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Synthesis of Termini-Differentiated 6-Carbon Stereotetrads: An Alkylative Oxidation Strategy for Preparation of the C21–C26 Segment of Apoptolidin[1]

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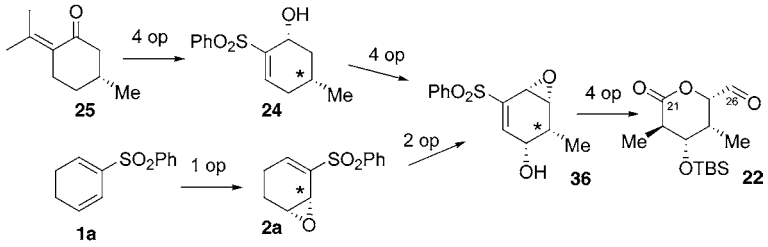
ABSTRACT



Two methods have been developed for the synthesis of epoxide 36. The first uses (+)-pulegone 25 as an enantiopure starting material and introduces the requisite intricacy of target 22 in 12 operations. The second method employs an enantiospecific catalytic Jacobsen epoxidation of 1a and is five operations shorter. The second sequence features an oxygen-directed alkylative oxidation reaction that re-establishes the dienyl sulfone functionality with concomitant 1,3-transposition of the sulfone moiety.

We have previously reported on vinyl epoxides **2a**[2a] and **2b**,[2b] which are available by enantiospecific epoxidation of the parent dienes **1a** and **1b**.[3] Elimination and epoxidation followed by nucleophilic addition places stereogenic centers at three of the four possible ring atoms (stars, Figure 1).

Cyclohexenones **4** with 4-hydroxy[4] and 4-alkyl[5] substituents are readily available in very high enantiopurity and are suitable starting points for accessing the remaining position in the triflate series since the parent compound is itself derived from cyclohexenone[6] The sulfone series either requires starting with enantiopure dienes **6** or **7** or, alternatively, devising a means of introducing functionality at the "unstarred" position of **3a**.

During our investigation, Arjona, Menchaca, and Plumet published their seminal study of polypropionate stereotetrad

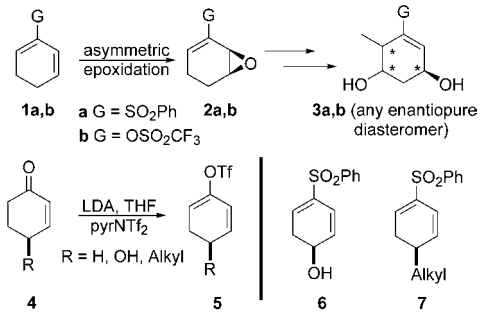


Figure 1.

(1) Syntheses via vinyl sulfones #88. Chiral Carbon Catalog 12.
(2) (a) Hentemann, M. F.; Fuchs, P. L. *Org. Lett.* **1999**, *1*, 355. (b) Hentemann, M. H.; Fuchs, P. L. *Tetrahedron. Lett.* **1999**, *40*, 2699.
(3) Hentemann, M. F.; Fuchs, P. L. *Tetrahedron Lett.* **1997**, *38*, 5615.
(4) Evarts, J.; Fuchs, P. L. *Tetrahedron. Lett.* **2001**, *42*, 3673.
(5) Evarts, J.; Torres, E.; Fuchs, P. L. *J. Am. Chem. Soc.* **2002**, *124*, 11093.
(6) All permutations of stereochemistry have been completed for the 4-hydroxy series. Evarts. J.; Fuchs, P. L. *Tetrahedron. Lett.* **1999**, *40*, 2703. The 4-methyl triflate series has also been investigated. Evarts, J. Ph.D. Thesis, Purdue University, West Lafayette, IN, 2001.

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synthesis using vinyl sulfones.[7] The absolute asymmetry was (or could be)[8] achieved by using 7-oxabicyclo [2.2.1] starting materials **10**[9] and **15** prepared by Diels−Alder reaction with furan **8**. Key features of their methodology included use of the bridging oxygen as a leaving group during nucleophilic methylation of **11** and **16** as well as highly selective Schreiber ozonolysis to establish the termini-differentiated stereotetrads. Figure 2 shows two examples, but the entire family of eight diastereomeric tetrads was prepared.

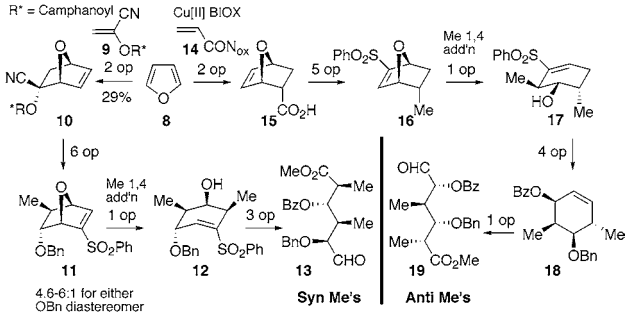

Figure 2.

In conjunction with synthesis of apoptolidin **20**[10] (Figure 3), we sought to construct the C21−C26 lactone precursor **22** of intermediate **21** via oxidative cleavage of the 6-carbon vinyl sulfone **23**. Enantiopure **23** can be accessed from both methyl vinyl sulfone **24** and epoxy vinyl sulfone **2a**.

Our initial synthesis began with the known epoxidation of (*R*)-(+)-pulegone **25** followed by treatment with sodium thiophenoxide providing α-ketosulfide **26.**[11] mCPBA oxidation of **26** gave sulfoxide **27** in a 71% overall yield from **25**. Reaction of **27** with acetic anhydride and methanesulfonic acid effects Pummerer elimination generating vinyl sulfide **28** in 94% yield.[12] Luche reduction of ketone **28** followed by addition to oxone-methanol gave sulfone **24** (Figure 4). Conversion of alcohol **24** to the corresponding mesylate followed by careful, low-temperature treatment with LiHMDS cleanly gave diene **29**. Epoxidation with mCPBA resulted in an unexpectedly inseparable 3:2 mixture of diastereomeric epoxides **30** and **31**. Attempts to improve this oxidation by employing double stereoselection with Jacobsen asymmetric epoxidation[3] provided a 55% yield of **30/31** in 6:1 selectivity accompanied by 35% aromatization.

To avoid the separation and yield problem created by the **30/31** mixture, we returned to vinyl sulfone **24** and examined base-catalyzed equilibration of this intermediate. Isomerization of **24** (Figure 5) with 5 mol % DBU for 15 h generated a 1:2.5 equilibrium mixture of **24/32**, which upon crystallization provided a first crop 46% yield of pure **32.**[13] Two

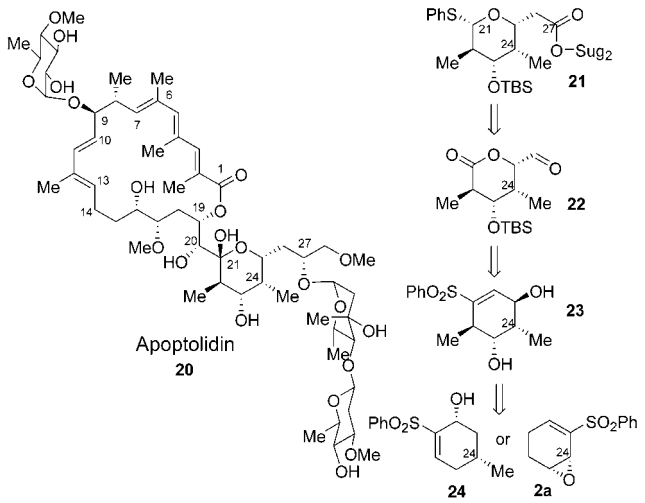

Figure 3.

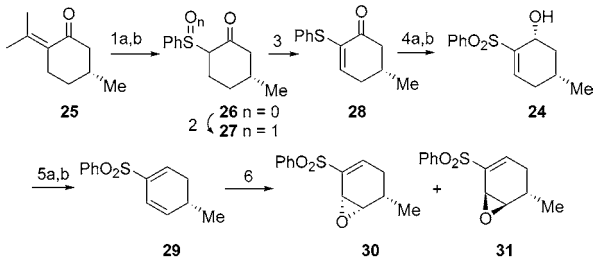

Figure 4. (1) (a) 30% H_2O_2, LiOH, MeOH, 25 °C, 8 h 94%; (b) PhSNa, THF reflux, 18 h 84%. (2) mCPBA, CH_2Cl_2, −30 °C, 2 h 90%. (3) Ac_2O, CH_3SO_3H (cat.), CH_2Cl_2, 25 °C, 14 h, 94%. (4) (a) $CeCl_3$, $NaBH_4$, MeOH, 25 °C, 30 min, 95%; (b) oxone, H_2O, MeOH, 25 °C, 24 h, 95%. (5) (a) MsCl, Et_3N, CH_2Cl_2, 0°C, 1 h; (b) LiHMDS, THF, −78 °C, 90%. (6) mCPBA, CH_2Cl_2, 25 °C, 3 h, 84% (**30**:**31** = 3:2), or (*R*,*R*)-Mn(salen)Cl (5 mol %), 30% H_2O_2, CH_2Cl_2/MeOH (1:1), 0 °C, 8 h, 55% (**30**:**31** = 6:1).

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(8) Compound **15** was used as a racemic mixture (Acena, J. L.; Arjona, O.; Leon, M.; Plumet, J. *Tetrahedron Lett.* **1996**, *37*, 8957), but enantiopure material is now available via a chiral-catalyzed Diels−Alder reaction of furan and prochiral vinyl amide-oxazolidinone: Evans, D. A.; Barnes, D. M. *Tetrahedron Lett.* **1997**, *38*, 57. Two additional high-yielding operations are included to formally enable comparisons in the enantiopure series.

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(12) Monteiro, H. J.; Gemal, A. L. *Synthesis* **1975**, *75*, 437.

(13) Structure verified by X-ray crystallography. X-ray data for compounds **32** and **33** have been submitted to the Cambridge Crystallographic database.

additional crops of **32** were collected via further equilibration of the crystallization residues for a final yield of 79%. mCPBA epoxidation of **32** in methylene chloride at 25 °C was slow, but afforded **33**[13] in 86% yield. Sequential treatment of **33** with mesyl chloride and 2 equiv of LiHMDS smoothly generated dienyl sulfone **35** in 92% yield, presumably via the intermediacy of epoxyvinyl sulfone **30** (Figure 5).

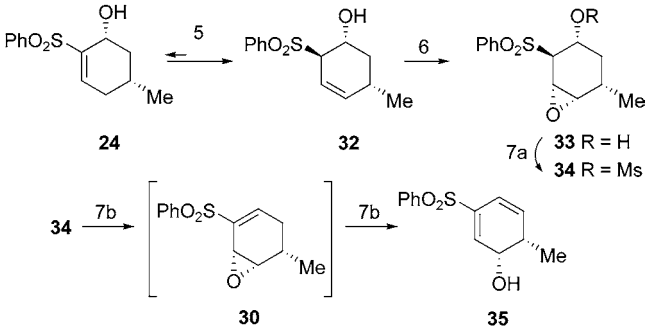

Figure 5. (5) DBU (5 mol %), CH_2Cl_2, 79%. (6) mCPBA, CH_2Cl_2, 3 days, 25 °C, 86%. (7) MsCl, 2 equiv of LiHMDS, −78 °C, 15 min, 92%.

Directed catalytic epoxidation[14] of alcohol **35** with $Mo(CO)_6$ (5 mol %) and TBHP in benzene at reflux for 1 h smoothly gave **36** as a single diastereomer in 94% yield. Treatment of alcohol **36** with trimethylaluminum in the presence of a catalytic amount of methylcopper[15] affords **37** in 91% yield. The nucleophilic methylation reaction has the potential of both 1,2- and 1,4-addition modes. In this instance, any competitive 1,2-trans-addition results in formation of the *enantiomer* of **37**, an especially serious consequence. Fortunately, chiral HPLC demonstrates that the enantiomeric excess of **37** is >98%, which indicates a 1,4-/1,2-selectivity ratio of >49:1 in the methylation process (Figure 6).

The allylic hydroxyl of diol **37** can be selectively inverted using the Mitsunobu reaction to give **23** in 95% yield. Sequential treatment of **23** with excess *tert*-butyldimethylsilyl chloride, followed by cleavage of the less-hindered silyl ether with 1 equiv of TBAF delivers **38** in 84% yield. Finally, ozonolysis of **38** in methylene chloride gives aldehyde **22**. For long-term storage, **22** is reduced with $LiAlH(O\text{-}tBu)_3$ to afford alcohol **39** in 50% overall yield from **38**. (Figure 6).

Although acceptable in terms of material supply, the synthesis was longer than desired. A superior synthesis of key fragment **36** begins with scale-up and improvement of the Jacobsen epoxidation reaction.[3] Beginning with dienyl sulfone **1a**,[16] we now produce epoxyvinyl sulfone **2a**[2] in 60% yield on 50 g scale and >97% ee by using a 6-fold-reduced catalyst load (2.5 vs 15%).

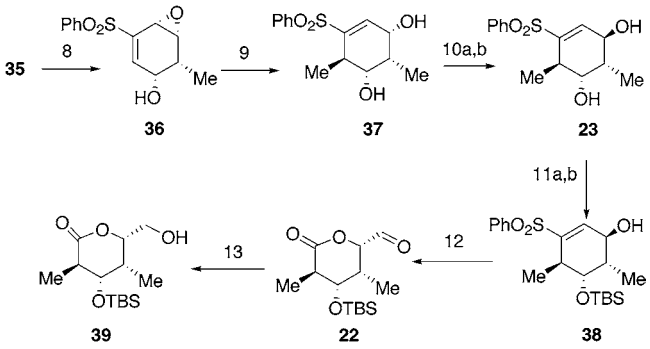

Figure 6. (8) $Mo(CO)_6$ (5 mol %), TBHP, C_6H_6, reflux, 1.5 h, 94%. (9) $AlMe_3$, 2.2 equiv, CuMe (cat), THF, from −78 to 25 °C, 10 h, 91%. (10) (a) PPh_3, DEAD, HCO_2H, THF, 2 h; (b) $NaHCO_3$, MeOH, 30 min, 95%, two steps. (11) (a) TBSCl, 4 equiv of imidazole, DMF, 70 °C, 20 h; (b) TBAF, 1.1 equiv of THF, 25 °C, 30 min, 84%, two steps. (12) (a) O_3, $NaHCO_3$, CH_2Cl_2, −30 °C, 1 h; (b) $(CH_3)_2S$, 25 °C, 5 h. (13) $LiAlH(O\text{-}tBu)_3$, THF, −78 °C, 1 h, 50%, two steps.

Reaction of epoxyvinyl sulfone **2a** with LiHMDS affords oxido diene **40**, which may be isolated as the dienyl alcohol if desired.[2] In most instances, we no longer isolate this intermediate. For example, addition of 1.1 equiv of LiHMDS to **2a** followed by 2.5 equiv of MeLi generates dianion **41**. Further addition of $(PhS)_2$ results in regiospecific capture of allyl sulfonyl anion **41** to produce vinyl sulfide **43** (isolated as the alcohol) in 82% yield after stirring for 8 h at 25 °C. As has been shown in the seven-membered ring series,[17] formation of intermediate **42** proceeds via conjugate addition of methyllithium followed by γ-sulfenylation. *The unusual γ-regiochemistry of this process appears to result from the interplay of the weak sulfenylation reagent in concert with the high steric demand imposed by the proximally methylated α-sulfonyl center.*

NMR studies confirm that initial intermediate **42** suffers thermodynamic base-catalyzed equilibration to γ-phenylthioallyl sulfone **43**. TMS-triflate-promoted, lone-pair-assisted[18] elimination of the crude diastereomeric mixture **44** to dienyl sulfide **45** was readily accomplished in 94% yield by heating **44** with 5.0 equiv of TMSOTf and 6.0 equiv of Et_3N in methylene chloride at reflux for 4 h. The mixture was then cooled to 0 °C, and 2.5 equiv of mCPBA was added in portions; the mixture was left stirring for 6 h at 25 °C to afford dienyl sulfone **35**.

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(17) Torres, E.; Chen, Y.; Kim, I.; Fuchs, P. L. Submitted for publication.

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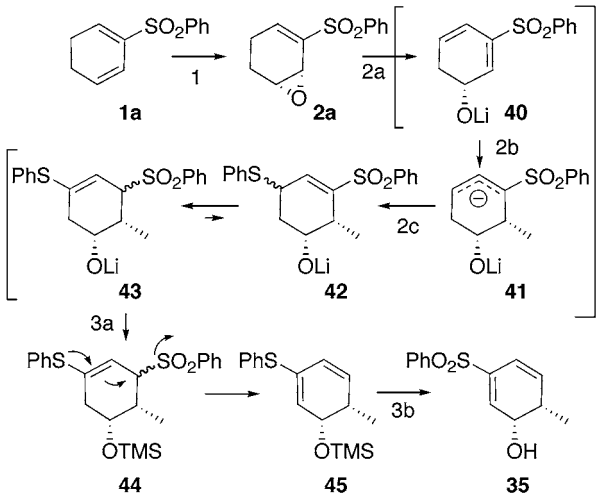

Figure 7. (2) (a) LiHMDS, THF, −78 °C, 98%; (b) 2.5 equiv of MeLi, THF, −78 °C; (c) $(PhS)_2$, THF, −78 → 25 °C, 82%. (3) (a) 5.0 equiv of TMSOTf, 6.0 equiv of Et_3N, CH_2Cl_2, reflux 4 h; (b) 2.5 equiv of mCPBA, 0 → 25 °C, 6 h, 89%.

The net effect of the sulfenylation/elimination sequence is the transposition of the sulfur-substituted dienyl system with simultaneous and stereospecific introduction of a methyl group at a previously inaccessible position.

In conclusion, two methods have been developed for the synthesis of epoxide **36**. The first uses (+)-pulegone **25** as an enantiopure starting material and introduces the requisite intricacy of target **22** in 12 operations. The second method employs an enantiospecific catalytic Jacobsen epoxidation of **1a** and is five operations shorter.

Using a pair of formulas devised for analysis of organic synthesis,[19] it can be seen that the overall synthesis from **25** is efficient in terms of yield per operation (EQ = 87%) but suffers badly from the overall number of operations, resulting in an IQ (intricacy quotient) of only 0.50. The second synthesis from **1a** is lower-yielding per operation but enjoys an IQ of ~0.7, which places it in the middle of a group of the "top 40" syntheses employed as the basis set to devise the two analytical tools (Figure 8).

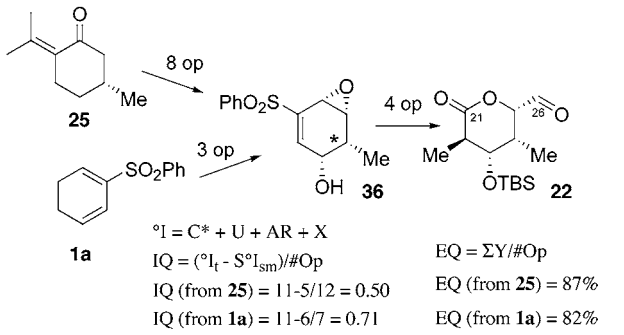

Figure 8.

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Supporting Information Available: Experimental procedures and copies of ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

OL026377M

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