Synthesis of Termini-Differentiated 6-Carbon Stereotetrads: An Alkylative Oxidation Strategy for Preparation of the C21–C26 Segment of Apoptolidin¹

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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-hydroxy⁴ and 4-alkyl⁵ 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 cyclohexenone⁶ The sulfone series either requires starting with enantiopure dienes **6** or **7** or, alterna-

(1) Syntheses via vinyl sulfones #88. Chiral Carbon Catalog 12.
(2) (a) Hentemann, M. F.; Fuchs, P. L. Org. Lett. 1999, 1, 355. (b)

(4) Evarts, J.; Fuchs, P. L. *Tetrahedron. Lett.* **2001**, *42*, 3673.

tively, 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





^{(2) (}a) Hentemann, M. H., Fuchs, F. L. *Org. Lett.* **1999**, 40, 2699. (3) Hentemann, M. F.; Fuchs, P. L. *Tetrahedron. Lett.* **1999**, 40, 2699.

⁽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.

synthesis using vinyl sulfones.⁷ The absolute asymmetry was (or could be)⁸ achieved by using 7-oxabicyclo [2.2.1] starting materials 10⁹ 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.





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 methane-

(7) Arjona, O.; Menchaca, R.; Plumet, J. J. Org. Chem. 2001, 66, 2400. (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-vielding operations are included to formally enable comparisons in the enantiopure series

(9) Vieira, E.; Vogel, P. Helv. Chim. Acta 1983, 66, 1865.

(10) Hayakawa, Y.; Kim, J. W.; Adachi, H.; Shin-ya, K.; Fujita, K.-I.; Seto, H. J. Am. Chem. Soc. 1998, 120, 3524. For efforts directed toward the synthesis of apoptolidin, see: Nicolaou, K. C.; Li, Y.; Weyershausen, B.; Wei, H.-X. Chem. Commun. 2000, 307. Sulikowski, G. A.; Lee, W.-M.; Jin, B.; Wu, B. Organic Lett. 2000, 2, 1439. Schuppan, J.; Wehlan, H.; Keiper, S.; Koert, U. Angew. Chem., Int. Ed. 2001, 40, 2063. Schuppan, J.; Ziemer, B.; Koert, U. Tetrahedron Lett. 2000, 41, 621. Toshima, K.; Arita, T.; Kato, K.; Tanaka, D.; Matsumura, S. Tetrahedron Lett. 2001, 42, 8873. Nicolaou, K. C.; Li, Yiwei; F., Konstantina, C.; Mitchell, H. J.; Wei, H.-X.; Weyershausen, B. Angew. Chem., Int. Ed. 2001, 40, 3849. Nicolaou, K. C.; Li, Y.; Fylaktakidou, K. C.; Mitchell, H. J.; Sugita, K. Angew. Chem., Int. Ed. 2001, 40, 3854.

(11) (a) Mutti, S.; Daubie, C.; Decalogne, F.; Fournier, R.; Rossi, P. Tetrahedron Lett. 1996, 37, 3125. (b) Caine, D.; Procter, K.; Cassell, R. A. J. Org. Chem. 1984, 49, 2647. (c) Avery, M. A.; Chong, W. K. M.; Jennings-White, C. J. Am. Chem. Soc. 1992, 114, 974. (d) Nangia, A.; Prasuna, G. Synth. Commun. 1994, 24, 1989.

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



Figure 3.

sulfonic 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



Figure 4. (1) (a) 30% H₂O₂, LiOH, MeOH, 25 °C, 8 h 94%; (b) PhSNa, THF reflux, 18 h 84%. (2) mCPBA, CH₂Cl₂, -30 °C, 2 h 90%. (3) Ac₂O, CH₃SO₃H (cat.), CH₂Cl₂, 25 °C, 14 h, 94%. (4) (a) CeCl₃, NaBH₄, MeOH, 25 °C, 30 min, 95%; (b) oxone, H₂O, MeOH, 25 °C, 24 h, 95%. (5) (a) MsCl, Et₃N, CH₂Cl₂, 0°C, 1 h; (b) LiHMDS, THF, -78 °C, 90%. (6) mCPBA, CH₂Cl₂, 25 °C, 3 h, 84% (30:31 = 3:2), or (*R*,*R*)-Mn(salen)Cl (5 mol %), 30% H₂O₂, $CH_2Cl_2/MeOH$ (1:1), 0 °C, 8 h, 55% (**30:31** = 6:1).

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 epoxidation³ 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

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

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 %), CH₂Cl₂, 79%. (6) mCPBA, CH₂-Cl₂, 3 days, 25 °C, 86%. (7) MsCl, 2 equiv of LiHMDS, -78 °C, 15 min, 92%.

Directed catalytic epoxidation¹⁴ 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 methylcopper¹⁵ 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-*t*Bu)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) AlMe₃, 2.2 equiv, CuMe (cat), THF, from -78 to 25 °C, 10 h, 91%. (10) (a) PPh₃, DEAD, HCO₂H, THF, 2 h; (b) NaHCO₃, 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) O₃, NaHCO₃, CH₂Cl₂, -30 °C, 1 h; (b) (CH₃)₂S, 25 °C, 5 h. (13) LiAlH(O-*t*Bu)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-assisted¹⁸ 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 Et₃N 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**.

⁽¹⁴⁾ Broom, S. J.; Ede, R. M.; Wilkins, A. L. *Tetrahedron Lett.* **1992**, *33*, 3197. Sharpless, K. B.; Michaelson, R. C. J. Am. Chem. Soc. **1973**, *95*, 6136.

⁽¹⁵⁾ Saddler, J. C.; Fuchs, P. L. J. Am. Chem. Soc. 1981, 103, 2112.

⁽¹⁶⁾ Myers, D.; Fuchs, P. L. J. Org. Chem. 2002, 60, 200–204. The 2-phenylsulfonyl-1,3-cycloheptadiene 1a precursor to 2a is commercially available from Aldrich.

⁽¹⁷⁾ Torres, E.; Chen, Y.; Kim, I.; Fuchs, P. L. Submitted for publication.
(18) While ionization of the γ-phenylsulfonyl moiety of acyclic vinyl ethers and vinyl sulfides is known to generate enones and enals (Trost, B. M.; Ghadiri, M. R. Bull. Soc. Chim. Fr. 1993, 130, 433. Craig, D.; Etheridge, C. J. Tetrahedron Lett. 1993, 34, 7487. Harmata, M.; Fletcher, V. R.; Claassen, R. J., II. J. Am. Chem. Soc. 1991, 113, 9861. Ogura, K.; Iihama, T.; Takahashi, K.; Iida, H. Tetrahedron Lett. 1984, 25, 2671. Craig, D.; Etheridge, C. J.; Smith, A. M. Tetrahedron Lett. 1992, 33, 7445–7446), the corresponding reaction for cyclic substrates is less common. Kim, S. H.; Jin, Z.; Fuchs, P. L. Tetrahedron Lett. 1995, 36, 4537. Jin, Z.; Fuchs, P. L. J. Am. Chem. Soc. 1995, 117, 3022; J. Am. Chem. Soc. 1994, 116, 5995.



Figure 7. (2) (a) LiHMDS, THF, $-78 \,^{\circ}$ C, 98%; (b) 2.5 equiv of MeLi, THF, $-78 \,^{\circ}$ C; (c) (PhS)₂, THF, $-78 \rightarrow 25 \,^{\circ}$ C, 82%. (3) (a) 5.0 equiv of TMSOTf, 6.0 equiv of Et₃N, CH₂Cl₂, reflux 4 h; (b) 2.5 equiv of mCPBA, $0 \rightarrow 25 \,^{\circ}$ 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).

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

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(19) Fuchs, P. L. Tetrahedron 2001, 57, 6855.