Combined Osmium−Rhenium Approach to Synthesis of Naturally Occurring Polyethers

Subhash C. Sinha,*,† Anjana Sinha-Bagchi,† and Ehud Keinan*,†,‡

Department of Molecular Biology
The Scripps Research Institute
10666 North Torrey Pines Road
La Jolla, California 92037
Department of Chemistry
Technion—Israel Institute of Technology
Technion City, Haifa 32000, Israel

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Transition-metal chemistry allows chemists to design synthetic strategies that are different from those observed in nature to construct complex molecules, such as macrolide antibiotics,[1] polyether antibiotics,[2] and marine toxins.[3] The biosynthesis of polyketide natural products, for example, involves multistep assembly of a polycarbonyl skeleton followed by manipulation of the oxygen functions.[4] Alternatively, using the osmium-based, Sharpless asymmetric dihydroxylation (AD) reaction,[5] one can selectively place the oxygen functions on a naked carbon skeleton, as has been recently demonstrated by our short syntheses of (+)-aspicilin and antibiotic (−)-AZ6771B.[6]

Of particular interest are members of the rapidly growing family of the annonaceous acetogenins, which are characterized by long, polyoxygenated carbon skeletons. Many of these polyketide, fatty acid derivatives, isolated from plants in the Annonaceae family, have shown cytotoxic, antitumor, antimalarial, immunosuppressive, pesticidal, and antifeedant activities.[7] Although more than 100 members of this family have already been discovered, information concerning their absolute configuration by either physical methods[8] or total synthesis[9] is still quite limited. We have recently used the above-mentioned strategy to prepare (+)-solamin and (+)-reticulatacin, the first members of this family to be synthesized in their naturally occurring stereochemistry.[10] Here we proceed one step further and show that merging the excellent enantioselectivity of the osmium-based AD reaction with the high stereoselectivity of Kennedy's rhenium-based oxidative cyclization technique[11] creates a powerful methodology for asymmetric synthesis of polyoxygenated aliphatic structures, with immediate applications in the annonaceous acetogenin family.

Aiming at a general approach to monotetrahydrofuranoid acetogenins, we took advantage of the significantly higher reactivity of AD reagents toward (*E*)-alkenes relative to (*Z*)-alkenes,[5] which enables selective dihydroxylation of the former in the presence of the latter. Thus, reaction of the (*E*,*Z*)-diene **2**[12] with AD-mix-β resulted in selective oxidation of the *E* double bond to give hydroxylactone **3**.[13] Oxidative cyclization with dirhenium heptoxide and periodic acid (Scheme 1) produced **4** as a single diastereomer in 75% yield.[14] Apparently, this oxidation with Re(VII) is far more selective than that with Cr(VI) oxide, which is incompatible with primary and secondary alcohols either in the starting material or in the product and may even degrade the carbon skeleton.[15]

Compound **4** provides a convenient entry to the relatively rare members of monotetrahydrofuranoid acetogenins, which are characterized by a threo-*trans*-erythro stereochemistry around the THF ring,[7] e.g., annonacin A,[16] *cis*- and *trans*-annonacin-A-one,[17] jetein and otivarin,[18] *cis*- and *trans*-bullatalicinone,[19] and squamostatin A.[20] Inversion of the configuration of the carbinol center[21] in **4** produced alcohol **5**, which is a useful intermediate in the synthesis of the more abundant

† The Scripps Research Institute.

‡ Technion—Israel Institute of Technology.

(1) Kirst, H. In *Recent progress in the chemical synthesis of antibiotics*; Lukacs, G., Ohno, M., Eds.; Springer-Verlag: Berlin, 1990; pp 39−63.

(2) Yonemitsu, O.; Horita, K. In *Recent progress in the chemical synthesis of antibiotics*; Lukacs, G., Ohno, M., Eds.; Springer-Verlag: Berlin, 1990; pp 447−466.

(3) Yasumoto, T.; Murata, M. *Chem. Rev.* **1993**, *93*, 1897.

(4) (a) Vederas, J. C. *Nat. Prod. Rep.* **1987**, *4*, 227. (b) Simpson, T. J. *Nat. Prod. Rep.* **1987**, *4*, 339.

(5) (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) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.*, in press.

(6) (a) Sinha, S. C.; Keinan, E. *J. Org. Chem.* **1994**, *59*, 949. (b) Sinha, S. C.; Sinha-Bagchi, A.; Keinan, E. *J. Org. Chem.* **1993**, *58*, 7789.

(7) (a) Rupprecht, J. K.; Hui, Y.-H.; McLaughlin, J. L. *J. Nat. Prod.* **1990**, *53*, 237. (b) Fang, X.-P.; Rieser, M. J.; Gu, Z.-M.; Zhao, G.-X.; McLaughlin, J. L. *Phytochem. Anal.* **1993**, *4*, 27−67.

(8) For a method to establish the absolute configuration of these compounds using NMR data of their Mosher ester derivatives, see: Rieser, M. J.; Hui, Y.-H.; Rupprecht, J. K.; Kozlowski, J. F.; Wood, K. V.; McLaughlin, J. L.; Hanson, P. R.; Zhuang, Z.; Hoye, T. R. J. *Am. Chem. Soc.* **1992**, *114*, 10203.

(9) (a) Trost, B. M.; Shi, Z. *J. Am. Chem. Soc.* **1994**, *116*, 7459. (b) Hoye, T. R.; Hanson, P. R.; Kovelesky, A. C.; Ocain, T. D.; Zhuang, Z. *J. Am. Chem. Soc.* **1991**, *113*, 9369. (c) Figadere, B.; Harmange, J.-C.; Hai, L. X.; Cave, A. *Tetrahedron Lett.* **1992**, *33*, 5189. (d) Bertrand, P.; Gesson, J.-P. *Tetrahedron Lett.* **1992**, *33*, 5177. (e) Harmange, J.-C.; Figadere, B.; Cave, A. *Tetrahedron Lett.* **1992**, *33*, 5749. (f) Harmange, J.-C.; Figadere, B.; Hocquemiller, R. *Tetrahedron: Asymmetry* **1991**, *2*, 347. (g) Hoye, T. R.; Hanson, P. R. *Tetrahedron Lett.* **1993**, *34*, 5043. (h) Hoppe, R.; Flasche, M.; Scharf, H.-D. *Tetrahedron Lett.* **1994**, *35*, 2873.

(10) Sinha, S. C.; Keinan, E. *J. Am. Chem. Soc.* **1993**, *115*, 4891.

(11) (a) Tang, S.; Kennedy, R. M. *Tetrahedron Lett.* **1992**, *33*, 3729. (b) Tang, S.; Kennedy, R. M. *Tetrahedron Lett.* **1992**, *33*, 5299. (c) Tang, S.; Kennedy, R. M. *Tetrahedron Lett.* **1992**, *33*, 5303. (d) Boyce, R. S.; Kennedy, R. M. *Tetrahedron Lett.* **1994**, *35*, 5133.

(12) (4*E*,8*Z*)-Ethyl eicosa-4,8-dienoate (**2**) was prepared as follows: Monobenzylation of butane-1,4-diol with benzyl bromide and NaH in DMF, PCC oxidation of the free alcohol to aldehyde, reaction with vinylmagnesium bromide in THF, and treatment of the resultant allylic alcohol with triethyl orthoacetate and catalytic amounts of propionic acid produced ethyl 8-benzyloxyoct-4-enoate. Debenzylation with $BCl_3{\cdot}SMe_2$ in CH_2Cl_2 followed by PCC oxidation in CH_2Cl_2 afforded aldehyde **1**. The latter was reacted with a Wittig reagent (which was prepared from tridecyltriphenylphosphonium bromide and potassium hexamethyldisilazide in THF−HMPA at −78 °C to 0 °C) to give compound **2**.

(13) Monoprotection of a vicinal diol in the form of a γ-lactone has been used in the synthesis of other natural products. See: (a) Reference 10. (b) Wang, Z.-M.; Zhang, X.-L.; Sharpless, K. B.; Sinha, S. C.; Sinha-Bagchi, A.; Keinan, E. *Tetrahedron Lett.* **1992**, *33*, 6407. (c) Keinan, E.; Sinha, S. C.; Sinha-Bagchi, A.; Wang, Z.-M.; Zhang, X.-L.; Sharpless, K. B. *Tetrahedron Lett.* **1992**, *33*, 6411. (d) Sinha-Bagchi, A.; Sinha, S. C.; Keinan, E. *J. Org. Chem.* submitted.

(14) Compound **3** (1 mmol) was dissolved in dry dichloromethane, H_5IO_6 (2 mmol) and Re_2O_7 (1.5 mmol) were added, and the mixture was stirred at room temperature for 35 min and then quenched with aqueous $NaHSO_3$. Workup with CH_2Cl_2−H_2O and column chromatography (silica gel, hexane:ethyl acetate 1:1) afforded pure **4** in 75% yield.

(15) (a) McDonald, F. E.; Towne, T. B. *J. Am. Chem. Soc.* **1994**, *116*, 7921. (b) Hammock, B. D.; Gill, S. S.; Casida, J. E. *J. Agric. Food Chem.* **1974**, *22*, 379. (c) Walba, D. M.; Stoudt, G. S. *Tetrahedron Lett.* **1982**, *23*, 727. (d) Schlecht, M. F.; Kim, H. *Tetrahedron Lett.* **1985**, *26*, 551. (e) Schlecht, M. F.; Kim, H. *J. Org. Chem.* **1989**, *54*, 583. (f) Chakraborty, T. K.; Chandrasekaran, S. *Tetrahedron Lett.* **1984**, *25*, 2895. (g) Chakraborty, T. K.; Chandrasekaran, S. *Chem. Lett.* **1984**, *25*, 2895. (h) Corey, E. J.; Ha, D.-C. *Tetrahedron Lett.* **1988**, *29*, 3171. (i) Waddell, T. G.; Carter, A. D.; Miller, T. J.; Pagni, R. M. *J. Org. Chem.* **1992**, *57*, 381. (j) Baskaran, S.; Islam, I.; Chandrasekaran, S. *J. Chem. Res. (M)* **1992**, 2213.

(16) Lieb, F.; Nonfon, M.; Wachendorff-Neumann, U.; Wendisch, D. *Planta Med.* **1990**, *56*, 317.

(17) Zhao, G.-X.; Rieser, M. J.; Hui, Y.-H.; Miesbauser, L. R.; Smith, D. L.; McLaughlin, J. L. *Phytochemistry* **1993**, *33*, 1065.

(18) Cortes, D.; Myint, S. H.; Leboeuf, M.; Cave, A. *Tetrahedron Lett.* **1991**, *43*, 6133.

(19) Hui, Y.-H.; Wood, K. V.; McLaughlin, J. L. *Phytotherapy Res.* **1991**, *5*, 124.

(20) Fujimoto, Y.; Murasaki, C.; Kakinuma, K.; Eguchi, T.; Ikekawa, N.; Furuya, M.; Hirayama, K.; Ikekawa, T.; Sahai, M.; Gupta, Y. K.; Ray, A. B. *Tetrahedron Lett.* **1990**, *31*, 535.

(21) Attempts to use the Mitsunobu reaction (Mitsunobu, O. *Synthesis* **1981**, 1.) failed to give the inverted benzoate but produced an enol ether instead, via elimination of H_2O. The desired transformation was achieved by converting **4** to its methanesulfonate ester, followed by treatment with cesium propionate and ester hydrolysis.

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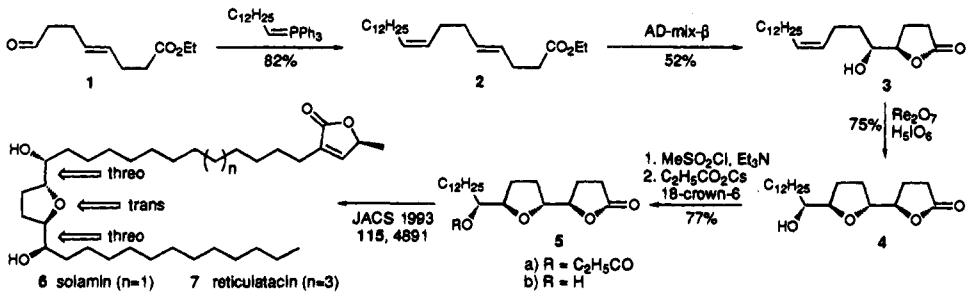
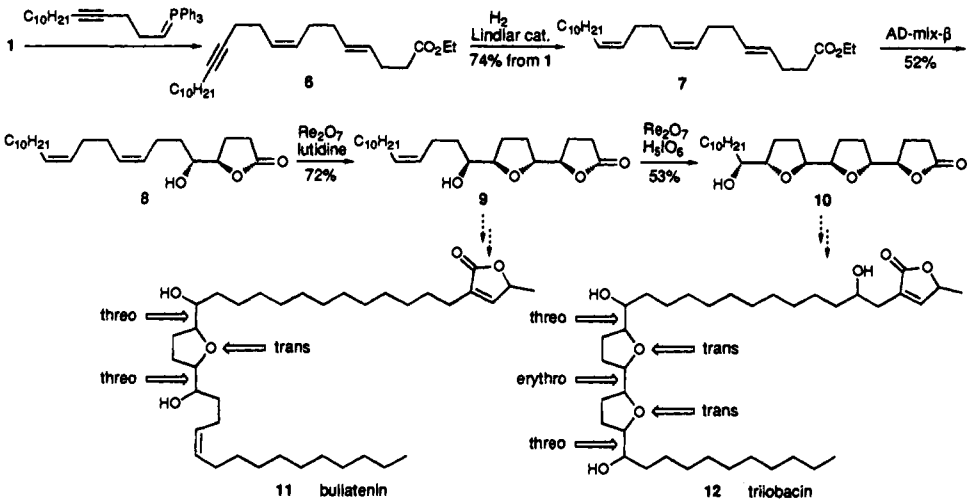
Scheme 1



Scheme 2



threo-*trans*-threo members. Alcohol **5** has already been described[10] in our synthesis of solamin (**6**) and reticulatacin (**7**). Scheme 1, therefore, represents a formal total synthesis of **6** and **7**.

The functional similarity between the starting material and the product (both having one free hydroxyl group) provides attractive synthetic opportunities to generate many asymmetric centers in a single step via tandem oxidative cyclizations of polyolefins. To check this we synthesized the (*Z,Z,E*)-triene **7** via Wittig olefination of aldehyde **1**, followed by catalytic hydrogenation of the resultant ynediene, **6**, over Lindlar's catalyst (Scheme 2). Dihydroxylation of **7** with AD-mix-β produced hydroxylactone **8** as the major product. Reaction of **8** with a mixture of Re_2O_7 and 2,6-lutidine afforded the monocyclized product **9** (Scheme 2).[22] Treatment of the latter with the more reactive mixture, Re_2O_7 (2 equiv) and H_5IO_6 (3 equiv) in dry dichloromethane, for 1 h indeed effected the second oxidative cyclization, producing compound **10** in 53% yield. Both cyclizations could be carried out in a single step by treatment of dienol **8** with Re_2O_7 (3 equiv) and H_5IO_6 (4 equiv) in dry dichloromethane for 2 h, producing the bis-THF product **10** in 25% yield. Even under these conditions, the first cyclization is approximately one order of magnitude faster than the subsequent one, offering a synthetic advantage of stopping the reaction after the first step. This differential activity could mirror inhibition by the polyoxygenated product which, by functioning as a polydentate ligand, inhibits further coordination of rhenium to the next olefinic bond.

Both compounds **9** and **10** are useful intermediates for synthesis of naturally occurring acetogenins, and bistetrahydrofuranoid ones in particular. For example, compound **9** could be a key intermediate in the synthesis of bullatenin (**13**),[23] and compound **10** could be used in the synthesis of trilobacin (**14**).[24] Since the absolute configuration of **11** and **12** is unknown, we are currently preparing both enantiomeric forms of each, using either AD-mix-α or AD-mix-β for dihydroxylation of **7**.

In conclusion, the advantage of merging the Sharpless AD reaction with the Kennedy oxidative cyclization for asymmetric oxygenation of polyenes has been demonstrated here by an efficient preparation of key intermediates for synthesis of naturally occurring annonaceous acetogenins. A formal asymmetric synthesis of solamin and reticulatacin has been achieved. The total synthesis of bullatenin and trilobacin will be reported shortly.

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Supplementary Material Available: Spectral data of compounds **1**–**4** and **8**–**10** (1 page). This material is contained in many 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.

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(22) Reactions proceed much slower with 2,6-lutidine[11] than with periodic acid, probably via coordination to the metal. We used it here to stop the reaction after a single cyclization step. Thus, dienol **8** (1 mmol) was stirred with Re_2O_7 (2 mmol) and 2,6-lutidine (4 mmol) in dry CH_2Cl_2 at room temperature for 16 h. The mixture was worked up with 2 M NaOH, acidified, extracted with CH_2Cl_2, and treated with *p*-toluenesulfonic acid to give compound **9** (72%).

(23) Hui, Y.-H.; Wood, K. V.; McLaughlin, J. L. *Nat. Toxins* **1992**, *1*, 4.

(24) Zhao, G.-X.; Hui, Y.-H.; Rupprecht, J. K.; McLaughlin, J. L.; Wood, K. V. *J. Nat. Prod.* **1992**, *55*, 347.