Chiral Sulfoxides in Asymmetric Synthesis: Enantioselective Synthesis of the Lactonic Moiety of (+)-Compactin and (+)-Mevinolin. Application to a Compactin Analogue

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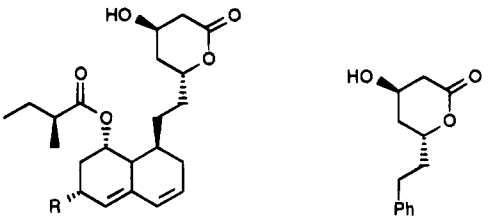
The lactonic part of (+)-compactin and (+)-mevinolin as well as a compactin analogue were synthesized in an enantioselective way from a β,δ-diketo sulfoxide easily obtained by the reaction of the trianion of methyl 3,5-dioxohexanoate with (−)-menthyl (*S*)-*p*-toluenesulfinate. The main reaction was the two-step stereoselective reduction of β,δ-diketo sulfoxide without any protective group.

Since their discovery at the end of the seventies, compactin (**1a**) and mevinolin (**1b**) have attracted a growing interest for their biological activity as potent inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMGR). As seen from their structure, the lactonic moiety, a masked dihydroxy acid, is closely related to the natural substrates of HMGR, which catalyzes the conversion of 3-hydroxy-3-methylglutaryl coenzyme A to mevalonic acid. This enzyme is one of the most important enzymes involved in the biosynthesis of cholesterol in the cells, and its regulation for the control of cholesterol level in the blood is of prime importance.[1]

Many syntheses of these substances have been already reported and reviewed[2] as well as the synthesis of new analogues in which only the lactonic part, which, in its open form mimics mevalonic acid, was retained, the southern lipophilic moiety being replaced by more accessible aromatic derivatives.[2]

A large number of publications reported mainly the synthesis of the lactonic moiety of compactin with two asymmetric carbons in the (*R*,*R*) configuration. Different strategies have been used: many started from the chiral pool [(*S*)-malic acid,[3a] L-glutamic acid,[3b,c] tartaric acid,[3d] or carbohydrates[3e–g]; others described asymmetric syntheses [asymmetric Diels–Alder reaction,[3b] diastereoselective aldol condensation,[3i] or enantioselective reduction



1a, R=H, (+) compactin
1b, R=Me, (+) mevinolin

(R,R)-2

Figure 1.

of β,δ-diketo esters with a chiral Ruthenium catalyst[3j] or bakers' yeast[3k,l]].

We report in this paper a short and efficient asymmetric synthesis of a compactin analogue (+)-(*R*,*R*)-**2**, based on the stereoselective reduction of (+)-(*R*) methyl 3,5-dioxo-6-(*p*-tolylsulfinyl)hexanoate (**4**) as shown on the retrosynthetic Scheme 1. Compound **4** was prepared in one step by reaction of the trianion of methyl 3,5-dioxohexanoate with (−)-menthyl (*S*)-*p*-toluenesulfinate.

The diketo ester **6** was readily obtained in one step by a known procedure[4] from commercially available dehydro acetic acid **5** (Scheme 2). The trianion of **6**, prepared in THF at 0 °C with 1 equiv of NaH and 2 equiv of t-BuLi or *sec*-BuLi, reacted rapidly at 0 °C with (−)-menthyl (*S*)-*p*-toluenesulfinate[5] to afford the corresponding diketo sulfoxide (+)-(*R*)-**4**. This new method is a convenient and short route to diketo sulfoxides which were obtained in our previous studies either by reaction of the anion of (*R*)-methyl-*p*-tolyl sulfoxide[6] on a β-keto ester, or dianions of β-diketones[7] on menthyl *p*-toluenesulfinate, or dianion of (*R*)-(*p*-tolylsulfinyl)-2-propanone[8] on an ester. ^{1}H NMR of compound **4** showed as expected[6–8] that only the δ-carbonyl was entirely enolized (one vinylic hydrogen giving a singlet at 5.65 ppm). Therefore, following our previous results,[6–8] the enantioselective reduction of the β-carbonyl of the (*R*)-β,δ-dicarbonyl sulfoxide **4** was carried out with 2 equiv of DIBAL in THF at −78 °C. Only one diastereomer of the resulting [5(*S*),S(*R*)]-methyl 5-hydroxy-3-oxo-6-(*p*-tolylsulfinyl)hexanoate, **7**, was detected by 200 MHz ^{1}H NMR of the crude product. The yield in isolated product was

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(1) (a) Hoeg, J. M.; Brewer, H. B. *J. Am. Med. Assoc.* **1987**, *258*, 3532. (b) Endo, A. J. *J. Med. Chem.* **1985**, *28*, 401. (c) Hoffman, W. F.; Alberts, A. W.; Anderson, P. S.; Chen, J. S.; Smith, R.L.; Williard, A. K. *J. Med. Chem.* **1986**, *29*, 849; d) Kuo, C. H.; Patchett, A. A.; Wendler, N. L. *J. Org. Chem.* **1983**, *48*, 1991. e) Lee, T. J.; Holtz, W. J.; Smith, R. L. *J. Org. Chem.* **1982**, *47*, 4750.

(2) Chapleur, Y. in Progress in the Chemical Synthesis of Antibiotics and Related Microbial Products; Luckacs, G., Ed.; Springer Verlag: Berlin, 1993, Vol. 2, pp 829–837.

(3) (a) Majewski, M.; Clive, D. L. J.; Anderson, P. C. *Tetrahedron Lett.* **1984**, *25*, 2101. (b) Hanessian, S.; Roy, P. J.; Petrini, M.; Hodges, P. J.; Di Fabio, R.; Carganico, G. *J. Org. Chem.* **1990**, *55*, 5766. (c) Menges, M.; Brückner, R. *Synlett* **1993**, 901. (d) Minami, T.; Takahashi, K.; Hiyama, T. *Tetrahedron Lett.* **1993**, *34*, 513. (e) Miyazawa, K.; Yoshida, N. *Chem. Lett.* **1993**, 1529. (f) Ernolenko, M. S.; Olesker, A.; Luckacs, G. *Tetrahedron Lett.* **1994**, *35*, 711. (g) Ernolenko, M. S.; Olesker, A.; Luckacs, G. *Tetrahedron Lett.* **1994**, *35*, 715. (h) Terada, M.; Mikami, K.; Nakai, T. *Tetrahedron Lett.* **1991**, *32*, 935. (i) Lynch, J. E.; Volante R. P.; Wttley, R. V.; Sinkai, I. *Tetrahedron Lett.* **1987**, *28*, 1385. (j) Shao, L.; Seki, T.; Kwano, H.; Saburi, M. *Tetrahedron Lett.* **1991**, *32*, 7699. (k) Bennett, F.; Knight, D. W.; Fenton, G. *J. Chem. Soc. Perkin Trans. 1*, **1991**, 133. (l) Ansari, M. H.; Kusumoto, T.; Hiyama, T. *Tetrahedron Lett.* **1993**, *34*, 8271.

(4) Batelaan, J. G. *Synth. Commun.* **1976**, *6*, 81.

(5) Solladié, G.; Hutt, J.; Girardin, A. *Synthesis* **1987**, 173.

(6) Solladié, G.; Ghiatou, N. *Tetrahedron Asymmetry* **1992**, *3*, 33.

(7) Solladié, G.; Ghiatou, N. *Tetrahedron Lett.* **1992**, *33*, 1605.

(8) Solladié, G.; Dominguez, C. *J. Org. Chem.* **1994**, *59*, 3898.

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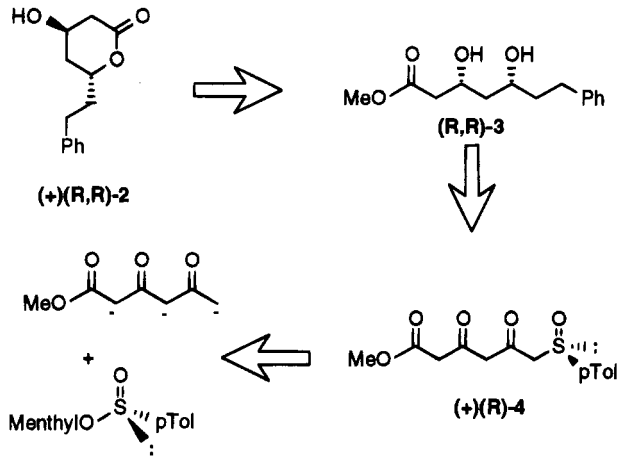
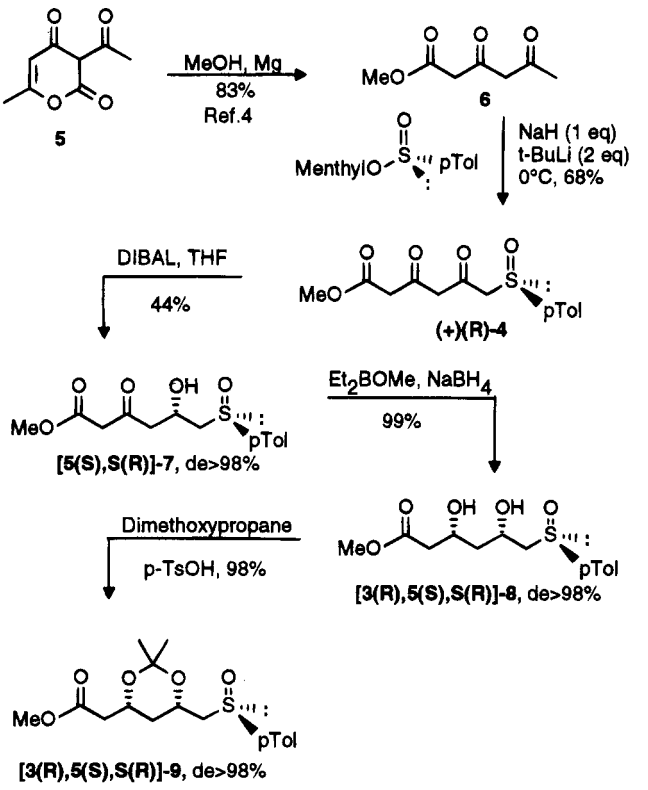
Scheme 1



Scheme 2

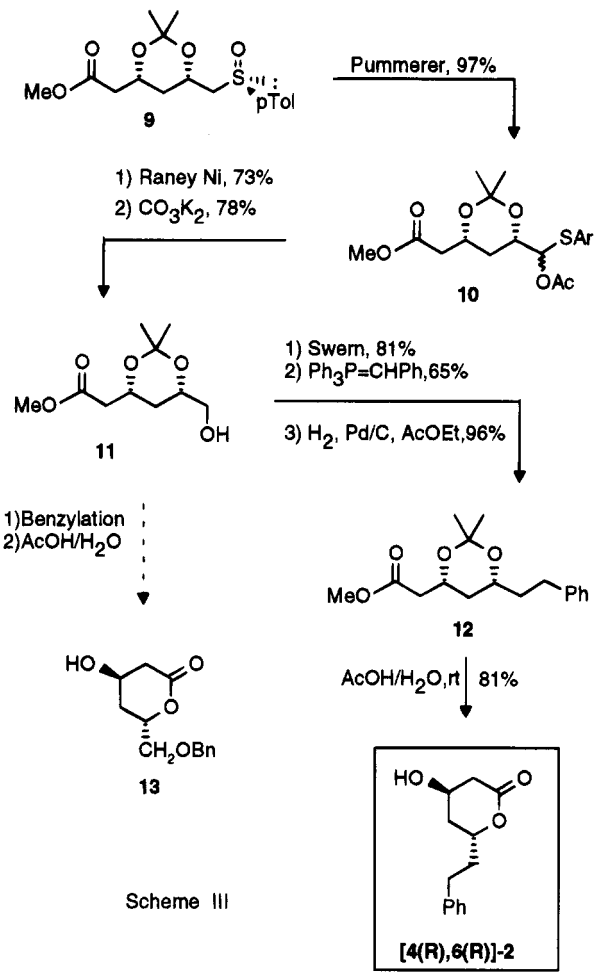


only 44%, due to some product decomposition (about 15%) during the chromatographic purification on metal-free silica gel. However this yield is still acceptable because of the absence of any additional step to protect the other reducible groups. The (*S*) absolute configuration of the created hydroxylic center was deduced from our previous studies[7,8] and will be confirmed in the known final product.

The ketone in compound **7** was only 9% enolized (one doublet at 4.12 ppm, $J = 3.4$ Hz, corresponding to OH). It was diastereoselectively reduced in the next step with diethylmethoxyborane and sodium borohydride,[9] giving in quantitative yield the *syn*-diol **8** (de > 98%), which was finally transformed to the corresponding acetonide **9**.

The relative syn configuration was confirmed by ^{13}C NMR of the acetonide: the two methyl groups at 20.0

Scheme 3



and 30.2 ppm are characterictics of a *syn*-diol acetonide according to literature[10] (the values for an *anti*-diol acetonide are between 24 and 25.5 ppm).

Pummerer reaction, desulfurization, and acetate hydrolysis of the intermediate allowed finally a high yield transformation of the sulfinyl acetonide **9** into the hydroxy ester (3*R*,5*S*)-**11** (Scheme 3). Finally the primary alcohol of compound **11** was transformed by Swern oxidation into the corresponding aldehyde which was submitted to a Wittig reaction with benzyltriphenylphosphonium ylide and the resulting olefin (a 85/15 *Z*/*E* mixture) catalytically reduced with Pd/C to the ester **12**.

Acetic acid hydrolysis of the acetonide led finally directly to the 4(*R*),6(*R*) lactone **2**, a compactin analogue showing all the characteristics described in literature.[10]

This method can be easily extended to the synthesis of all the four possible stereomers of molecule **2** by using a (*R*) or (*S*) configuration at sulfur and reducing the corresponding β-hydroxy-δ-keto sulfoxide into a *syn*-diol (as in this paper) or an *anti*-diol (with tetramethylammonium triacetoxyborohydride, a reagent we used already for nonactic acid synthesis[8]). We would like also to point out that protection of the primary hydroxylic group in the intermediate **11** with a benzyl group would allow the formation of the functionalized lactone **13** which can be used for the total synthesis of compactin itself or mevinolin.

(9) Chen, K. M.; Hardtmann, G. E.; Prasad, K.; Repic, O.; Shapiro, M. J. *Tetrahedron Lett.* **1987**, *28*, 155.

(10) Rychnovsky, S. D.; Griesgraber, G.; Zeller; Shalitzky, D. J. *J. Org. Chem.* **1991**, *56*, 5161.

Experimental Section.

Methyl 3,5-Dioxohexanoate (6). The dioxo ester **6** was synthesized according to literature.[4] The crude product was distilled under reduced pressure (91 °C/0.6 mmHg) to afford a colorless liquid in 83% yield. The ^{1}H NMR indicated the presence of 83% of an enol form. ^{1}H NMR (200 MHz, $CDCl_3$): enol, δ 15.08 (br s, 1H), 5.60 (s, 1H), 3.73 (s, 3H), 3.33 (s, 2H), 2.06 (s, 3H); ketone, 3.73 (s, 5H), 3.56 (s, 2H), 2.24 (s, 3H). ^{13}C NMR ($CDCl_3$): enol, δ 190.7, 187.7 168.6, 101.1, 45.5, 53.0, 24.9; ketone: 202.2, 197.4, 57.8, 49.7, 31.3.

(+)-(*R*)-Methyl 3,5-Dioxo-6-(*p*-tolylsulfinyl)hexanoate (4). To a suspension of NaH (2.2 g, 1.2 equiv) in dry THF (250 mL) was dropwise added at 0 °C a solution of methyl 3,5-dioxohexanoate (**6**) (12.1 g, 0.0765 mol) in THF (25 mL). The mixture became rapidly a thick white suspension. At 0 °C, *tert*-butyllithium (10 g of a 1.5 M pentane solution, 2.04 equiv) was then quickly added with a cannula over a period of 15 min. The solution turned yellow, orange, and finally deep red as the addition progressed. The (−)-menthyl (*S*)-*p*-toluenesulfinate[5] (11.31 g, 0.5 equiv) in solution in THF (35 mL) was then dropwise added within 20 min. Stirring at 0 °C was continued for an additional 40 min until all the sulfinate was consumed (TLC). The reaction was quenched with saturated NH_4Cl (10 mL), diluted with AcOEt (250 mL), and then acidified to pH 1 with 1 N HCl (170 mL) and concd H_2SO_4. The aqueous layer was extracted with AcOEt (3 × 150 mL). The combined organic layers were washed with brine (100 mL), dried over $MgSO_4$, and filtered before concentrated. The crude oily residue was purified by rapid chromatography on metal-free silica gel[11] (hexane and CH_2Cl_2) to give an orange oil which was crystallized (CH_2Cl_2/diethyl ether) to afford **4** as pale yellow prisms (7.73 g, 68%). $[\alpha]_D$ = +261 (c = 0.98; $CHCl_3$); mp = 55−56 °C. ^{1}H NMR (200 MHz, $CDCl_3$): This product was entirely enolized; δ 14.51 (br s, 1H), 7.51 (A fragment of an $(AB)_2$ system, 2H, J_{AB} = 8 Hz, $\Delta\nu$ = 37 Hz), 7.32 (B fragment of an $(AB)_2$ system, 2H, J_{AB} = 8 Hz, $\Delta\nu$ = 37 Hz), 5.65 (s, 1H), 3.72 (s, 3H,), 3.69 (A fragment of an AB system, 1H, J_{AB} = 14 Hz, $\Delta\nu$ = 17 Hz), 3.58 (B fragment of an AB system, 1H, J_{AB} = 14 Hz, $\Delta\nu$ = 17 Hz), 3.35 (s, 2H), 2.40 (s, 3H). ^{13}C NMR ($CDCl_3$), δ 188.9, 167.4, 179.6, 142.4, 139.6, 130.2, 124.1, 102.8, 64.9, 45.3, 52.6, 21.6. Anal. Calcd for $C_{14}H_{16}O_5S$: C, 56.74; H, 5.44. Found: C, 56.67; H, 5.53.

(+)-[5(*S*),S(*R*)]-Methyl 5-Hydroxy-3-oxo-6-(*p*-tolylsulfinyl)hexanoate (7). To a solution of the β,δ-diketo sulfoxide **4** (5.88 g, 0.0198 mol) in THF (350 mL) was dropwise added (15 min) at −78 °C a solution of DIBAL-H (40.5 mL of a 1 M solution in toluene, 2 equiv). Stirring was continued for 15 min before adding MeOH (80 mL). After 1 h, the solution was stirred 0.5 h at room temperature and then evaporated to afford a fine orange powder which was dissolved in AcOEt (300 mL), and saturated disodium L-tartrate dihydrate (20 mL) was added. This mixture was stirred overnight at room temperature and then acidified to pH 4 with concd HCl. The aqueous layer was extracted with AcOEt (2 × 150 mL) and saturated with NaCl and extracted with AcOEt (150 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated to afford a solid residue. The crude product was purified by rapid chromatography on metal-free silica gel[11] (AcOEt/CH_2Cl_2: 1/1) and the resulting solid recrystallized (CH_2Cl_2/diethyl ether) to give colorless crystals (2.61 g, 44%, de > 98%, 9% of enol form identified by a doublet at 4.12 ppm, J = 3.4 Hz). $[\alpha]_D$ = +213 (c = 1.48; $CHCl_3$), $[\alpha]_D$ = +153 (c = 0.90, acetone), mp = 120−121 °C. ^{1}H NMR (200 MHz, $CDCl_3$), δ 7.52 (A part of an $(AB)_2$ system, 2H, J_{AB} = 8 Hz, $\Delta\nu$ = 33 Hz), 7.35 (B part of an $(AB)_2$ system, 2H, J_{AB} = 8 Hz, $\Delta\nu$ = 33 Hz), 4.62 (m, 1H, X part of an ABX system), 4.21 (d, 1H, J = 2 Hz), 3.71 (s, 3H), 2.90 (AB fragment of an ABX system, 2H, J_{AB} = 13.4 Hz, J_{AX} = 9.4 Hz, J_{BX} = 2.4 Hz, $\Delta\nu$ = 59 Hz), 3.47 (s, 2H), 2.79 (d, 2H, J = 6 Hz), 2.42 (s, 3H). ^{13}C NMR ($CDCl_3$), δ 201.5, 167.2, 141.8, 139.2, 130.2, 124.0, 63.5, 60.4, 49.6, 49.0, 52.5, 21.4. Anal. Calcd for $C_{14}H_{18}O_5S$: C, 56.36; H, 6.08. Found: C, 56.30; H, 6.21.

(11) Hubbard, J. S.; Harris, T. M. *J. Org. Chem.* **1981**, *46*, 2566.

(+)-[3(*R*),5(*S*),S(*R*)]-Methyl 3,5-Dihydroxy 6-(*p*-tolylsulfinyl)hexanoate (8). A solution of the hydroxy sulfoxide **7** (1.089 g, 3.65 mmol) in a THF/MeOH mixture (35 mL/7 mL; 5:1) was cooled at −78 °C. After rapid addition (2 min) of a solution of 1 M Et_2BOMe in THF (4 mL, 1.1 equiv), a white precipitate appeared. Stirring was continued during 20 min before addition of $NaBH_4$ (178 mg, 1.3 equiv) at one time which led to a homogeneous solution. After 4 h at −78 °C, AcOH (4 mL) and saturated $NaHCO_3$ (60 mL) were added at room temperature until pH 7. The aqueous layer was extracted with AcOEt (3 × 150 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated. The yellow oil was then submitted three times to azeotropic distillation with MeOH (3 × 50 mL). The product was then purified by rapid chromatography on treated silica gel[11] (AcOEt) to afford a light yellow oil, which crystallized at low temperature (4 °C), (1.09 g, 99.4%, de > 98%). $[\alpha]_D$ = +220 (c = 1.03; $CHCl_3$), $[\alpha]_D$ = +219 (c = 0.49; $CHCl_3$), mp = 92−94 °C. ^{1}H NMR (200 MHz, $CDCl_3$), δ 7.47 (A part of an $(AB)_2$ system, 2H, J_{AB} = 8 Hz, $\Delta\nu$ = 39.6 Hz), 7.27 (B part of an $(AB)_2$ system, 2H, J_{AB} = 8 Hz, $\Delta\nu$ = 39.6 Hz), 5.05 (br s, 1H), 4.43 (m, 1H), 4.27 (m, 2H), 3.61 (s, 3H), 2.83 (AB part of an ABX system, 2H, J_{AB} = 13.2 Hz, J_{AX} = 9.8 Hz, J_{BX} = 2.5 Hz, $\Delta\nu$ = 30 Hz), 2.43 (d, 2H, J = 6 Hz), 2.35 (s, 3H), 1.76−1.49 (m, 2H). ^{13}C NMR ($CDCl_3$), δ 172.9, 142.2, 140.3, 130.6, 124.5, 68.1, 66.5, 64.2, 42.7, 42.2, 52.3, 21.9. Anal. Calcd for $C_{14}H_{20}O_5S$: C, 55.98; H, 6.71. Found: C, 56.23; H, 6.72

(+)-[3(*R*), 5(*S*),S(*R*)]-Methyl *syn*-3,5-(Isopropylidenedioxy)-6-(*p*-tolylsulfinyl)hexanoate (9). The dihydro sulfoxide **8** (1.17 g, 3.89 mmol) and catalytic *p*-TsOH (15 mg, 0.13% w/w) were dissolved in acetone (62 mL) and 2,2-dimethoxypropane (6.25 mL). Stirring at room temperature (3 h) was continued until all starting material disappeared (TLC). All solvents were removed, the crude product was then diluted in CH_2Cl_2 (100 mL), and saturated $NaHCO_3$ (10 mL) was added. The mixture was stirred 15 min at room temperature and diluted with water (50 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL), and the combined organic layers were washed with water (100 mL), dried ($MgSO_4$), and concentrated to afford **9** as sharp colorless needles (1.3 g, 98%). $[\alpha]_D$ = +195 (c = 1.37, $CHCl_3$), mp = 110−111 °C. ^{1}H NMR ($CDCl_3$), δ 7.43 (A part of an $(AB)_2$ system, 2H, J_{AB} = 8 Hz, $\Delta\nu$ = 42.2 Hz), 7.21 (B part of an $(AB)_2$ system, 2H, J_{AB} = 8 Hz, $\Delta\nu$ = 42.2 Hz), 4.47−4.31 (m, 1H), 4.30−4.14 (m, 1H), 3.53 (s, 3H), 2.43 (m, 2H), 2.32 (AB part of an ABX system, 2H, J_{AB} = 15.6 Hz, J_{AX} = 7 Hz, J_{BX} = 6 Hz, $\Delta\nu$ = 37.5 Hz), 2.26 (s, 3H), 1.49 (dt, 1H, J_{gem} = 12 Hz. ^3J = 2 Hz), 1.40 (s, 3H), 1.27 (s, 3H), 1.27−1.05 (m, 1H). ^{13}C NMR ($CDCl_3$), δ 171.2, 141.9, 141.8, 99.8, 130.3, 124.1, 66.0, 63.7, 65.0, 41.3, 36.2, 51.9, 30.2, 21.7, 20.0. Anal. Calcd for $C_{17}H_{24}O_5S$: C, 59.98; H, 7.11. Found: C, 60.04; H, 7.33.

(3*R*,5*S*)-Methyl 6-Acetoxy-*syn*-3,5-(isopropylidenedioxy)-6-(*p*-tolylthio) hexanoate (10). Anhydrous sodium acetate (4.4 g, 10 equiv) was added to the sulfoxide **9** (1.80 g, 5.28 mmol). Acetic anhydride (130 mL) was then added, and the mixture was refluxed for 10 h at 135 °C. After cooling, the brown heterogeneous solution was filtered over Celite and the solvent removed by azeotropic distillation with toluene (4 × 50 mL). The resulting solid deep brown was diluted in CH_2Cl_2 (50 mL) and filtered on Celite. The crude product was purified by column chromatography on silica gel (CH_2Cl_2) to afford **10** as an orange brown oil (1.98 g, 97%), a mixture of the two isomers at the C_6 position in a 54/46 ratio which were not separated; one is solid and the other liquid. ^{1}H NMR (200 MHz, $CDCl_3$), δ 7.35 (A part of an $(AB)_2$ system, 2H, J_{AB} = 8 Hz, $\Delta\nu$ = 56.2 Hz), 7.07 (B part of an $(AB)_2$ system, 2H, J_{AB} = 8 Hz, $\Delta\nu$ = 56.2 Hz), 6.00 (d, 1H, J = 5.4 Hz, major isomer), 5.94 (d, 1H, J = 5.4 Hz, minor isomer), 4.30−4.15 (m, 1H), 4.10−3.90 (m, 1H), 3.64 (s, 3H), 2.45 (AB part of an ABX system, 2H, J_{AB} = 15.8 Hz, J_{AX} = 7 Hz, J_{BX} = 6 Hz, $\Delta\nu$ = 36.5 Hz), 2.28 (s, 3H), 2.01 (s, 3H),1.74 (dt, 1H, J_{gem} = 12,8 Hz, ^3J = 2.4 Hz, major isomer), 1.65 (dt, 1H, J_{gem} = 14.4 Hz, ^3J = 2.4 Hz, minor isomer), 1.38 (s, 3H, major isomer), 1.34 (s, 3H, major isomer), 1.36 (s, 3H, minor isomer), 1.34 (s, 3H, minor isomer), 1.46−1.22 (m, 1H). ^{13}C NMR ($CDCl_3$), δ 171.6, 170.2, 170.0, 139.1, 139.0, 128.6, 128.2, 99.9, 99.8, 134.7, 134.3, 130.3,

130.2, 83.3, 83.1, 70.8, 70.1, 66.0, 65.9, 41.5, 33.1, 32.6, 51.2, 30.3, 21.7, 21.5, 21.4, 20.0. Anal. Calcd for $C_{19}H_{26}O_6$: C, 59.67; H, 6.85. Found: C, 56.00; H, 5.00.

(+)-(3*R*,5*S*)-Methyl 6-Hydroxy-*syn*-3,5-(isopropylidenedioxy) hexanoate (11). (1) Nickel Raney was added by portions to a solution of compound **10** (1.29 g, 3.37 mmol) in MeOH (90 mL, 0.04 M). The reaction at room temperature was followed by TLC (AcOEt/ CH_2Cl_2 1:1). The mixture was carefully filtered on Celite and the solid washed with MeOH. After evaporating the solvent, the product could be purified by rapid chromatography on silica gel (AcOEt/CH_2Cl_2 1:1) to afford white crystals (0.641g, 73%) of (+)-(3*R*,5*S*)-methyl 6-acetoxy-3,5-(isopropylidenedioxy)hexanoate. $[\alpha]_D = +12$ (c = 0.92, $CHCl_3$); mp = 49−50 °C. ^{1}H NMR (200 MHz, $CDCl_3$), δ 4.32 (tdd, 1H, J = 12 Hz, J = 6 Hz, J = 3 Hz), 4.17−4.05 (m, 1H), 4.04−3.94 (m, 2H), 3.67 (s, 3H), 2.47 (AB part of an ABX system, 2H, J_{AB} = 15.7 Hz, J_{AX} = 6.7 Hz, J_{BX} = 6.2 Hz, $\Delta\nu$ = 39 Hz), 2.06 (s, 3H), 1.61 (dt, 1H, J_{gem} = 12.6 Hz, ^3J = 2.4 Hz), 1.45 (s, 3H), 1.37 (s, 3H), 1.33−1.13 (m, 1H). ^{13}C NMR ($CDCl_3$), δ 171.8, 171.5, 99.7, 67.7, 66.1, 67.6, 41.7, 43.2, 52.3, 30.5, 21.5, 20.2. Anal. Calcd for $C_{12}H_{20}O_6$: C, 55.37; H, 7.74. Found: C, 55.41; H, 7.81.

(2) An aqueous solution of K_2CO_3 (927 mg/6 mL) was dropwise added to a stirred solution of the preceding compound (706 mg, 2.7 mmol) in MeOH (70 mL). The colorless solution turned to light yellow with a white precipitate. After stirring at room temperature for 3 h, water (50 mL) and solid NH_4Cl were added until pH 7. AcOEt (50 mL) was added and the aqueous layer was extracted with AcOEt (3 × 50 mL), then saturated with solid NaCl and extracted again with AcOEt (3 × 50 mL). The combined organic layers were dried ($MgSO_4$) and evaporated to afford **11** as a colorless liquid (459 mg, 78%). $[\alpha]_D = +9.7$ (c = 1.85, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$), δ 4.33 (tdd, 1H, J = 11.4 Hz, J = 6.4 Hz, J = 2.6 Hz), 4.00 (m, 1H), 3.67 (s, 3H), 3.53 (AB part of an ABX system, 2H, J_{AB} = 11.5 Hz, J_{AX} = 6.0 Hz, J_{BX} = 2.5 Hz, $\Delta\nu$ = 26 Hz), 2.47 (AB part of an ABX system, 2H, J_{AB} = 15.6 Hz, J_{AX} = 6.9 Hz, J_{BX} = 6.1 Hz, $\Delta\nu$ = 39 Hz), 2.18 (br s, 1H), 1.50 (dt, 1H, J_{gem} = 13.2 Hz, ^3J = 2.8 Hz), 1.46 (s, 3H), 1.37 (s, 3H), 1.40−1.21 (m, 1H). ^{13}C NMR ($CDCl_3$), δ 171.8, 99.5, 70.1, 66.0, 66.3, 41.6, 32.4, 52.1, 30.4, 20.2. Anal. Calcd for $C_{10}H_{18}O_5$: C, 55.03; H, 8.31. Found: C, 54.92; H, 8.19

(+)-(3*R*,5*R*)-Methyl 7-Phenyl-3,5-(isopropylidenedioxy)-heptanoate (12). (1) DMSO (0.320 mL, 6 equiv) was dropwise added at −75 °C to a solution of oxalyl chloride (0.200 mL, 3 equiv) in CH_2Cl_2 (5 mL). After 10 min the alcohol **11** (156.9 mg, 0.718 mmol) diluted in CH_2Cl_2 (5 mL) was slowly added. The heterogeneous mixture was stirred for 1.5 h and the temperature raised to −40 °C. The flask was cooled at −50 °C before adding NEt_3 (1.2 mL, 12 equiv) and then stirred at room temperature for 1 h. CH_2Cl_2 (4 mL) was added to get a homogenous solution. After completion (TLC) the reaction was first quenched with CH_2Cl_2 (20 mL) and saturated NH_4Cl (20 mL) and then neutralized with 10% HCl (2 mL). The organic layer was washed with water (3 × 50 mL) and brine (20 mL) and then dried ($MgSO_4$). Evaporation of the solvent afford (3*R*,5*S*)-methyl 6-formyl-*syn*-3,5-(isopropylidenedioxy)hexanoate (slight yellow oil, 125 mg, 80.7%) which was used in the next step without further purification. ^{1}H NMR (200 MHz, $CDCl_3$), δ 9.53 (s, 1H), 4.41−4.19 (m, 8H), 3.65 (s, 3H), 2.46 (AB part of an ABX system, 2H, J_{AB} = 15.8 Hz, J_{AX} = 6.9 Hz, J_{BX} = 6.0 Hz, $\Delta\nu$ = 35 Hz), 1.81 (dt, 1H, J_{gem} = 12.8 Hz, ^3J = 2.8 Hz), 1.45 (s, 3H), 1.41 (s, 3H), 1.4−1.2 (m, 1H). ^{13}C NMR ($CDCl_3$), δ 201.4, 171.5, 99.9, 74.3, 65.9, 41.5, 31.2, 52.3, 30.2, 19.9.

(2) To a solution containing benzyl triphenylphosphonium bromide (204 mg, 1.13 equiv) in dry THF (5 mL) was added at room temperature a solution of nBuLi in hexane (1.5 M, 0.320 mL, 1.15 equiv). After stirring for 10 min the preceding aldehyde (90 mg, 0.416 mmol) diluted in dry THF (10 mL) was dropwise added to the red-orange Wittig reagent. The reaction was stirred for 4 h at room temperature to afford a yellow solution with a white precipitate. Then CH_2Cl_2 (50 mL) and a saturated solution of NH_4Cl (60 mL) were added until pH 6. The aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated, and the crude product was purified by column chromatography on silica gel (CH_2Cl_2) giving (3*R*,5*S*)-methyl 7-phenyl-*syn*-3,5-(isopropylidenedioxy)-6-heptenoate as a 85/15 *Z*/*E* mixture of a slight yellow oil and white crystals (79.1 mg, 65.5%).^{1}H NMR (200 MHz, $CDCl_3$), δ 7.40−7.21 (m, 5H), 6.62 (d, 1H, J = 11.4 Hz, *Z* and *E* isomer), 6.61 (d, 1H, J = 16.4 Hz, *E* isomer), 6.16 (dd, 1H, J = 16 Hz, J = 6.2 Hz, *E* isomer), 5.60 (dd, 1H, J = 11.4 Hz, J = 8.6 Hz, *Z* isomer), 4.81 (ddd, 1H, J = 11 Hz, J = 9 Hz, J = 2.6 Hz, *Z* isomer), 4.62−4.52 (m, 1H, *E* isomer),), 4.5−4.3 (m, 1H, Hx of ABX system, *E* isomer), 4.32 (m, 1H, Hx from ABX system, *Z* isomer), 3.67 (s, 3H, *Z* isomer), 3.69 (s, 3H, *E* isomer), 2.48 (AB fragment of an ABX system, 2H, J_{AB} = 15.6 Hz, J_{AX} = 7 Hz, J_{BX} = 6 Hz, $\Delta\nu$ = 40 Hz, *Z* isomer), 1.65 (dt, 1H, J_{gem} = 12.8 Hz, ^3J = 2.8 Hz, *Z* isomer), 1.50 (s, 3H, *Z* isomer), 1.44 (s, 3H, *Z* isomer), 1.47−1.38 (m, 1H, *Z* isomer). ^{13}C NMR ($CDCl_3$), δ 171.9, 142.3, 99.7, 137.1, 133.3, 132.1, 130.2, 129.3, 129.1, 128.9, 128.3, 128.1, 127.1, 66.3, 66.2, 41.8, 37.1, 52.3, 30.8, 20.5.

(3) The reduction of the preceding olefinic compound (30.4 mg, 0.104 mmol) dissolved in AcOEt (6 mL) was carried out with hydrogen and 5% Pd/C (25 mg). After stirring for 24 h the solution was filtered on Celite, washed with CH_2Cl_2, and concentrated to give **12** as a colorless liquid (29.3 mg, 96%) which was used without further purification. $[\alpha]_D = +23$ (c = 1.45, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$), δ 7.32−7.13 (m, 5H), 4.26 (tdd, 1H, Hx of ABX system, J = 12 Hz, J = 6.5 Hz, J = 2.6 Hz), 3.88−3.75 (m, 1H), 3.68 (s, 3H), 2.82−2.61 (m, 2H), 2.46 (AB fragment of an ABX system, 2H, J_{AB} = 15.4 Hz, J_{AX} = 6.7 Hz, J_{BX} = 6.3 Hz, $\Delta\nu$ = 41 Hz), 1.93−1.63 (m, 2H), 1.56 (dt, 1H, J_{gem} = 12 Hz, ^3J = 2.6 Hz), 1.43 (s, 3H), 1.40 (s, 3H), 1.33−1.12 (m, 1H). ^{13}C NMR ($CDCl_3$), δ 172.1, 142.6, 99.5, 129.2, 129.0, 126.4, 68.2, 66.6, 41.9, 38.5, 37.2, 31.7, 52.3, 30.8, 20.4. Anal. Calcd for $C_{17}H_{24}O_4$: C, 69.84; H, 8.27. Found: C, 69.05; H, 8.55.

(+)-(4*R*,6*R*)-4-Hydroxy-6-(2-phenylethyl)-tetrahydro-2*H*-pyran-2-one (2). The ester **12** (27 mg, 0.092 mmol) in acetic acid (2 mL) and water (0.5 mL) was heated at 92 °C for 2 h. After 2 h at room temperature the solution was then diluted with CH_2Cl_2 (20 mL) and water (10 mL) and neutralized with saturated $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2 (4 × 10 mL), and the combined organic layers were washed with brine (10 mL) and dried ($MgSO_4$). The crude product was purified by column chromatography on silica gel giving **2** (16 mg, 81%) as white crystals which was recrystallized (CH_2Cl_2/hexane). $[\alpha]_D = +71$ (c = 0.94, $CHCl_3$), mp = 108 °C, lit.[10] mp = 106−107 °C, $[\alpha]_D = +67.2$ (c = 0.67, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$), δ 7.09−7.44 (m, 5H), 4.71 (m, 1H), 4.37 (m, 1H), 2.96−2.64 (m, 4H), 2.17−1.69 (m, 4H), 2.46 (m, 1H). ^{13}C NMR ($CDCl_3$), δ 171.3, 141.7, 129.2, 129.1, 126.8, 75.7, 63.3, 41.7, 39.3, 38.0, 31.8. Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.89; H, 7.39. Found: C, 70.78; H, 7.12.

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