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Modeling a Macrocyclic Bis[spirodiepoxide] Strategy to Erythronolide A

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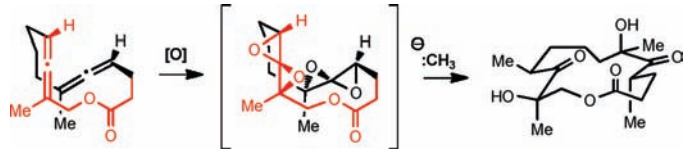
ABSTRACT



A concise route to functionalized 14-membered macrolides related to erythronolide A was achieved. Key steps include the simultaneous formation of bis[allenic] substrates, efficient macrolactonization, highly stereoselective oxidation to the corresponding bis[spirodiepoxide], and nucleophilic spirodiepoxide opening. The structure and reactivity of these macrolides, and the strategy that led to their evaluation, are discussed.

Here we present a study designed to model some of the key steps in a planned synthesis of erythronolide A by way of precursor **1**. The routes to this archetypal macrocyclic polypropionate form a gallery of elegant strategies and methods for chemical synthesis.[1] As indicated in Figure 1, this target contains two identical stereotriads. Despite this long-recognized structural redundancy and the established routes to this structure, the target still poses a substantive synthetic challenge. Most routes to **1** require over 30 preparative steps in the longest linear sequence. The shortest require near 25 preparative steps. Aside from Patterson's route, which realized midstage cyclization and subsequent macrocyclic functionalization of a C5−C6 olefin, all other routes sculpted fully elaborated linear substrates that were cyclized in the final steps.

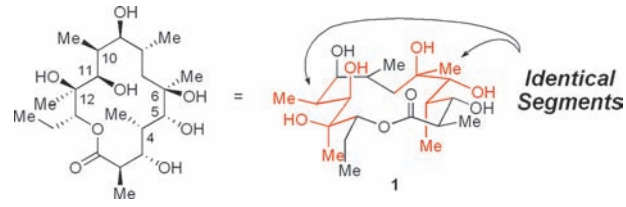


Figure 1. 9(*S*)-Dihydroerythronolide A.

Our aim was to evaluate a strategy of simultaneous formation of the identical C4−C6 and C10−C12 segments in a macrocyclic context. In this case, oxidation would be followed by elaboration of the twin motifs. Late stage introduction of heterofunctionality introduces significant risks related to planning flexibility.[2] However, this approach has the potential advantage to significantly increase tempo and efficiency.

(1) For lead references, see: (a) Paterson, I.; Mansuri, M. M. *Tetrahedron* **1985**, *41*, 3569–3624. (b) Paterson, I.; Rawson, D. J. *Tetrahedron Lett.* **1989**, *30*, 7463–7466. (c) Mulzer, J. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1452–1454. (d) Stürmer, R.; Ritter, K.; Hoffmann, R. W. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 101–103. (e) Martin, S. F.; Hida, T.; Kym, P. R.; Loft, M.; Hodgson, A. *J. Am. Chem. Soc.* **1997**, *119*, 3193–3194. (f) Evans, D. A.; Kim, A. S.; Metternich, R.; Novack, V. J. *J. Am. Chem. Soc.* **1998**, *120*, 5921–5942. (g) Peng, Z.-H.; Woerpel, K. A. *J. Am. Chem. Soc.* **2003**, *125*, 6018–6019. (h) Hergenrother, P. J.; Hodgson, A.; Judd, A. S.; Lee, W.-C.; Martin, S. F. *Angew. Chem., Int. Ed. Engl.* **2003**, *42*, 3278–3281. (i) Muri, D.; Lohse-Fraefel, N.; Carreira, E. M. *Angew. Chem., Int. Ed. Engl.* **2005**, *44*, 4036–4038.

(2) Flexibility is paramount since the route fails with one mis-synthetic step. For a discussion, see: Corey, E. J.; Cheng, X.-M. *The Logic of Chmical Synthesis*; John Wiley & Sons, Inc.: New York, 1989; p 4.

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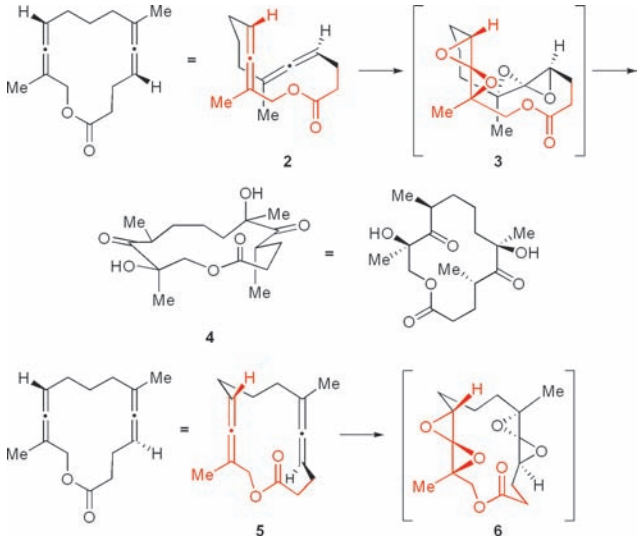
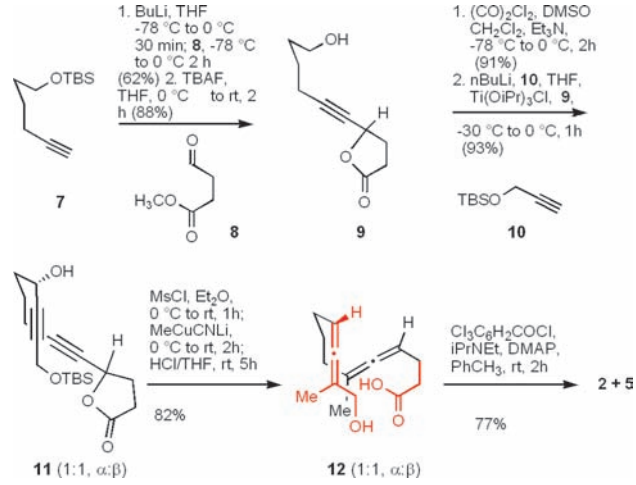
Scheme 1



Scheme 2



Our primary target was compound **4** (Scheme 1, cf. **1**). Oxidation of allene **2** to the corresponding spirodiepoxide[3] **3**, followed by nucleophilic opening (→**4**), suggested a direct means of entry to the goal structure. Of course, in the total synthesis the requisite functionality at C1, C2, C8, C9, and C13 would need to be installed probably prior to the epoxidation sequence.

Many of the planned steps of this strategy seemed highly speculative. There is little precedent to guide expectations with regard to the formation and stability of macrocyclic bis[allenes] of type **2**,[4] bis[spirodiepoxides] of type **3**,[5] and necessarily, nucleophilic substitution of **3**. However, the possibility of the successful conversion of **3** to **4**, and the implications of the sequence on strategic planning of this and other targets, encouraged us to proceed with this study. The stereochemical outcome of the epoxidation/addition sequence became the focal point, and the epoxidation of both allene **2** and isomer **5** was evaluated.

The synthesis of **2** and **5** began with commercial aldehyde[6] **8** and readily available alkyne **7**[7] (Scheme 2). Careful lithium alkynylide addition to **8** minimized competitive addition to the ester moiety and effected spontaneous lactone formation, which we recognized might be sufficiently reactive to serve as an allene precursor. Removal of the silyl group (→**9**) and then oxidation of the primary alcohol gave the corresponding aldehyde. The combination of titanium chloride triisopropoxide and lithium alkynylide[8] derived from **10** effected the selective conversion of this aldehyde to a 1:1 mixture of propargyl alcohols **11** without complication from the electrophilic lactone.

We explored the single flask conversion of the two propargyl moieties in **11** to the corresponding double allene of **12**.[9] Even though not highly activated, the propargyl lactone could serve as the immediate precursor to the corresponding C4−C6 allene. The goal, therefore, was to activate the C10−C12 propargyl alcohol and then to add excess cuprate directly to the reaction vessel. This proved successful. Furthermore, it was unnecessary to isolate the silyl ether product. Instead, subsequent addition of aqueous acid in tetrahydrofuran to the reaction mixture effected silyl cleavage and provided seco acid **12** as a 1:1 mixture of isomers in excellent overall yield. Thus, the sequential addition of reagents for propargyl alcohol activation, subsequent double allene formation, and then deprotection effected the single flask conversion of **11** to **12** in 82% overall yield.

Macrolactonization often requires high temperature, high dilution, and very slow addition.[10] Cyclization of **12** occurred readily at room temperature, with slow addition of reagents over 2 h and a final concentration of substrate of 0.01 M. This simple procedure gave the macrocyclic bis[allenes] **2** and **5** in a 1:1 ratio as a separable mixture in good yield. Both **2** and **5** proved to be stable, well-behaved oils.

(3) (a) Katukojvala, S.; Barlett, K. N.; Lotesta, S. D.; Williams, L. J. *J. Am. Chem. Soc.* **2004**, *126*, 15348–15349. (b) Lotesta, S. D.; Hou, Y.; Williams, L. J. *Org. Lett.* **2007**, *9*, 869–872. (c) Ghosh, P.; Lotesta, S. D.; Williams, L. J. *J. Am. Chem. Soc.* **2007**, *129*, 2438–2439. (d) Lotesta, S. D.; Kiren, S.; Sauers, R. R.; Williams, L. J. *Angew. Chem., Int. Ed. Engl.* **2007**, *46*, 7108–7111. (e) Shangguan, N.; Kiren, S.; Williams, L. J. *Org. Lett.* **2007**, *9*, 1093–1096. (f) Wang, Z.-H.; Shangguan, N.; Cusick, J. R.; Williams, L. J. *Synlett* **2008**, *2*, 213–216.

(4) For cyclic bis[allenes], see: (a) Garratt, P. J.; Nicolaou, K. C.; Sondheimer, F. *J. Chem. Soc. D, Chem. Commum.* **1970**, *121*, 9–1220. (b) Baker, R.; Garratt, P. J.; Nicolaou, K. C.; Sondheimer, F. *Tetrahedron Lett.* **1972**, 3425–3428. (c) Garratt, P. J.; Nicolaou, K. C.; Sondheimer, F. *J. Am. Chem. Soc.* **1973**, *95*, 4582–4592.

(5) (a) No bis[spirodiepoxides] are known. The only cyclic spirodiepoxide reported was derived from 1,2-cyclononadiene. (b) Crandall, J. K.; Batal, D. J.; Sebesta, D. P.; Ling, F. *J. Org. Chem.* **1991**, *56*, 1153–1166.

(6) Also conveniently prepared from γ-butyrolactone, see: Corey, E. J.; Albright, J. O.; Barton, A. E.; Hashimoto, S.-I. *J. Am. Chem. Soc.* **1980**, *102*, 1435–1436.

(7) This known substance was prepared from the corresponding alcohol. Marron, B. E.; Spanevello, R. A.; Elisseou, M. E.; Serhan, C. N.; Nicolaou, K. C. *J. Org. Chem.* **1989**, *54*, 5522–5527.

(8) Normally, these mild conditions are used to effect nonchelation controlled addition, cf.: Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 556–569.

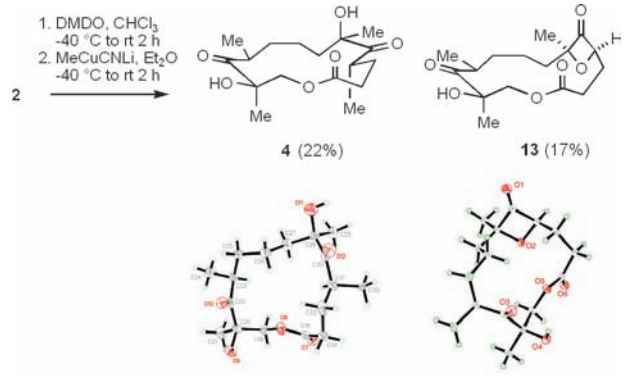
(9) The generality of these findings is under evaluation and will be reported separately.

(10) Parenty, A.; Moreau, X.; Campagne, J.-M. *Chem. Rev.* **2006**, *106*, 911–939.

Molecular modeling of **2** suggests that its low energy conformer closely resembles the structure shown in Scheme 1. The intrinsic facial bias for approach of reagent to the π-faces of an allene appears to be reenforced by cyclization.[11] Still, the selective conversion of **2** to bis[spirodiepoxide] **3** was not ensured, as each oxygen would be delivered to the substrate sequentially, and the topography and conformation of each possible intermediate on the path to **3** differ somewhat.

The synthesis of the erythronolide model proceeded smoothly. Structure assignments, including the relative stereochemistry of **2** and **5**, are inferred but unambiguous based on X-ray crystallographic analysis, as described below and illustrated in Schemes 3 and 4. Exposure of **2** to DMDO

Scheme 3



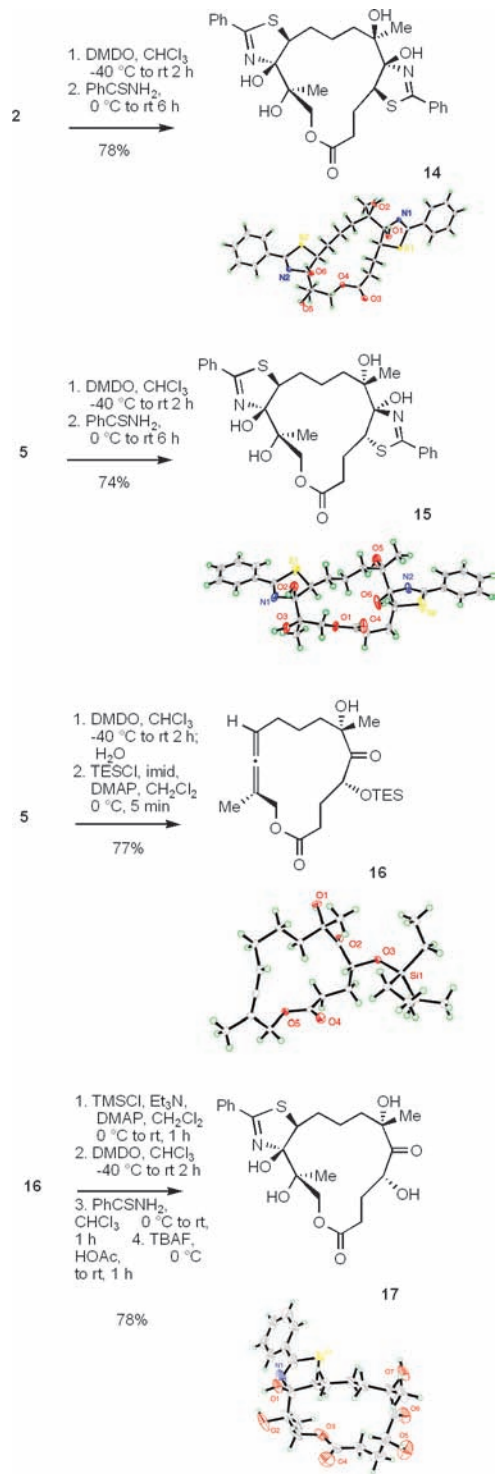
*crystal structures of **4** and **13***

(6 equiv) followed by addition of the methyl cuprate to the spirodiepoxide[3c] gave **4** (Scheme 3). Hence, exhaustive epoxidation of the cyclic bis[allene] generated the corresponding bis[spirodiepoxide] and effected the conversion of the two allene axes of chirality into six stereogenic centers. The 22% isolated yield of **4** represents the combined overall efficiency for the introduction of four oxygens as the bis[spirodiepoxide] and its subsequent conversion to the two ketones, two tertiary alcohols, and two methyl groups and thereby the selective installation of four noncontiguous stereocenters.[12]

Several other minor products were also observed. The most abundant of these, **13**, was found to contain an oxetanone in the C4−C6 sector and the desired substitution in the C10−C12 sector. The only published report of oxetanone formation from spirodiepoxide rearrangement (a single example) was effected under flash vacuum pyrolysis conditions.[5b] Presumably, **13** arises from Lewis acid mediated rearrangement of the spirodiepoxide.

In contrast to the conversion of **2** to **4**, epoxidation of **2** followed by reaction with thiobenzamide gave a 78% yield

Scheme 4



of **14**, a functionalized bis[thiazoline] (Scheme 4).[3d] Two rings and six stereogenic centers were installed by this exercise. The stereochemistry of the aminols at C5 and C11 is consistent with minimization of steric repulsion of the thiazoline substituents.

The behavior of **5** mirrored that of **2**. Molecular modeling suggested that the rendering shown in Scheme 2 is a good approximation of the low energy conformer for this sub-

(11) For a discussion of intrinsic bias and stereochemical models of spirodiepoxide formation, see: Zhang, Y.; Cusick, J. R.; Ghosh, P.; Shangguan, N.; Katukojvala, S.; Inghrim, J.; Emge, T. J.; Williams, L. J. (submitted).

(12) All products were obtained as single isomers, including **4** and **13**−**17**. There was no evidence of the formation of isomeric mixtures.

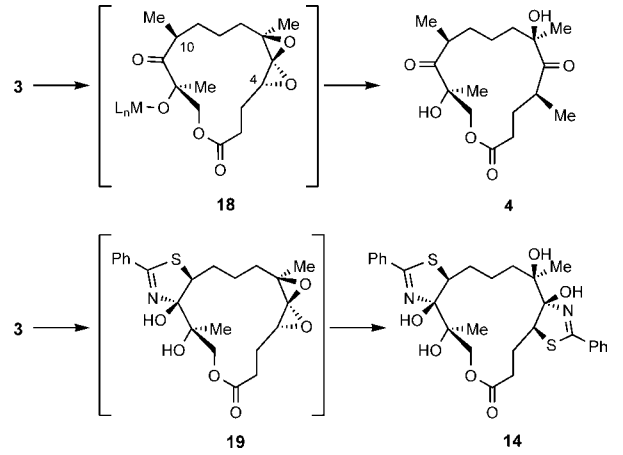
stance. DMDO oxidation of **5** gave the isomeric bis[spirodiepoxide], which we assign as **6**. Addition of thiobenzamide to this bis[spirodiepoxide] gave bis[thiazoline] **15** in excellent yield as well (74%, Scheme 4).

In the course of these studies, we noticed that the DMDO oxidation of **2** and **5** led to rapid and selective formation of mono[spirodiepoxide] intermediates. The second allene oxidized slowly at low temperature. Hence, in the presence of only 3 equiv of DMDO at 0 °C the mono[spirodiepoxide] was efficiently prepared. As shown for **5**, selective generation of the mono[spirodiepoxide] followed by addition of water gave the corresponding ketodiol. This substance is an oil at room temperature. The TES ether, **16**, however, is a crystalline solid. X-ray analysis of this material established that the spirodiepoxide was derived from the more electron-rich allene. The mono[spirodiepoxidation] was stereoselective, as expected given the conversion of **5** to **15**; water addition and silyl protection were regioselective; and the overall yield of **16** from **5** was 77%.

The differences in allene oxidation rates offer the opportunity to incorporate two divergent nucleophiles to the macrocyclic core. Accordingly, **16** was silylated and then converted to the corresponding spirodiepoxide. Thiobenzamide addition to the spirodiepoxide followed by liberation of the secondary and tertiary alcohols gave **17**. Crystallographic analysis of this material unambiguously confirmed the structural assignment.

The efficiency of these transformations, which is good for **4** and excellent for **14**−**17**, coupled with the structural diversity and complexity of the macrolides obtained illustrate the advantage of the macrocycle scaffold strategy. We suggest that the difference in efficiency for the formation of **4** and **14** from **2** stems from the behavior of the corresponding intermediates (e.g., **18** and **19**, Scheme 5). The intermediate derived from cuprate addition (**18**) differs substantially from the intermediate derived from thiobenzamide addition (**19**). Since cuprate addition to spirodiepoxides is accompanied by precipitation of the product complex, rate retardation associated with heterogeneous cuprate addition to species such as **18** could lower the overall yield for the conversion of **2** to **4** and increase the likelihood of side

Scheme 5



product formation (cf. **13**, Scheme 3). In contrast, the thiazoline intermediates, e.g., **19**, are soluble. Regardless, this strategy provides rapid and stereoselective access to targets of high complexity.

In summary, elaborated macrocycles **4** and **14**−**17** were prepared from scaffolds **2** and **5**. These precursors were readily obtained in a seven-step sequence that included the efficient single flask conversion of the two propargyl moieties to the seco acid (**11**→**12**). Whereas **16** and **17** were fashioned via multistep manipulations, model compound **4** and related structures **14** and **15** were prepared in one oxidation/addition maneuver, for a total of eight steps from commercial reagents. This strategy and studies on fully elaborated scaffolds are under evaluation and will be disclosed accordingly.

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Supporting Information Available: Synthetic methods and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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