

Short Synthesis of (+)-Aspicilin via Asymmetric Hexahydroxylation of a Triene

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Summary: Asymmetric synthesis of the 18-membered lichen macrolide (+)-aspicilin has been achieved in 14 steps and 11% overall yield, starting from an achiral hydrocarbon, (3*E*)-hexadeca-1,3,15-triene. All four stereogenic carbinol centers have been introduced by three Sharpless asymmetric dihydroxylation (AD) reactions, using both AD-mix- β and AD-mix- α to produce the hexol with very high regio- and enantioselectivity (epimeric excess of 88% at position 2, 96% at positions 3 and 4, and 86% at position 15).

Nature synthesizes polyoxygenated carbon skeletons by multistep assembly of polyketide chains followed by manipulation of the oxygen functions.¹ Mimicking nature, chemists have also been using carbonyl chemistry as the main tool for synthesis of macrolide antibiotics,² polyether antibiotics,³ marine toxins,⁴ etc. An alternative strategy, one that selectively places the oxygen functions onto a naked carbon skeleton, could facilitate the synthesis of such compounds. Here, we demonstrate this idea by a short synthesis of the 18-membered lichen macrolide (+)-aspicilin, 1,⁵ starting from an achiral, unsaturated hydrocarbon.

Introduction of four stereogenic carbinol centers with the correct absolute configuration represents the crucial part in any synthesis of aspicilin.⁶ We reasoned that hexahydroxylation of triene 2,⁷ using the Sharpless asymmetric dihydroxylation (AD) reaction,⁸ would engender all four asymmetric centers with high enantiomeric purity. However, retrosynthetic analysis indicates that in order to achieve the 5*R*,6*S*,7*R*,18*S* configuration of aspicilin, this operation cannot be carried out in a single AD step. Introduction of six oxygen functions into 2 with the

absolute configuration shown in 9 (Scheme 1) requires a sequence of three regioselective AD steps, using both AD-mix- β and AD-mix- α .⁹ Consequently, the question of regioselective dihydroxylation of a polyene¹⁰ became the crucial issue of the entire synthetic strategy. Therefore, we studied the relative reactivity of the three double bonds in 2 toward AD-mix- β using increasing amounts of the reagent (Table 1).

The relative proportions of diols 3–5 produced under conditions of low conversion (entry 1) indicate that the disubstituted double bond is approximately five times more reactive than the two monosubstituted ones,¹¹ each of which exhibits comparable reactivity. As has already been observed in AD reactions with conjugated dienes,^{12,13} dihydroxylation of one double bond strongly inhibits the reactivity of the remaining one toward further dihydroxylation, probably due to increased steric demands. Thus, further dihydroxylation of dienes 3 and 4 occurs exclusively at the C-15 double bond, producing tetrols 6 and 7, respectively (entries 2–5). The relatively low proportions of 7 observed under increased concentration of oxidant reflect the high preference of 5 to produce 6 rather than 7. Expectedly, further dihydroxylation of 6 and 7 to hexols appears to be slow even with 0.5% catalyst (9% after 8 h and 20% after 18 h, entries 4 and 6). This is supported by the observed yields of isolated 7 which follow faithfully its GC-determined relative proportions in the mixture (entries 2–5).

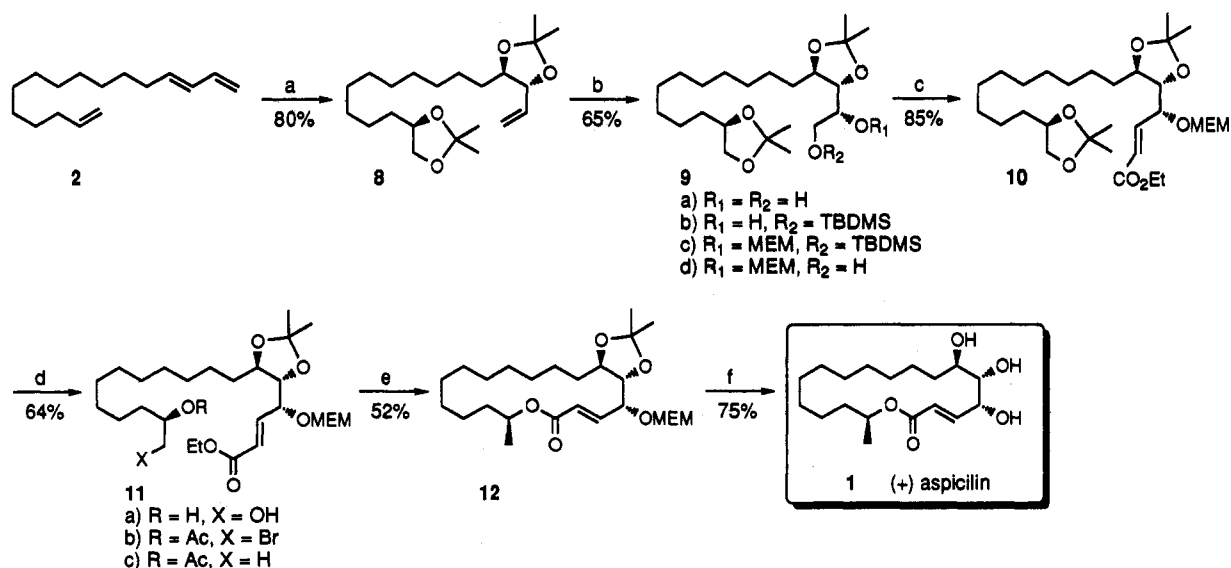
Isolation of the bis-acetonide 8, [α]_D -10.0 (*c* = 2.50, CHCl₃), in 80% yield from the AD reaction of 2 (using 2 or more equiv of AD-mix- β followed by treatment with dimethoxypropane) set the stage for a short and efficient synthesis of (+)-aspicilin (Scheme 1). The enantiomeric purity of 8 was found to be 83% (86% epimeric excess¹⁴ at position 15 and 96% at positions 3 and 4), as determined by ¹H NMR of the appropriate Mosher ester derivatives.¹⁵ Reaction of 8 with AD-mix- α in 2-methyl-2-propanol–water at 0 °C for 48 h produced the desired (2*R*)-1,2-dihydroxy derivative 9a in 77% yield, along with 10% of its 2*S* epimer.

Having all asymmetric centers in place, we turned to the next key step, i.e., two-carbon extension of the carbon skeleton to form an α,β -unsaturated carboxyl function, a transformation that could be achieved via Wittig–Horner

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• Abstract published in *Advance ACS Abstracts*, February 15, 1994.(1) (a) Vederas, J. C. *Nat. Prod. Rep.* 1987, 4, 227. (b) Simpson, T. *J. Nat. Prod. Rep.* 1987, 4, 339.(2) Kirst, H. In *Recent progress in the chemical synthesis of antibiotics*; Lukacs, G., Ohno, M., Eds.; Springer-Verlag: Berlin, 1990; pp 39–63.(3) Yonemitsu, O.; Horita, K. *Ibid.* pp 447–466.(4) Yasumoto, T.; Murata, M. *Chem. Rev.* 1993, 93, 1897.(5) (a) For isolation of aspicilin see: Hesse, O. *J. Prakt. Chem.* 1900, 62, 430; 1904, 70, 449. (b) For basic structure determination see: Huneke, S.; Schreiber, K.; Steglich, W. *Tetrahedron* 1973, 29, 3687. (c) For X-ray structure determination see: Quinkert, G.; Heim, N.; Bats, J. W.; Oechkinat, H.; Kessler, H. *Angew. Chem., Int. Ed. Engl.* 1985, 24, 987.(6) (a) For synthesis of (+)-1 from D-mannose, see: Quinkert, G.; Fernholz, E.; Eckes, P.; Neumann, D.; Dürner, G. *Helv. Chim. Acta* 1989, 72, 1753. For synthesis from (S)-methyloxirane, see: (b) Quinkert, G.; Heim, N.; Glenneberg, J.; Döller, U.; Eichhorn, M.; Billhardt, U.-M.; Schwarz, C.; Zimmermann, G.; Bats, J. W.; Dürner, G. *Helv. Chim. Acta* 1988, 71, 1719. (c) Quinkert, G.; Becker, H.; Dürner, G. *Tetrahedron Lett.* 1991, 32, 7397. (d) For synthesis of (–)-1 from (+)-diethyl L-tartrate and (R)-methyloxirane see: Waanders, P. P.; Thijs, L.; Zwanenburg, B. *Tetrahedron Lett.* 1987, 28, 2409. (e) For asymmetric synthesis of (–)-1 utilizing a chiral sulfoxide group, see: Solladié, G.; Fernandez, I.; Maestro, C. *Tetrahedron Asymmetry* 1991, 2, 801.(7) (3*E*)-Hexadeca-1,3,15-triene, 2, has been prepared in 57% yield from tridec-12-enal in a sequence of four steps: (i) Wittig–Horner reaction with triethylphosphonoacetate and NaH in THF at 0 °C; (ii) DIBAL-H reduction to the corresponding primary alcohol; (iii) PCC oxidation to penta-2,14-dienal; and (iv) Wittig reaction with methylenephosphorane (obtained from methyltriphenylphosphonium bromide and *n*-BuLi in THF).(8) (a) Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem.* 1992, 57, 2768. (b) Crispino, G. A.; Jeong, K.-S.; Kolb, H. C.; Wang, Z.-M.; Xu, D.; Sharpless, K. B. *J. Org. Chem.* 1993, 58, 3785. (c) Johnson, R. A.; Sharpless, K. B. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH Publishers Inc.: New York, 1993; pp 227–272.(9) AD-mix- α (Aldrich no. 39275-8), AD-mix- β (Aldrich no. 39276-6).(10) Soler, M.; Sharpless, K. B. submitted to *Tetrahedron*.(11) Andersson, P. G.; Sharpless, K. B. *J. Am. Chem. Soc.* 1993, 115, 7047.(12) Xu, D.; Crispino, G. A.; Sharpless, K. B. *J. Am. Chem. Soc.* 1992, 114, 7570.(13) Sinha, S. C.; Sinha-Bagchi, A.; Keinan, E. *J. Org. Chem.* 1993, 58, 7789.(14) We propose a new term: *epimeric excess* (epe) to describe a "local enantiomeric excess" in a molecule containing more than one asymmetric center.

Scheme 1^a

^a Key: (a) (i) AD-mix- β , MeSO_2NH_2 , $t\text{-BuOH-H}_2\text{O}$, 0°C , 8 h; (ii) dimethoxypropane, acetone, TsOH , 60°C , 1 h; (b) (i) AD-mix- α , MeSO_2NH_2 , $t\text{-BuOH-H}_2\text{O}$, 0°C , 48 h; (ii) TBDMS-Cl, Et_3N , DMAP, rt, 24 h; (iii) methoxyethoxymethyl chloride, $i\text{-Pr}_2\text{EtN}$, DMAP, rt, 18 h; (iv) TBAF, THF, rt, 1 h; (c) (i) Me_2S , NCS, toluene, -25°C , 2 h, then Et_3N , rt, 15 min; (ii) triethylphosphonoacetate, NaH, THF, 0°C , 20 min; (d) (i) AcOH , H_2O , rt; (ii) $(\text{EtO})_3\text{CMe}$, Me_3SiBr , CH_2Cl_2 , 0°C , 1 h; (iii) Bu_3SnH , AIBN, benzene, 80°C , 2.5 h; (e) (i) LiOH, THF- H_2O , $40\text{--}50^\circ\text{C}$, 12 h, then oxalic acid, 0°C ; (ii) 2,4,6-trichlorobenzoyl chloride, Et_3N , THF, rt, 2 h then DMAP, toluene, 90°C , 3.5 h; (f) $(\text{CH}_2\text{SH})_2$, BF_3 , CH_2Cl_2 , 0°C , 2 h.

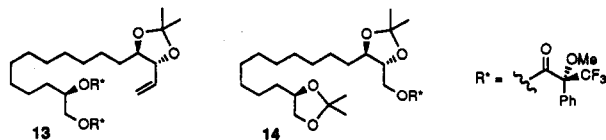
olefination of the appropriate aldehyde. To that end diol **9a** was monoprotected to give **9d** in a three-step sequence: (i) selective protection of the primary alcohol as a silyl ether using *tert*-butyldimethylchlorosilane (1 equiv), triethylamine and (dimethylamino)pyridine in dichloromethane to produce **9b** (97%); (ii) protection of the secondary alcohol as a MEM ether using methoxyethoxymethyl chloride and ethyldiisopropylamine in dichloromethane to give **9c** (88%); and (iii) desilylation with tetrabutylammonium fluoride in THF, affording the desired alcohol **9d** (97%), $[\alpha]_D +33.6$ ($c = 3.30$, CHCl_3). The latter alcohol was oxidized with *N*-chlorosuccinimide, dimethylsulfide, and triethylamine in toluene¹⁶ to produce the corresponding aldehyde which was immediately reacted with triethyl phosphonoacetate/NaH in THF at 0°C to give ethyl enoate **10**, $[\alpha]_D -26.9$ ($c = 5.09$, CHCl_3).

Reductive deoxygenation at the ω -position was carried out according to our recently developed approach to

Table 1. Product Distribution in the AD Reaction of **2**^a

entry	AD-mix- β^b (equiv)	2 (%)	3 (%)	4 (%)	5 (%)	6 ^c (%)	7 (%)	AD hexols (%)
1 ^d	1	64	26	3	5	2		
2	1 ^e	3	52	3	6	36 (30)		
3	2		16	2	3	67 (63)	9	3
4	2 ^{e,f}		1			89 (80)	1	9
5	3		2			83 (77)	6	9
6	2 ^e					80		20

(15) Enantiomeric purity was determined by ^1H NMR of the (*R*)-Mosher esters **13** and **14** (Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* 1969, 34, 2543).



Compound **13** was prepared in two steps from **8**: (i) selective hydrolysis of the less sterically hindered acetonide (acetic acid/water, 2 h) to diol and (ii) double esterification with (*S*)-(+)- α -methoxy- α -(trifluoromethyl)-phenylacetyl chloride and DMAP in CH_2Cl_2 . The integration ratio between the two methoxy singlets at 3.48 and 3.40 ppm (representing the 15*R* epimer) and the two singlets at 3.44 and 3.42 (representing the 15*S* epimer) was found to be 93:7, respectively. Compound **14** was prepared from **8** in a sequence of four steps: (i) dihydroxylation of the terminal double bond using OsO_4 and quinuclidine; (ii) cleavage of the resultant diol to aldehyde with aqueous NaIO_4 in CH_2Cl_2 ; (iii) NaBH_4 reduction in MeOH to produce the primary alcohol; and (iv) esterification with Mosher acid chloride described above. The integration ratio between the two sets of double doublets at 4.47 and 4.36 ppm (representing the (2*R*,3*R*) diastereomer) and the two sets at 4.42 and 4.39 (representing the (2*S*,3*S*) diastereomer) was found to be 98:2.

(16) Corey, E. J.; Kim, C. U. *J. Am. Chem. Soc.* 1972, 94, 7586.

^a All reactions were carried out with **2** (0.25 mmol), AD-mix- β (containing either 0.2 or 0.5 mol % osmium), and methanesulfonamide (25 mg in entries 1 and 2, 50 mg in entries 3 and 4, and 75 mg in entry 5) in 1:1 2-methyl-2-propanol/water (5 mL in entries 1 and 2, 10 mL in entries 3 and 4, and 15 mL in entry 5) at 0°C for 18 h. The crude mixture of diols was converted to the corresponding acetonide derivatives by mixing with 1:1 acetone/dimethoxypropane and catalytic TsOH . Product ratio was determined by GC. In some cases this GC analysis was confirmed by ^1H NMR. ^b The amount of 1.4 g of AD-mix- β (usually employed for dihydroxylation of 1 mmol of alkene)⁷ contains potassium osmate (0.002 mmol), $\text{K}_3\text{Fe}(\text{CN})_6$ (3 mmol), K_2CO_3 (3 mmol), and 1,4-bis(9-*O*-dihydroquinidiny)phthalazine (0.01 mmol). Thus, 1 equiv represents here 0.35 g of AD-mix- β . ^c The numbers in parentheses represent the yield of isolated bis-acetonide, **8**. ^d This reaction was interrupted after 5 h at 0°C . ^e Increased amounts of potassium osmate (0.005 instead of 0.002 mmol/equiv) were employed. ^f The reaction was interrupted after 8 h.

methylcarbinols using a three-step sequence:¹³ (i) selective hydrolysis of the less sterically hindered acetonide using aqueous acetic acid to give diol 11a (88%); (ii) conversion of this diol to 18-bromo-17-acetoxy derivative 11b (84%) using triethyl orthoacetate and bromotrimethylsilane in dichloromethane; and (iii) debromination with tributyltin hydride and catalytic AIBN in refluxing benzene to produce 11c (86%), $[\alpha]_D -21.0$ ($c = 2.68$, CHCl_3). The two esters within 11c were hydrolyzed to the protected seco-acid of aspicilin using LiOH in aqueous THF (45 °C, 12 h) which was then lactonized without further purification, using the mixed anhydride approach,^{6a,17} to give lactone 12, $[\alpha]_D -21.9$ ($c = 2.68$, CHCl_3). Finally, deprotection of 12 was carried out in dichloromethane using $\text{BF}_3\text{-Et}_2\text{O}$ and ethanedithiol,^{6e} affording aspicilin, 1, that was recrystallized from hexane/diethyl ether to give colorless needles (75%), mp 154–156 °C (lit.^{6c} 154–156 °C, lit.^{5b} 153–154 °C), $[\alpha]_D = +38.5$ ($c = 1.05$, CHCl_3) (lit.^{6c} +39.4 ($c = 0.868$, CHCl_3), lit.^{5b} +32 ($c = 2.31$, CHCl_3)).

(17) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* 1979, 52, 1989.

Our synthetic 1 was found to be identical by ^1H NMR, ^{13}C NMR, IR, and MS to the naturally occurring compound.⁶

In conclusion, asymmetric synthesis of (+)-aspicilin has been achieved in 14 steps and 11% overall yield, starting from an achiral hydrocarbon, hexadecatriene. All asymmetric centers have been introduced in two AD steps with very high regio- and enantioselectivity, demonstrating the advantages of the AD methodology in synthesis of polyoxygenated carbon skeletons.¹⁸

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Supplementary Material Available: Experimental procedures and characterization data for 8, 9a–d, 10, 11a–c, and 12 (5 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(18) For previous work in this series see ref 13 and: Sinha, S. C.; Keinan, E. *J. Am. Chem. Soc.* 1993, 115, 4891.