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Studies toward the Synthesis of Pinolidoxin, a Phytotoxic Nonenolide from the Fungus *Ascochyta pinodes*. Determination of the Configuration at the C-7, C-8, and C-9 Chiral Centers and Stereoselective Synthesis of the C_6-C_{18} Fragment

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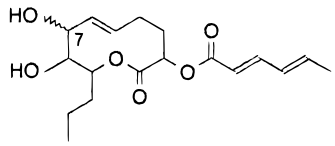
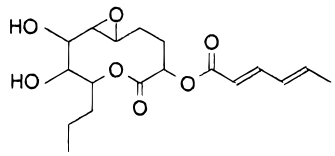
The absolute stereochemistry at the C-7, C-8, and C-9 chiral centers of pinolidoxin (**1**) has been determined by chemical and spectral methods. First, the synthesis of four stereoisomeric fully benzoylated 2,3-*erythro*-1,2,3,4-heptanetetrols, corresponding to the C_6-C_{18} portion of the natural substance, has been accomplished starting from *meso*-tartaric acid. As next step, the selection of the synthetic tetrabenzoate possessing "natural" stereochemistry (**10a′**), suitable for absolute configuration determination, has been carried out by correlation with its "natural" homologue derived from degradation of pinolidoxin. Determination of the stereochemistry at the title chiral centers has been carried out by application of the Mosher's method both to **7a′**, a compound stereochemically related to **10a′**, and to pinolidoxin itself. The stereoselective synthesis of a protected form of the C_6-C_{18} portion of pinolidoxin, to be used in its total synthesis, has also been accomplished starting from commercially available D-erythronolactone.

Introduction

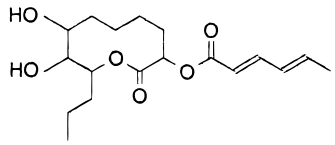
Fungi of *Aschochyta* species have considerable phytopatological and agrarian relevance because they are responsible for diseases of important crops used for animal and human feed, such as legumes and cereals.[2] Some years ago, one of us undertook a study aimed at isolating the toxic metabolites produced by *Ascochyta pinodes*, the causal agent of anthracnose of pea (*Pisum sativum* L.) causing severe lesions and necrosis of leaves and pods of the host plant. The main phytotoxin, named pinolidoxin (**1**, Figure 1), was isolated and characterized as a new tetrasubstituted nonenolide, namely 2-(2,4-hexadienoiloxy)-7,8-dihydroxy-9-propyl-5-nonen-9-olide.[3] Later, from the same fungus three new toxic nonenolides closely related to pinolidoxin, namely 7-epi- (**2**), 5,6-dihydro-, and 5,6-epoxypinolidoxin (Figure 1), were isolated in lower amounts.[4] Among the isolated substances pinolidoxin showed high phytotoxicity toward host (pea) and nonhost (bean) plants. This finding stimulated structure−activity relationship studies, which were carried out both on the natural pinolidoxins and on some unnatural derivatives of **1** by assaying their phytotoxicity on weeds and crop plants, zootoxicity, and antifungal activity.[5] The results obtained indicated in



pinolidoxin (1), 7-epipinolidoxin (2)



5,6-epoxypinolidoxin



5,6-dihydropinolidoxin

Figure 1.

(1) Part of the present work is taken from the degree thesis of D.P. performed under the supervision of V.P. and G.P., Università di Napoli "Federico II", 1996.

(2) Vurro, M.; Zonno, M. C.; Evidente, A.; Capasso R.; Bottalico A. *Mycotox. Res.* **1992**, *8*, 17−20.

(3) Evidente, A.; Capasso, R.; Abouzeid, M. A.; Lanzetta, R.; Vurro, M.; Bottalico, A. *J. Nat. Prod.* **1993**, *56*, 1937−1943.

(4) Evidente, A.; Lanzetta, R.; Capasso, R.; Vurro, M.; Bottalico A. *Phytochemistry* **1993**, *34*, 999−1003.

(5) Evidente, A.; Capasso, R.; Andolfi, A.; Vurro, M.; Zonno, M. C. *Nat. Toxins* **1998**, *6*, 183−188.

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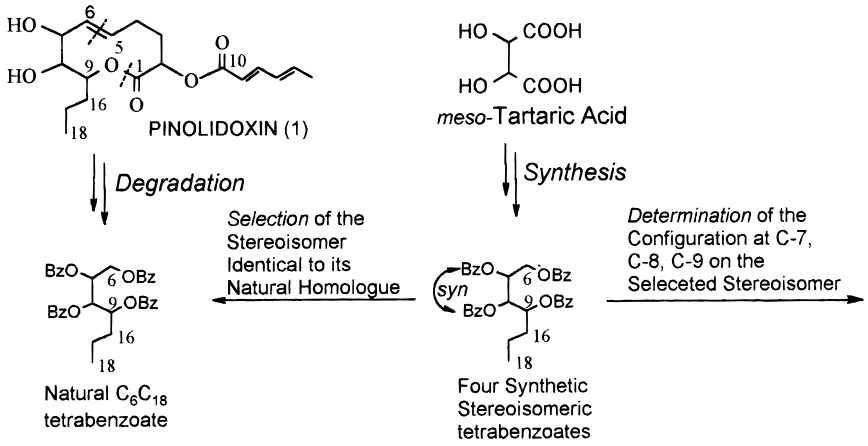
Scheme 1



particular that primarily important structural features for the phytotoxicity of pinolidoxin are the unmodified C-7/C-8 diol system and the C-5/C-6 double bond (7-epi- and 5,6-epoxypinolidoxins as well as C-7,C-8-protected derivatives of **1** exhibited low or no phytotoxicity) while the sorbic acid side chain does not seem to affect the activity (hexahydropinolidoxin is also strongly phytotoxic possibly due to its increased lipophilicity and, therefore, the easier cell penetration).

The possible direct use of toxins produced by plant pathogens as natural herbicides has been reviewed.[6] Recently, Vurro and Ellis[7] have shown the ability of some phytotoxins, including pinolidoxin, to strongly suppress PAL (phenylalanine-ammonia lyase) induction in poplar cells, suggesting a role of these substances in suppressing specific defense responses in plant cells during pathogenesis. From a practical point of view, these results suggest the use of phytotoxins in an integrated weed control program in which subtoxic amounts of these substances could be administered in combination with weed pathogens in order to induce reduction of defense mechanisms of the undesired weed, thus helping the pathogen to cause its disease. Therefore, in view of the possible use of pinolidoxin in the biocontrol of noxious plants, we embarked on its total synthesis.[8] This would allow us to obtain sufficient amounts of the toxin, isolated at low levels from the fungal culture filtrates, to test its activity also in greenhouse or field experiments and to prepare suitably modified derivatives and analogues of the natural metabolite for further structure−activity relationship studies. In this paper, we report the results of a preliminary study that sets the basis for the accomplishment of the stereoselective total synthesis of pinolidoxin (**1**).[9]

Strategy

As a first step toward the synthesis of pinolidoxin, we had to cope with the elucidation of its stereochemistry that could not be determined by previous NMR studies and X-ray experiments.[3] In particular, the stereochemical information on the molecule, comprising four chiral centers, was confined to the knowledge of the *E* configuration of the C5/C6 double bond, deduced from the large value (15.8 Hz) of the coupling constant between the pertinent protons. In addition, the easy formation of an acetonide derivative involving the C-7/C-8 diol system was suggestive of a syn relationship between the hydroxyl groups at these carbons. Though the acetonide formation could not conclusively secure the syn relationship within the C-7/C-8 diol system (due to the conformational freedom of the 10-membered ring also an anti diol system at C-7/C-8 could form an acetonide derivative), as a first approximation we decided to assume this stereochemical feature to be correct. This assumption, that strongly semplified the synthetic work we have accomplished, was later demonstrated to be indeed correct.

The present paper deals with the determination of the configuration at the C-7, C-8, and C-9 chiral centers of pinolidoxin, carried out along the general lines detailed below and schematically shown in Scheme 1, as well as the stereoselective synthesis of its C_6-C_{18} portion, starting from commercially available D-erythronolactone. In particular:

(1) Four of the eight possible stereoisomers corresponding to the C_6-C_{18} fragment of pinolidoxin, namely those displaying a syn relationship between the C-7 and C-8 hydroxyl groups, were synthesized in the form of fully benzoylated 2,3-*erythro*-1,2,3,4-heptanetetrols. These materials appeared to be easily accessible both by synthesis (see Scheme 2) and from degradation of natural pinolidoxin (see Scheme 3), whose amount at disposal was very limited (few milligrams);

(2) The synthetic tetrabenzoate possessing the "natural" stereochemistry was selected via correlation with its "natural" equivalent derived from degradation of pinolidoxin (see Scheme 4);

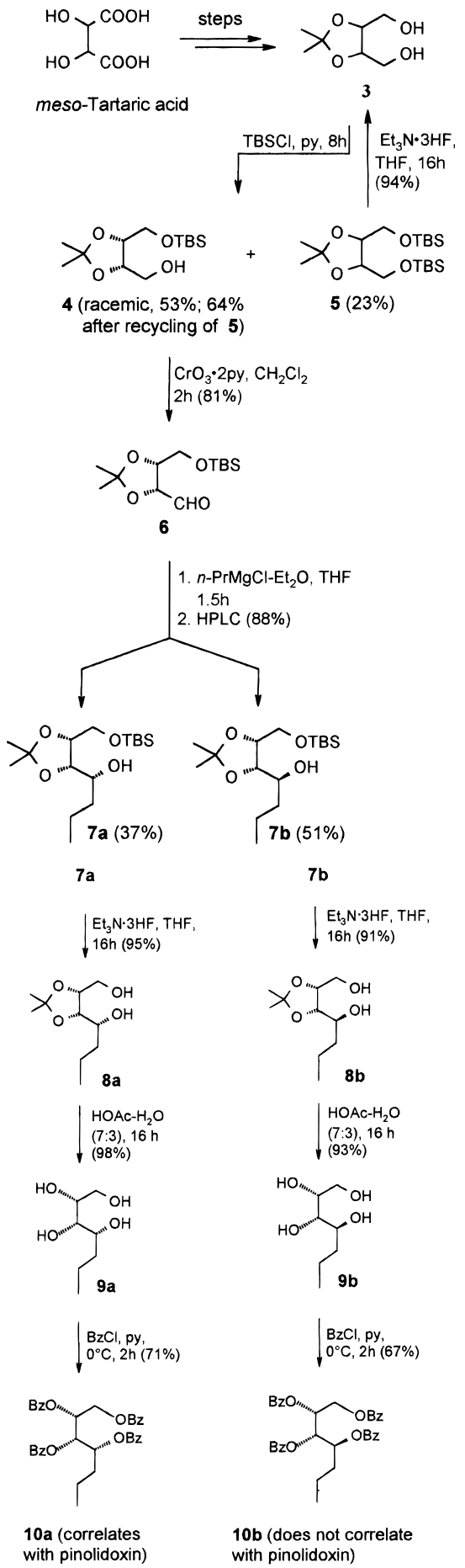
(6) (a) Strobel, G. A.; Kenfield, D.; Bunkers, G.; Sugawara, F.; Clardy, J. Phytotoxins as potential herbicides. In *Phytotoxins and their involvement in plant diseases*; Ballio, A., Graniti, A., Eds. *Experientia* **1991**, *47*, 819−826. (b) Evidente, A. Bioactive metabolites from phytopathogenic fungi and bacteria. In *Recent research developments in phytochemistry*; Pandalai, S. G., Ed.; Research Signpost: Trivandrum, India, 1997; pp 255−292.

(7) Vurro, M.; Ellis, B. E. *Plant Sci.* **1997**, *126*, 29−38.

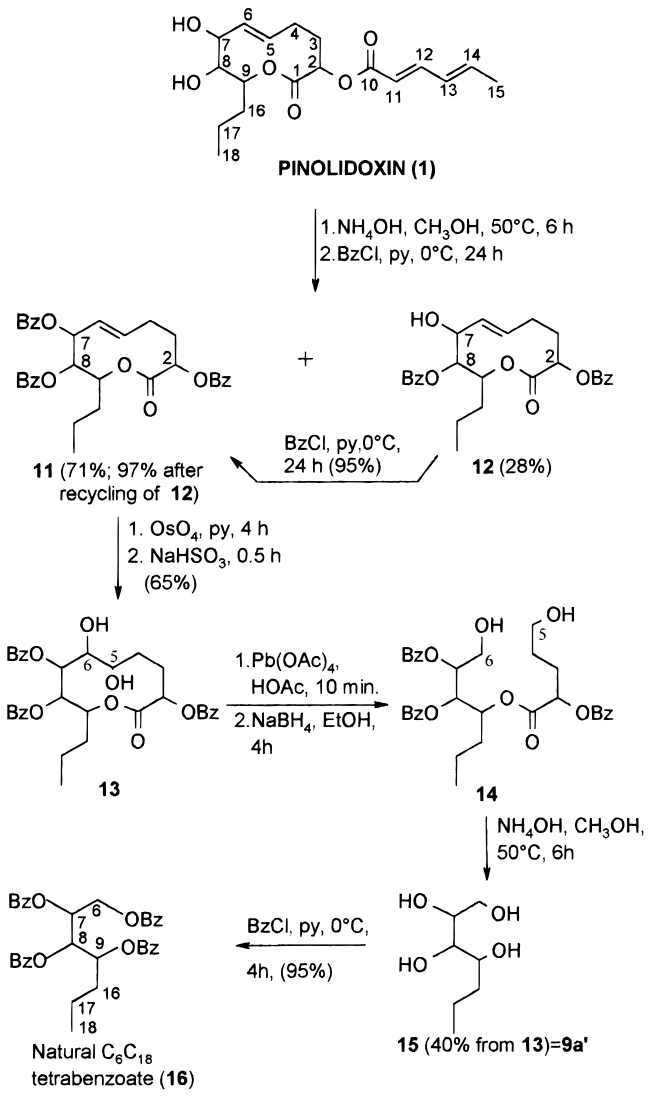
(8) Preliminary results were presented at the 9th International Congress of Pesticide Chemistry, London, 2−7 Aug, 1998; De Napoli, L.; Evidente, A.; Lasalvia, M.; Piccialli, G.; Piccialli, V.

(9) For a review on the synthesis of medium-sized lactone rings, see: Rousseau, G. *Tetrahedron* **1995**, *51*, 2777−2849. For a list of papers dealing with the synthesis of 10-membered lactones, see, in particular, pp 2830−2832. For more recent papers on the synthesis of natural substances containing 10-membered lactone rings, see: (a) Fürstner, A.; Müller, T. *Synlett* **1997**, 1010−1012. (b) Jones, G. B.; Huber, R. S.; Chapman, B. J. *Tetrahedron*: *Asymmetry* **1997**, *8*, 1797−1809. (c) Andrus, M. B.; Shih, T.-L. *J. Org. Chem.* **1996**, *61*, 8780−8785. (d) Moricz, A.; Gassmann, E.; Bienz, S.; Hesse, M. *Helv. Chim. Acta* **1995**, *78*, 663−669.

Scheme 2



Scheme 3



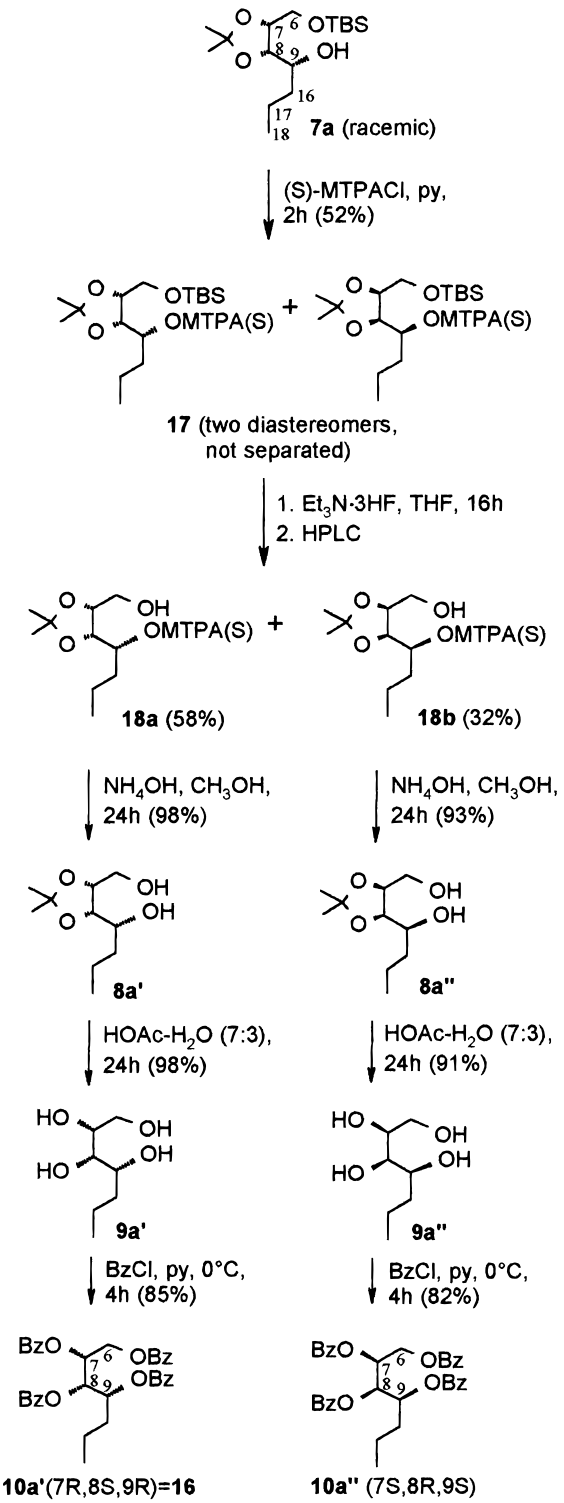
(3) The absolute configuration at the C-7, C-8, and C-9 stereogenic centers in a compound (**7a′**) stereochemically related to the selected synthetic material was determined (see Schemes 5 and 6), and the stereoselective synthesis of the C_6-C_{18} portion of pinolidoxin accomplished starting from commercially available D-erythronolactone (see Scheme 7).

Synthesis of the Four Stereoisomeric Fully Benzoylated 2,3-*erythro*-1,2,3,4-Heptanetetrols Corresponding to the C_6-C_{18} Fragment of Pinolidoxin. The synthesis of the desired four stereoisomeric tetrabenzoates (two racemic mixtures) corresponding to the C_6-C_{18} fragment of pinolidoxin (Scheme 2; for the racemic materials one enantiomer is shown) began with the conversion of commercially available *meso*-tartaric acid into 2,3-*O*-isopropylideneerythritol **3** through simple chemical transformations (see the Supporting Information for experimental details).

Reaction of diol **3** with TBSCl in pyridine for 8 h provided the racemic monosilylated alcohol **4** in 53% yield along with a 23% amount of the disilylderivative **5** that was converted to the synthetically useful compound **4** by hydrolysis to diol **3** (Et_3N·3HF, THF, 16 h, 94%)[10]

(10) Pirrung, M. C.; Steven, W. S.; Lever, D. C.; Fallon, L. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 1345−1346.

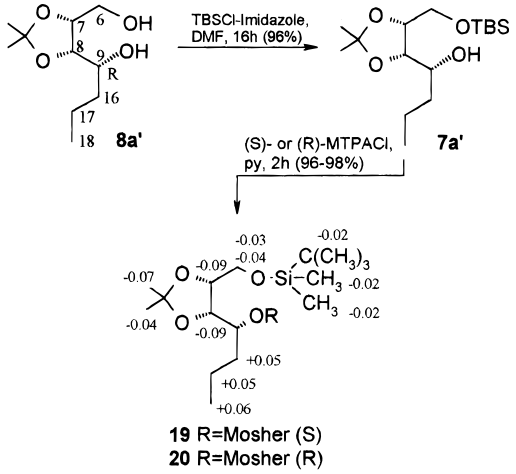
Scheme 4



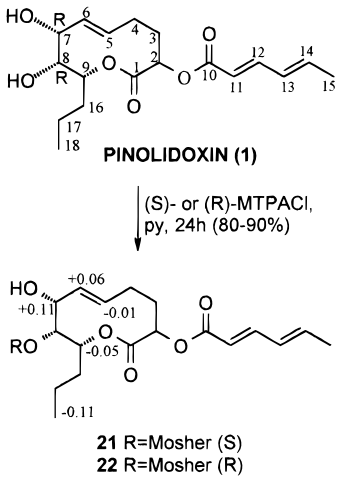
followed by treatment with TBSCl in pyridine as above. After this recycling step, compound **4** was obtained in 64% overall yield from **3**. Silylation with the alternative procedure using TBSCl (1.5 equiv)/imidazole (2.5 equiv) in DMF,[11] resulted less convenient for our porposes affording a higher amount of the undesired bis-silyl-derivative in the resulting mixture (ratio of mono- and bis-silylderivative, 1:2). Oxidation of alcohol **4** with the CrO_3·2py complex, generated in situ from CrO_3 and

(11) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190−6191.

Scheme 5



Scheme 6

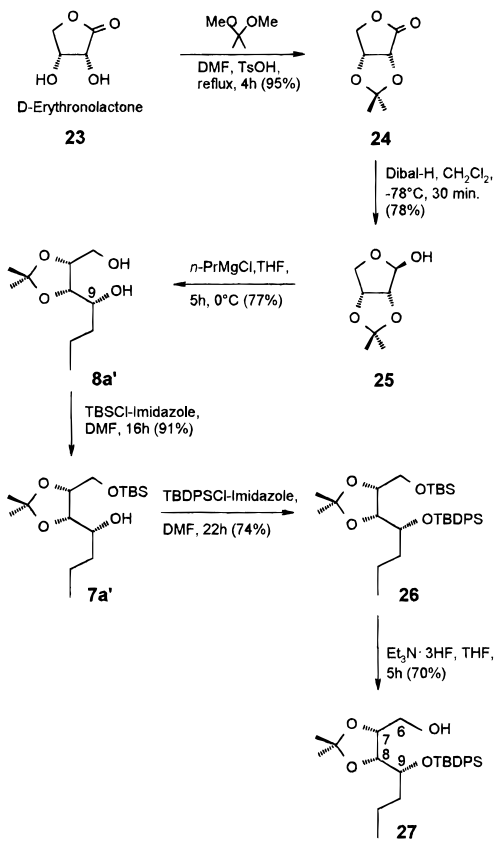


pyridine in CH_2Cl_2,[12] afforded the aldehyde **6** (81% yield) that was immediately treated with *n*-PrMgCl in THF at 25 °C to give a mixture of the diastereoisomeric alcohols **7a** and **7b**, in 88% combined yield. HPLC separation of this material (silica, hexanes−EtOAc, 92:8) afforded the two racemic alcohols **7a** and **7b** in 37% and 51% yields, respectively.[13] It is to be noted at this stage that the stereochemistry of compounds **7a** and **7b** is specified for sake of clarity and is, anyway, the correct ("natural") one as determined through the work carried out afterward and detailed below. As a next step, we had to select the racemic alcohol (**7a** or **7b**) correlating with pinolidoxin from which the enantiomer having the "natural" stereochemistry could be isolated and used for the stereochemistry determination at its C-7, C-8, and C-9 chiral centers. This was accomplished by transforming **7a** and **7b** into the corresponding tetrabenzoates, **10a** and **10b**, respectively, as shown in Scheme 2. In particular, deprotection of the primary alcoholic functions both in **7a** and **7b** by treatment with Et_3N·3HF in THF provided diols **8a** and **8b** in 95% and 91% yields, respectively. Removal of the isopropylidene protecting group with $CH_3COOH-H_2O$ (7:3) at room temperature for 16 h and subjection of the resulting tetrols (**9a** and **9b**) to benzoylation with benzoyl

(12) Ratcliffe, R.; Rodehorst, R. *J. Org. Chem.* **1970**, *35*, 4000−4002.

(13) For the synthesis of related 1,2-protected 1,2,3,4-heptanetetrols, see: (a) Cha, J. K.; Christ, W. J.; Kishi, Y. *Tetrahedron Lett* **1983**, *24*, 3943−3946. (b) Cha, J. K.; Christ, W. J.; Kishi, Y. *Tetrahedron* **1984**, *40*, 2247−2255.

Scheme 7



chloride in pyridine at 0 °C for 2 h afforded the tetrabenzoylated derivatives **10a** and **10b** (71% and 67% yields from **8a** and **8b**, respectively) that could be compared with their "natural" homologue **16**, derived from pinolidoxin through the degradative route shown in Scheme 3.

Degradation of Pinolidoxin and Correlative Work. Degradation of pinolidoxin was carried out as shown in Scheme 3, through simple classical chemical transformations. In particular, treatment of **1** with NH_4OH in CH_3OH at 50 °C for 6 h produced the cleavage of the sole sorbic acid side chain while leaving intact the 10-membered lactone ring, suggesting that the carbonyl function of the 10-membered lactone was inaccessible due to steric congestion. Benzoylation of the crude material obtained from the previous reaction with BzCl−pyridine at 0 °C for 24 h afforded a mixture of the 2,7,8-tribenzoyl lactone **11** and the 2,8-dibenzoyl lactone **12**, the C7-OH group being unaffected in the latter compound. The different propensity to benzoylation of the C-7 and C-8 hydroxyl groups of the C-2 deacylated pinolidoxin has been fruitfully used in a late stage of the present work when the absolute configuration at C-8 in **1** was accomplished by the application of the Mosher's method (see Scheme 6). Separation of the above di- and tribenzoylated derivatives of pinolidoxin by HPLC (silica, hexane−EtOAc, 8:2) afforded pure **11** and **12** in 71% and 28% yields, respectively. Resubjection of the unwanted partially benzoylated derivative **12** to benzoylation as above gave, after purification, another amount of **11** (yield for the conversion of **12** to **11**, 95%) bringing its overall yield to 97%. The degradation sequence continued with the scission of the C_5-C_6 double bond in **11** by reaction of this compound with excess OsO_4 in pyridine for 4h, followed by treatment with aqueous $NaHSO_3$ (0.5 h) that gave diol **13** in 65% yield after HPLC purification. Scission of the diol system in **13** with $Pb(OAc)_4$[14] in CH_3COOH gave a dialdehyde product that was treated, without purification, with $NaBH_4$ in EtOH to yield the tribenzoate dihydroxyester **14**. The ^1H NMR spectrum of a small amount of this material revealed it to be ca. 80% pure. Treatment of crude **14** with NH_4OH in CH_3OH at 50 °C for 6 h produced the scission of the ester functions in **14** providing tetrol **15** (40% from **13**). Finally, treatment of crude **15** with BzCl−pyridine at 0 °C for 4 h afforded, after HPLC purification (hexane−EtOAc, 8:2), the tetrabenzoylated fragment **16** (95%) suitable for comparison with the synthetic diastereoisomeric tetrabenzoates **10a** and **10b**, obtained as above (Scheme 2). In particular, synthetic **10a** displayed NMR spectra and chromatographic properties (HPLC co-injections of **16** with both **10a** and **10b**) identical to those exhibited by the degradation product of pinolidoxin **16**. This result demonstrated that our initial assumption on the syn relationship of the C-7/C-8 OH groups was correct.

As a consequence, the selection of the enantiomer possessing the "natural" stereochemistry, to be used for stereochemistry determination as planned, should be carried out on one of the racemic materials belonging to the "**a**" series, that is among compounds **7a**−**10a**. Of these, **7a**, being protected at its C-6, C-7, and C-8 hydroxyl groups, was a good candidate for the accomplishment of the next steps because its C-9 OH group could serve as an anchorage of a suitable chiral appendage likely necessary in its resolution. In addition, we reasoned that the free OH group at C-9 could also serve for the formation of the C-9 Mosher's esters of the "natural" enantiomer, to be used for the determination of the configuration at this stereocenter, once this had been isolated.

Scheme 4 depicts the route leading to the isolation of the enantiomer possessing the "natural" stereochemistry belonging to the racemic mixture **7a**. First, the resolution of **7a** was attempted by HPLC using a chiral column and various eluent mixtures. Unfortunately, all the separations obtained in this way were unsatisfactory. Therefore, the pair of enantiomers composing **7a** was transformed into the diastereoisomeric compounds **17** by reacting **7a** with (*S*)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride ((*S*)-MTPACl) in pyridine in 52% overall yield. Frustratingly, also this mixture did not give a reasonable HPLC separation in various HPLC conditions. Nevertheless, after removal of the silyl protecting group at C-6 a successful HPLC separation (silica, hexane−EtOAc, 8:2) of the two diastereoisomers, **18a** and **18b**, composing the resulting mixture, could be easily achieved. Each of these substances was then subjected to the removal of the ester (NH_4OH/CH_3OH, 24 h), and acetonide [CH_3COOH/H_2O (7:3), rt, 24 h] protecting groups and perbenzoylated with BzCl−pyridine at 0 °C for 4 h, to give the two tetrabenzoylated fragments **10a′** and **10a″** (81% and 69% from **18a** and **18b**, respectively) that could be compared with their "natural" tetrabenzoate homologue **16** derived from degradation of pinolidoxin as above-described (Scheme 3). Optical rotation data and circular dicroism spectra (see Supporting Information) obtained for **16**, **10a′** and **10a″** unequivocally indicated **10a′** to be identical to the "natural" fragment **16**.

Determination of the Configuration at the C-7, C-8, and C-9 Stereogenic Centers of Pinolidoxin. We had now to determine the absolute configuration of the

three chiral centers C-7, C-8, and C-9 in one of the compounds of the "**a′**" series, namely compounds **8a′**−**10a′**, or in the MTPA(S) derivative **18a**, all shown in Scheme 4. This proved to be more time-consuming than we could initially suppose. In fact, X-ray crystallographic analysis on one of these substances could not be accomplished due to the difficulties encountered in obtaining well-grown crystals of these substances. Thus, we turned our attention to the application of the Mosher's method[15] on a derivative of **8a′**. In particular, the determination of the chirality at C-9 was accomplished by transforming diol **8a′** into the mono-Mosher derivatives **19** and **20** (Scheme 5) by selective silylation of the primary hydroxyl group with TBSCl (1.9 equiv) in DMF in the presence of imidazole (2.5 equiv) for 16 h, to give alcohol **7a′** in 96% yield, followed by its treatment with either (*S*)- or (*R*)-α-methoxy-α-(trifluoromethyl)phenylacetyl chlorides [(*S*)- and (*R*)-MTPACl] and analyzing the resulting diastereoisomeric alcohols, **19** and **20**, respectively, by ^{1}H NMR in the usual way. The observed $\Delta\delta$ ($\delta_S - \delta_R = \delta_{19} - \delta_{20}$) values for the two substances, shown on the structure, clearly indicated the configuration of the C-9 chiral center in **7a′** to be *R* (for a tridimensional view of **19** and **20**, see the Supporting Information). Note that in **7a′** and **8a′** also the configuration at C-7 and C-8 is the correct ("natural") one as established later (see Scheme 6).

At this stage, however, we discarded the possibility of determining the configuration at the C-7 and C-8 stereocenters through the application of Mosher's method on one of the synthetic compounds **7a′**−**10a′** or **18a**, because this would have required a rather long manipulative work aimed at obtaining the (*S*)- and (*R*)-MTPA ester derivatives at the sole C-7 or C-8 position in these substances. Instead, the determination of the chirality at these centers was carried out on pinolidoxin itself. This was possible because, as established through the degradative work carried out on pinolidoxin (Scheme 3), the C-7 hydroxyl group could be benzoylated at a slower rate than the C-8 OH group. We reasoned that this could also be the case using the Mosher's chlorides. Indeed, when pinolidoxin was treated with (*S*)- or (*R*)-MTPACl (Scheme 6), the (*S*)- and (*R*)-MTPA derivatives of the natural molecule at C-8, **21** and **22**, respectively, were obtained as the major reaction products. The usual ^{1}H NMR analysis of these compounds (diagnostic $\Delta\delta$ values are shown on the formula) established the *R* configuration at C-8. Note that the structurally corresponding C-8 carbon in the fragment **10a′** = **16** (Scheme 4) has the opposite *S* configuration simply due to a different substitution pattern. The above result also fixed the *R* configuration at the C-7 carbon, standing the syn relationship between the C(7)−OH and C(8)−OH groups in the natural substance (the Supporting Information includes a tridimensional view of the (*S*)- and (*R*)-MTPA derivatives).

Stereoselective Synthesis of the C_6−C_{18} Fragment of Pinolidoxin. With the above stereochemical information at hand, we were now in a position to carry out the stereoselective synthesis of a protected form of the C_6−C_{18} portion of pinolidoxin by selecting a suitable chiral precursor. The synthesis was straightforwardly accomplished through a six-step sequence starting from commercially available D-erythronolactone[16] (**23**) as depicted in Scheme 7. This substance possesses four of the seven carbons of the target fragment with the required stereochemistry at its C-2 and C-3 carbons, corresponding to the C-8 and C-7 carbons of pinolidoxin, respectively, and a functionalization at C-1 that allows the easy attachment of a three-carbon chain needed to complete the carbon backbone of the C_6−C_{18} segment. Thus, protection of D-erythronolactone as its acetonide derivative **24** was accomplished in 95% yield by reaction with excess 2,2-dimethoxypropane in DMF in the presence of a catalytic amount (3%) of *p*-toluensulfonic acid at reflux for 4 h. A diastereoselective reduction of the ester function of **24** with diisobutylaluminum hydride (Dibal-H)[17] in CH_2Cl_2 at −78 °C for 30 min gave 2,3-*O*-isopropylidene-*β*-D-erythrofuranose[18] in 78% yield. The singlet shape of the signal for the anomeric proton, resonating at δ 5.42 in the proton spectrum of this compound, pointed to a trans relationship between H-1 and H-2.[18] Gratifyingly, the reaction of this material with *n*-PrMgCl[19] in THF at 0 °C proceeded with a good diastereoselectivity level affording diol **8a′**, possessing the desired *R* configuration at C-9, in 77% yield. Finally, temporary protection of the primary alcohol in **8a′** to obtain the TBS-derivative **7a′** (TBSCl-imidazole, DMF, 90%), followed by protection of the C-9 alcohol function with the more robust TBDPS group to give the bis-silylderivative **26** (TBDPSCl-imidazole, DMF, 74%), and selective removal of the C-6 alcohol function by treatment with $Et_3N{\cdot}3HF$ in THF, delivered the desired synthetic alcohol **27** (70% yield) protected as silyl ether at the sole C-9 position. Compound **27** was now ready to be oxidized at C-6 and coupled to a suitably protected form of the right-hand, C_1−C_5, portion of pinolidoxin.

Conclusion

In conclusion, in the present work we have carried out the determination of the absolute configuration at the stereogenic centers C-7, C-8, and C-9 of pinolidoxin through a combination of chemical and spectral methods as well as the stereoselective synthesis of its C_6−C_{18} portion in a protected form suitable for its total synthesis. Also worth of mentioning is that the degradative work performed on pinolidoxin has disclosed interesting information on its reactivity which could be fruitfully used to prepare suitable C-2, C-7, or C-8 derivatives of the natural substance. Completion of the synthesis of pinolidoxin requires the determination of the configuration

(14) (a) Fieser, L. F.; Fieser, M. *Reagents for Organic Synthesis*, Wiley: New York, 1967; Vol. 1, pp 537−563. (b) Criegee, R. In *Oxidation in Organic Chemistry*; Wiberg, K. B., Ed.; Academic Press: New York, 1965; Part A.

(15) (a) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543−2549. (b) Dale, J. A.; Mosher, H S. *J. Am. Chem. Soc.* **1973**, *95*, 512−519. (c) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092−4096.

(16) For previous works dealing with the use of D-erythronolactone as a chiral precursor in organic synthesis, see, for example: (a) Musich, J. A.; Rapoport, H. *J. Am. Chem. Soc.* **1978**, *100*, 4865−4872. (b) Ireland, R. E.; Wilcox, C. S.; Thaisrivongs, S. *J. Org. Chem.* **1978**, *43*, 786−787.

(17) (a) Paquette L. A. *Encyclopedia of Reagents for Organic Synthesis*; John Wiley & Sons: New York, 1995; Vol. 3, pp 1908−1912. (b) Vidari, G.; Ferriño, S.; Grieco, P. A. *J. Am. Chem. Soc.* **1984**, *106*, 3539−3548

(18) (a) De Bernardo, S.; Weigele, M. *J. Org. Chem.* **1976**, *41*, 287−290. (b) Maehr, H.; Williams, T. H.; Leach, M.; Stempel, A. *Helv. Chim. Acta* **1974**, *57*, 212−213. (c) Stevens, J. D.; Hewitt, G. F., Jr. *J. Org. Chem.* **1968**, *33*, 1799−1805.

(19) (a) Stork, G.; Raucher, S. *J. Am. Chem. Soc.* **1976**, *98*, 1583−1584. (b) Hanessian, S. *Total Synthesis of Natural Products: the Chiron Approach*; Baldwin, J. E., FRS Ed.; Pergamon Press: New York, 1993.

at C-2, the enantioselective synthesis of a suitably protected form of the C_1-C_5 portion and its coupling with the C_6-C_{18} fragment (trans-stereoselective formation of the C_5-C_6 double bond through, for example, a Julia−Lythgoe olefination sequence,[20] followed by lactonization), and attachment of the sorbic acid side chain. The results of this work will be reported in due course.

Experimental Section

General Methods. Melting points are uncorrected. When necessary, solvents and reagents were dried in the traditional fashion prior to use. Routine monitoring of reactions was performed using precoated silica gel TLC plates (Merck 60 F_{254} 0.25 mm thick). Spots were visualized by UV light and/or spraying an aqueous solution of sulfuric acid and heating the plate in an oven, or with I_2. Column chromatography was carried out on Merck silica gel 40 (70−230 mesh). *J* values are in hertz. Fourier transform IR (FTIR) spectra were taken as films on a NaCl plate. Circular dicroism spectra are expressed in $\Delta\epsilon$ vs λ. Mass spectra were run by direct sample introduction: $R = 10^4$, $T_{source} = 120$ °C, emission current 500 μA, electron energy 70 eV. Probe accurate mass measurement using PFK as reference standard. High-performance liquid chromatographies (HPLC) were performed using dual cell refractometer or UV detectors, generally using Si-60 (250 × 10 mm, 7 μm, and 250 × 4 mm, 5 μm) columns; attempts to separate the diastereoisomers composing the mixture **17** were carried out on the columns specified in the pertinent section. A sample of pinolidoxin was obtained as white needles from the filtrates of *Ascochyta pinodes* according to a reported procedure.[3]

Mono-TBS Ether Alcohol 4. To a stirred solution of diol **3** (780 mg, 4.81 mmol) in pyridine (8 mL) was added 725 μL (1 equiv) of a stock solution prepared by dissolving 1.0 g of TBSCl in pyridine (1 mL). After 8 h at room temperature, TLC monitoring indicated the complete transformation of the starting product to two less polar products ($R_f = 0.7$ and 0.9; $CHCl_3-CH_3OH$ 99:1). The solution was diluted with 5 mL of a 5% aqueous $NaHCO_3$ solution and extracted with $CHCl_3$. The combined organic extracts were washed with water, dried (Na_2SO_4), filtered, and concentrated. Column chromatography (eluent $CHCl_3$) afforded 700 mg (53%) of the monosilyl ether **4** and 430 mg (23%) of the bis-silyl ether **5** as clear oils. The unwanted disilylated material **5** (430 mg) was desilylated by treatment with $Et_3N{\cdot}3HF$ (1.6 mL, 10 equiv) in dry THF (3.5 mL). After being stirred at room temperature for 16 h, the reaction mixture was diluted with Et_3N (3 mL), evaporated, and chromatographed (eluent: $CHCl_3-CH_3OH$ 9:1) to give 195 mg (94%) of diol **3**. This material was resubjected to silylation as above to afford further 170 mg (51%) of silyl ether **4** after chromatography. The overall yield of **4** after this recycle step was of 64%.

Data for mono-TBS **4**: IR (film) 3483 (br, OH), cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 4.35 (ddd, $J = 5.9, 5.9, 5.9$ Hz, 1H), 4.23 (ddd, $J = 8.8, 5.9, 4.4$ Hz, 1H), 3.78 (overlapped multiplets, 3H), 3.67 (dd, $J = 10.6, 4.4$ Hz, 1H), 3.00 (dd, $J = 6.9, 6.9$ Hz, 1H), 1.41, 1.35 (s's, 3H each), 0.90 (s, 9H), 0.10 (s, 6H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 108.2, 77.2, 76.7, 61.4, 60.7, 27.7, 25.1, 25.6, 18.1, −5.5; MS *m/z* (assignment, relative intensity) 261 ($M^+ - CH_3$, 65), 219 ($M^+ - C(CH_3)_3$, 40); HRMS calcd for $C_{12}H_{25}O_4Si$ ($M^+ - CH_3$) 261.1522, found 261.1531; TLC $R_f = 0.7$ ($CHCl_3-CH_3OH$, 99:1).

Data for bis-TBS **5**: ^1H NMR ($CDCl_3$, 200 MHz) δ 4.17 (m, 2H), 3.73 (AB system further coupled, A part $J = 10.8, 5.6$ Hz, B part $J = 10.8, 5.6$ Hz, 4H), 1.43, 1.34 (s's, 3H each), 0.89 (s, 9H), 0.06 (s, 6-H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 108.3, 77.7, 62.0, 27.8, 25.2, 25.8, 18.3, −5.4; MS *m/z* (assignment, relative intensity) 375 ($M^+ - CH_3$, 15), 333 ($M^+ - C(CH_3)_3$, 20), 275 ($M^+ - SiC(CH_3)_3(CH_3)_2$, 37); HRMS calcd for $C_{18}H_{39}O_4Si_2$ ($M^+ - CH_3$) 375.2387, found 375.2388; TLC $R_f = 0.9$ ($CHCl_3/CH_3OH$, 99:1).

Aldehyde 6. To a stirred solution of pyridine (950 μL, 12 mmol) in CH_2Cl_2 (5 mL) was added CrO_3 (600 mg, 6 mmol) under nitrogen at room temperature, and the resulting mixture was stirred for 15 min. Then, a solution of the alcohol **4** (276 mg, 1 mmol) dissolved in CH_2Cl_2 (600 μL) was added in one portion, causing the immediate formation of a black precipitate. After 2 h, the mixture was filtered and the residue was washed several times with Et_2O. The ethereal phase was washed with a 5% NaOH solution and brine and dried (Na_2SO_4). Evaporation of the solvent gave 222 mg (81%) of aldehyde **6** as a clear oil. The unpurified product (ca. 90% pure by ^1H NMR) was subjected without hesitation to the next step.

Data for **6**: ^1H NMR ($CDCl_3$, 250 MHz) δ 9.69 (s, 1H), 4.46 (m, 2H), 3.73 (AB system further coupled, A part, $J = 10.7$, 3.4 Hz, B part $J = 10.7$, 2.4 Hz, 2H), 1,57, 1.38 (s's, 3H each), 0.88 (s, 9H), 0.05, 0.04 (s's, 3H each); TLC $R_f = 0.6$ ($CHCl_3-CH_3OH$, 99:1).

Alcohols 7a and 7b. Aldehyde **6** (200 mg, 0.73 mmol) obtained as above was azeotropically dried with two 5 mL portions of anhydrous toluene and dissolved in anhydrous THF (6 mL). To the stirred solution was added *n*-PrMgCl (2M in Et_2O, 730 μL, 1.46 mmol) via syringe over 5 min, at room temperature. After 1 h, another 300 μL of the Grignard reagent was added, and the mixture was stirred for a further 30 min, after which time the reaction was quenched with saturated NH_4Cl solution (5 mL). The aqueous layer was separated and extracted with ether. The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. Purification of the resulting oil by HPLC (column: LiChrosorb Si-60 250 × 10 mm, 7 μm; eluent: hexane−EtOAc, 92:8; flow: 2.5 mL/min) gave the two diastereoisomeric alcohols **7a** (86 mg, 37%; $t_R = 7.4$ min) and **7b** (116 mg, 51%; $t_R = 8.8$ min).

Data for **7a**: IR (film) 3477 (br, OH) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 4.22 (ddd, $J = 10.4, 5.5, 3.7$ Hz, 1H), 4.02 (dd, $J = 9.2, 5.5$ Hz, 1H), 3.87 (bd, $J = 3.0$ Hz, 1H), 3.79 (dd, $J = 10.4, 10.4$ Hz, 1H), 3.79 (m, superimposed to another signal, 1H), 3.57 (dd, $J = 10.4, 3.7$ Hz, 1H), 1.78−1.37 (overlapped multiplets, 2H), 1.37, 1.33 (s's, 3H each), 0.94 (t, $J = 7.3$ Hz, 3H); 0.91 (s, 9H), 0.13, 0.12 (s's, 3H each); ^{13}C NMR ($CDCl_3$, 62.8 MHz) δ 108.3, 80.8, 77.2, 68.7, 62.0, 36.1, 28.1, 25.3, 25.7, 18.3, 18.1, 14.1, −5.5, −5.6; MS *m/z* (assignment, relative intensity) 303 ($M^+ - CH_3$, 10); HRMS calcd for $C_{15}H_{31}O_4Si$ ($M^+ - CH_3$) 303.3199, found 303.3187; TLC $R_f = 0.8$ (hexane/EtOAc, 8:2). Anal. Calcd for $C_{16}H_{34}O_4Si$: C, 60.34; H, 10.76; Si, 8.82. Found: C, 60.54; H, 10.65; Si, 8.64.

Data for **7b**: IR (film) 3494 (br, OH) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 4.15 (ddd, $J = 6.8, 4.4, 4.4$ Hz, 1H), 4.02 (dd, $J = 6.3, 4.4$ Hz, 1H), 3.91 (dd, $J = 10.7, 6.8$ Hz, 1H), 3.78 (m, 1H), 3.72 (dd, $J = 10.7, 4.4$ Hz, 1H), 2.70 (d, $J = 5.4$ Hz, 1H), 1.47, 1.36 (s's, 3H each), 1.30−1.60 (overlapped multiplets, 4H), 0.95 (t, $J = 6.8$ Hz, 3H), 0.90 (s, 9H), 0.09 (s, 6H); ^{13}C NMR ($CDCl_3$, 62.8 MHz) δ 107.8, 79.7, 77.4, 68.6, 61.8, 36.6, 27.3, 25.0, 25.8, 19.0, 18.1, 13.9, −5.5, −5.7; MS *m/z* (assignment, relative intensity) 303 ($M^+ - CH_3$, 15); HRMS calcd for $C_{15}H_{31}O_4Si$ ($M^+ - CH_3$) 303.3199, found 303.3207; TLC $R_f = 0.7$ (hexane/EtOAc, 8:2). Anal. Calcd for $C_{16}H_{34}O_4Si$: C, 60.34; H, 10.76; Si, 8.82. Found: C, 60.48; H, 10.73; Si, 8.70.

Diols 8a and 8b. Alcohol **7a** (12 mg, 0.038 mmol) was dissolved in dry THF (1 mL), and excess $Et_3N{\cdot}3HF$ (50 μL, 0.38 mmol) was added at room temperature under stirring. After 16 h, Et_3N (3 mL) was added and the mixture taken to dryness and chromatographed (eluent: $CHCl_3-CH_3OH$, 9:1) to give 7.3 mg (95%) of diol **8a** as a white solid. An analogous procedure applied to the alcohol **7b** (12 mg) afforded 7.0 mg (91%) of diol **8b** as a white solid.

Data for **8a**: IR (film) 3388 (br, OH) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 4.28 (ddd, $J = 7.2, 5.4, 5.4$ Hz, 1H), 3.97 (dd, $J = 8.6, 5.4$ Hz, 1H), 3.83 (m, H-9, 2H), 3.70 (dd, $J = 11.4, 5.4$ Hz, 1H), 2.88 (bs, 2H), 1.80−1.30 (overlapped multiplets, 4H), 1.40, 1.35 (s's, 3H each), 0.95 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ: 108.2, 80.0, 77.2, 69.3, 60.8, 36.3, 27.8, 25.3, 18.3,

(20) (a) Julia, M.; Paris, J.-M. *Tetrahedron Lett.* **1973**, *14*, 4833−4836. (b) Kocienski, P. J.; Lythgoe, B.; Ruston, S. *J. Chem. Soc., Perkin Trans. 1* **1978**, 829−834. (c) Kocienski, P. J.; Lythgoe, B.; Waterhouse, I. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1045−1050. For a review, see: Kocienski, P. *Phosphorus Sulfur* **1985**, *24*, 97−127.

14.0; MS *m/z* (assignment, relative intensity) 189 ($M^+ - CH_3$, 75); HRMS calcd for $C_9H_{17}O_4$ ($M^+ - CH_3$) 189.1127, found 189.1134; TLC $R_f = 0.6$ ($CHCl_3/CH_3OH$ 9:1).

Data for **8b**: mp 68.5−69.5 (from EtOAc by evaporation); IR (film) 3414 (br, OH) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 4.19 (ddd, $J = 6.5, 5.4, 5.4$ Hz, 1H), 4.02 (dd, $J = 6.5, 3.0$ Hz, 1H), 3.75 (m, 2H), 3.71 (m, 1H), 2.92 (bs, 2H), 1.65−1.30 (overlapped multiplets, 4H), 1.50, 1.37 (s's, 3H each), 0.93 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 108.2, 79.2, 77.4, 68.7, 61.0, 37.0, 27.2, 25.0, 19.0, 13.9; MS *m/z* (assignment, relative intensity) 189 ($M^+ - CH_3$, 50); HRMS calcd for $C_9H_{17}O_4$ ($M^+ - CH_3$) 189.1127, found 189.1136; TLC $R_f = 0.6$ ($CHCl_3/CH_3OH$ 9:1).

Tetrols 9a and 9b. To 10.0 mg of diol **8a** was added 2 mL of a CH_3COOH/H_2O (7:3) solution. After 16 h, the mixture was concentrated by rotary evaporation, and acetic acid was azeotropically removed by addition and evaporation of four 2 mL portions of *n*-heptane. Purification by preparative TLC afforded 8.0 mg (98%) of tetrol **9a** as a white solid. An analogous procedure applied to diol **8b** (10.0 mg) gave 7.6 mg (93%) of tetrol **9b** as a white solid.

Data for **9a**: IR (film) 3280 (br, OH's) cm^{-1}; ^1H NMR (C_5D_5N, 250 MHz) δ: 4.51, 4.38, 4.26 (partly overlapped m's, 2H, 2H, 1H, respectively), 2.12, 1.90, 1.65 (partly overlapped m's, 1H, 2H, 1H, respectively), 0.95 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (C_5D_5N, 62.8 MHz) δ 76.2, 75.0, 73.8, 65.1, 35.9, 19.5, 14.6; MS *m/z* (assignment, relative intensity) 273 ($M^+ - CH_3COO$, 10); HRMS for the tetraacetate calcd for $C_{13}H_{21}O_6$ ($M^+ - CH_3COO$) 273.1338, found 273.1343; TLC $R_f = 0.2$ ($CHCl_3/CH_3OH$ 9:1).

Data for **9b**: IR (film) 3348 (br, OH) cm^{-1}; ^1H NMR (C_5D_5N, 200 MHz) δ 4.51, 4.34, 4.11 (the first two signals appear as partly overlapped multiplets; the third signal appears as a clean dd, $J = 7.3, 1.9$ Hz, 3H, 1H, 1H, respectively), 2.14−1.44 (overlapped m's, 4H), 0.90 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (C_5D_5N, 50.3 MHz) δ 75.0, 73.6, 70.8, 65.4, 37.0, 19.9, 14.5; MS data for the tetraacetate *m/z* (assignment, relative intensity) 273 ($M^+ - CH_3COO$, 15), calcd for $C_{13}H_{21}O_6$ ($M^+ - CH_3COO$) 273.1338, found 273.1340; TLC $R_f = 0.2$ ($CHCl_3/CH_3OH$ 9:1).

Tetrabenzoates 10a and 10b. To a cooled (0 °C) and stirred solution of **9a** (8.0 mg, 0.048 mmol) in pyridine (1 mL) was added benzoyl chloride (45 μL, 0.48 mmol). After 2 h, a saturated $NaHCO_3$ solution (2 mL) was added, and the solution was stirred at 0 °C for 30 min and then diluted with $CHCl_3$, poured into a separatory funnel, and extracted with $CHCl_3$. The combined organic extracts were washed with water, dried (Na_2SO_4), filtered, and concentrated. The resulting yellow oil was purified by HPLC (column: LiChrosorb Si-60 250 × 4 mm, 5 μm; eluent: hexane−EtOAc, 8:2; flow: 1.0 mL/min; $t_R = 19.2$ min) to afford 19.8 mg (71%) of **10a** as a clear oil. Perbenzoylation of tetrol **9b** (11.8 mg, 0.072 mmol) as above-reported for **9a**, followed by HPLC purification (above conditions, $t_R = 20.2$ min) gave 18.7 mg (67%) of **10b** as a clear oil.

Data for **10a**: IR (film) 1724 (C=O's), 1265 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 8.10−7.91 (overlapped multiplets, 8H), 7.64−7.19 (overlapped multiplets, 12H), 5.95 (m, 2H), 5.67 (ddd, $J = 8.4, 3.7, 3.7$ Hz, 1H), 4.94 (dd, $J = 11.9, 2.3$ Hz, 1H), 4.59 (dd, $J = 11.9, 5.7$ Hz, 1H), 1.92, 1.47 (m's, 2H each), 0.92 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 166.1, 165.8, 165.5, 165.2, 133.4, 132.2, 133.0, 132.9, 129.8, 129.7, 129.3, 128.5, 128.5, 128.3, 72.6, 72.6, 70.4, 63.1, 32.2, 18.6, 13.7; MS *m/z* (assignment, relative intensity) 580 (M^+, 0.5), 336 ($M^+ -$ 2PhCOOH, 20), 105 (100), 77 (87); HRMS calcd for $C_{35}H_{32}O_8$ (M^+) 580.2096, found 580.2091; TLC $R_f = 0.58$ (benzene/EtOAc 95:5); $R_f = 0.5$ (hexane/EtOAc 8:2).

Data for **10b**: IR (film) 1724 (C=O's), 1265 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 8.12−7.90 (overlapped multiplets, 8H), 7.64−7.32 (overlapped multiplets, 12H), 5.92 (dd, $J = 6.7, 4.2$ Hz, 1H), 5.78 (ddd, $J = 6.7, 6.7, 3.4$ Hz, 1H), 5.67 (ddd, $J = 6.7, 6.7, 4.2$ Hz, 1H), 4.85 (dd, $J = 12.7, 3.4$ Hz, 1H), 4.55 (dd, $J = 12.7, 6.7$ Hz, 1H), 1.80, 1.43 (m's, 2H), 0.91 (t, $J = 6.8$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 166.0, 165.7, 165.4, 165.4, 133.5, 133.2, 133.0, 133.0, 129.8, 129.7, 129.4, 128.5, 128.3, 72.1, 71.6, 69.9, 62.7, 33.2, 18.5, 13.8; MS *m/z* (assignment, relative intensity) 580 (M^+, 0.3), 336 ($M^+ -$ 2PhCOOH, 15), 105 (100), 77 (75); HRMS calcd for $C_{35}H_{32}O_8$ (M^+) 580.2096, found 580.2010; TLC $R_f = 0.54$ (benzene/EtOAc 95:5); $R_f = 0.5$ (hexane−EtOAc 8:2).

2,7,8-Tribenzoyllactone 11 and 2,8-Dibenzoyllactone 12. To a solution of pinolidoxin (**1**, 5.0 mg, 0.015 mmol) in CH_3OH (0.5 mL) was added a 32% aqueous NH_3 solution (0.5 mL), and the mixture was stirred at 50 °C for 6 h. After evaporation of the solvent, the crude 2-deacylated pinolidoxin ($R_f = 0.3$, $CHCl_3$−2-propanol, 95:5) was azeotropically dried with three 1 mL portions of anhydrous toluene and dissolved in anhydrous pyridine (200 μL). Then, benzoyl chloride (50 μL, 0.4 mmol) was added, and the mixture was stirred at 0 °C. After 24 h, saturated aqueous $NaHCO_3$ (1 mL) was added and the solution was stirred at room temperature for a further 30 min and extracted with $CHCl_3$. The combined organic extracts were washed with water, dried (Na_2SO_4), filtered, and concentrated to give a white solid. HPLC separation (LiChrospher Si-60 250 × 4 column, 5 μm; eluent: hexane−EtOAc 8:2; flow: 1 mL/min) afforded 6.0 mg (71%) of 2,7,8-tribenzoylpinolidoxin **11** ($t_R = 9.2$ min) and 2.0 mg (28%) of 2,8-dibenzoylpinolidoxin **12** ($t_R = 14.3$ min). The partially benzoylated product **12** was converted into the synthetically useful fully benzoylated derivative **11** in the above conditions to give, after HPLC purification, additional 2.2 mg (95%) of this material, bringing the total yield of **11** to 8.2 mg (97%).

Data for **11**: $[\alpha]_D$ +64.0 ($c = 0.10$, $CHCl_3$); IR (film) 1728 (C=O's), 1266, cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 8.19, 8.14, 7.86 (dd's, $J = 7.7, 1.7$ Hz, 2H each), 7.73−7.30 (overlapped multiplets, 9H), 6.07 (bs, $W_{1/2}$=6.7 Hz, 1H), 5.88 (bd, $J = 15.9$ Hz, 1H), 5.78 (ddd, $J = 10.5, 10.5, 3.9$ Hz, 1H), 5.62 (bd, $J = 15.9$ Hz, 1H), 5.53 (bd, $J = 3.9$ Hz, 1H), 5.19 (dd, $J = 8.7, 2.0$ Hz, 1H), 2.54 (m, 1H), 2.45−2.12, 1.73−1.18 (m's, 6H), 0.81 (t, $J = 7.1$ Hz, 3H); MS *m/z* (assignment, relative intensity) 556 (M^+, 2), 451 ($M^+ -$ PhCO, 2), 434 ($M^+ -$ PhCOOH, 4), 312 ($M^+ -$ 2PhCOOH, 8), 190 ($M^+ -$ 3PhCOOH, 14), 105 (100), 77 (92); TLC $R_f = 0.6$ (hexane/EtOAc, 7:3).

Data for **12**: IR (film) 3448 (br, OH), 1728 (C=O's), 1262 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 8.13, 8.04 (dd's, $J = 7.4, 1.8$ Hz, 2H each), 7.70−7.41 (overlapped multiplets, 6H), 5.83 (bd, $J = 15.6$ Hz, 1H), 5.75 (bd, $J = 15.6$ Hz, 1H) 5.59 (ddd, $J = 9.6, 9.6, 4.0$ Hz, 1H), 5.49 (bd, $J = 4.0, 1.5$ Hz, 1H), 5.02 (dd, $J = 9.7, 2.0$ Hz, 1H), 4.60 (bs, $W_{1/2}$=4.6 Hz, 1H), 2.55 (m, 2H), 2.45−2.00, 1.70−1.20 (m's, 6H), 0.80 (t, $J = 7.4$ Hz, 3H). MS *m/z* (assignment, relative intensity) 347 ($M^+ - 105$, 1), 105 (100), 77 (92); TLC $R_f = 0.4$ (hexane/EtOAc, 7:3).

Dioltribenzoate 13. To a stirred solution of 6.0 mg (0.011 mmol) of tribenzoate **11** in pyridine (1 mL) was added over a 5 min period 5.5 mg (0.022 mmol) of OsO_4. After 4 h, 1 mL of a solution prepared dissolving 200 mg of $NaHSO_3$ in 3 mL of H_2O and 2.5 mL of pyridine was added. After being stirred for 30 min, the orange solution was extracted with $CHCl_3$ and the organic phase was washed with water, dried (Na_2SO_4), filtered, and concentrated. Purification by HPLC (LiChrospher Si-60 250 × 4 column, 5 μm; eluent: $CHCl_3$; flow: 1 mL/min) gave 4.0 mg (65%) of diol **13** ($t_R = 2.5$ min) as an oil.

Data for **13**: ^1H NMR ($CDCl_3$, 200 MHz) δ 8.08, 8.01, 7.96 (dd's, $J = 7.7, 1.8$ Hz for all, 2H each), 7.67−7.41 (overlapped multiplets, 9H), 5.72 (bs, 1H), 5.63 (dd, $J = 6.1, 2.4$ Hz, 1H), 5.46 (m, 1H), 5.33 (dd, $J = 6.7, 2.5$ Hz, 1H), 4.18 (bs, 1H), 4.02 (bs, 1H), 0.82 (t, $J = 7.1$ Hz, 3H); TLC $R_f = 0.8$ ($CHCl_3-CH_3OH$, 9:1).

Tetrol 15. To a solution of dioltribenzoate **13** (4.0 mg, 0.008 mmol) in CH_3COOH (2 mL) was added crystalline $Pb(OAc)_4$ (4.0 mg, 0.01 mmol)[14] over a 5 min period under stirring. The stirring was continued for further 5 min, then the reaction mixture was quenched by addition of two drops of ethylene glicole, diluted with ice−water, and extracted with $CHCl_3$. The organic phase was washed with a saturated aqueous $NaHCO_3$ solution and water, dried (Na_2SO_4), filtered, and evaporated to give 4.0 mg of a crude dialdehyde product: ^1H NMR ($CDCl_3$, 200 MHz) (selected data from the crude reaction mixture) δ 9.85, 9.83 (two apparent s's, 2H), 8.19, 7.86 (overlapped multiplets, 6H), 7.62−7.30 (overlapped multiplets, 9H), 5.86,

5.74 (m's, 1H each), 5.62 (m, 1H), 5.35 (m, 1H), 0.90 (t, J = 7.0 Hz, 3H).

The unpurified dialdehyde obtained as above (4.0 mg, 0.008 mmol) was dissolved in EtOH (2 mL), and $NaBH_4$ (12.0 mg, 0.32 mmol) was added. After the mixture was stirred for 4 h at room temperature, CH_3COOH (two drops) was added and the reaction mixture was extracted with $CHCl_3$. The organic phase was washed with water, dried (Na_2SO_4), filtered, and evaporated to give 4.0 mg of a product whose chromatographyc mobility (R_f = 0.8; $CHCl_3/CH_3OH$ 9:1) was in agreement with that of the expected 5,6-dihydroxy-2,7,8-tribenzoyl-5,6-seco-pinolidoxin **14**. The unpurified substance was subjected to the next step of the sequence.

To a solution of the crude dioltribenzoate **14**, obtained as above, in CH_3OH (1 mL) was added aqueous 32% NH_3 (1.5 mL), and the solution was stirred at 50 °C for 6h. Then the mixture was extracted with $CHCl_3$, the organic phase was dried (Na_2SO_4), filtered, and evaporated. Preparative TLC afforded 1.0 mg (40% from **13**) of tetrol **15** as a withe solid: $[\alpha]_D$ −14.5 (*c* 0.1, CH_3OH). Spectral data (^{1}H NMR, ^{13}C NMR, IR, MS), and chromatographic properties (TLC R_f = 0.2; $CHCl_3/CH_3OH$ 9:1) of this material were identical to those exhibited by the synthetic racemic tetrol **13a**, obtained as above, and the enantiomerically pure tetrol **9a′** (see later and Scheme 5). In addition, the $[\alpha]_D$ value of **15** well matched that exhibited by **9a′**.

Tetrabenzoate 16. Perbenzoylation of tetrol **15** (1.0 mg, 0.006 mmol) in the same conditions used to perbenzoylate racemic tetrol **9a** (BzCl, py, 0 °C, 4 h) gave, after purification as described for **9a**, 3.5 mg (95%) of tetrabenzoate **16**: $[\alpha]_D$ +30.8 (*c* 0.3, $CHCl_3$). Spectral data (^{1}H NMR, ^{13}C NMR, IR, MS), and chromatographic properties (co-injection of **16** with both **10a** and **10b** on a LiChrosorb Si-60 250 × 4 column, 5 μm; eluent hexane−EtOAc, 8:2; flow: 1.0 mL/min) were identical to those exhibited by the synthetic racemic tetrabenzoate **10a** obtained as above-described. The $[\alpha]_D$ value for **16** is in good agreement with that exhibited by enantiomerically pure **10a′** obtained as described later (Scheme 4).

Mosher's Ester Derivatives 17. To a solution of the racemic alcohol **7a** (10.0 mg, 0.031 mmol) in pyridine (500 μL) was added (*S*)-MTPA chloride (30 μL, 0.19 mmol). After the mixture was stirred for 2 h at room temperature, a saturated $NaHCO_3$ solution (1 mL) was added and the solution was stirred for further 30 min then transferred into a separatory funnel and extracted with $CHCl_3$. The combined organic extracts were washed with water, dried (Na_2SO_4), filtered, and concentrated. HPLC purification (Hibar LiChrosorb Si-60 250 × 10 column; eluent: hexane−EtOAc, 8:2; flow: 2.5 mL/min) afforded 10 mg (52%) of a mixture of the two diastereoisomeric (*S*)-MTPA derivatives **17** (one peak at t_R = 12.0 min) as an oil. TLC R_f = 0.65 (hexane/EtOAc, 8:2).

The following attempts to separate the two diastereoisomers composing the mixture **17** were unsuccessful: (1) column: LiChrospher Si-60 (250 × 4 mm), 5 μm; eluent: hexane−EtOAc 98:2; flow: 0.7 mL/min; t_R = 22.5 min; (2) column: Supelcosil LC-®-DNB−PG (250 × 4.6 mm), 5 μm; eluent: hexane−EtOAc, 98:2; 0.7 mL/min; t_R = 19.5 min; (3) column: Whatman Partisphere C-18 (15 × 4 mm); eluent: CH_3OH; flow: 0.7 mL/min; t_R = 7.9 min; (4) column: Hibar Supersphere RP-18 (250 × 4 mm), 5 μm; eluent: CH_3OH or CH_3OH-H_2O (95:5); flow: 0.7 mL/min; t_R = 4 or 9 min, respectively.

Alcohols 18a and 18b. To a stirred solution of **17** (10 mg, 0.016 mmol) in dry THF (750 μL) was added 100 μL (0.51 mmol) of $Et_3N{\cdot}3HF$ at room temperature. After 16 h, the mixture was diluted with Et_3N (2 mL), evaporated, and filtered through a short pad of silica gel (eluent $CHCl_3-CH_3OH$, 9:1) to give a mixture of the alcohols **18** as an oil. HPLC separation (LiChrospher Si-60 250 × 4 mm column, 5 μm; eluent: hexane−EtOAc, 8:2; flow: 1 mL/min) of this material afforded 3.7 mg (58%) of **18a** (t_R = 11.5 min) and 2.3 mg (32%) of **18b** (t_R = 13.0 min).

Data for **18a**: $[\alpha]_D$ +28.7 (*c* 0.86, $CHCl_3$); IR (film) 3489 (br, OH), 1747 (C=O), 1250 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz) δ: 7.55 (m, 2H), 7.41 (m, 3H), 5.26 (ddd, J = 7.0, 7.0, 5.0 Hz, 1H), 4.18 (dd, J = 7.0, 5.8 Hz, 1H), 4.07 (ddd, J = 5.8, 5.8, 5.8 Hz, 1H), 3.55 (s, 3H), 3.44 (t, J = 5.8 Hz, 2H), 1.85−1.62 (m, 4H), 1.38, 1.33 (s's, 3H each), 0.93 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 165.7, 131.9, 129.7, 128.4, 127.3, 121.0, 108.6, 77.4, 76.2, 73.8, 61.1, 55.4, 33.7, 27.7, 25.4, 17.7, 13.9; MS *m/z* (assignment, relative intensity) 405 (M^+-CH_3, 40), 389 (M^+-OCH_3, 20); HRMS calcd for $C_{19}H_{24}O_6F_3$ ($M^+ - CH_3$) 405.1525, found 405.1505; TLC R_f = 0.2 (hexane/EtOAc, 8:2).

Data for **18b**: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.55 (m, 2H), 7.41 (m, 3H), 5.30 (ddd, J = 7.0, 7.0, 5.0 Hz, 1H), 4.22 (dd, J = 7.0, 5.8 Hz, 1H), 4.16 (ddd, J = 5.8, 5.8, 5.8 Hz, 1H), 3.53 (a 3H singlet overlapped to a 2H multiplet), 1.46, 1.36 (s's, 3H each), 0.90 (t, J = 7.0 Hz, 3H); MS *m/z* (assignment, relative intensity) 405 ($M^+ - CH_3$, 30), 389 ($M^+ - OCH_3$, 25); HRMS calcd for $C_{19}H_{24}O_6F_3$ ($M^+ - CH_3$) 405.1525, found 405.1519; TLC R_f = 0.2 (hexane/EtOAc, 8:2).

Diols 8a′ and 8a″. To a solution of **18a** (5.0 mg, 0.01 mmol) in CH_3OH (1 mL) was added 32% aqueous NH_3 (1.5 mL), and the mixture was stirred at room temperature for 24 h. Evaporation of the solvent and chromatography (eluent: $CHCl_3-CH_3OH$, 9:1) afforded 2.0 mg (98%) of diol **8a′** as a white solid. An analogous procedure applied to **18b** (5.0 mg, 0.01 mmol) followed by chromatography in the same conditions used for the purification of **8a′** gave 1.9 mg (93%) of diol **8a″** as a white solid.

Data for **8a′**: $[\alpha]_D$ −33.3 (*c* = 0.30, $CHCl_3$); spectral data (^{1}H NMR, ^{13}C NMR, IR, MS), and chromatographic properties (TLC R_f = 0.6; $CHCl_3/CH_3OH$ 9:1) of this material were identical to those exhibited by the synthetic racemic diol **8a** obtained as above-described.

Data for **8a″**: $[\alpha]_D$ +32.4 (*c*= 0.25, $CHCl_3$).

Tetrols 9a′ and 9a″. To 5.0 mg (0.026 mmol) of diol **8a′** was added 1.5 mL of a CH_3COOH/H_2O (7:3) solution. After 24 h, the mixture was evaporated and the residual acetic acid was azeotropically removed by addition of *n*-heptane (4 × 2 mL). Purification by preparative TLC ($CHCl_3-CH_3OH$, 8:2) afforded 4.0 mg (98%) of tetrol **9a′** as a white solid. An analogous procedure applied to diol **8a″** (2.0 mg, 0.010 mmol) gave 1.5 mg (91%) of tetrol **9a″** as a white solid.

Data for **9a′**: $[\alpha]_D$ −13.1 (*c* 0.35, CH_3OH); mp 115−117 °C (microneedles from pyridine/$CHCl_3$, 1:1). Spectral data (^{1}H NMR, ^{13}C NMR, IR, MS) and chromatographic properties (TLC R_f = 0.2; $CHCl_3-CH_3OH$, 9:1) were identical to those exhibited by tetrol **15** derived from degradation of pinolidoxin, and synthetic racemic tetrol **9a** obtained as described above.

Data for **9a″**: $[\alpha]_D$= +14.0 (*c* 0.15, CH_3OH).

Tetrabenzoates 10a′ and 10a″. Tetrols **9a′** and **9a″** were perbenzoylated as described above for **9a** and **9b** and purified by HPLC in the same conditions. From 4.0 mg (0.024 mmol) of tetrol **9a′** were obtained 11.9 mg (85%) of tetrabenzoate **10a′**, while 1.5 mg (0.009 mmol) of tetrol **9a″** gave 4.3 mg (82%) of tetrabenzoate **10a″**, both as oils.

Data for **10a′**: $[\alpha]_D$ +32.2 (*c* 1.1, $CHCl_3$); spectral data (^{1}H NMR, ^{13}C NMR, IR, MS) and chromatographic properties (TLC R_f = 0.5; hexane/EtOAc, 8:2) were identical to those exhibited by tetrabenzoate **16**, derived from degradation of pinolidoxin, and synthetic racemic tetrol **10a** obtained as described above. Anal. Calcd for $C_{35}H_{32}O_8$: C, 72.40; H, 5.56. Found: C, 72.29; H, 5.63.

Data for **10a″**: $[\alpha]_D$ −31.1 (*c* 0.34, $CHCl_3$). Anal. Calcd for $C_{35}H_{32}O_8$: C, 72.40; H, 5.56. Found: C, 72.48; H, 5.59.

Mosher's Ester Derivatives 19 and 20. A mixture of diol **8a′** (5.0 mg, 0.024 mmol), imidazole (4.1 mg, 0.060 mmol), and *tert*-butyldimethylsilyl chloride (6.0 mg, 0.046 mmol) in DMF (1 mL) was stirred overnight at room temperature, quenched with water (3 mL), and extracted with $CHCl_3$. The organic solution was dried (Na_2SO_4) and concentrated. Purification of the residue by HPLC (column: LiChrosorb Si-60 250 × 10 mm, 7 μm; eluent: hexane−EtOAc, 92:8; flow: 2.5 mL/min) delivered 7.3 mg (96%) of alcohol **7a′** as an oil.

Data for **7a′**: $[\alpha]_D$ −13.2 (*c* 0.71, $CHCl_3$); spectral data (^{1}H NMR, ^{13}C NMR, IR, MS) and chromatographic properties (TLC R_f = 0.8; hexane/EtOAc, 8:2) were identical to those exhibited by synthetic racemic alcohol **7a** obtained as described above.

To a solution of the alcohol **7a′** obtained as above (3.0 mg, 0.009 mmol) in pyridine (400 μL) was added (*S*)-MTPA chloride

(30 μL, 0.054 mmol). After the solution was stirred for 2 h at room temperature, a saturated $NaHCO_3$ solution (1 mL) was added, and the mixture was stirred for 30 min and then transferred into a separatory funnel and extracted with $CHCl_3$. The combined organic extracts were washed with water, dried (Na_2SO_4), filtered, and concentrated. HPLC purification on a Hibar LiChrosorb Si-60 (250 × 4) column (eluent: hexane−EtOAc, 8:2) afforded 4.7 mg (98%) of the (*S*)-MTPA derivative **19** as a clear oil. Using the (*R*)-MTPA chloride and the above procedure, alcohol **7a′** (2.5 mg, 0.008 mmol) gave 4.0 mg (96%) of the (*R*)-MTPA derivative **20** as a clear oil after HPLC purification in the above conditions.

Data for **19**: $[\alpha]_D$ +23.0 (*c* 0.15, $CHCl_3$); IR (film) 1748 (C=O), 1254 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.55, 7.39 (m's, 2H and 3H, respectively), 5.42 (ddd, *J* = 5.0, 6.4, 6.4 Hz, 1H), 4.16 (dd, *J* = 6.4, 6.4 Hz, 1H), 4.04 (ddd, *J* = 6.4, 5.7, 4.6 Hz, 1H), 3.59 (AB system further coupled, A part *J* = 11.5, 4.6 Hz, B part *J* = 11.5, 5.7 Hz, 2H), 3.55 (bs, 3H), 1.73 (m, 2H), 1.37, 1.29 (s's, 3H each), 1.50−1.20 (m, 2H), 0.91 (t, *J* = 7.1 Hz, 3H), 0.90 (s, 9H), 0.06, 0.05 (s's, 3H each); TLC R_f = 0.7 (hexane−EtOAc, 85:15).

Data for **20**: $[\alpha]_D$ −20.0 (*c* 0.10, $CHCl_3$); IR (film) 1748 (C=O), 1259 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.56, 7.39 (m's, 2H and 3H, respectively), 5.42 (ddd, *J* = 7.4, 5.2, 5.2 Hz, 1H), 4.25 (dd, *J* = 5.2, 5.2 Hz, 1H), 4.14 (ddd, *J* = 5.6, 5.2, 5.2 Hz, 1H), 3.64 (AB system further coupled, A part *J* = 11.5, 5.2 Hz, B part *J* = 11.5, 5.7 Hz, 2H), 3.54 (bs, 3H), 1.67 (m, 2H), 1.45, 1.33 (s's, 3H each), 1.40−1.15 (m, 2H), 0.88 (s, 9H), 0.85 (t, *J* = 7.2 Hz, 3H), 0.04, 0.03 (s's, 3H each); TLC R_f = 0.7 (hexane−EtOAc, 85:15).

C-8 Mosher's Ester Derivatives of Pinolidoxin (21 and 22). To a stirred solution of pinolidoxin **1** (2.0 mg, 0.006 mmol) in pyridine (100 μL) was added (*S*)-MTPA chloride (90 μL, 0.009 mmol). After 5 h, a saturated $NaHCO_3$ solution (300 μL) was added, and the mixture was stirred for 30 min and then extracted with $CHCl_3$. The combined organic extracts were washed with water, dried (Na_2SO_4), filtered, and concentrated. HPLC purification on a Hibar LiChrosorb Si-60 (250 × 4) column (eluent: cyclohexane−EtOAc, 8:2) afforded 3.0 mg (90%) of the C-8 (*S*)-MTPA derivative of pinolidoxin **21** as an oil. Using the (*R*)-MTPA chloride (200 μL, 0.02 mmol) and the above procedure, pinolidoxin (2.0 mg, 0.006 mmol) gave 2.6 mg (80%) of the C-8 (*R*)-MTPA derivative of pinolidoxin **22** as an oil, after HPLC purification as described for **21**. In this case, the reaction required 24 h to go to completion.

Data for **21**: IR (film) 3415 (br, OH), 1734 (3 × C=O), 1260 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 7.60−750, 7.43−4.38 (m's, 5H), 7.32 (dd, *J* = 15.4, 9.8 Hz, 1H), 6.25 (m, 2H), 5.88 (d, *J* = 15.4 Hz, 1H), 5.69 (bd, *J* = 14.8 Hz, 1H), 5.61 (bdd, 14.8, 14.8 Hz, 1H), 5.36 (ddd, *J* = 9.4, 9.4, 2.8 Hz, 1H), 5.27 (dd, *J* = 5.6, 1.7 Hz, 1H), 4.95 (dd, *J* = 9.4, 2.5 Hz, 1H), 4.60 (bs, 1H), 3.61 (s, 3H), 2.46 (m, 1H), 2.30−1.93 (overlapped multiplets, 4H), 1.91 (bd, *J* = 5.5 Hz, 3H), 1.0−1.3 (overlapped multiplets, 3H), 0.69 (t, *J* = 7.3 Hz, 3H); TLC R_f = 0.4 (cyclohexane/EtOAc 8:2).

Data for **22**: IR (film) 3426 (br, OH), 1730 (3 × C=O), 1262 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.60−750, 7.45−4.35 (m's, 5H), 7.32 (dd, *J* = 15.4, 9.7 Hz, 1H), 6.25 (m, 2H), 5.88 (d, *J* = 15.4 Hz, 1H), 5.63 (bd, *J* = 14.8 Hz, 1H), 5.62 (bdd, 14.8, 14.8 Hz, 1H), 5.41 (ddd, *J* = 9.5, 9.5, 2.6 Hz, 1H), 5.27 (dd, *J* = 5.6, 1.7 Hz, 1H), 4.96 (dd, *J* = 9.5, 2.5 Hz, 1H), 4.49 (bs, 1H), 3.61 (s, 3H), 2.46 (m, 1H), 2.30−1.93 (overlapped multiplets, 4H), 1.91 (bd, *J* = 5.5 Hz, 3H), 1.0−1.3 (overlapped multiplets, 3H), 0.80 (t, *J* = 7.3 Hz, 3H); TLC R_f = 0.5 (cyclohexane/EtOAc 8:2).

Acetonide Lactone 24. A mixture of D-erythronolactone **23** (947 mg, 8.02 mmol), *p*-tolenesulfonic acid monohydrate (40 mg), and 2,2-dimethoxypropane (8 mL) in DMF (10 mL) was refluxed for 4 h. Then saturated $NaHCO_3$ solution (1 mL) was added, and excess 2,2-dimethoxypropane was evaporated in vacuo. Extraction with $CHCl_3$, filtration, anhydrification (Na_2SO_4), and evaporation delivered 1.206 g (95%) of acetonide lactone **24** as an oil. An analytical sample of **24** was obtained by preparative TLC (hexane−EtOAc, 7:3).

Data for **24**: $[\alpha]_D$ −104.4 (*c* 1.67, $CHCl_3$);[21] IR (film) 1780 (C=O), cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 4.85 (ddd, *J* = 5.7, 3.8, 1.2 Hz, 1H), 4.73 (d, *J* = 5.7 Hz, 1H), 4.41 (AB system further coupled, A part *J* = 14.3 Hz, B part *J* = 14.3, 3.8 Hz, 2H), 1.44, 1.35 (s's, 3H each); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 174.2, 113.8, 75.4, 74.5, 70.1, 26.6, 25.4; EIMS (assignment, relative intensity) *m*/*z* 158 (M^+, 10), 120 ($M^+ - CO_2$, 92); TLC R_f = 0.5 (hexane−EtOAc, 1:1).

Lactol 25. A cold (−78 °C) solution of lactone **24** (65 mg, 0.41 mmol) in CH_2Cl_2 (2 mL) was treated with diisobutylaluminum hydride (284 μL of a 1 M solution in CH_2Cl_2) during 5 min, stirred for 30 min at this temperature, and quenched with saturated NH_4Cl (2 mL). The reaction mixture was stirred at room temperature for further 30 min and diluted with CH_2Cl_2 (2 mL). The separated aqueous phase was extracted with CH_2Cl_2, and the combined organic solutions were dried (Na_2SO_4), filtered, and concentrated. Preparative TLC ($CHCl_3$−CH_3OH, 9:1) afforded 51 mg (78%) of lactol **25** as a clear oil.

Data for **25**: $[\alpha]_D$ −58.5 (*c* 1.53, $CHCl_3$); IR (film) 3418 (br, OH) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ: 5.47 (bs, 1H), 4.84 (dd, *J* = 5.8, 3.3 Hz, 1H), 4.57 (d, *J* = 5.8 Hz, 1H), 4.04 (AB system further coupled, A part *J* = 10.3, 3.3 Hz, B part *J* = 10.3 Hz, 2H), 2.88 (bs, 1H), 1.47, 1.32 (s's, 3H each); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 112.3, 101.8, 85.1, 79.9, 71.9, 26.2, 24.7; EIMS (assignment, relative intensity) *m*/*z* 160 (M^+, 10), 143 (M^+ − OH, 68); TLC R_f = 0.5 ($CHCl_3$−CH_3OH, 9:1).

Diol 8a′. To a stirred and cold (0 °C) solution of lactol **25** (248 mg, 1.55 mmol) in THF (2 mL) was added *n*-PrMgCl (2 M in Et_2O, 2.3 mL, 4.65 mmol) via syringe over a 5 min period. TLC monitoring (hexane−EtOAc, 7:3, double migration) showed the reaction to be complete after some 5 h. To the mixture, diluted with Et_2O (10 mL), was added a saturated NH_4Cl solution (10 mL), and the whole was transferred into a separatory funnel. The aqueous layer was separated and extracted with Et_2O. The combined organic layers were dried (Na_2SO_4), filtered, concentrated, and chromatographed (eluent $CHCl_3$−CH_3OH, 9:1) to give 240 mg (77%) of diol **8a′** as a white solid.

Data for **8a′**: $[\alpha]_D$ −32.7 (*c* 0.33, $CHCl_3$). Spectral data (^1H NMR, ^{13}C NMR, IR, MS) and chromatographic properties (TLC R_f= 0.6; $CHCl_3$−CH_3OH, 9:1) were identical to those exhibited by synthetic **8a′** obtained as described above (Scheme 4).

Silyl Ether 7a′. A mixture of diol **8a′** (231 mg, 1.13 mmol), imidazole (115 mg, 1.69 mmol), and *tert*-butyldimethylsilyl chloride (205 mg, 1.36 mmol) in DMF (500 μL) was stirred for 16 h at room temperature, quenched with water (3 mL), and extracted with $CHCl_3$. The organic solution was dried (Na_2SO_4), filtered, and concentrated. Purification by HPLC as described above for this compound afforded 270 mg (91%) of **7a′** as an oil.

Data for **7a′**: $[\alpha]_D$ −13.3 (*c* 0.25, $CHCl_3$). Spectral data (^1H NMR, ^{13}C NMR, IR, MS) and chromatographic properties (TLC R_f= 0.8; hexane−EtOAc, 8:2) were identical to those exhibited by synthetic **7a′** obtained as described above (Scheme 5).

Disilyl Ether 26. A mixture of alcohol **7a′** (268 mg, 0.84 mmol), imidazole (200 mg, 2.94 mmol), and *tert*-butyldiphenylsilyl chloride (647 μL, 2.53 mmol) in DMF (1 mL) was stirred for 22 h at room temperature, quenched by addition of water (3 mL), and extracted with $CHCl_3$. The organic phase was dried (Na_2SO_4), filtered, concentrated, and chromatographed (eluent: petroleum ether−EtOAc, 95:5) to give 345 mg (74%) of **26** as an oil.

Data for **26**: $[\alpha]_D$ +15.5 (*c* 2.97, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz) δ: 7.78−7.64, 7.44−7.30 (m's, 10H), 4.13 (overlapped multiplets, 2H), 3.95 (ddd, *J* = 4.9, 4.9, 4.9 Hz, 1H), 3.73 (A part of an AB system further coupled, *J* = 13.5, 3.3 Hz, 1H), 3.55 (B part of an AB system further coupled, *J* = 13.5, 7.5 Hz, 1H), 1.57−1.11 (overlapped signals, 2H), 1.46, 1.31 (s's,

(21) The $[\alpha]_D$ value for the enantiomer of compound **24** is reported to fall in the range +105 to +116.3°. (a) Hudlicky, T.; Luna, H.; Price, J. D.; Rulin, F. *J. Org. Chem.* **1990**, *15*, 4683−4687. (b) Vanhessche, K.; Van der Eyken, E.; Vanderwalle, M.; Röeper, H. *Tetrahedron Lett.* **1990**, *16*, 2337−2340. (c) Munier, P.; Giudicelli, M.-B.; Picq, D.; Anker, D. *J. Carboydr. Chem.* **1996**, *6*, 739−762.

3H each), 1.05 (s, 9H), 0.85 (s, 9H), 0.66 (t, $J = 7.0$ Hz, 3H), −0.01, −0.02 (s's, 3H each); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ: 136.0, 135.8, 134.2, 133.7, 129.6, 127.4, 107.7, 79.1, 78.4, 71.4, 63.3, 36.4, 27.8, 25.4, 26.9, 25.9, 19.4, 18.3, 18.2, 13.9, −5.3; MS *m/z* (assignment, relative intensity) 541 ($M^+ - CH_3$, 10), 499 ($M^+ - C_4H_9$, 20), 441 ($M^+ - SiC(CH_3)_3(CH_3)_2$, 55); HRMS calcd for $C_{31}H_{49}O_4Si_2$ ($M^+ - CH_3$) 541.3169, found 541.3182; TLC $R_f = 0.6$ (hexane−EtOAc, 9:1).

Alcohol 27. To a solution of disilyl ether **26** (35 mg, 0.063 mmol) in THF (1 mL) was added excess $Et_3N{\cdot}3HF$ (102 μL, 0.63 mmol) under stirring at room temperature. After 5 h, the mixture was diluted with Et_3N (2 mL) and evaporated. Preparative TLC (hexane−EtOAc. 7:3) afforded 18 mg (70%) of alcohol **27** as an oil.

Data for **27**: $[\alpha]_D$ +2.6 (*c* 0.83, $CHCl_3$); IR (film) 3479 (br, OH) cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 7.76−7.64, 7.46−7.33 (m's, 10H), 4.19 (m, 1H), 4.12 (dd, $J = 5.4$, 5.4 Hz, 1H), 3.99 (ddd, $J = 4.8$, 4.8, 4.8 Hz, 1H), 3.60 (m, 2H), 2.42 (bs, 1H), 1.49, 1.35 (s's, 3H each), 1.07 (s, 9H), 0.91 (t, $J = 7.7$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ: 136.1, 135.9, 133.8, 133.0, 129.8, 127.5, 107.9, 78.5, 71.3, 62.0, 36.9, 28.0, 25.6, 27.0, 19.3, 18.1, 13.8; MS *m/z* (assignment, relative intensity) 427 ($M^+ - CH_3$, 15), 385 ($M^+ - C_4H_9$, 12); HRMS calcd for $C_{25}H_{35}O_4Si$ ($M^+ - CH_3$) 427.2305, found 427.2321; TLC $R_f = 0.5$ (hexane−EtOAc, 7:3). Anal. Calcd for $C_{26}H_{38}O_4Si$: C, 70.57; H, 8.66; Si, 6.35. Found: C, 70.69; H, 8.51; Si, 6.20.

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Supporting Information Available: Experimental details for the transformation of *meso*-tartaric acid into 2,3-*O*-isopropylideneerythritol **3**, stereochemical view of Mosher's ester derivatives **19**−**22**, ^{1}H NMR spectra for compounds **4**−**6**, **7a**−**10a**, **7b**−**10b**, **11**−**13**, **18a**,**b** (mixture), **18a**, **18b**, **19**−**22**, **24**, **26**, and **27**, and HPLC chromatograms and CD spectra for compounds **16**, **10a′**, and **10a″**. This material is available free of charge via the Internet at http://pubs.acs.org.

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