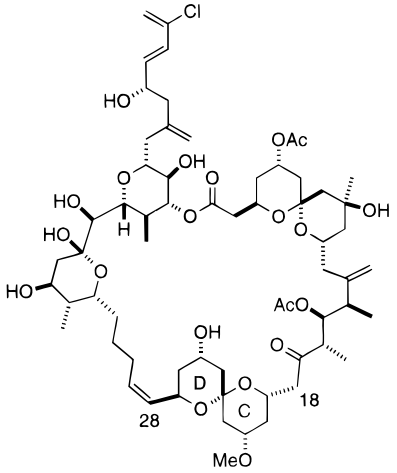
A Method for Constructing the C18−C28 Dispiroacetal Moiety of Altohyrtin A

Christopher J. Hayes and Clayton H. Heathcock*

Department of Chemistry, University of California, Berkeley, California 94720

Received January 30, 1997

The altohyrtins,[1,2] the spongistatins,[3] and cinachyrolide A[4] represent a growing group of related marine-derived macrolides, which show extremely potent cancer cell growth inhibitory activity. It is of particular interest that many of these compounds have displayed extreme cytotoxicity toward a subset of chemoresistant tumor types. Altohyrtin A (**1**) is the only member of this family for which the absolute stereochemistry has been determined. Profound biological activity and unusual chemical structure couple to make **1** a desirable target for total synthesis.



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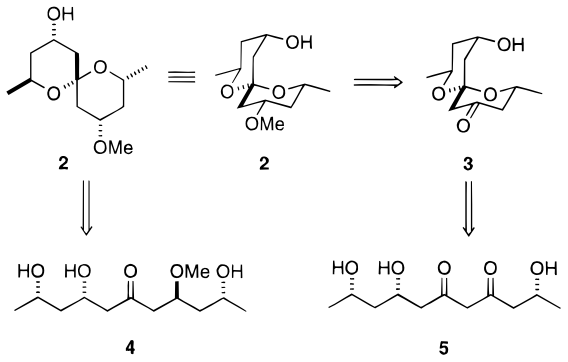
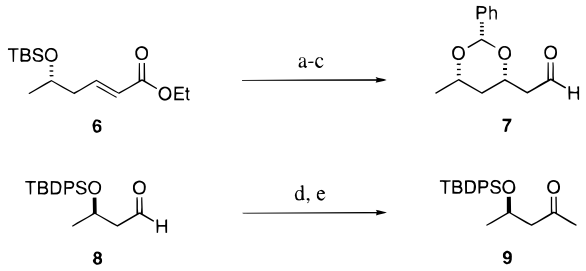
As part of our research directed toward a total synthesis of **1**,[5] we had reason to synthesize the spiroacetal **2**, which is a model for the C−D, C18−C28 fragment of **1**. Retrosynthetic analysis of **2** (Scheme 1) revealed the triol **4** as a potential precursor. Preliminary molecular mechanics and semiempirical calculations, however, suggested that the spiroacetalization of **4** might result in low selectivity for the desired acetal configuration. Therefore, we decided to explore an alternative approach. Thus, disconnection of **2** revealed the ketohydroxy spiroacetal **3** as a key intermediate, which might result from spiroacetalization of the triol−dione **5**. In this case, molecular modeling suggested that the desired *R*-spiroacetal configuration should be favored. In order to test this hypothesis, we required an expedient synthesis of the triol−dione **5**.

Scheme 1



Scheme 2[a]



[a] Reagents: (a) HF(48% aqueous), MeCN (91%); (b) KHMDS, PhCHO, THF, 0 °C (73%); (c) DIBALH, CH_2Cl_2, −95 °C (94%); (d) MeMgBr, Et_2O, 0 °C; (e) Dess-Martin, CH_2Cl_2 (94%).

We envisioned **5** as being readily derived from the known ester **6**[6] and aldehyde **8**[5a] (Scheme 2). Thus, deprotection of **6** with 48% aqueous HF in acetonitrile first provided the corresponding secondary alcohol. Stereoselective installation of the C3 stereocenter and concomitant benzylidene acetal formation were achieved using the method developed by Evans and co-workers.[7] Reduction of the resultant ethyl ester with 1 equiv of DIBALH afforded the aldehyde **7**. The synthesis of **9** from **8** was readily accomplished in two steps by addition of methylmagnesium bromide and Dess−Martin periodinane oxidation.[8] Condensation of **7** with the lithium enolate of **9** afforded the corresponding aldol product, which was oxidized with Dess−Martin periodinane to yield the dione **10** in good yield (Scheme 3). The synthesis of **5** was completed by deprotection of the TBDPS ether with tetrabutylammonium fluoride followed by removal of the benzylidene acetal using catalytic hydrogenation. A number of solvents were screened for the hydrogenation reaction, and it was found that in ethyl acetate spiroacetalization of **5** occurred *in situ*. The acetalization is presumably catalyzed by trace amounts of acid present in the solvent. Our original prediction regarding the stereoselective acetalization of **5** was shown to be correct. A ^{1}H NMR spectrum of the crude reaction mixture showed that the diastereomeric spiroacetals **3** and **11** were formed in a ratio of approximately 5:1. Owing to problems associated with the volatility of **11** and particularly **3**, the diastereoisomers were not separated at this stage. Treatment of a mixture of **3** and **11** with *tert*-butyldimethylsilyl trifluoromethanesulfonate and 2,6-lutidine at low temperature (−78 °C) afforded a 5:1 mixture of the corresponding silyl ethers **12** and **13**

(1) Kobayashi, M.; Aoki, S.; Kitagawa, I. *Tetrahedron Lett.* **1994**, *35*, 1243.
(2) Kobayashi, M.; Aoki, S.; Sakai, H.; Kawazoe, K.; Kihara, N.; Sasaki, T.; Kitagawa, I. *Tetrahedron Lett.* **1993**, *34*, 2795.
(3) Bai, R.; Taylor, G. F.; Cichacz, Z. A.; Herald, C. L.; Kepler, J. A.; Pettit, G. R.; Hamel, E. *Biochemistry* **1995**, *34*, 9714. See also references cited therein.
(4) Fusetani, N.; Shinoda, K.; Matsunaga, S. *J. Am. Chem. Soc.* **1993**, *115*, 3977.
(5) (a) Claffey, M. M.; Heathcock, C. H. *J. Org. Chem.* **1996**, *61*, 7646. See also: (b) Paterson, I.; Oballa, R. M.; Norcross, R. D. *Tetrahedron Lett.* **1996**, *37*, 8581.
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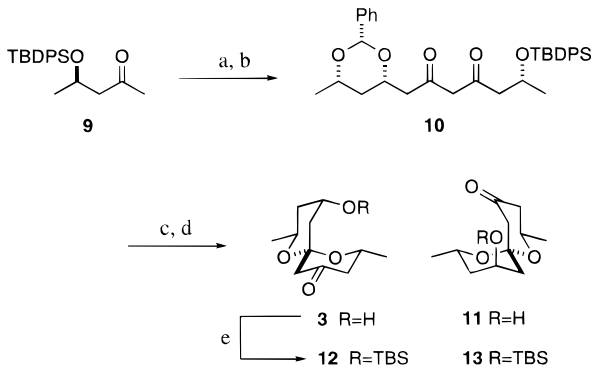
(7) Evans, D. A.; Gauchet-Prunet, J. A. *J. Org. Chem.* **1993**, *58*, 2446.
(8) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.

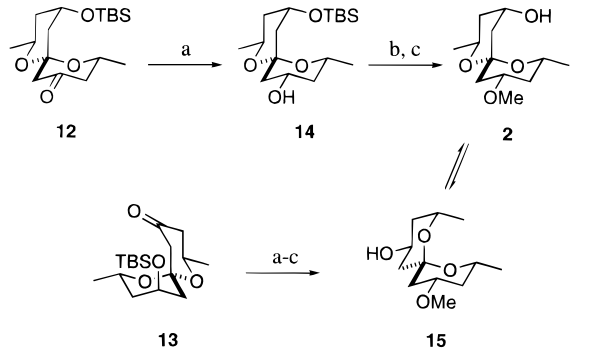
S0022-3263(97)00170-9 CCC: $14.00

Scheme 3[a]



[a] Reagents: (a) LDA, −78 °C, THF then **7**, THF (81%); (b) Dess−Martin, CH_2Cl_2 (84%); (c) TBAF, THF (92%); (d) H_2, $Pd(OH)_2$, EtOAc; (e) TBSOTf, 2,6-lutidine, CH_2Cl_2, −78 °C (74%, two steps).

Scheme 4[a]



[a] Reagents: (a) K/NH_3, MeOH; (b) NaH, MeI, THF; (c) TBAF, THF.

in excellent yield. The diastereoisomers were easily separated at this point by column chromatography.

Reduction of **12** using potassium in liquid ammonia at low temperature (−78 °C) resulted in the selective formation of the equatorial secondary alcohol **14** (Scheme 4). Methyl ether formation and removal of the TBS protecting group, following standard procedures, yielded the desired spiroacetal target **2**. The relative configuration of **2** was confirmed by a series of NOE difference NMR experiments. In addition to the synthesis of **2**, we were able to synthesize the diastereomeric spiroacetal **15** from **13** using an identical sequence of reactions to those described above. We found that under a variety of acidic conditions, an equilibrium between **15** and **2** could be established (Table 1). A number of equilibration conditions were examined in an attempt to favor **2** over **15**. The best conditions were found to be trifluoroacetic acid in methylene chloride, giving a ratio of 55:45 of **2** and **15** at equilibrium. Since the two isomers were readily separable by column chromatography, we had a method to convert the undesired spiroacetal isomer **15** into the desired product **2**. Thus, three equilibration/separation cycles allowed us to convert isomerically pure **15** into isomerically pure **2** in 90% isolated yield. Subsequent to the aforementioned studies, we found that the separation of **12** and **13** was not necessary. The mixture of diastereoisomers could be carried through the reduction, methyl ether formation and deprotection reactions, producing **2** and **15** in a ratio paralleling the initial ratio of **12** and **13** used. For example, a 5:1 mixture of **12** and **13** produced a 5:1 mixture of **2** and **15** in 64% overall yield. The separated **15** was then converted into **2** using two equilibration/separation cycles. This overall process afforded the desired acetal **2** in 60% isolated yield (from the mixture of **12** and **13**) along with 2% of **15**. Although we were hoping for a better ratio than 55:45 of **2**:**15** in the equilibration step, this result supports our original prediction that the spiroacetalization of **4** would not be selective for the desired acetal configuration.

Table 1

condns	ratio **15**:**2**	condns	ratio **15**:**2**
TFA, CH_2Cl_2	45:55	TFA, hexanes	55:45
HCl, $CDCl_3$	45:55	HF_{aq}, MeCN	85:15

In summary, a stereoselective synthesis of the desired model **2** has been accomplished. We have shown that acetalization of the triol **5** leads to selective formation of the spiroacetal **3** possessing the desired *R*-spiroacetal configuration and how this intermediate can be elaborated into **2**. In addition, we have described how the minor *S*-spiroacetal isomer **11** can also be used to access the desired target **2** in good yield. The strategy developed for stereocontrolled synthesis of **2** is directly applicable to the synthesis of the C−D, C18−C28 spiroacetal of altohyrtin A (**1**), and studies directed toward this end are currently underway.

Acknowledgment. This work was supported by a research grant from the United States Public Health Service (GM 15067).

Supporting Information Available: Experimental procedures and spectral data for all compounds (13 pages).

JO9701703