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Double Lawton S_N2' Addition to Epoxyvinyl Sulfones: Selective Construction of the Stereotetrads of Aplyronine A†

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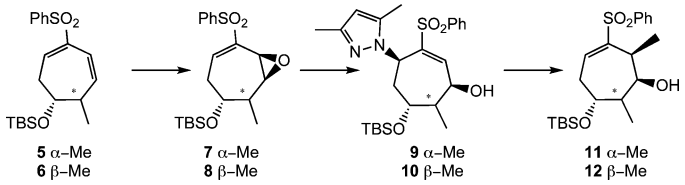
ABSTRACT



Enantiopure epoxyvinyl sulfones function as templates for the diastereoselective construction of the three stereotetrads of aplyronine A. Lawton S_N2' addition of 3,5-dimethylpyrazole followed by its displacement in an alcohol-directed Lawton S_N2' reaction establishes the required product stereochemistry with high selectivity.

Aplyronine A (**1**), a polypropionate marine natural product, was isolated and partially characterized in 1993.[1] Its absolute stereochemistry was fully proven one year later.[2] Remarkable antineoplastic activity against several tumor cell lines,[1] scarcity of supply from natural sources, and structural complexity kindled synthetic efforts of several research groups.[3] Among the structural features of aplyronine A, three stereotetrads, carbons 7−10, 23−26, and 29−32, and a 24-membered macrolactone have been central issues of the previous studies (Figure 1).

In conjunction with our program exploiting sulfone chemistry for creating stereodefined polypropionate fragments,[4] we needed a new method for preparation of segments **2**−**4** of aplyronine A (**1**) (Figure 1).

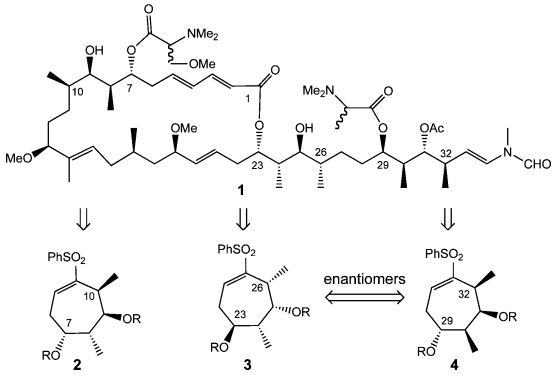


Figure 1. Aplyronine A and its stereotetrad precursors.

† Synthesis via vinyl sulfones 92; chiral carbon catalog 14.

(1) Yamada, K.; Ojika, M.; Ishigaki, T.; Yoshida, Y.; Ekimoto, H.; Arakawa, M. *J. Am. Chem. Soc.* **1993**, *115*, 11020−11021.

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Previous studies from our laboratory have demonstrated methods for stereocontrolled Lawton S_N2' addition (hybrid conjugate addition, S_N2' reaction[5]) of nucleophiles to epoxyvinyl sulfones from either diastereotopic face (α- or β-1,4).[6] We have also effected direct opening of epoxyvinyl sulfones with inversion of configuration at the epoxide-bearing carbon (β-1,2). The aplyronine synthesis now presents an opportunity to complete the synthetic toolkit by providing a strategy for α-1,2-addition to the epoxide with net retention of stereochemistry (red structure, Figure 2).

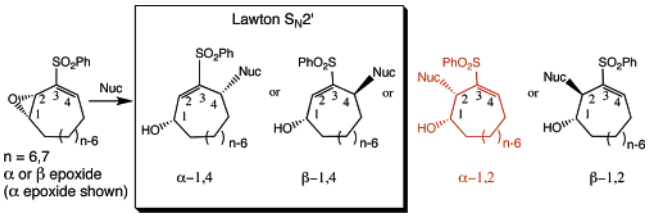
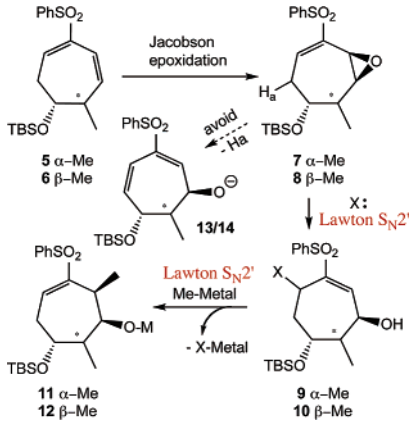


Figure 2. Addition of nucleophiles to cross-conjugated epoxyvinyl sulfones.

The synthesis begins with enantiopure cross-conjugated dienyl sulfones **5** and **6**, which are both available on the decagram scale.[4a] Double stereoselective epoxidation of **5** with Jacobsen's catalyst[7] yields epoxide **7** in 79% yield[8] (Scheme 1). 1,4-Addition of a group with hybrid nucleophilic/nucleofugic character to the epoxyvinyl sulfone moiety should afford a new substrate **9** bearing a proximal oxygen moiety appropriate for chelate-mediated S_N2' methylation.

Scheme 1. General Strategy for Stereotetrad Assembly

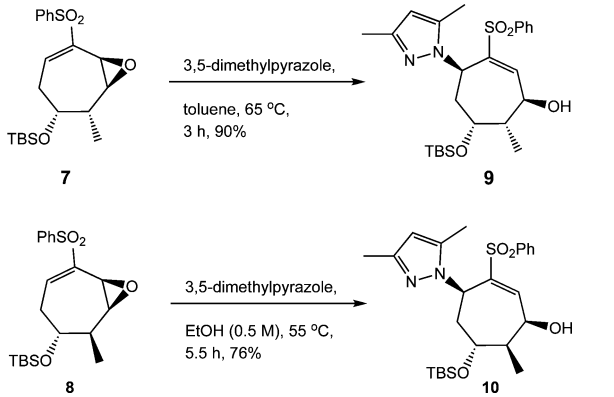


Because Jacobsen epoxidation is also applicable to dienyl sulfone **6**,[8] this strategy represents a general framework for the stereodefined construction of **2**−**4**. Furthermore, because two of the three stereotetrads of aplyronine A are enantiomeric, viz., **3** and **4**, the synthetic task simplifies to the preparation of two relative stereochemical relationships.

The appropriate nucleophile for the above strategy should fulfill certain criteria. Our desire to introduce the second methyl group via an S_N2' reaction requires that the nucleophile serves as a good leaving group. That means that it presumably must have a low pK_a. Moreover, it must initially undergo regiospecific Lawton S_N2' addition to the vinyl epoxide (α- or β-1,4 addition; Figure 2). Finally, its pK_a must be sufficiently low so that it does not affect base-promoted epoxide rearrangement of **7**/**8** to the undesired (in this case) dienylic alcohols **13**/**14**.

Finding a nucleophile that fulfilled the above criteria was a demanding task. Ethylthiol, pyrrole, lithium diethyl phosphite, and acetone cyanohydrin all returned the starting material. Thiolates, imidazole, and iodide exclusively gave 1,2-addition. Cyanide fostered base-promoted epoxide rearrangement. We had previously shown in five- and six-membered systems that secondary amines gave the desired 1,4-addition products.[9] However, because these basic amines required an additional nitrogen alkylation step to enable bond scission, we turned to the azole functionality as a compromise between nucleophilicity and nucleofugacity. Although pyrrole was totally unreactive, treatment of epoxide **7** with 3,5-dimethylpyrazole[10] resulted in a virtually quantitative yield of the coveted Lawton S_N2' product **9** as a single diastereomer (Scheme 2).

Scheme 2. Addition of 3,5-Dimethylpyrazole to **7** and **8**



On the other hand, diastereomeric epoxide **8** yielded a 5.8:

(5) For references to the evolution of the Lawton reaction, see: Brocchini, S. J.; Eberle, M.; Lawton, R. G. *J. Am. Chem. Soc.* **1988**, *110*, 5211−5212 and references therein.

(6) Jiang, W.; Lantrip, D. A.; Fuchs, P. L. *Org. Lett.* **2000**, *2*, 2181−2184 and reference 4d.

(7) (a) Jacobsen, E. N.; Zhang, W.; Muci, A. R.; Ecker, J. R.; Deng, L. *J. Am. Chem. Soc.* **1991**, *113*, 7063−7064. (b) Hentemann, M. F.; Fuchs, P. L. *Tetrahedron Lett.* **1997**, *38*, 5615−5618.

(8) Torres, E. Ph.D. Thesis, Purdue University, May 2004.

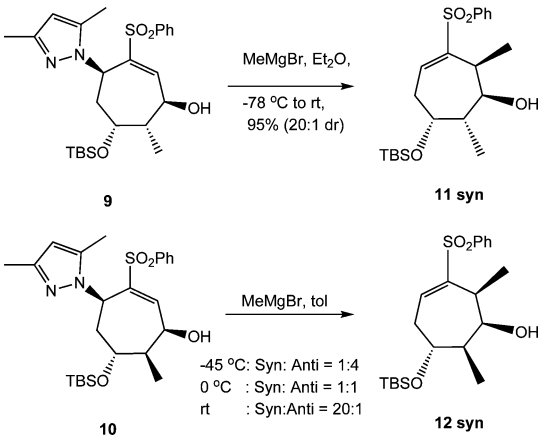
(9) Pan, Y.; Hardinger, S. A.; Fuchs, P. L. *Synth. Commun.* **1989**, *19*, 403−416. Pan, Y.; Hutchinson, D. K.; Nantz, M. H.; Fuchs, P. L. *Tetrahedron* **1989**, *45*, 467−478. Hutchinson, D. K.; Fuchs, P. L. *J. Am. Chem. Soc.* **1985**, *107*, 6137−6138. Hutchinson, D. K.; Fuchs, P. L. *J. Am. Chem. Soc.* **1987**, *109*, 4755−4756. Hutchinson, D. K.; Hardinger, S. A.; Fuchs, P. L. *Tetrahedron Lett.* **1986**, *27*, 1425−1428.

(10) Grekov, A. P.; Veselov, V. Y. *Russ. Chem. Rev.* **1978**, *47*, 631−648.

1[11] mixture of isomeric products under the same set of conditions.[12] Numerous reaction conditions were examined, and the best variant involved ethanol as the solvent (Scheme 2) and resulted in a 13:1 ratio in favor of the desired product **10**. Recrystallization gave **10** in ca. 30:1 ratio and 76% yield,[13] obviating tedious chromatography.[14]

Attention was then directed toward Lawton S_N2' methylation (Scheme 3). Expecting hydroxyl group direction of the

Scheme 3. Lawton S_N2' Methylation



methylation reaction, we screened a number of alternative methylating agents. Methyllithium (2.2 equiv) resulted in complicated product mixtures. Trimethylaluminum plus methyllithium yielded a single diastereomer yet failed to deliver more than 50% conversion. Finally, the use of 3 equiv of methyl Grignard reagent in ether proved optimal, yielding the stereotetrad in more than 95% conversion and 20:1 ratio in favor of the desired **11 syn**.

The reaction of **10** with MeMgBr under conditions identical to those of **9** resulted in a 10:1 ratio of epimers in favor of the desired product **12 syn**. Attempts to increase the selectivity by running the reaction at 0 °C instead of at ambient temperature resulted in a disappointing 1:1 mixture of **12 syn/anti** epimers. Excitingly, when the reaction was run at −45 °C,[15] it gave a 4:1 ratio favoring **12 anti**.[16] Finally, when the reaction was run completely at ambient temperature, a 20:1[17] selectivity was obtained in favor of the desired **12 syn**. This temperature-dependent selectivity was not paralleled in the case of **9**, which was totally inert to methylmagnesium bromide at temperatures below −30 °C for more than 40 h.

To explain the temperature-dependent reversal of selectivity, equilibrium between two conformations of the magnesium alkoxide **10A** and **10B** is postulated (Figure 3).

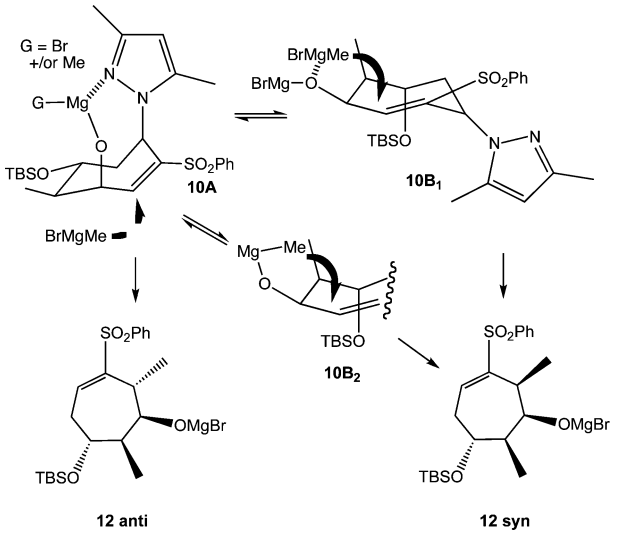


Figure 3. Temperature-dependent reversal of selectivity in the addition of MeMgBr to **10**.

Conformation **10A** has the magnesium coordinated to both the alkoxide and the nitrogen of the pyrazole ring, which results in blockage of the β-face of the seven-membered ring, and consequently, addition of the methyl group is only possible from the α-face, resulting in an anti relationship between the alkoxide and the new methyl group. This conformation is preferred in the crystal structure of **10**, which shows a hydrogen bond between the hydroxyl group and the pyrazole nitrogen.[18] Evidence for the hydrogen bond in solution is provided by the ^{1}H NMR spectrum, which exhibits the hydroxyl hydrogen resonance at 6.9 δ, indicative of hydrogen bonding to the nitrogen atom of the pyrazole ring. Furthermore, that hydrogen exhibits a coupling constant of 11.1 Hz[19] with the hydrogen vicinal to it. That value indicates a rigid trans-diaxial relationship between both hydrogens, which puts the hydroxyl hydrogen in an ideal position for hydrogen bonding with the nitrogen atom. In conformation **10B**, the magnesium ion is not coordinated to the pyrazole nitrogen and directs the attack of the methyl group from the β-face either after Schlenck equilibrium and replacement of the bromide by a methyl ligand or from another methylmagnesium bromide molecule in the same aggregate. Because addition of the methyl group to conformation **10B** is an intramolecular event, whereas addition to conformation **10A** is an intermolecular event, the desired epimer prevails at ambient temperature via rapid equilibration of **10A** and **10B**. However, at −45 °C, the equilibrium presumably greatly favors conformation **10A** resulting in skewing the product ratio in favor of the undesired epimer.

(11) Unless otherwise specified, diastereomeric ratios are based on crude ^{1}H NMR integration.

(12) Attempts to isolate and characterize the minor product by chromatography resulted in its conversion to three inseparable compounds.

(13) The yield after flash column chromatography is 90%.

(14) The relative and absolute stereochemistries were determined by X-ray analysis of a single crystal. See Supporting Information.

(15) The reaction is very slow at −45 °C requiring 3 days for completion.

(16) The relative stereochemistry of the alternate epimer was confirmed by X-ray analysis of a single crystal.

(17) After flash column chromatography, the ratio becomes 50:1.

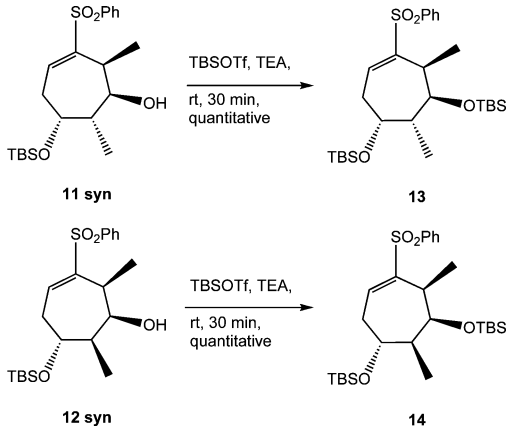
(18) See crystal structure in Supporting Information.

(19) The fact that directly attached electronegative atoms tend to reduce J values further corroborates the degree of the conformational rigidity. See: Friebolin, H. *Basic One- and Two-Dimensional NMR Spectroscopy*, 3 ed.; Wiley-VCH: Weinheim, 1998; Chapter 3, p 93.

It is remarkable that, although vinyl sulfones are amenable to S_N2 attack by Grignard reagents, **11 syn** and **12 syn** do not further react under the above reaction conditions, and no trimethyl products were isolated even using 2.6 equiv of methylmagnesium bromide, which indicates a significant difference in reactivity between the starting material and product.

Di-TBS protected **13** and **14** were found to be crystalline, which permitted X-ray confirmation[18] of the relative and absolute stereochemistries of **11 syn** and **12 syn** (Scheme 4). Having stereotetrad **12 syn** in hand guarantees the

Scheme 4. Preparation of Crystalline Derivatives of **16** and **17**



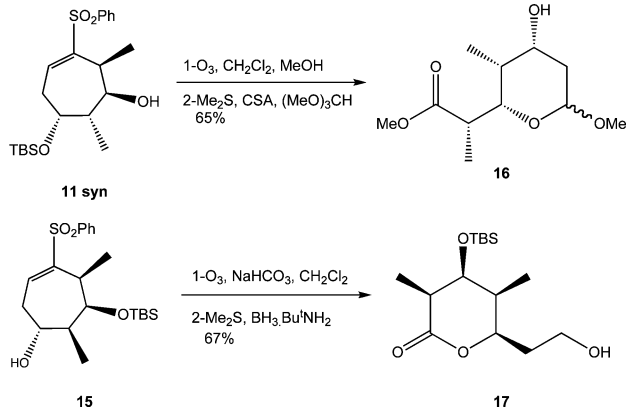
preparation of the enantiomeric stereotetrad **3**.

Oxidative cleavage of the stereotetrads **11 syn** and **15**[20] yielded termini differentiated stereotetrads **16** and **17** (Scheme 5) which are being advanced with other fragments for assembly of aplyronine A.

In conclusion, we have developed a unified strategy for the synthesis of the polypropionate fragments of aplyronine

(20) Obtained by selective deprotection of **14**. See Supporting Information.

Scheme 5. Oxidative Cleavage of Vinyl Sulfone Stereotetrads



A. The method relies on catalytic asymmetric and substrate-directed reactions for stereocontrol, thereby avoiding the use of chiral auxiliaries. Two sequential highly chemo- and stereoselective Lawton S_N2' reactions serve to establish the desired product stereochemistry. Progress toward the synthesis of aplyronine A, and further extension of this methodology for the construction of other polypropionate fragments, will be published in due course.

Acknowledgment. A.E. dedicates this work to Ahmad Shams, an inspiring high school chemistry teacher. We thank Arlene Rothwell and Karl Wood for providing MS data.

Supporting Information Available: Experimental procedures and characterization data for all new compounds, including X-ray data for **10**, **11 anti** di-TBS, **13**, and **14** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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