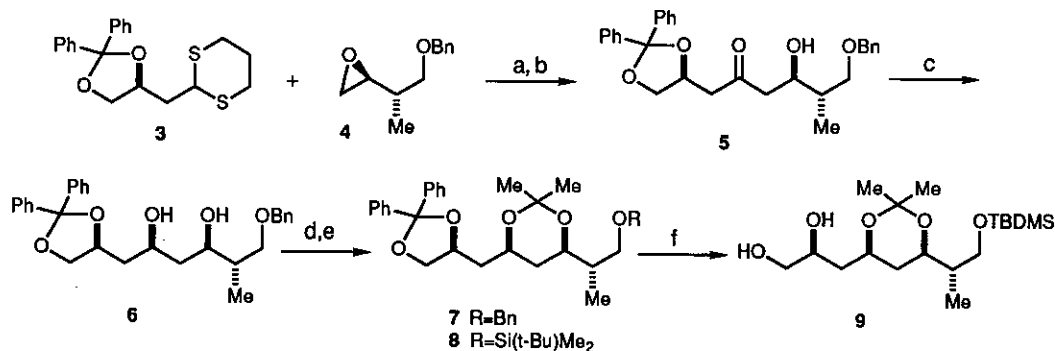
Synthesis of 1,3-polyols in a stereocontrolled manner is considerable interest since syn- and anti-diols are recurring units of various polyacetate-derived natural products, such as polyene macrolide antibiotics,¹ and convergent strategies to prepare alternating polyol chains have been developed.² Over 200 polyene macrolides are known, but the complete structure and stereochemistry have been determined only in several cases.³ Roxaticin (**1**) is a representative of this family and the structure have been established by X-ray crystallographic analysis.⁴

As a part of our program of synthetic studies on 1,3-polyols,⁵ we have chosen **1** as a synthetic target. Retrosynthetic analysis led us to disconnections at C11-C12 and C27-C28 bonds to provide the C12-C27 polyol fragment. We now report an approach for the synthesis of the suitably protected and optically active fragment (**2**) using a four-carbon chain extension methodology.



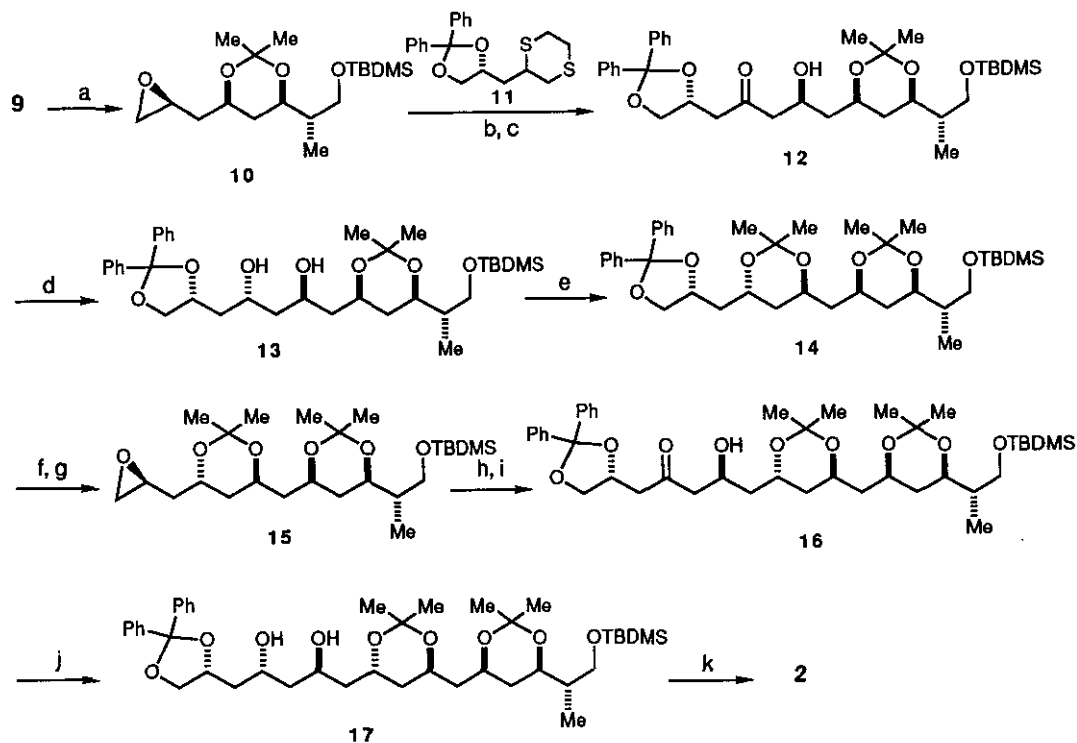
Reaction of epoxide (**4**)⁶ with the lithiated anion of **3** gave the bisalkylated dithiane in 74% yield. Subsequent to dithiane cleavage into **5**, the resulting hydroxy ketone (**5**) could be a substrate for diastereoselective reduction to syn-diol (**6**). Our original method utilizing lithium aluminum hydride in the presence of lithium iodide^{5a} gave **6** in a ratio of 3:1. The low selectivity would be attributed to the bulky diphenylmethylene ketal which prevents the chelation of lithium cation with an oxygen of the dioxorane ring. Complete control of the syn-reduction was realized by the procedure of Prasad and co-workers,⁷ giving **6** in 95% yield with a 99.7:0.3 diastereoselectivity analyzed by hplc.

The stereochemical outcome of the reduction was confirmed by the method developed by Rychnovsky.⁸ The ¹³C nmr spectrum of **7** showed two acetonide methyl signals at 19.7 and 30.1 ppm, indicating the syn-1,3-diol relationship. In order to deprotect the diphenylmethylene ketal, the benzyl group of **7** was replaced by a silyl group to afford **8** (80%), which was then subjected to dissolving metal-ammonia reduction to give diol (**9**) in 81% yield.



(a) **3**, *n*-BuLi, THF, -30°C, 2 h, then **4**, -25°C, 15 h (74%); (b) MeI, CaCO₃, MeCN-H₂O, 16 h (88%); (c) NaBH₄, Et₂BOMe, THF-MeOH, -78°C, 3 h (95%); (d) Me₂C(OMe)₂, PPTS, CH₂Cl₂, 20 min (90%); (e) i) H₂, Pd(OH)₂-C, EtOAc, 30 min (81%); ii) TBDMS-Cl, imidazole, DMF, 3.5 h (99%); (f) Li, liq. NH₃-THF, *i*-PrOH, -70°C, 15 min (81%)

Second coupling of epoxide (**10**), obtained from **9** *via* tosylate in 65% yield, with the anion of **11**, an enantiomer of **3**, formed hydroxy ketone (**12**) (62%) after dithiane hydrolysis. Directed reduction of **12** with Evans' reagent [Me₄NBH(OAc)₃]⁹ led to **13** (93%) as a 97:3 mixture of separable diastereomers. It is worthy to note that the anti-reduction of a hydroxy ketone prepared from dithiane (**3**) and epoxide (**10**) afforded a 5:1 mixture of anti and syn-diols. The relative stereochemistry of **13** was proved by ¹³C nmr analysis⁸ of the diacetonide (**14**), which showed one syn-1,3-diol (19.8 and 30.2 ppm) and one anti-1,3-diol (24.6 and 24.7 ppm) acetonides. The Birch reduction of **14** followed by pivaloylation, mesylation, and treatment with base yielded epoxide (**15**) in 69% overall yield.



(a) i) TsCl, Py, 0°C, 2.5 h; ii) *t*-BuOK, Et₂O-MeOH, 1.5 h (65%, two steps); (b) 11, *n*-BuLi, THF, -30°C, 2 h, then 10, -25°C, 15 h (91%); (c) MeI, CaCO₃, MeCN-H₂O, 16 h (68%); (d) Me₄NBH(OAc)₃, MeCN-AcOH, -25°C, 20 h (93%); (e) Me₂C(OMe)₂, PPTS, CH₂Cl₂, 40 min (100%); (f) Li, liq. NH₃-THF, *i*-PrOH, -78°C, 30 min (86%); (g) i) *t*-BuCOCl, Py, 0°C, 30 min (92%); ii) MsCl, Et₃N, CH₂Cl₂, 0°C, 45 min; iii) *t*-BuOK, Et₂O-MeOH, 3.5 h, (87%, two steps); (h) same as (b) (71%); (i) same as (c) (80%); (j) same as (d) (77%); (k) same as (e) (98%)

Final coupling of **15** with **11** followed by hydrolysis of dithioketal group provided hydroxy ketone (**16**) in 59% yield. The anti-1,3-diol stereochemical relationship in **17** was established by reduction of **16** with Me₄NBH(OAc)₃ to afford a 97:3 mixture of anti and syn diastereomers from which **17** was isolated in 77% yield. Protection of the diol gave **2** corresponding to the C12-C27 fragment of roxaticin (**1**).

In summary, synthesis of the polyhydroxylated chain of roxaticin has been accomplished in a stereocontrolled manner using three chiral building blocks (**3**, **4**, and **11**). Further studies on the synthesis of **1** are in progress.

REFERENCES

1. S. Ohmura and H. Tanaka, *'Macrolide Antibiotics: Chemistry, Biology, and Practice,'* S. Ohmura, Ed., Academic Press, New York, 1984, pp. 351-404.
2. (a) S. D. Rychnovsky, G. Griesgraber, S. Zeller, and D. J. Skalitzky, *J. Org. Chem.*, 1991, **56**, 5161. (b) T. Oishi and T. Nakata, *Synthesis*, **1990**, 635 and references cited therein.
3. (a) P. Ganis, G. Avitabile, W. Mechlinsky, and C. P. Schaffner, *J. Am. Chem. Soc.*, 1971, **93**, 4560. (b) S. L. Schreiber and M. T. Goulet, *J. Am. Chem. Soc.*, 1987, **109**, 8120. (c) J. Prandi, and J.-M. Beau, *Tetrahedron Lett.*, 1989, **30**, 4517. (d) J.-M. Lancelin and J.-M. Beau, *J. Am. Chem. Soc.*, 1990, **112**, 4060. (e) J. Pawlak, K. Nakanishi, T. Iwashita, and E. Borowski, *J. Org. Chem.*, 1987, **52**, 2896. (f) T. Nakata, N. Hata, T. Suenaga, and T. Oishi, Symposium Papers, 30th Symposium on the Chemistry of Natural Products; Fukuoka, Japan, October, 1988, pp. 540-547.
4. R. Maehr, R. Yang, L.-N. Hong, C.-M. Liu, M. H. Hatada, and L. J. Tadaro, *J. Org. Chem.* 1989, **54**, 3816.
5. (a) Y. Mori, M. Kuhara, A. Takeuchi, and M. Suzuki, *Tetrahedron Lett.*, 1988, **29**, 5419. (b) Y. Mori, A. Takeuchi, H. Kageyama, and M. Suzuki, *Tetrahedron Lett.*, 1988, **29**, 5423. (c) Y. Mori and M. Suzuki, *Tetrahedron Lett.*, 1989, **30**, 4383. (d) Y. Mori and M. Suzuki, *Tetrahedron Lett.*, 1989, **30**, 4387.
6. J. D. Aebi, M. S. Sutter, D. Wasmuth, and D. Seebach, *Liebigs Ann. Chem.*, **1983**, 2114.
7. K.-M. Chen, G. E. Hardtmann, K. Prasad, O. Repic, and M. J. Shapiro, *Tetrahedron Lett.*, 1987, **28**, 155.
8. S. D. Rychnovsky and D. J. Skalitzky, *Tetrahedron Lett.*, 1990, **31**, 945.
9. D. A. Evans, K. T. Chapman, and E. M. Carreira, *J. Am. Chem. Soc.*, 1988, **110**, 3560.

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