Sulfoxide-Mediated Asymmetric Synthesis of Glycosidase Inhibitor Precursors

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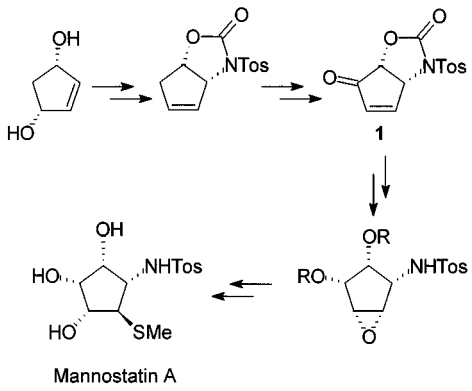
The highly diastereoselective DIBALH and DIBALH/$ZnBr_2$ reduction of enantiomerically pure (5*S*,-(S)*S*)-3-ethoxy-5-(*p*-tolylsulfinyl)cyclopentenone (**9**) is used as a key step to the synthesis of oxazolidinone **2**, a precursor of glycosidase inhibitor mannostatin. Compound **9** was obtained from 3-ethoxycyclopentenone by direct sulfinylation with (*S*)-*N*-benzyl-*N*-(*p*-tolylsulfinyl)propionamide.

Introduction

Glycosidase inhibitors possess a wide range of biological properties[1] including antitumoral and antiviral activities. Some of these compounds share the common structural features of an aminopolyhydroxycyclopentane[2] or cyclohexane[3] moiety with defined stereochemistry. The potential of these enzyme inhibitors as therapeutic agents as well as their challenging structures have stimulated intensive efforts in recent years directed toward their stereocontrolled total synthesis.[4] Several research groups have focused attention on five-membered-ring derivatives of the trehazolin[5] and mannostatin[6] family. One of the routes to racemic mannostatin was reported by Trost[6d,f] in 1994 (Scheme 1), but this strategy failed to provide enantiomerically pure materials.[6f]

Scheme 1



In connection with our research devoted to the use of sulfoxides in asymmetric synthesis,[7] we found that reduction of both cyclic[8] and acyclic[8b] β-keto sulfoxides could be effected in a highly stereocontrolled manner giving rise, after elimination of the sulfinyl group, to enantiomerically pure carbinols. We successfully applied this strategy to the synthesis of several natural macrolides[9] and various cyclohexanols.[10] We decided to extend this methodology to the synthesis of highly functionalized cyclopentanols as an approach to glycosidase inhibitors. In this paper, we report the asymmetric synthesis of the oxazolidinone **2**, a precursor of **1** (Scheme 1) in high optical purity, utilizing β-keto sulfoxide reduction as a key step to achieve the proper absolute stereochemistry.

Results and Discussion

Our retrosynthetic analysis for **1** (Scheme 2) indicated that compound **3** could be considered a potential precursor because it could generate both the oxazolidinone ring (by stereoselective intramolecular nucleophilic addition at the vinyl sulfoxide moiety) and the enonic system (ketal hydrolysis and desulfinylation). The synthesis of **3** could be achieved from **4** through conventional trans-

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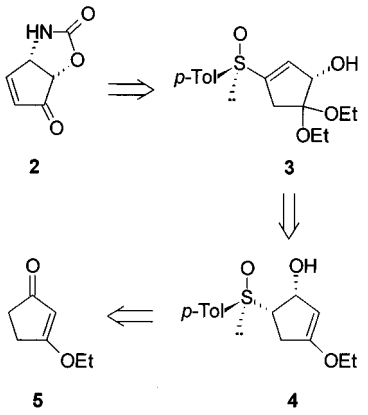
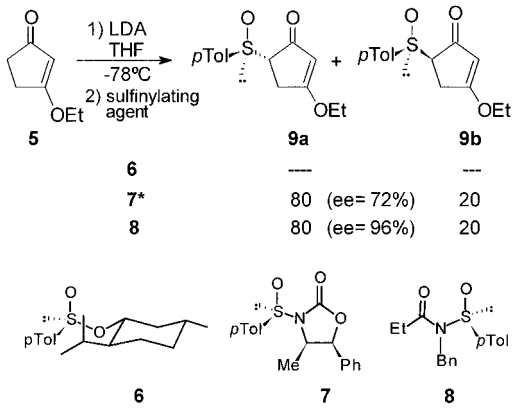
S0022-3263(96)01774-4 CCC: $14.00

Scheme 2



Scheme 3

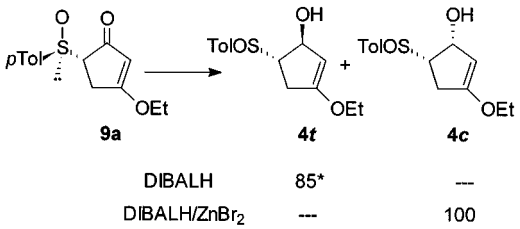


* The configuration in sulfoxide achieved with **7** is opposite to the one obtained with **8**

formations, whereas **4** could be easily obtained from **5**[11] by sulfinylation and further stereoselective reduction.

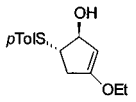
According to previously described methodology for the synthesis of cyclic β-keto sulfoxides,[8a,12] we attempted direct sulfinylation of α' enolate of **5**,[13] with menthyl *p*-toluenesulfinate (**6**) (Scheme 3). Unfortunately treatment of **5** with LDA followed by sulfinate **6** did not provide the desired β-keto sulfoxides. The sodium or magnesium enolates of **5** likewise failed to react. These results are probably due to the low reactivity of both the nucleophile (a doubly conjugated enolate) and the electrophile (menthyl *p*-toluenesulfinate). We therefore tried the more reactive, optically pure sulfinylating agents, (4*R*,5*S*,(S)*R*)-4-methyl-5-phenyl-3-*p*-tolylsulfinyloxazolidin-2-one (**7**)[14] and (*S*)-*N*-benzyl-*N*-(*p*-tolylsulfinyl)propionamide (**8**).[15] Sulfinylation of the lithium enolate of **5** with **7** afforded a 80:20 mixture[16] of [5*S*,(S)*R*]-**9a** and [5*R*,(S)*R*]-**9b** in a 68% combined yield. The ee of the major isomer was 72%.[17] The use of the sulfinylamide **8** afforded a higher yield (75%) of **9a** + **9b** in the same 80:20 ratio, but in this case the ee of the major isomer **9a** was 96%. Repeated crystallizations of the 80:20 epimeric mixture of **9a** and **9b** from ether containing 1 drop of 1 N NaOH solution afforded diastereomerically pure **9a**.

Scheme 4



DIBALH	85*	---
DIBALH/$ZnBr_2$	---	100

* 15% of *trans* thioether **10*t*** was also obtained



10*t*

As expected from previous β-keto sulfoxide reductions,[8b,18] the treatment of **9a** with DIBALH or DIBALH/$ZnBr_2$ afforded carbinols with the opposite configurations at the hydroxyl center (Scheme 4). In the absence of $ZnBr_2$, an excess of DIBALH (3.5 equiv) was neccesary to achieve a complete reaction. However, a 85:15 mixture of *trans*-hydroxy sulfoxide **4*t*** and the overreduced *trans*-hydroxy thioether **10*t*** was formed in these conditions. The reaction with DIBALH and $ZnBr_2$ cleanerly formed *cis*-hydroxy sulfoxide **4*c*** as the sole isolated product. The configurations shown in Scheme 4 were assigned according to the established mechanism of these reductions.[8b,c]

All attempts to isolate and purify compounds **4*c*** or **4*t*** were unsuccessful due to their instability.[19] Thus, the synthesis was continued using **4*c*** directly from the reduction without further purification. As depicted in Scheme 5, iodo acetal **11** was obtained by treatment of **4*c*** with NIS in EtOH.[20] The stereochemistry of **11** was assigned on the basis of similar known reactions of alkoxy-2-cyclopentene derivatives.[21] Thus, the intermediate iodonium ion (**I**) should be formed from the sterically less encumbered face of the starting hydroxy sulfoxide, and the regioselective nucleophilic attack of ethanol afforded **11** in a totally stereoselective process. A pure sample of **11** could be obtained by crystallization from hexane/ether at low temperature (−20 °C) but

(11) Gannon, W. F.; House, H. O. *Organic Synthesis*; Wiley: New York, 1963; Collect. Vol. IV, p 539.

(12) Carreño, M. C.; García Ruano, J. L.; Pedregal, C.; Rubio, A. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1335.

(13) With regard to the regioselectivity of cyclopentenone deprotonation (α' or γ) see: Liang Chen, Y.; Mariano, P. S.; Little, G. M.; O'Brian, D.; Huesmann, P. L. *J. Org. Chem.* **1981**, *46*, 4643. Koreeda, M.; Mislankar, S. G. *J. Am. Chem. Soc.* **1983**, *105*, 7203.

(14) Evans, D. A; Faul, M. M.; Colombo, J. J.; Basaha, J.; Clardy, J.; Cherry, D. *J. Am. Chem. Soc.* **1992**, *114*, 5977.

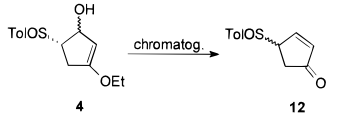
(15) García Ruano, J. L.; Alonso, R.; Zarzuelo, M. M.; Noheda, P. *Tetrahedron: Asymmetry* **1995**, 6, 1133. Enantiomer (*R*)-**8** is also available using (+)-menthol as quiral auxiliary.

(16) The absolute configuration of **9a** and **9b** was established by comparison of their NMR data with those of 2-sulfinylcyclopentanones previously described; see ref 8b.

(17) The enantiomeric excess was determined by using the chiral shift reagent Eu(tfc)$_3$ and confirmed in a further step by means of Mosher's esters of the hydroxy derivative **3**.

(18) (a) Barros, D.; Carreño, M. C.; García Ruano, J. L.; Maestro, M. C. *Tetrahedron Lett.* **1992**, 33, 2733. (b) Bueno, A. B.; Carreño, M. C.; García Ruano, J. L.; Peña, B.; Rubio, A.; Hoyos, M. A. *Tetrahedron* **1994**, *50*, 9355.

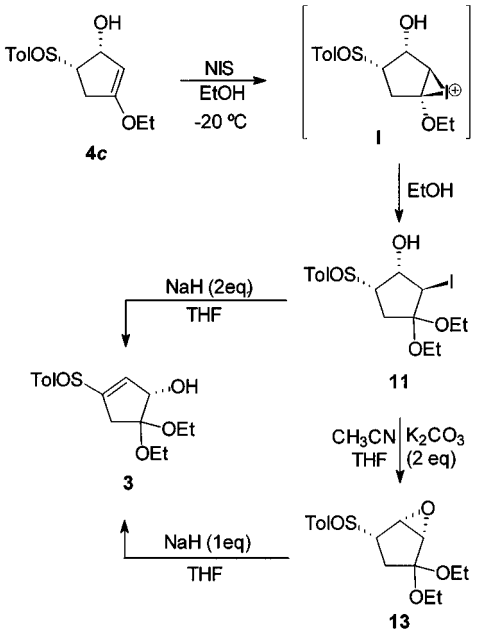
(19) Chromatographic purification of the hydroxy sulfoxides **4** yielded 4-(*p*-tolylsulfinyl)-2-cyclopenten-1-one (**12**) (the corresponding thioether was derived from compound **10**), as a result of the hydrolysis of the enol ether moiety and the dehydration of the carbinol.



(20) (a) Poutsma, M. L.; Kartch, J. L. *J. Am. Chem. Soc.* **1967**, *89*, 6595. (b) Middleton, D. S.; Simpkins, N. S. *Synth. Commun.* **1989**, *19*, 21. (c) Dalla, V.; Pale, P. *Tetrahedron Lett.* **1992**, *33*, 7857.

(21) Maag, H.; Rydzewski, R. M. *J. Org. Chem.* **1992**, *57*, 5823.

Scheme 5

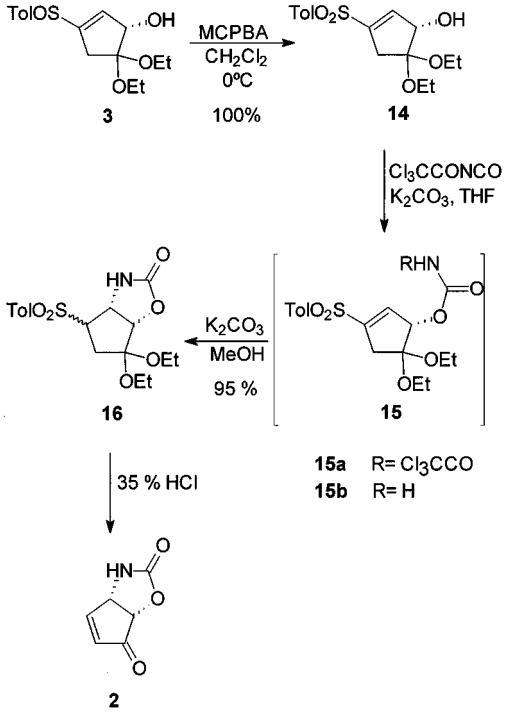


decomposition to **12** took place quickly at room temperature. Thus, the iodohydrin was used directly without further purification, and the yield of this step was not determined.

Transformation of compound **11** into the epoxide **13** was effected by treatment with K_2CO_3 in 80% conversion. The formation of **13** confirmed the *trans* disposition between the iodine atom and the hydroxy group in **11**. Further treatment of **13** with a stronger base (NaH) yielded vinyl sulfoxide **3**. The transformation of **11** into **3** could be directly achieved by using 2 equiv of NaH. Thus, **3** was isolated in a 60% overall yield from the *β*-keto sulfoxide **9a**. The (*S*) absolute configuration at the hydroxylic center of **3** as well as its optical purity (96%) were established by ^{1}H-NMR of the α-methoxy-α-(trifluoromethyl)phenylacetate (MTPA) esters. Both (S_2,*R*)-MTPA and (R_2,*R*)-MTPA esters were prepared from racemic **3**. The differences observed in the chemical shifts of the carbinol substituents in both diastereomers allowed the configurational correlation according to the model developed by Mosher and Dale.[22] Thus, the absolute configuration of **3** could be established as (2*S*)-1,1-diethoxy-2-hydroxy-4-(*p*-tolylsulfinyl)cyclopenten-3-one.

In order to obtain the cyclic carbamate present in **2**, an intramolecular Michael addition was required. Since the sulfinyl group[23] does not activate this process enough, it was necessary to transform compound **3** into the sulfone **14** (Scheme 6), which was quantitatively formed by *m*-CPBA oxidation. Reaction of sulfone **14** with trichloroacetyl isocyanate[24] in the presence of K_2CO_3 and addition of another equivalent of K_2CO_3 in MeOH/CH_2Cl_2, provided **16** as a 75:25 mixture of C-4 epimers. Several steps are involved in this transformation. First,

Scheme 6



trichloroacetyl imide **15a** is formed by the reaction of the carbinol with trichloroacetyl isocyanate. Methanolysis of the imide group yields the carbamate **15b**, detectable by H^1 NMR. The nucleophilic attack of the nitrogen on the vinyl sulfone moiety took place through the favored *cis*-cyclization process, giving rise to oxazolidinone **16**. The configurational integrity of the alkoxy and amino stereogenic centers of **16** was further confirmed. In a single additional step the treatment of **16** with 35% HCl allowed the isolation of oxazolidinone **2** in 62% yield. The keto sulfone resulting from the hydrolysis of the ketal was not detected. The elimination of the sulfone took place, presumably due to the stability of the resulting conjugate enone.

The structure of oxazolidinone **2** could be established on the basis of its NMR parameters (see the Experimental Section), which are very similar to those of the tosyl derivative analogous previously synthesized by Trost.[6f]

Conclusion

Enantiomerically pure sulfinylcyclopentenones **9** readily available from 3-ethoxycyclopent-2-en-1-one and the sulfinylating agent (*S*)-*N*-benzyl-*N*-(*p*-tolylsulfinyl)propionamide (**8**), provide access to glycosidase inhibitor precursors. Our synthesis features the preparation of oxazolidinone (*S*,*S*)-**2**,[25] using the highly diastereoselective DIBALH/$ZnBr_2$ reduction of **9** as a key step. Transformation of the resulting hydroxy sulfoxide into **2** occurs uneventfully.

Experimental Section

(5*S*,(S)*S*)-3-Ethoxy-5-(*p*-tolylsulfinyl)cyclopent-2-en-1-one (9). A solution of 341 mg (2.7 mmol) of 3-ethoxycyclopent-2-en-1-one (**5**) in 7 mL of THF was added under argon to a solution of 2.7 mmol of LDA in 7 mL of anhydrous THF at

(22) See: (a) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512. (b) Yamaguchi, S. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1983; Vol. 1, p 125. (c) Chan, T. H.; Nwe, K. T. *J. Org. Chem.* **1992**, *57*, 6107.

(23) The reaction of **3** with trichloroacetyl isocyanate in the presence of K_2CO_3 followed by addition of base in MeOH/CH_2Cl_2 failed to yield the corresponding sulfinylcarbamate.

(24) (a) Hirama, M.; Hioki, H.; Itô, S. *Tetrahedron Lett.* **1988**, *29*, 3125. (b) Blas, J. de; Carretero, J. C.; Domínguez, E. *Tetrahedron Lett.* **1994**, *35*, 4603.

(25) The use of the readily available (*R*)-**8** (see ref 15) would give access to (*R*,*R*)-**2**, which possesses the same stereochemistry as mannostatin.

−78 °C over 20 min. The solution was stirred for 1 h at −78 °C. The enolate was added by cannula at the same temperature over a solution of 1.63 g (5.4 mmol) of (+)-(*S*)-*N*-benzyl-*N*-(*p*-tolylsulfinyl)propionamide (**8**) in 15 mL of anhydrous THF over 2 min. After the mixture was stirred for 1 h, saturated NH_4Cl was added, and the mixture was allowed to reach rt. The aqueous layer was extracted with CH_2Cl_2 (4 × 20 mL). The organic layers were combined and dried over $MgSO_4$. The solvents were removed in vacuo, and the residue was purified by chromatography (EtOAc/hexane 1:2) to give 293 mg of a 80:20 mixture of **9a**/**9b** as a yellow solid (75% yield). Compound **9a** was isolated diastereomerically pure by repeated recrystallizations from ether containing a drop of 1 N NaOH solution. **9a:** $[\alpha]_D = -554°$ (*c* 1, $CHCl_3$); ^{1}H NMR δ 7.49 and 7.33 (AA′BB′ system, 4H), 5.38 (t, J = 1.1 Hz, 1H), 4.08 (m, 2H), 3.57 (dd, J = 7.4, 3.1 Hz, 1H), 3.05 (ddd, J = 18.0, 3.1, 1.1 Hz, 1H), 2.42 (s, 3H), 2.32 (ddd, J = 18.0, 7.4, 1.1 Hz, 1H), 1.40 (m, 3H); ^{13}C NMR δ 197.5, 189.8, 141.4, 138.6, 129.9 (2C), 123.7 (2C), 104.9, 68.3, 68.0, 25.1, 21.3, 13.9. **9b** (from an 80:20 mixture of **9a:9b**): ^{1}H NMR δ 7.47 and 7.30 (AA′BB′ system, 4H), 4.95 (m, 1H), 4.28 (m, 1H), 3.83 (m, 2H), 2.95−2.66 (m, 2H), 2.39 (s, 1H), 1.23 (m, 3H); ^{13}C NMR δ 197.5, 189.4, 141.9, 138.6, 129.3 (2C), 125.2 (2C), 104.8, 68.3, 68.0, 27.3, 21.3, 13.9; mp 129−131 °C; IR ($CHCl_3$) 3000, 1680, 1590, 1380 cm^{-1}. Anal. Calcd for $C_{14}H_{16}O_3S$: C, 63.61; H, 6.10; N, 0.00. Found: C, 63.53; H, 5.91; N, 0.03 (from the mixture **9a**:**9b**).

(1*R*,5*S*,(S)*S*)-3-Ethoxy-5-(*p*-tolylsulfinyl)cyclopent-2-en-1-ol (4*c*). A solution of 100 mg (0.38 mmol) of 3-ethoxy-5-(*p*-tolylsulfinyl)cyclopent-2-en-1-one (**9a**) and 171 mg (0.76 mmol) of $ZnBr_2$ in 4 mL of THF was stirred at rt under argon for 1 h. This mixture was added to a solution of 0.95 mL (0.95 mmol) of DIBALH (1 M in hexane) in 4 mL of THF at −78 °C over 20 min. After the mixture was stirred at this temperature for 3 h, 1 mL of methanol was added. The mixture was allowed to reach rt and was transferred to an Erlenmeyer flask containing 60 mL of aqueous saturated potassium−sodium tartrate and 60 mL of EtOAc. The two layers were stirred for 15 min and separated. The aqueous layer was extracted with EtOAc (4 × 20 mL), and the organic layers were combined and dried over Na_2SO_4. After removal of the solvents in vacuo, 120 mg of **4c** as a yellow oil was obtained: ^{1}H NMR δ (from the crude mixture) 7.86 and 7.35 (AA′BB′ system, 4H), 4.92 (m, 1H), 4.67 (m, 1H), 3.87 (m, 3H), 3.17 (m, 1H), 2.50 (m, 1H), 2.45 (s, 3H), 1.30 (t, J = 7.0 Hz, 3H). This mixture was used without purification.

(1*S*,5*S*,(S)*S*)-3-Ethoxy-5-(*p*-tolylsulfinyl)cyclopent-2-en-1-ol (4*t*). A solution of 100 mg (0.38 mmol) of 3-ethoxy-5-(*p*-tolylsulfinyl)cyclopent-2-en-1-one (**9a**) was added to a solution of 1.33 mL (1.33 mmol) of DIBALH (1 M in hexane) in 4 mL of THF at −78 °C. After the mixture was stirred for 4 h, 1 mL of methanol was added, and the mixture was allowed to reach rt. The treatment of the mixture was performed as previously described for **4*c*** in the DIBALH/$ZnBr_2$ reduction, affording **4*t*** as a yellow oil: ^{1}H NMR δ (from the crude mixture) 7.50 and 7.30 (AA′BB′ system, 4H), 5.16 (m, 1H), 4.55 (m, 1H), 3.77 (q, J = 7.0 Hz, 2H), 3.20 (ddd, J = 9.0, 5.5, 3.6 Hz, 1H), 2.73 (m, 1H), 2.41 (s, 3H), 2.31 (m, 1H), 1.26 (t, J = 7.0 Hz, 3H).

(2*R*,3*S*,4*S*,(S)*S*)-3-hydroxy-2-iodo-4-(*p*-tolylsulfinyl)cyclopentan-1-one Diethyl Acetal (11). The crude mixture of **4*c*** was diluted in 4 mL of a 1:1 mixture of CH_2Cl_2/ethanol at −20 °C, and 102 mg (0.46 mmol) of NIS was added in small portions with stirring. After 10 min, a saturated solution of Na_2SO_3 was added dropwise until decoloration occurred, and the mixture was allowed to warm to rt. The solvents were removed in vacuo, and the mixture was dissolved in CH_2Cl_2, washed with saturated $NaHCO_3$, and concentrated, affording **11**. Compound **11** was used without further purification: ^{1}H NMR δ 7.56 and 7.32 (AA′BB′ system, 4H), 4.57 (ddd, J = 12.0, 6.3, 1.3 Hz, 1H), 4.24 (t, J = 1.3 Hz, 1H), 4.08 (d, J = 12 Hz, 1H), 3.94 (dq, J = 9.2, 7.1 Hz, 2H), 3.62 (m, 1H), 3.49 (q, J = 7.0 Hz, 2H), 2.95 (ddd, J = 15.4, 4.9, 2.0 Hz, 1H), 2.41 (s, 3H), 2.06 (dd, J = 15.4, 11.7 Hz, 1H), 1.27 (t, J = 7.0 Hz, 3H), 1.21 (t, J = 7.0 Hz, 3H); ^{13}C NMR δ 141.2, 139.7, 129.7 (2C), 124.1 (2C), 109.3, 79.1, 76.3, 64.8, 58.5, 27.0, 21.2, 15.1, 14.6.

(2*S*,3*R*,4*S*,(S)*S*)-2,3-Epoxy-4-(*p*-tolylsulfinyl)cyclopentan-1-one Diethyl Acetal (13). Compound **11** was diluted in 3 mL of CH_3CN/THF (2:1), and 114 mg (0.82 mmol) of K_2CO_3 was added at rt. After 23 h, saturated Na_2SO_3 (5 mL) was added, and the aqueous layer was extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4, and the solvents were removed in vacuo. The residue was purified by chromatography (EtOAc/hexane 1:3) to yield pure **13** (overall 65% yield from **9a**): ^{1}H NMR δ 7.62 and 7.35 (AA′BB′ system, 4H), 3.63 (m, 4H), 3.53 (m, 1H), 3.19 (m, 2H), 2.43 (s, 3H), 2.21 (m, 1H), 2.03 (m, 1H), 1.24 (t, J = 7.0 Hz, 3H), 1.15 (t, J = 7.0 Hz, 3H).

(2*S*,(S)*S*)-2-Hydroxy-4-(*p*-tolylsulfinyl)cyclopent-3-en-1-one Diethyl Acetal (3). A solution of **11** in 3 mL of THF was added under argon to a suspension of 22 mg (0.92 mmol) of NaH in 1 mL of THF at rt. After 15 min, the mixture was quenched with saturated NH_4Cl, extracted with CH_2Cl_2, and dried over Na_2SO_4. The solvents were removed in vacuo, and the compound was purified by chromatography (EtOAc/hexane 1:2), affording 71 mg of **3** as a white solid (60% yield from **9a**): $[\alpha]_D = -126°$ (*c* 0.66, $CHCl_3$); mp 87−88 °C; ^{1}H NMR δ 7.49 and 7.30 (AA′BB′ system, 4H), 6.43 (bs, 1H), 4.67 (d, J = 9.1 Hz, 1H), 3.6−3.2 (m, 4H), 3.09 (d, J = 9.1 Hz, 1H), 2.76 (m, 1H), 2.41 (s, 3H), 2.19 (m, 1H), 1.14 (t, J = 7.0 Hz, 3H), 1,13 (t, J = 7.0 Hz, 3H); ^{13}C NMR δ 146.4, 141.8, 138.5, 135.9, 129.9 (2C), 124.8 (2C), 107.0, 78.8, 58.2, 57.3, 34.7, 21.4, 15.1, 15.0; IR ($CHCl_3$): 3600, 2990, 2910, 1220 cm^{-1}; Anal. HRMS calcd for $C_{16}H_{22}O_4S$ 310.1239, found 310.1233. Calcd for $C_{16}H_{22}O_4S$: C, 61.91; H, 7.15; N, 0.00. Found: C, 62.00; H, 7.35; N, 0.08.

Procedure for Preparation of MTPA Esters. To a solution of 15 mg (0.05 mmol) of **3** and 12.4 mg (0.10 mmol) of DMAP in 3 mL of CH_2Cl_2 was added 0.015 mL (0.083 mmol) of (*R*)-MTPACl, and the mixture was stirred for 1 h at rt. The reaction was quenched with water (1 mL) and Et_2O (3 mL) and stirred for 15 min. The solution was washed with 1 N HCl (4 mL), 1 N NaOH (4 mL), and brine and dried over $MgSO_4$. The solvent was removed in vacuo, and the corresponding MTPA ester was obtained and characterized without further purification (80% yield): ^{1}H NMR δ (2*S*,*R*)-MTPA ester 7.57−7.27 (m, 9H), 6.61 (ABX system, J = 2.3, 1.2 Hz, 1H), 5.68 (d, J = 2.8 Hz, 1H), 3.61−3.13 (m, 4H), 3.50 (s, 3H), 2.48 and 2.36 (ABX system, J = 15.3, 1.2 Hz, 2H), 2.41 (s, 3H), 1.08 (t, J = 7.0 Hz, 3H), 1.05 (t, J = 7.0 Hz, 3H) (2*R*,*R*)-MTPA ester 7.57−7.27 (m, 9H), 6.48 (ABX system, J = 2.3, 1.2 Hz, 1H), 5.81 (d, J = 2.8 Hz, 1H), 3.61−3.13 (m, 4H), 3.56 (s, 3H), 2.48 and 2.36 (ABX system, J = 15.3, 1.2 Hz, 2H), 2.41 (s, 3H), 1.08 (t, J = 7.0 Hz, 3H), 1.05 (t, J = 7.0 Hz, 3H).

(2*S*)-2-Hydroxy-4-(*p*-tolylsulfonyl)cyclopent-3-en-1-one Diethyl Acetal (14). To a solution of 100 mg (0.32 mmol) of vinyl sulfoxide **3** in 3 mL of CH_2Cl_2 at 0 °C was added a solution of 110 mg (0.32 mmol) of *m*-CPBA (50% aqueous) in 5 mL of CH_2Cl_2. After the mixture was stirred for 15 min, 1 mL of a saturated solution of Na_2SO_3 was added, and the mixture was warmed to rt over 15 min. The organic layer was washed with saturated aqueous $NaHCO_3$ and dried over Na_2SO_4, and the solvent was removed in vacuo, yielding 105 mg of **14** as a colorless oil (95% yield): $[\alpha]_D = -57°$ (*c* 0.3, $CHCl_3$); ^{1}H NMR δ 7.76 and 7.35 (AA′BB′ system, 4H), 6.52 (m, 1H), 4.69 (d, J = 9.4 Hz, 1H), 3.52 (m, 4H), 3.05 (d, J = 9.4 Hz, 1H), 2.86 (m, 1H), 2.52 (m, 1H), 2.45 (s, 3H), 1.14 (t, J = 7.0 Hz, 3H), 1.13 (t, J = 7.0 Hz, 3H); ^{13}C NMR δ 144.9, 142.5, 140.5, 135.4, 129.9 (2C), 128.2 (2C), 107.5, 78.8, 58.5, 57.3, 21.6, 15.1, 15.0; IR ($CHCl_3$) 3540 (b), 3000, 2980, 1220 cm^{-1}.

4,4-Diethoxy-6-(*p*-tolylsulfonyl)cyclopentane[5,4-*d*]-(3a*S*,6a*S*)-oxazolidin-2-one (16). To a solution of 100 mg (0.31 mmol) of **14** in 1 mL of anhydrous THF was added 48 mg (0.34 mmol) of K_2CO_3. After the solution was stirred for 30 min, 0.045 mL (0.37 mmol) of trichloroacetyl isocyanate was added. The mixture was stirred overnight at rt. The solvent was removed in vacuo, the residue was diluted with 2 mL of a 1:1 mixture of CH_2Cl_2/methanol, and 48 mg (0.34 mmol) of K_2CO_3 was added. The mixture was stirred for 7 h, and then CH_2Cl_2 was added and the solution was washed with saturated aqueous NH_4Cl. The organic layers were combined and dried over $MgSO_4$ and concentrated in vacuo to give 108 mg of **16** as a 72:28 epimeric mixture (95% yield): mp 184−185 °C; ^{1}H

NMR δ (diastereomeric mixture) 7.77 and 7.41 (AA′BB′ system, 1.2H), 7.76 and 7.40 (AA′BB′ system, 2.8H), 5.78 (bs, 0.7H), 5.12 (bs, 0.3H), 4.82−4.48 (m, 2H), 3.72−3.18 (m, 5H), 2.49 (s, 0.3H), 2.34−2.19 (m, 2H), 1.20 (t, J = 7.0 Hz, 2.2H), 1.15 (t, J = 7.0 Hz, 1.6H), 1.09 (t, J = 7.0 Hz, 2.2H); ^{13}C NMR δ (diastereomeric mixture) 157.8, 157.3, 145.8, 145.5, 135.8, 134.4, 130.4, 130.2, 128.3, 106.3, 105.9, 82.4, 80.4, 68.6, 63.6, 59.3, 59.1, 57.8, 56.3, 54.6, 53.8, 32.8, 30.8, 30.7, 21.6, 15.1, 14.9; IR ($CHCl_3$) 3420, 2990, 1770, 1150 cm^{-1}; HRMS calcd for $C_{17}H_{23}NO_6S$ 369.1246, found 369.1234.

4-Oxocyclopent-5-en[5,4-*d*]-(3a*S*,6a*S*)-oxazolidin-2-one (2). A solution of 32 mg (0.09 mmol) of **16** in 2 mL of 35% HCl was stirred at rt for 4 h. The mixture was diluted with CH_2Cl_2, washed with saturated aqueous $NaHCO_3$, and dried over Na_2SO_4. Solvents were removed in vacuo, and chromatography of the residue (EtOAc/hexane 1:1) gave 7.5 mg of **2** (62% yield): $[\alpha]_D$ = −140° (*c* 0.2, $CHCl_3$); ^{1}H NMR δ 7.69 (dd, J = 6.0, 2.1 Hz, 1H), 6.57 (bs, 1H), 6.49 (dd, J = 6.0, 0.8 Hz, 1H), 4.82 (m, 2H); ^{13}C NMR δ 199.4, 160.2, 157.7, 135.7, 74.35, 54.9; IR ($CHCl_3$): 3400, 2990, 2860, 2400, 1730, 1200 cm^{-1}; HRMS calcd for $C_6H_5NO_3$ 139.0260, found 139.0269.

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Supporting Information Available: Copies of ^{1}H NMR spectra of compounds **2**, **3**, **9a**, **12**, **14**, **16**, the MTPA-esters of **3**, and the acetyl derivate of **11** (8 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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