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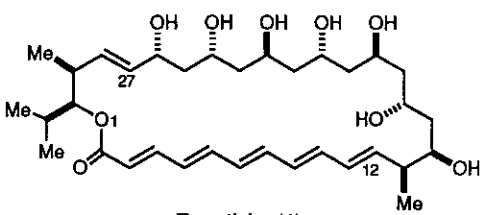
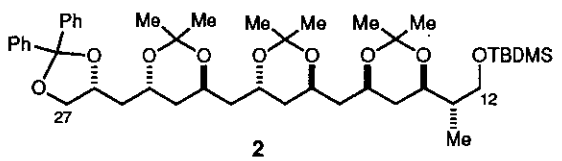
Abstract - The polyol fragment of roxaticin containing eight chiral centers has been prepared in a reiterative manner using coupling reactions of chiral dithianes with epoxides followed by stereoselective reduction.

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.



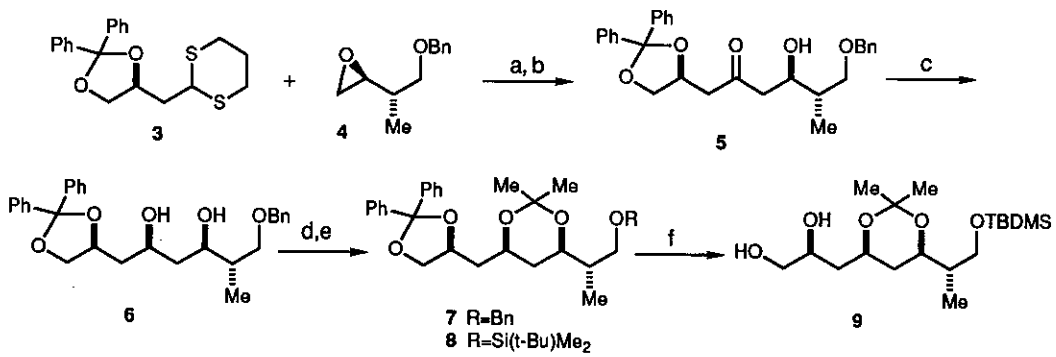
Roxaticin (**1**)



2

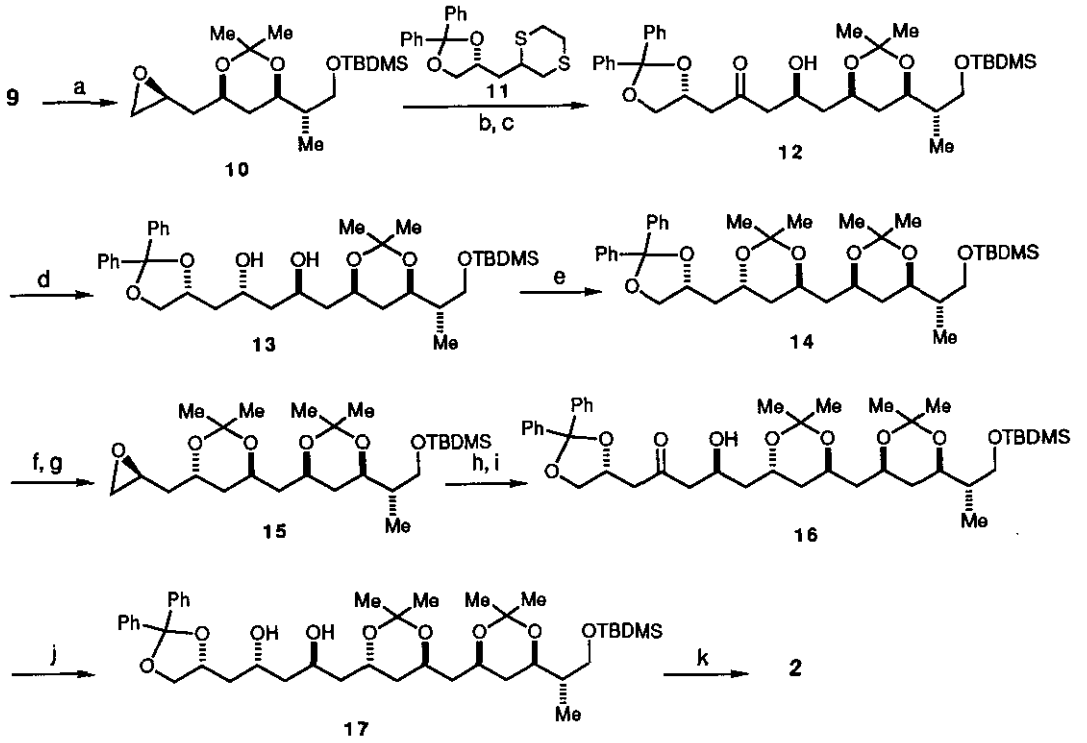
Reaction of epoxide (**4**)[6] with the lithiated anion of **3** gave the bisalkylated dithiane in 74% yield. Subsequent to dithiane cleavage into **5**, the resulting hydroxy ketone (**5**) could be a substrate for diastereoselective reduction to syn-diol (**6**). Our original method utilizing lithium 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 ^{13}C 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, $CaCO_3$, MeCN-H_2O, 16 h (88%); (c) $NaBH_4$, Et_2BOMe, THF-MeOH, -78°C, 3 h (95%); (d) $Me_2C(OMe)_2$, PPTS, CH_2Cl_2, 20 min (90%); (e) i) H_2, $Pd(OH)_2$-C, EtOAc, 30 min (81%); ii) TBDMS-Cl, imidazole, DMF, 3.5 h (99%); (f) Li, liq. NH_3-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 [$Me_4NBH(OAc)_3$][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 ^{13}C nmr analysis[8] 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, Et_2O-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, $CaCO_3$, MeCN-H_2O, 16 h (68%); (d) $Me_4NBH(OAc)_3$, MeCN-AcOH, -25°C, 20 h (93%); (e) $Me_2C(OMe)_2$, PPTS, CH_2Cl_2, 40 min (100%); (f) Li, liq. NH_3-THF, i-PrOH, -78°C, 30 min (86%); (g) i) t-BuCOCl, Py, 0°C, 30 min (92%); ii) MsCl, Et_3N, CH_2Cl_2, 0°C, 45 min; iii) t-BuOK, Et_2O-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 $Me_4NBH(OAc)_3$ 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.*

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