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Asymmetric Synthesis of the Tetrahydropyran Ring, C32–C38 Fragment, of Phorboxazoles

Yasmin Brinkmann,[†,‡] M. Carmen Carreño,*[,†] Antonio Urbano,[†] Françoise Colobert,*[,‡] and Guy Solladié*[,‡]

Departamento de Química Orgánica (C-I), Universidad Autónoma de Madrid, Cantoblanco, 28049-Madrid, Spain, and Laboratoire de Stéréochimie associé au CNRS, Université Louis Pasteur, E.C.P.M., 25 rue Becquerel, 67087 Strasbourg Cedex 2, France

carmen.carrenno@uam.es

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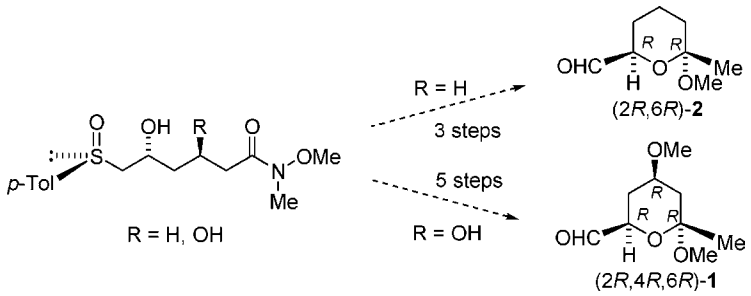
ABSTRACT



The asymmetric synthesis of a model aldehyde (2*R*,6*R*)-2 and the C32–C38 fragment of phorboxazoles, (2*R*,4*R*,6*R*)-1, is described using a sulfoxide as chiral auxiliary. Key advances include the stereoselective reductions of *β*-keto- or *β*,*γ*-diketosulfoxides, the acid-catalyzed cyclization of enantiopure sulfinyl hydroxy ketone precursors to the tetrahydropyran ring, and the Pummerer reaction on the pendant sulfoxide to create the formyl group.

Phorboxazoles A and B are unique tetrahydropyranoxazole-based macrolides isolated in 1995 by Searle and Molinski from a species of Indian Ocean sponge.[1] Both compounds were shown to inhibit growth of a wide range of different tumoral cells.[2] Their novel structure and potent biological activity have combined to make the scarcely available phorboxazoles attractive synthetic targets for the chemistry community.[3]

Phorboxazole A has been synthesized by Forsyth et al. in 1998,[4] by Smith et al. in 2001,[5] and by Williams et al.[6] and Pattenden et al.[7] in 2003. Phorboxazole B has been prepared by Evans et al. in 2000.[8]

The phorboxazole skeleton consists of two 2,4-disubstituted oxazoles and four tetrahydropyrans, and 15 stereogenic centers organized into a macrolide (C1−C26) and a side-

[†] Universidad Autónoma de Madrid.
[‡] Université Louis Pasteur.

(1) Searle, P. A.; Molinski, T. F. *J. Am. Chem. Soc.* **1995**, *117*, 8126−8131.

(2) (a) Searle, P. A.; Molinski, T. F.; Brzezinski, L. J.; Leahy, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 9422−9423. (b) Molinski, T. F. *Tetrahedron Lett.* **1996**, *37*, 7879−7880.

(3) For a review on the total synthesis of the phorboxazoles, see: Haustedt, L. O.; Hartung, I. V.; Hoffmann, H. M. R. *Angew. Chem., Int. Ed.* **2003**, *42*, 2711−2716.

(4) Forsyth, C. J.; Ahmed, F.; Cink, R. D.; Lee, Ch. S. *J. Am. Chem. Soc.* **1998**, *120*, 5597−5598.

(5) (a) Smith, A. B., III; Verhoest, P. R.; Minbiole, K. P.; Schelhaas, M. *J. Am. Chem. Soc.* **2001**, *123*, 4834−4836. (b) Smith, A. B., III; Minbiole, K. P.; Verhoest, P. R.; Schelhaas, M. *J. Am. Chem. Soc.* **2001**, *123*, 10942−10953.

(6) Williams, D. R.; Kiryanov, A. A.; Emde, U.; Clark, M. P.; Berliner, M. A.; Reeves, J. T. *Angew. Chem., Int. Ed.* **2003**, *42*, 1258−1262.

(7) (a) González, M. A.; Pattenden, G. *Angew. Chem., Int. Ed.* **2003**, *42*, 1255−1258. (b) Pattenden, G.; González, M. A.; Little, P. B.; Millan, D. S.; Plowright, A. T.; Tornos, J. A.; Ye, T. *Org. Biomol. Chem* **2003**, *1*, 4173−4208.

(8) (a) Evans, D. A.; Cee, V. J.; Smith, T. E.; Fitch, D. M.; Cho, P. S. *Angew. Chem., Int. Ed.* **2000**, *39*, 2533−2536. (b) Evans, D. A.; Fitch, D. M.; *Angew. Chem., Int. Ed.* **2000**, *39*, 2536−2540. (c) Evans, D. A.; Fitch, D. M.; Smith, T. E.; Cee, V. J. *J. Am. Chem. Soc.* **2000**, *122*, 10033−10046.

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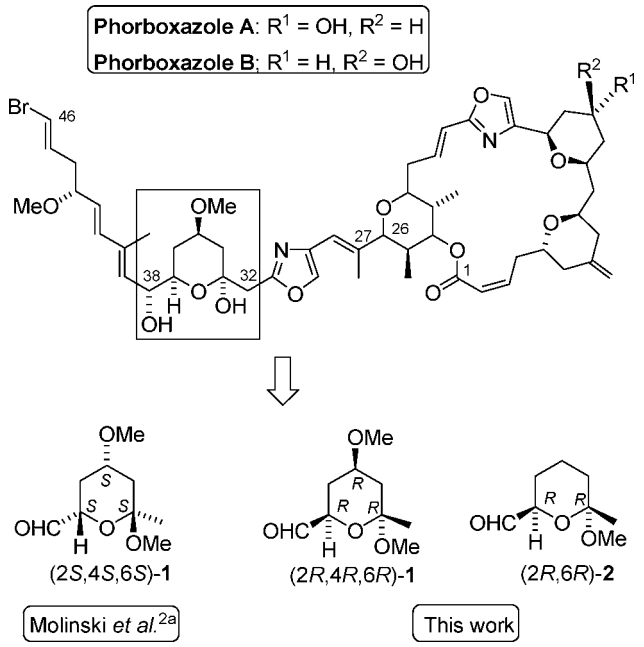
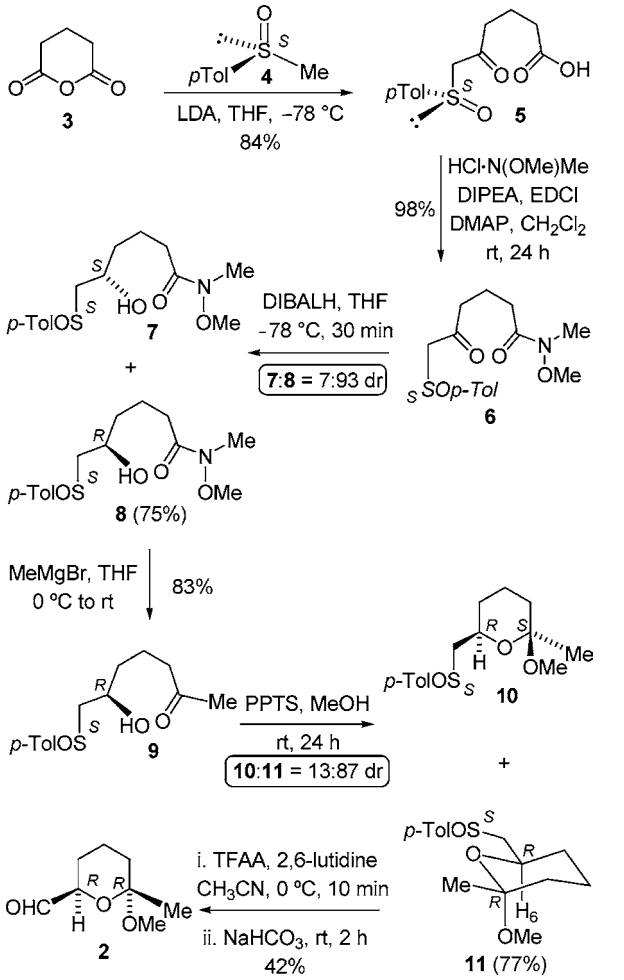


chain substructure (C27−C46). Of the four THP rings, only one, the C33−C37 fragment, possesses a hemiketal functionality and three stereogenic centers. Besides the synthetic efforts achieved for the stereoselective construction of this portion in the total syntheses of phorboxazoles, several groups have reported different strategies for the enantioselective assembly of this THP-hemiketal ring.[9] Among them, it is worth mentioning the first stereoselective approach to this fragment published by Molinski et al. in 1996,[2a] where derivative (2*S*,4*S*,6*S*)-**1**, bearing three stereogenic centers with the configuration opposite to that present in the natural phorboxazoles, was synthesized using malic acid as starting material. This synthesis of a model compound and the use of different NMR techniques served for the elucidation of the absolute configuration of 14 out of the 15 stereocenters in phorboxazoles.[2a]

In connection with a program devoted to asymmetric synthesis mediated by sulfoxides,[10] we have recently described a highly stereoselective approach to different sized *cis*-disubstituted oxygenated heterocycles (five-, six-, and seven-membered rings) based on the reductive cyclization of the corresponding enantiopure hydroxy sulfinyl ketones.[11] In this communication, we report the synthesis of several hydroxy sulfinylated intermediates and their use for the enantioselective construction of the C32−C38 THP fragment of phorboxazoles, illustrated with the asymmetric synthesis of (2*R*,6*R*)-**2**, a model compound lacking the OMe group at C-4, and (2*R*,4*R*,6*R*)-**1**, the enantiomer of the derivative prepared by Molinski, bearing the three stereogenic centers with the correct absolute configuration present in the natural phorboxazoles.

The synthesis of the model compound (2*R*,6*R*)-**2**, depicted in Scheme 1, began with the condensation of commercially

Scheme 1. Asymmetric Synthesis of Model Compound (2*R*,6*R*)-**2**



available glutaric anhydride (**3**) and the carbanion of (−)-(*SS*)-methyl-*p*-tolyl sulfoxide (**4**)[12] to give enantiopure *β*-ketosulfoxide (*SS*)-**5**,[13] in 84% yield. The transformation of the carboxylic group of (*SS*)-**5** into the Weinreb amide (*SS*)-**6** was effected, in 98% yield, by treatment with *N*,*O*-dimethylhydroxylamine hydrochloride in the presence of diisopro-

(9) (a) Ahmed, F.; Forsyth, C. J. *Tetrahedron Lett.* **1998**, *39*, 183−186. (b) Pattenden, G.; Plowright, A. T.; Tornos, J. A.; Ye, T. *Tetrahedron Lett.* **1998**, *39*, 6099−6102. (c) Wolbers, P.; Hoffmann, H. M. R. *Synthesis* **1999**, 797−802. (d) Williams, D. R.; Clark, M. P.; Emde, U.; Berliner, M. A. *Org. Lett.* **2000**, *2*, 3023−3026. (e) Marshall, J. A.; Yanik, M. M. *Tetrahedron Lett.* **2000**, *41*, 4717−4721. (f) Li, R. D.; Tu, Y. Q.; Lin, G.-Q.; Zhou, W.-S. *Tetrahedron Lett.* **2003**, *44*, 8729−8732. (g) Yadav, J. S.; Rajaiah, G. *Synlett* **2004**, 1743−1746.

(10) Overviews: (a) Hanquet, G.; Colobert, F.; Lanners, S.; Solladié, G. *ARKIVOC* **2003**, *7*, 328−401. (b) Carreño, M. C. *Chem. Rev.* **1995**, *95*, 1717−1760. Recent work: (c) Carreño, M. C.; Sanz-Cuesta, M. J.; Colobert, F.; Solladié, G. *Org. Lett.* **2004**, *6*, 3537−3540. (d) Bonini, C.; Chiummiento, L.; Pullez, M.; Solladie, G.; Colobert, F. *J. Org. Chem.* **2004**, *69*, 5015−5022. (e) Carreño, M. C.; García-Cerrada, S.; Urbano, A. *Chem. Eur. J.* **2003**, *9*, 4118−4131. (f) Carreño, M. C.; Garcia-Cerrada, S.; Sanz-Cuesta, M. J.; Urbano, A. *J. Org. Chem.* **2003**, *68*, 4315−4321.

(11) (a) Colobert, F.; Des Mazery, R.; Solladié, G.; Carreño, M. C. *Org. Lett.* **2002**, *4*, 1723−1725. (b) Carreño, M. C.; Des Mazery, R.; Urbano, A.; Colobert, F.; Solladié, G. *J. Org. Chem.* **2003**, *68*, 7779−7787. (c) Carreño, M. C.; Des Mazery, R.; Urbano, A.; Colobert, F.; Solladié, G. *Org. Lett.* **2004**, *6*, 297−299.

(12) Solladié, G.; Hutt, J.; Girardin, A. *Synthesis* **1987**, 173−175.

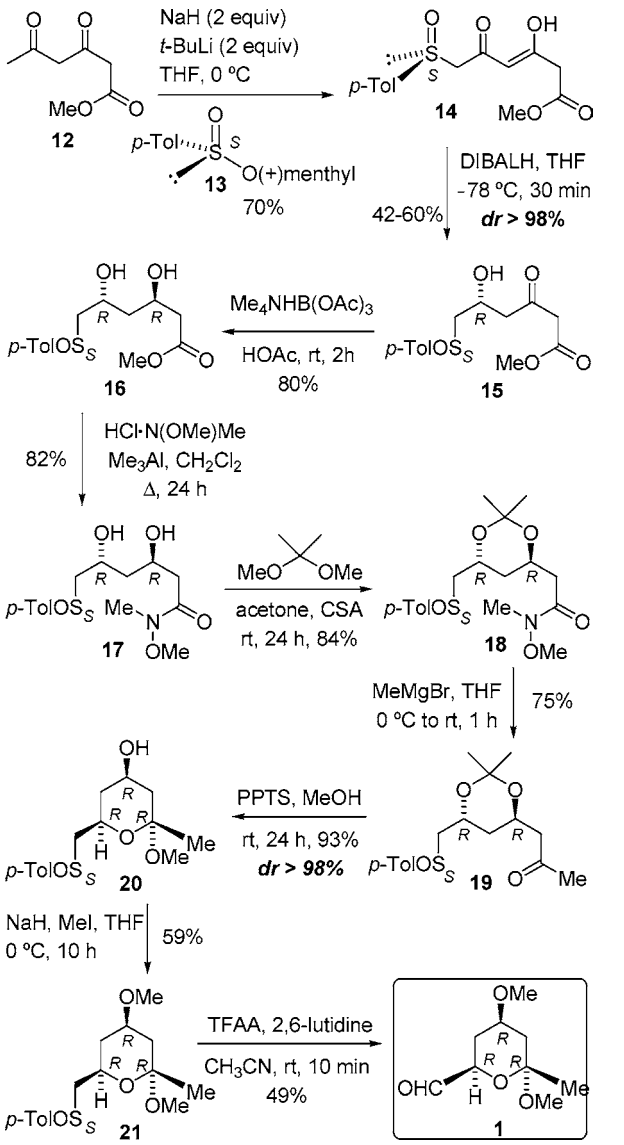
(13) (*SR*) enantiomer: Solladié, G.; Maestro, M. C.; Rubio, A.; Pedregal, C.; Carreno, M. C.; García Ruano, J. L. *J. Org. Chem.* **1991**, *56*, 2317−2322.

pylethylamine (DIPEA) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) and a catalytic amount of DMAP.[14] The stereoselective reduction of derivative (*SS*)-**6** with diisobutylaluminum hydride (DIBALH) afforded a 7:93 mixture of diastereoisomeric alcohols (5*S*,*SS*)-**7** and (5*R*,*SS*)-**8**, from which diastereoisomer (5*R*,*SS*)-**8** was isolated pure after chromatographic separation in 75% yield (based on recovered starting material). Without protection of the OH group, amide (5*R*,*SS*)-**8** reacted with an excess of methylmagnesium bromide in THF at room temperature, affording enantiopure methyl ketone (6*R*,*SS*)-**9** in 83% yield. The cyclization of δ-hydroxy ketone (6*R*,*SS*)-**9** into the corresponding THP-ketal ring was carried out by treatment with pyridinium *p*-toluenesulfonate (PPTS) in methanol giving rise to a 13:87 mixture of cyclic derivatives (2*S*,6*R*,*SS*)-**10** and (2*R*,6*R*,*SS*)-**11** from which the major diastereoisomer (2*R*,6*R*,*SS*)-**11** {$[\alpha]^{20}_D = -270$ (*c* 1.0, $CHCl_3$)} was separated in 77% yield after flash chromatography. Preferred formation of the α-anomer **11** was expected on the basis of the higher stability of the axially positioned OMe ketal group.[15] The structural assignment for **11** was verified by NOESY experiments (interaction of H-6 with the OMe group and not with the Me group). Finally, the treatment of sulfoxide (2*R*,6*R*,*SS*)-**11** under the typical Pummerer reaction conditions[16] [(i) trifluoroacetic anhydride (TFAA), 2,6-lutidine; (ii) $NaHCO_3$] gave rise, after flash chromatography on deactivated silica gel (see Supporting Information), to aldehyde (2*R*,6*R*)-**2** {$[\alpha]^{20}_D = -40$ (*c* 0.36, CH_2Cl_2)} in 42% yield, as an unstable colorless oil.

Having demonstrated the feasibility of this strategy for the stereoselective construction of the THP-hemiketal ring of phorboxazoles, we turned our attention to enantioselective synthesis of the C32−C38 fragment present in the natural derivatives. The synthetic sequence leading to enantiomerically pure ketone (4*R*,6*R*,*SS*)-**19**, immediate precursor of the tetrahydropyran moiety of (2*R*,4*R*,6*R*)-**1**, is outlined in Scheme 2.

Methyl 3,5-diketohexanoate (**12**)[17] was submitted to treatment with sodium hydride (1 equiv) and *tert*-butyllithium (2 equiv) to give the corresponding trianion intermediate, whose sulfinylation at C-6 occurred in the presence of (+)-menthyl-(*SS*)-(*p*-toluene)sulfinate (**13**).[12] Under these conditions, diketosulfoxide (*SS*)-**14** was obtained in 70% yield, showing the carbonyl group at C-3 totally enolized.[18a] The reduction of (*SS*)-**14** with DIBALH[18b,c] took place chemoselectively at the C-5 carbonyl group, probably as a consequence of the aluminum atom of the DIBALH coordinating the sulfinyl oxygen,[19] affording the hydroxysulfoxide (5*R*,*SS*)-**15**. This reaction was highly stereoselective, but the formation of two byproducts characterized as the starting material

Scheme 2. Asymmetric Synthesis of Compound (2*R*,4*R*,6*R*)-**1**, the C32−C38 Fragment of Phorboxazoles



12 and *p*-ditolyl disulfide could not be avoided. Purification of **15** by flash chromatography led to further degradations. Finally, a careful washing of the crude reduction mixture with cold ether and recrystallization (CH_2Cl_2/ether) afforded pure **15** in yields ranging from 42% to 60%. The remaining ketone was stereoselectively reduced to the corresponding *anti*-diol (3*R*,5*R*,*SS*)-**16**,[18b] in 80% yield, following the Evans protocol using tetramethylammonium triacetoxyborohydride, $Me_4NHB(OAc)_3$, as the reducing agent.[20]

The treatment of methyl ester (3*R*,5*R*,*SS*)-**16** with *N*,O-dimethylhydroxylamine hydrochloride in the presence of trimethyl aluminum[21] furnished the Weinreb amide (3*R*,5*R*,*SS*)-**17** in 82% yield (Scheme 2). Protection of the diol unit of

(14) Satoshi, S.; Mori, K. *Eur. J. Org. Chem.* **1999**, 1679−1686.
(15) (a) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon Press: Oxford, 1983; pp 5−20. (b) Smith, M. B.; March, J. *Advanced Organic Chemistry. Reactions, Mechanisms and Structure*, 5th ed.; Wiley-Interscience: New York, 2001; p 176.
(16) Sugihara, H.; Tanikaga, R.; Kaji, A. *Synthesis* **1978**, 881.
(17) Batelaan, J. G. *Synth. Commun.* **1976**, *6*, 81−83.
(18) (a) Solladié, G.; Bauder, C.; Rossi, L. *J. Org. Chem.* **1995**, *60*, 7774−7777. (b) Solladié, G.; Colobert, F.; Denni, D. *Tetrahedron: Asymmetry* **1998**, *9*, 3081−3094. (c) Solladié, G.; Wilb, N.; Bauder, C. *Eur. J. Org. Chem.* **1999**, 3021−3026.
(19) Carreño, M. C.; García Ruano, J. L.; Martín, A.; Pedregal, C.; Rodríguez, J. H.; Rubio, A.; Sanchez, J.; Solladié, G. *J. Org. Chem.* **1990**, *55*, 2120−2128.
(20) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *116*, 3560−3578.

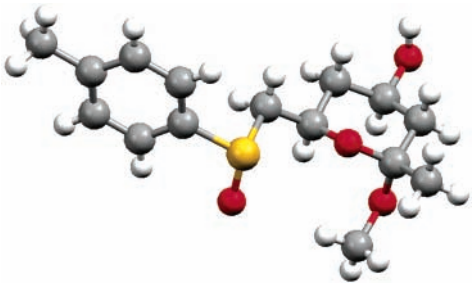


Figure 1. X-ray ORTEP for compound (2*R*,4*R*,6*R*,S*S*)-**20**.

17 (2,2-dimethoxypropane, camphorsulfonic acid, acetone, 24 h, 84%), followed by reaction of the acetonide (3*R*,5*R*,S*S*)-**18** with methylmagnesium bromide, gave rise to sulfinyl methyl ketone (4*R*,6*R*,S*S*)-**19** in 75% yield. In this case, the treatment of **19** with PPTS in MeOH afforded tetrahydropyran (2*R*,4*R*,6*R*,S*S*)-**20** $\{[\alpha]^{20}_D = -213$ (*c* 2.4, $CHCl_3)\}$ as the unique diastereoisomer in optically pure form, after initial deprotection of the acetonide of **19** and cyclization of the 4,6-dihydroxyketone intermediate. The structural assignment of **20** was initially based on its NMR parameters, including NOESY (interaction of H-4 and H-6 with the OMe group and not with the Me group) and COSY experiments. The (2*R*,4*R*,6*R*,S*S*) absolute configuration of all stereocenters present in derivative **20** was later confirmed by X-ray crystallography (Figure 1).

The free OH at C-4 on enantiopure derivative (2*R*,4*R*,6*R*,S*S*)-**20** (Scheme 2) was then methylated using NaH and MeI to furnish in 59% yield (based on recovered starting material) compound (2*R*,4*R*,6*R*,S*S*)-**21** $\{[\alpha]^{20}_D = -320$ (*c* 0.46, $CHCl_3)\}$. Upon Pummerer reaction [(i) TFAA, 2,6-lutidine; (ii) $NaHCO_3$], sulfoxide **21** was transformed into the desired aldehyde (2*R*,4*R*,6*R*)-**1** $\{[\alpha]^{20}_D = -66$ (*c* 0.28, $CHCl_3)\}$, bearing the C32−C38 fragment of phorboxazoles, in 49% yield. This transformation allowed the generation of the formyl-substituted heterocycle in the last step by the intermediacy of the sulfoxide. The three stereogenic centers of **1** have the same absolute configuration as the corresponding moiety in the natural enantiomers. Derivative (2*R*,4*R*,6*R*)-**1** showed physical and spectroscopic parameters identical to those described for the enantiomer (2*S*,4*S*,6*S*)-**1** reported by Molinski except in the sign of the optical rotation $\{[\alpha]^{20}_D = +52.5$ (*c* 0.28, $CHCl_3)\}$.[2a] The stereoselective generation of the carbinol group at C-38 of phorboxazoles with the correct (*R*) absolute configuration has been achieved by Evans et al.[8c] from an aldehyde similar to **1**.

In summary, our strategy, based on the stereoselective reduction of several β-keto sufoxides and the acid-catalyzed cyclization of the corresponding sulfinyl hydroxy ketones, has been exemplified with an approach to the ketal THP ring present in phorboxazoles. The asymmetric synthesis of model compound (2*R*,6*R*)-**2**, lacking the oxygenated group at C-4, has been achieved in six steps from commercially available glutaric anhydride, and that of derivative **1**, the C32−C38 fragment of natural phorboxazoles, in nine steps from methyl 3,5-diketohexanoate (**12**).

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Supporting Information Available: Experimental procedures, spectroscopic data, and copies of ^1H and ^{13}C NMR for all new compounds and X-ray data for derivative (2*R*,4*R*,6*R*,S*S*)-**20**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) (a) Levin, J. I.; Turos, E.; Weinreb, S. M. *Synth. Commun.* **1982**, *12*, 989−993. (b) Boukouvalas, J.; Fortier, G.; Radu, I. I. *J. Org. Chem.* **1998**, *63*, 916−917.