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Tetrahedron: *Asymmetry* 16 (2005) 1837–1843

Enantioselective synthesis of either enantiomer of α-alkyl-α-hydroxy-α-phenylacetic acids using chiral auxiliaries

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Received 2 March 2005; accepted 30 March 2005

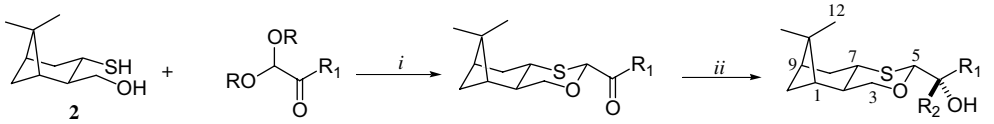
Abstract—The enantioselective synthesis of either enantiomer of α-alkyl-α-hydroxy-α-phenylacetic acids was achieved by using 2-acyloxathianes **1a**–**c** and the mixed acyl-S,O-acetals **7** and **8** as chiral auxiliaries, which can straightforwardly be prepared from (1*R*)-(−)-myrtenal. This procedure allowed the preparation of the title compounds in >95% enantiomeric excess (ee).

1. Introduction

α-Hydroxy acids represent a useful arrangement of functional groups widely used as building blocks for the synthesis of molecules with synthetic[1] or biological[2,3] interest. Most enantioselective syntheses of the title compounds involve the reduction of ketoesters by biomimetic[4] or by borane-mediated asymmetric reductions,[5] ring-opening of epoxyacids with metalated reagents,[6] asymmetric hydrogenation of enol acetates,[7] enzymatic protocols,[8] and through dynamic kinetic resolution,[9] although such procedures usually lead to only one enantiomer. As an extension of our research on the enantioselective preparation of chiral 1,2-diols using (1*R*)-(−)-myrtenal-derived chiral auxiliaries **1**, **7**, and **8**,[10] we herein report their use to synthesize either antipode of some representative chiral α-alkyl-α-hydroxy-α-phenylacetic acids. A comparative analysis concerning the advantage of the use of acyloxathianes **1** and acyl-S,O-acetals **7** and **8** is also described.

2. Results and discussion

The preparation of both enantiomers of α-hydroxyaldehydes can be achieved by diastereoselective nucleophilic additions to acylaminals[11] and acyloxathianes[12] used as chiral auxiliaries, in which the inclusion order of the two groups into the chiral auxiliary, either as the acyl group or as the nucleophilic reagent, determines the absolute



3a R = Et; R_1 = Ph
3b R = Me; R_1 = Me
3c R = Me; R_1 = Et

1a R_1 = Ph
1b R_1 = Me
1c R_1 = Et

4a R_1 = Ph; R_2 = Me
4b R_1 = Ph; R_2 = Et
4c R_1 = Me; R_2 = Ph
4d R_1 = Et; R_2 = Ph

Scheme 1. Preparation of acyloxathianes **1a**–**c** and their treatment with Grignard reagents. (i) C_6H_6, *p*-TsOH, reflux; (ii) R_2MgBr, THF, −78 °C.

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0957-4166/$ - see front matter © 2005 Published by Elsevier Ltd.
doi:10.1016/j.tetasy.2005.03.032

configuration of the new stereogenic center. In this context, and based on the excellent capabilities of acyloxathianes[10a,b] and mixed S,O-acetals[10c] as chiral auxiliaries, the use of both protocols to selectively prepare either desired enantiomer of the title compounds is described.

According to the first protocol, to achieve a representative synthesis of each antipode pair of two α-alkyl-α-phenylacetic acids, we choose to prepare the three acyloxathianes **1a**–**c**, having a benzoyl, acetyl or propionyl substituent as the acyl group, respectively, whose preparation (Scheme 1) was done as described.[10a,b] Thus, hydroxythiol **2** was treated with the corresponding α-ketoacetals **3a** and **3b** to yield the 2-acyloxathianes **1a** and **b**, respectively. Similarly, the new oxathiane **1c** was prepared in 32% isolated yield by condensing α-ketoacetal[13] **3c** with hydroxythiol **2**. As was previously done for oxathianes **1a** and **b**,[10a,b] the stereochemistry at C-5 of propionyloxathiane **1c** was confirmed by an NOE experiment, giving 5% and 8% enhancements in the NMR signals of H-3 axial and H-7, respectively, upon irradiation of H-5.

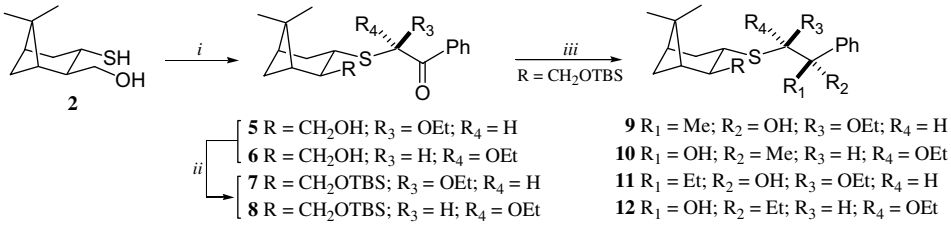
The nucleophilic addition of Grignard reagents on acyloxathianes **1a**–**c** were carried out as previously described.[10a,b] Accordingly, the addition of MeMgBr and EtMgBr on benzoyloxathiane **1a** gave adducts **4a** (R_1 = Ph; R_2 = Me) and **4b** (R_1 = Ph; R_2 = Et), respectively, while addition of PhMgBr on oxathianes **1b** and **c** gave adducts **4c** (R_1 = Me; R_2 = Ph) and **4d** (R_1 = Et; R_2 = Ph), respectively. The chemical yields of adducts **4a**–**d** range from 85% to 95% isolated yield, while the diastereomeric ratios (dr) were >99:1. The stereochemical outcome is consistent with the Cram chelated model,[10,12,14] while diastereomeric ratios were calculated by integrating the H-5 signals of each diastereoisomer in the NMR spectra.

For the second protocol, the synthesis of a mixture of S,O-acetals **5** and **6** (Scheme 2) was achieved in 83% yield in a 4:1 ratio.[10c] To increase the amount of S,O-acetal **6**, the above mixture was equilibrated to ca. 1:1 ratio after treatment with potassium carbonate in THF at room temperature for 24 h. The separation of this mixture can efficiently be done at this stage through column chromatography (silica gel 230–400; hexane:ethyl acetate 4:1), or after its conversion to the corresponding silyl derivatives **7** and **8** (silica gel 230–400, hexane:ethyl acetate 49:1). Preparation of the two later compounds proceeded without epimerization in 95%, by treatment of diastereoisomerically pure S,O-acetals **5** and **6**, respectively, with TBSCl in CH_2Cl_2 in the presence of DMAP (Scheme 2).[10c] Once separated, S,O-acetals **7** and **8** were submitted to nucleophilic addition using MeMgBr or EtMgBr, to give the derived diastereoisomeric carbinols **9**–**12** in good yields (>95%) and excellent diastereoselective ratios (>99:1).

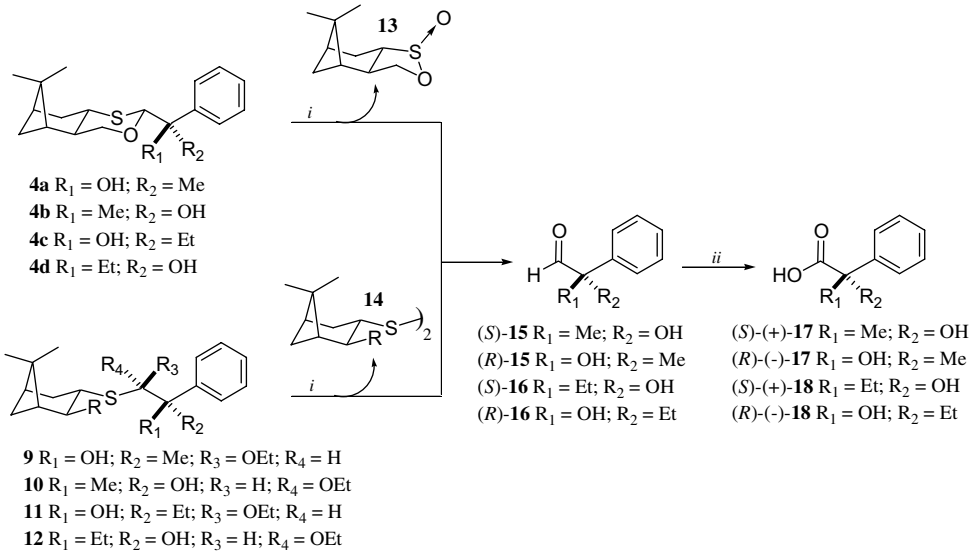
The oxidative hydrolyses of adducts **4a**–**d** and **9**–**12** were achieved using $AgNO_3$ and NCS in acetonitrile (Scheme 3), giving the corresponding aldehydes and the chiral auxiliary as sultine[10a,b] **13** (50–72% yield) or dimer **14** (91% yield), respectively. Aldehydes (*S*)-**15** and (*S*)-**16** were obtained from adducts **4a** and **b** in 58% and 63% yield, respectively, while hydrolysis of adducts **4c** and **d** gave aldehydes (*R*)-**15** and (*R*)-**16** in 67% and 72% yield, respectively.

Purification of aldehydes (*S*)-**15** and (*R*)-**15** through column chromatography failed since they showed a faster tendency to decompose than aldehydes (*S*)-**16** and (*R*)-**16**. The former aldehydes, even upon standing at room temperature, decomposed to yield acetophenone. To overcome this, oxidation of aldehydes (*S*)-**15** and (*R*)-**15** should be done as soon as they have been prepared. The oxidation process using Ag_2O, to afford carboxylic acids (*S*)-**17** and (*R*)-**17**, is in agreement with the formation of acetophenone as a side product.[12,15] At this stage, carboxylic acids (*S*)-**17** and (*R*)-**17** were purified by crystallization in $CHCl_3$. In turn, aldehydes (*S*)-**16** and (*R*)-**16** were also oxidized using the same reaction conditions to give carboxylic acids (*S*)-**18** and (*R*)-**18**. Spectroscopic data and specific rotations (see Experimental) of the above hydroxyacids are in agreement with those reported.[11b,12,16,17]

A comparison of the above two experimental protocols is of interest in order to attain a specific structural or stereochemical objective. The number of synthetic steps required from hydroxythiol **2** to the addition products **4a**–**d**, or **9**–**12**, are two or three, respectively. Both protocols hold identical procedures before and after these stages. However, in order to obtain two enantiomeric pairs of α-hydroxyacids **17** and **18**, it was necessary in the first protocol to carry out three separate reactions to prepare three different acyloxathianes **1a**–**c**, while in the second protocol, only one synthetic operation is required to obtain the diastereoisomeric acyl-S,O-acetals **5** and **6**. This fact would clearly favor the acyl-S,O-acetals protocol when the synthesis of a series of compounds bearing a common substituent, such as a



Scheme 2. Preparation of acyl-S,O-acetals **7** and **8** and their treatment with Grignard reagents. (i) Compound **3a**, CH_2Cl_2, *p*-TsOH, rt; (ii) TBSCl, CH_2Cl_2, DMAP, rt; (iii) MeMgBr or EtMgBr, THF, −78 °C.



Scheme 3. Oxidative hydrolysis of carbinols **4a–d** and **9–12** and preparation of the respective α-hydroxyacids. (i) $AgNO_3$, NCS, $CH_3CN{\cdot}H_2O$ (1:1), 0 °C; (ii) Ag_2O, $THF{\cdot}H_2O$ (1:1), 0 °C.

phenyl group, is the objective. This advantage of the acyl-S,O-acetals protocol, over the acyloxathiane protocol, is due to the diastereoisomeric relationship at the S,O-acetalic carbon in **7** and **8**, which is equivalent of having enantiomeric acyloxathianes, or to control the nature of the nucleophilic reagent and the acyl group at the oxathiane ring.

On the other hand, recovery of the chiral auxiliary is efficiently done in both protocols. Thus, the oxidative hydrolysis of carbinols **4a–d** yield the respective α-hydroxyaldehydes and sultine **13**, while hydrolysis of S,O-acetals **9–12** provides the expected α-hydroxyaldehydes and dimer **14**. Both sultine **13** and dimer **14** were reconverted to hydroxythiol **2** in 72 and 91% yield, respectively, with $LiAlH_4$. From there, hydroxythiol **2** leads directly to acyloxathianes **4**, while for the preparation of acyl-S,O-acetals **7** and **8**, two reaction steps and a separation are necessary. However, the additional reaction steps can well be compensated, since acyl-S,O-acetals can be obtained in higher yields than acyloxathianes.

3. Conclusion

In summary, when using acyloxathianes, the desired absolute configuration at the new stereogenic center can be determined by controlling both the nature of the acyl group attached to the chiral auxiliary and the incoming nucleophilic moiety of a Grignard reagent, while the same goal can be achieved by using either thioacetal **7** or **8** (Scheme 2), thus it being unnecessary to switch between the nucleophile and the acyl groups. Despite the existence of several enantioselective and diastereoselective methods to obtain optically active compounds, these methods normally give only one enantiomer of a given pair. In this context, our thioacetal protocol allows us to obtain any configuration of a given α-hydroxycarbonyl derivative in a more straightforward process, a situation that is strongly desired in the field of asymmetric synthesis.

4. Experimental

4.1. General

Melting points were determined on an electrothermal capillary melting point apparatus and are uncorrected. Optical rotations were measured at 589 nm using a 1 dm cell on a JASCO DIP-370 polarimeter. Infrared spectra were recorded on a Perkin–Elmer Spectrum 2000 spectrophotometer. ^1H and ^{13}C NMR spectra were obtained on a Varian Mercury spectrometer at 300 and 75.4 MHz, or in a Bruker DMX at 500 and 125 MHz, as specified, using $CDCl_3$ as solvent and TMS as the internal standard. The low resolution mass spectra (LRMS) were recorded on a Varian Saturn 2000 GC/Selective Mass Detector, either using EI (70 eV) or CI, as specified. The high resolution electron impact mass spectra (HREIMS) were recorded on a VG 7070 high resolution mass spectrometer at the UCR Mass Spectrometry Facility, University of California, Riverside, CA. Elemental analyses were determined by A-M-W laboratories, Phoenix, AZ. Thin-layer chromatograms were done on precoated TLC sheets of silica gel 60 F_{254} (E. Merck). Flash chromatography was carried out using Merck silica gel (230–400 mesh). THF used in the nucleophilic additions was distilled from Na immediately prior to use, and all other reagents were used without further purification.

4.2. (1*S*,2*R*,5*R*,7*S*,9*R*)-5-Propionyl-10,10-dimethyl-4-oxa-6-thiatricyclo[7.1.1.$0^{2,7}$]undecane 1c

A solution containing 200 mg (1.07 mmol) of hydroxythiol[10a] **2** and 184 mg (1.39 mmol) of ketoacetal **3c** in 40 mL of benzene was refluxed for 1.5 h. The reaction

mixture was poured into a cold saturated solution of $NaHCO_3$, extracted with ethyl ether, washed with a saturated solution of $NaHCO_3$ (2×20 mL), dried over anhydrous Na_2SO_4 and evaporated to dryness. The oily residue was flash chromatographed using a mixture of hexane:EtOAc (9:1) as the eluent, giving 94 mg (34% yield) of propionyloxathiane **1c** as a colorless syrup (R_f 0.43, hexane:EtOAc 9:1). $[\alpha]_D^{25} = -5.2$ (*c* 0.11, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 5.49 (s, 1H, H-5), 4.11 (dd, 1H, $J = 10.7$, 3.1 Hz, H-3eq), 3.82 (dt, 1H, $J = 8.5$, 10.2 Hz, H-7), 3.65 (t, 1H, $J = 11.3$ Hz, H-3ax), 2.66 (q, 2H, $J = 7.4$ Hz, H-2′), 2.62 (m, 1H, H-11eq), 2.48 (ddd, 1H, $J = 11.3$, 10.2, 3.1 Hz, H-2), 2.38 (m, 1H, H-8eq), 2.14 (bq, 1H, $J = 6.1$ Hz, H-9), 1.84 (bt, 1H, $J = 5.9$ Hz, H-1), 1.76 (m, 1H, H-8ax), 1.27 (s, 3H, Me-13), 1.16 (s, 3H, Me-12), 1.08 (t, 3H, $J = 7.3$ Hz, Me-3′), 1.02 (d, 1H, $J = 9.6$ Hz, H-11ax). ^{13}C NMR ($CDCl_3$) δ 204.9 (C-1′), 88.6 (C-5), 76.0 (C-3), 51.1 (C-2), 45.6 (C-1), 43.3 (C-9), 41.9 (C-7), 39.5 (C-11), 39.0 (C-10), 33.4 (C-8), 31.4 (C-2′), 29.5 (C-13), 24.5 (C-12), 7.3 (C-3′). IR (KBr) ν_{max}: 2917, 1722, 1458, 1129, 1058 cm^{-1}. EIMS m/z (rel. int): 255 (M^++1, 4), 197 (100), 135 (20), 107 (37), 93 (28), 79 (21). HREIMS calcd for $C_{14}H_{22}O_2S$: 254.1341. Found: 254.1349.

4.3. Preparation of acyl-S,O-acetals 5 and 6

A solution containing 5.2 g (28 mmol) of hydroxythiol **2**, 8.7 g (42 mmol) of 2,2-diethoxyacetophenone **3a** and 0.53 g (3.1 mmol) of *p*-TsOH in 30 mL of CH_2Cl_2 was stirred at room temperature for 5 h. After the addition of 150 mL of CH_2Cl_2, the reaction mixture was washed with a saturated solution of $NaHCO_3$ (4×50 mL), the organic layer dried over anhydrous Na_2SO_4 and concentrated to dryness, to give 12.5 g of a syrup. This mixture was filtered through a short chromatography column (5 cm diam. × 15 cm large of silica gel 230–400; hexane:EtOAc 4:1) to give a mixture of 8.1 g (83% yield) of S,O-acetals **5** and **6** in a ca. 4:1 ratio. Two gram of this mixture was then treated with 0.2 g of K_2CO_3 in 50 mL of THF at room temperature for 24 h to give a mixture of **5** and **6** in a ca. 1:1 ratio, whose separation was achieved through column chromatography (3 cm diam. × 40 cm large, silica gel mesh 230–400) using hexane:EtOAc 4:1 as eluent, giving 0.8 g of compound **5** and 0.6 g of compound **6**.

4.3.1. (1*S*,2*R*,3*S*,5*R*,2′*R*)-6,6-Dimethyl-3-(2′-ethoxy-1′-phenyl-1′-oxo-2′-ethylsulfanyl)-2-hydroxymethyl-bicyclo-[3.1.1]heptane 5. Colorless syrup (R_f 0.25, hexane:EtOAc 4:1). $[\alpha]_D^{28} = +8.2$ (*c* 0.529, EtOH). ^1H NMR ($CDCl_3$) δ 8.04 (dd, 2H, $J = 7.1$, 1.4 Hz, H-*o*), 7.57 (dd, 1H, $J = 7.1$, 1.4 Hz, H-*p*), 7.46 (dd, 2H, $J = 7.3$, 1.4 Hz, H-*m*), 5.86 (s, 1H, H-2′), 3.99 (dq, 1H, $J = 9.3$, 7.0 Hz, OCHa), 3.63 (dq, 1H, $J = 9.3$, 7.0 Hz, OCHb), 3.45 (d, 2H, $J = 6.0$ Hz, H-10), 3.09 (ddd, 1H, $J = 9.8$, 8.1, 5.8 Hz, H-3), 2.66 (m, 1H, H-4eq), 2.41 (m, 1H, H-7eq), 2.15 (m, 1H, H-4eq), 2.08 (m, 1H, H-5), 2.01 (m, 1H, H-2), 1.95 (m, 1H, H-1), 1.30 (t, 3H, $J = 7.0$ Hz, CH_2CH_3), 1.19 (s, 3H, Me-9), 1.02 (d, 1H, $J = 9.9$ Hz, H-7ax), 0.98 (s, 3H, Me-8). ^{13}C NMR ($CDCl_3$) δ 191.6 (C-1′), 134.4 (C-*i*), 133.4 (C-*p*), 128.9 (C-*o*), 128.6 (C-*m*), 85.0 (C-2′), 66.0 (C-10), 64.2 (OCH_2), 52.7 (C-2), 43.4 (C-5), 42.3 (C-1), 39.3 (C-4), 38.4 (C-6), 36.4 (C-3), 33.5 (C-7), 27.6 (Me-9), 23.6 (Me-8), 14.9 (CH_2CH_3). IR (CH_2Cl_2) ν_{max}: 3477, 3059, 2980, 2921, 2869, 1681, 1596, 1578, 1091, 1044, 689, 734 cm^{-1}. EIMS (70 eV) *m/z* (rel. int): 348 (M^+), 243 (73), 135 (48), 105 (52), 91 (40), 79 (100), 55 (16). EA calcd for $C_{20}H_{28}SO_3$: C, 68.96; H, 8.04; S, 9.19. Found: C, 68.72; H, 7.86; S, 8.92.

4.3.2. (1*S*,2*R*,3*S*,5*R*,2′*S*)-6,6-Dimethyl-3-(2′-ethoxy-1′-phenyl-1′-oxo-2′-ethylsulfanyl)-2′-hydroxymethyl-bicyclo-[3.1.1]heptane 6. Colorless syrup (R_f 0.16, hexane:EtOAc 4:1). $[\alpha]_D^{24} = +81.9$ (*c* 0.71, EtOH). ^1H NMR ($CDCl_3$) δ 8.05 (dd, 2H, $J = 6.8$, 1.3 Hz, H-*o*), 7.56 (dd, 1H, $J = 7.4$, 1.3 Hz, H-*p*), 7.46 (ddd, 2H, $J = 7.4$, 6.8, 1.5 Hz, H-*m*), 5.76 (s, 1H, H-2′), 3.97 (dq, 1H, $J = 9.2$, 7.0 Hz, OCHa), 3.79 (dd, 1H, $J = 10.9$ y 6.4, H-10a), 3.62 (m, 1H, OCHb), 3.62 (m, 1H, H-10b), 3.26 (ddd, 1H, $J = 10.1$, 7.5, 5.7 Hz, H-3), 2.46 (m, 1H, H-4eq), 2.34 (m, 1H, H-7eq), 2.14 (m, 1H, H-2), 2.06 (m, 1H, H-5), 1.85 (m, 1H, H-4ax), 1.85 (m, 1H, H-1), 1.32 (t, 3H, $J = 7.0$ Hz, CH_2CH_3), 1.17 (s, 3H, Me-9), 0.97 (d, 1H, $J = 8.4$, H-7ax), 0.96 (s, 3H, Me-8). ^{13}C NMR ($CDCl_3$) δ 191.5 (C-1′), 134.4 (C-*i*), 133.3 (C-*p*), 128.9 (C-*o*), 128.5 (C-*m*), 84.6 (C-2′), 66.4 (C-10), 64.5 (OCH_2), 53.9 (C-2), 43.8 (C-5), 41.9 (C-1), 38.3 (C-4), 38.0 (C-6), 35.9 (C-3), 33.1 (C-7), 27.4 (Me-9), 23.5 (Me-8), 14.8 (CH_2CH_3). IR (CH_2Cl_2) ν_{max}: 3453, 3058, 2981, 2920, 2869, 1682, 1596, 1578, 1093, 1044, 734, 686 cm^{-1}. EA calcd for $C_{20}H_{28}SO_3$: C, 68.96; H, 8.04; S, 9.19. Found: C, 68.78; H, 7.93; S, 8.98.

4.4. Preparation of acyl S,O-acetals 7 and 8

A solution of 6.63 g (19.0 mmol) of S,O-acetals **5** and **6**, 8.06 g (53.5 mmol) of TBSCl, 4.44 g (43.9 mmol) of triethylamine and 0.65 g (6.1 mmol) of DMAP in 40 mL of CH_2Cl_2 was stirred at room temperature under an N_2 atmosphere for 22 h, at which point were added 150 mL of CH_2Cl_2 and the reaction mixture washed (2×100 mL) with an HCl solution (0.5%). The organic layer was dried over anhydrous Na_2SO_4 and concentrated to dryness, to give 11.2 g of the crude reaction mixture, which was flash chromatographed (5 cm diam. × 20 cm large, silica gel 230–400 mesh) using hexane:EtOAc (30:1), giving 8.36 g (95% yield) of S,O-acetals **7** and **8**. A portion of 584 mg of **7** and **8** was efficiently separated through column chromatography (5 cm diam.) packed with silica gel mesh 230–400 (90 cm) and eluted with a mixture of hexane:EtOAc (49:1), giving 252 mg of compound **7** and 236 mg of compound **8**.

4.4.1. (1*S*,2*R*,3*S*,5*R*,2′*R*)-6,6-Dimethyl-3-(2′-ethoxy-1′-phenyl-1′-oxo-2′-ethylsulfanyl)-2-(O-*t*-butyl-dimethylsilyl-hydroxymethyl)-bicyclo[3.1.1]heptane 7. Obtained in 96% yield as a colorless syrup (R_f 0.79, hexane:EtOAc 9:1). $[\alpha]_D^{28} = -4.4$ (*c* 0.40, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 8.02 (dd, 2H, $J = 7.2$, 1.6 Hz, H-*o*), 7.55 (dd, 1H, $J = 7.9$, 1.6 Hz, H-*p*), 7.44 (dd, 2H, $J = 7.2$, 7.9 H-*m*), 5.84 (s, 1H, H-2′), 4.01 (dq, 1H, $J = 9.2$, 7.2 Hz, OCHa), 3.60 (dq, 1H, $J = 9.2$, 7.2 Hz, OCHb), 3.38 (t, 1H,

J = 10.0 Hz, H-10a), 3.20 (dd, 1H, J = 10.0, 4.2 Hz, H-10b), 2.85 (m, 1H, H-3), 2.77 (m, 1H, H-4eq), 2.38 (m, 1H, H-7eq), 2.18 (m, 1H, H-5), 2.11 (ddd, 1H, J = 13.8, 5.9, 2.4 Hz, H-4ax), 1.91 (m, 1H, H-1), 1.86 (m, 1H, H-2), 1.29 (t, 3H, J = 7.2 Hz, CH_2CH_3), 1.17 (s, 3H, Me-9), 0.98 (s, 3H, Me-8), 0.94 (d, 1H, J = 10.0 Hz, H-7ax), 0.77 (s, 9H, t-Bu), −0.12 (s, 3H, Me-Si), −0.14 (s, 3H, Me-Si). ^{13}C NMR ($CDCl_3$) δ 190.8 (C-1′), 134.4 (C-*i*), 133.2 (C-*p*), 128.8 (C-*o*), 128.5 (C-*m*), 84.3 (C-2′), 64.5 (C-10), 63.8 (OCH_2), 52.1 (C-2), 42.3 (C-1), 41.9 (C-5), 39.7 (C-4), 38.4 (C-6), 35.2 (C-3), 33.7 (C-7), 27.7 (Me-9), 25.9 (*t*-Bu), 23.4 (Me-8), 18.3 (CSi), 14.8 (CH_2 CH_3), −5.40 (Si–Me_2). IR (CH_2Cl_2) ν_{max}: 3059, 2926, 2857, 1686, 1597, 1579, 1250, 1087, 836, 776 cm^{-1}. EIMS (70 eV) *m/z* (rel. int): 357 (M^+−105, 8), 135 (100), 133 (16), 105 (44), 79 (93), 41 (19), 29 (18). EA calcd for $C_{26}H_{42}O_3SSi$: C, 67.51; H, 9.09; S, 6.92. Found: C, 67.69; H, 8.83; S, 7,20.

4.4.2. (1*S*,2*R*,3*S*,5*R*,2′*S*)-6,6-Dimethyl-3-(2′-ethoxy-1′-phenyl-1′-oxo-2′-ethylsulfanyl)-2-(*O*-*t*-butyl-dimethylsilyl-hydroxymethyl)-bicyclo[3.1.1]heptane 8. Obtained in 95% yield as a colorless syrup (R_f 0.84, hexane:EtOAc 9:1). $[\alpha]_D^{25}$ = +75.3 (*c* 0.51, EtOH). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01 (dd, 2H, J = 8.0, 1.2 Hz, H-*o*), 7.52 (dd, 1H, J = 7.5, 1.2 Hz, H-*p*), 7.41 (ddd, 2H, J = 8.0, 7.5, 1.2 Hz, H-*m*), 5.64 (s, 1H, H-2′), 3.98 (dq, 1H, J = 9.5, 7.0 Hz, OCHa), 3.63 (dd, 1H, J = 10.0, 4.5 Hz, H-10a), 3.57 (dq, 1H, J = 9.5, 7.0 Hz, OCHb), 3.56 (t, 1H, J = 10.0 Hz, H-10b), 3.01 (ddd, 1H, J = 10.0, 8.5, 6.0 Hz, H-3), 2.42 (ddd, 1H, J = 14.0, 10.0, 2.0 Hz, H-4eq), 2.31 (m, 1H, H-7eq), 2.19 (td, 1H, J = 6.0, 2.0 Hz, H-5), 1.98 (m, 1H, H-2), 1.84 (ddd, 1H, J = 14.0, 6.0, 3.0 Hz, H-4ax), 1.74 (ddd, 1H, J = 8.6, 6.0, 3.0 Hz, H-1), 1.29 (t, 3H, J = 7.0 Hz, CH_2CH_3), 1.13 (s, 3H, Me-9), 0.93 (s, 3H, Me-8), 0.87 (d, 1H, J = 10.0 Hz, H-7ax), 0.84 (s, 9H, *t*-Bu), 0.004 (Si–Me), 0.003 (Si–Me). ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.5 (C-1′), 134.4 (C-*i*), 133.2 (C-*p*), 128.9 (C-*o*), 128.4 (C-*m*), 84.2 (C-2′), 64.7 (C-10), 64.1 (OCH_2), 53.2 (C-2), 42.1 (C-1), 41.9 (C-5), 38.5 (C-4), 38.1 (C-6), 34.5 (C-3), 33.3 (C-7), 27.5 (Me-9), 25.9 (*t*-Bu), 23.4 (Me-8), 18.3 (*C*Si), 14.8 (CH_2CH_3), −5.29 (Si–Me_2). IR (CH_2Cl_2) ν_{max}: 3058, 2926, 2855, 1689, 1597, 1578, 1250, 1079, 836, 776 cm^{-1}. EIMS (70 eV) *m/z* (rel. int): 462 (M^+), 357 (21), 135 (99), 105 (49), 79 (100), 59 (16). EA calcd for $C_{26}H_{42}O_3SSi$: C, 67.51; H, 9.09; S, 6.92. Found: C, 67.72; H, 8.80; S, 7.24.

4.5. General procedure for the addition of Grignard reagents to acyloxathianes 1a–c and S,O-acetals 9–12

To a solution of acyloxathianes **1a**,[10b] **1b**,[10a] **1c**, and S,O-acetals **7** and **8** (1 equiv) in anhydrous THF was added the Grignard reagent (1.5–2 equiv) at −78 °C under an N_2 atmosphere. After stirring for 2 h at the same temperature, the reaction mixture was allowed to warm up to room temperature and further stirred for 1 h. The reaction mixture was quenched with 10 mL of a saturated solution of ammonium chloride; the THF was eliminated by evaporation under reduced pressure and the remaining emulsion extracted with ethyl ether. The organic layer was washed with a saturated solution of ammonium chloride, dried over anhydrous Na_2SO_4 and evaporated to dryness, to give the corresponding pure carbinols as colorless oils. Spectroscopic data for compounds **4a**–**c** are described.[10c]

4.5.1. (1*S*,2*R*,5*R*,7*S*,1′*R*)-5-(1′-Hydroxy-1′-phenyl-1′-propyl)-10,10-dimethyl-4-oxa-6-thia-tricyclo[7.1.1.0^{2,7}]-undecane 4d. Obtained in 78% yield as a colorless syrup (R_f 0.39, hexane:EtOAc 9:1). $[\alpha]_D^{20}$ = −46.7 (*c* 0.28, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 7.51–7.21 (m, 5H, Ar), 5.09 (s, 1H, H-5), 4.00 (dd, 1H, J = 11.0, 3.1 Hz, H-3eq), 3.65 (bq, 1H, J = 10.1 Hz, H-7), 3.57 (t, 1H, J = 11.0 Hz, H-3ax), 2.91 (bs, 1H, OH), 2.57 (m, 1H, H-11eq), 2.46–2.23 (m, 2H, H-2, H-8eq), 2.09 (bq, 1H, J = 5.4 Hz, H-9), 2.02 (q, 2H, J 7.3 Hz, H-2′), 1.78 (t, 1H, J = 5.6 Hz, H-1), 1.72 (m, 1H, H-8ax), 1.24 (s, 3H, Me-13), 1.10 (s, 3H, Me-12), 0.99 (d, 1H, J = 9.6 Hz, H-11ax), 0.75 (t, 3H, J = 7.3 Hz, Me-3′). ^{13}C NMR ($CDCl_3$) δ 142.5 (C-*i*), 127.8 (C-*m*), 127.0 (C-*p*), 116.2 (C-*o*), 93.9 (C-5), 78.3 (C-1′), 76.5 (C-3), 51.5 (C-2), 45.5 (C-1), 43.2 (C-9), 41.1 (C-7), 39.3 (C-11), 39.0 (C-10), 33.4 (C-8), 29.8 (C-2′), 29.5 (C-13), 24.4 (C-12), 7.5 (C-3′). IR (film) ν_{max}: 3501, 2921, 1448, 1368, 1258, 1063 cm^{-1}. EIMS (70 eV) *m/z* (rel. int): 314 (M^+−18, 1), 197 (100), 135 (30), 107 (32), 93 (30), 79 (22). HREIMS calcd for $C_{20}H_{28}O_2S$+H: 333.1888. Found: 333.1902.

4.5.2. (1*S*,2*R*,3*S*,5*R*,1′*R*,2′*S*)-6,6-Dimethyl-3-(1′-ethoxy-2′-phenyl-2′-hydroxy-1′-propylsulfanyl)-2-(*O*-*t*-butyl-dimethylsilyl-hydroxymethyl)-bicyclo[3.1.1]heptane 9. Obtained in 96% yield as a colorless syrup (R_f 0.79, hexane:EtOAc 4:1). $[\alpha]_D^{24}$ = +25.6 (*c* 0.90, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 7.60–7.20 (m, 5H, Ar), 4.62 (s, 1H, H-1′), 3.90 (dq, 1H, J = 9.0, 7.0 Hz, OCHa), 3.64 (dd, 1H, J = 10.0, 5.0 Hz, H-10a), 3.59 (t, 1H, J = 10.0 Hz, H-10b), 3.25 (dq, 1H, J = 9.0, 7.0 Hz, OCHb), 2.90 (m, 1H, H-3), 2.40 (m, 2H, H-4eq, H-7eq), 2.21 (t, 1H, J = 7.0 Hz, H-1), 2.15–1.95 (m, 3H, H-2, H-4ax, H-5) 1.62 (s, 3H, Me-3′), 1.20 (s, 3H, Me-9), 1.18 (t, 3H, J = 7.0 Hz, CH_2CH_3), 0.95 (d, 1H, J = 10.0 Hz, H-7ax), 0.93 (s, 3H, Me-8), 0.80 (s, 9H, t-Bu), 0.02 (Si–Me_2). ^{13}C NMR ($CDCl_3$) δ 144.7 (*C*-*i*), 127.6 (*C*-*m*), 127.0 (*C*-*p*), 126.0 (*C*-*o*), 95.6 (C-1′), 75.8 (C-2′), 65.7 (C-10), 65.5 (OCH_2), 53.0 (C-2), 42.3 (C-1), 42.1 (C-5), 38.8 (C-4), 38.2 (C-6), 37.1 (C-3) 33.2 (C-7), 27.7 (C-9), 25.9 (t-Bu), 25.3 (C-3′), 23.4 (C-8), 18.5 (Si*C*), 14.8 (CH_2CH_3), −5.2, −5.3 (Me_2Si). IR (film) ν_{max}: 3467, 2928, 2857, 1447, 1079, 699, 620 cm^{-1}. EIMS (70 eV) *m/z* (rel. int): 433 (4), 357 (73), 135 (100), 105 (58). HREIMS calcd for $C_{27}H_{46}O_3SSi$+Na: 501.2835. Found: 501.3725.

4.5.3. (1*S*,2*R*,3*S*,5*R*,1′*S*,2′*R*)-6,6-Dimethyl-3-(1′-ethoxy-2′-phenyl-2′-hydroxy-1′-propylsulfanyl)-2-(*O*-*t*-butyl-dimethylsilyl-hydroxymethyl)-bicyclo[3.1.1]heptane 10. Obtained in 98% yield as a colorless syrup (R_f 0.77, hexane:EtOAc 4:1). $[\alpha]_D^{25}$ = −122.4 (*c* 0.59, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 7.56 (d, 2H, J = 7.0 Hz, H-*o*), 7.33 (t, 2H, J = 7.0 Hz, H-*m*), 7.24 (t, 1H, J = 7.0 Hz, H-*p*),

4.54 (s, 1H, H-1′), 3.96 (dq, 1H, J = 9.9, 7.0 Hz, OCHa), 3.39 (dd, 1H, J = 5.0, 9.7 Hz, H-10a), 3.33 (dq, 1H, J = 9.9, 7.0 Hz, OCHb), 3.28 (s, 1H, OH), 3.22 (t, 1H, J = 9.7 Hz, H-10b), 2.44 (m, 1H, H-4eq), 2.36 (ddd, 1H, J = 9.7, 6.0, 6.0 Hz, H-7eq), 2.24 (ddd, 1H, J = 9.7, 9.7, 7.0 Hz, H-3), 2.14 (m, 1H, H-4ax), 2.14 (t, 1H, J = 6.0 Hz, H-1), 1.90 (m, 1H, H-2), 1.90 (m, 1H, H-5), 1.62 (s, 3H, H-3′), 1.20 (t, 3H, J = 7.0 Hz, CH_2CH_3), 1.16 (s, 3H, H-9), 1.00 (d, 1H, J = 9.7 Hz, H-7ax), 0.88 (s, 9H, *t*-Bu), 0.72 (s, 3H, H-8), 0.06 (s, 6H, $SiMe_2$). ^{13}C NMR ($CDCl_3$) δ 145.4 (C-*i*), 128.1 (C-*m*), 127.1 (C-*p*), 125.9 (C-*o*), 94.8 (C-1′), 76.7 (C-2′), 65.9 (C-10), 65.4 (OCH_2), 52.4 (C-2), 42.4 (C-1), 42.4 (C-5), 38.9 (C-6), 38.4 (C-4), 37.3 (C-3), 33.2 (C-7), 27.8 (C-8), 26.3 (*t*-Bu), 25.3 (C-3′), 23.4 (C-8), 18.6 (C-Si), 14.9 (CH_2CH_3), −4.8 (SiMe), −4.9 (SiMe). IR (film) ν_{max}: 3467, 3058, 2928, 2857, 1471, 1447, 1380, 1367, 1254, 1079, 837, 776, 699 cm^{-1}. EIMS (70 eV) *m*/*z* (rel. int): 460 (M^+−18), 433 (3), 357 (57), 179 (10), 121 (18), 105 (58). HREIMS calcd for $C_{27}H_{46}O_3SSi$+Na: 501.2835. Found: 501.2827.

4.5.4. (1*S*,2*R*,3*S*,5*R*,1′*R*,2′*S*)-6,6-Dimethyl-3-(1′-ethoxy-2′-phenyl-2′-hydroxy-1′-butylsulfanyl)-2-(*O*-*t*-butyl-dimethylsilyl-hydroxymethyl)-bicyclo[3.1.1]heptane 11. Obtained in 98% yield as a colorless syrup (R_f 0.66, hexane:EtOAc 9:1). $[\alpha]_D^{25}$ = +46.2 (*c* 0.80, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 7.60–7.20 (m, 5H, Ar), 4.60 (s, 1H, H-1′), 3.90 (dq, 1H, J = 9.0, 7.0 Hz, OCHa), 3.59 (dd, 1H, J = 10.0, 5.0 Hz, H-10a), 3.59 (t, 1H, J = 10.0 Hz, H-10b), 3.30 (dq, 1H, J = 9.0, 7.0 Hz, OCHb), 2.82 (m, 1H, H-3), 2.40 (m, 2H, H-4eq, H-7eq), 2.20–1.80 (m, 4H, H-1, H-2, H-5, H-4ax), 2.04 (q, 2H, J = 7.1 Hz, H-3′), 1.20 (t, 6H, J = 7.2 Hz, CH_2CH_3, Me-9), 0.91 (d, 1H, J = 10.0 Hz, H-7ax), 0.86 (s, 3H, Me-8), 0.80 (s, 9H, t-Bu), 0.72 (t, 3H, J = 7.1 Hz, Me-4′), 0.04 (Si–Me). ^{13}C NMR ($CDCl_3$) δ 142.3 (*C*-*i*), 127.6 (*C*-*m*), 126.7 (*C*-*p*), 126.4 (*C*-*o*), 95.6 (C-1′), 78.5 (C-2′), 65.5 (C-10), 65.3 (OCH_2), 53.2 (C-2), 42.2 (C-1), 42.1 (C-5), 38.8 (C-4), 38.3 (C-6), 37.0 (C-3) 33.2 (C-7) 30.2 (C-3′), 27.6 (C-9), 26.0 (Ct-Bu), 23.4 (C-8), 18.3 (CSi), 14.8 (CH_2CH_3), 7.5 (C-4′), −5.2 (SiMe), −5.3 (SiMe). IR (film) ν_{max}: 3467, 2928, 2857, 1448, 1079, 701, 665 cm^{-1}. EIMS (70 eV) *m*/*z* (rel. int): 447 (2), 357 (53), 135 (100), 107 (39). HREIMS calcd for $C_{28}H_{48}O_3SSi$+Na: 515.2991. Found: 515.3092.

4.5.5. (1*S*,2*R*,3*S*,5*R*,1′*S*,2′*R*)-6,6-Dimethyl-3-(1′-ethoxy-2′-phenyl-2′-hydroxy-1′-butylsulfanyl)-2′-(*O*-*t*-butyl-dimethylsilyl-hydroxymethyl)-bicyclo[3.1.1]heptane 12. Obtained in 96% yield as a colorless syrup (R_f 0.63, hexane:EtOAc 9:1). $[\alpha]_D^{25}$ = +67.8 (*c* 0.64, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 7.5 (d, 2H, J = 7.0 Hz, H-*o*), 7.32 (t, 2H, J = 7.0 Hz, H-*m*), 7.23 (t, 1H, J = 7.0 Hz, H-*p*), 4.56 (s, 1H, H-1′), 3.98 (dq, 1H, J = 9.5, 7.0 Hz, OCHa), 3.37 (dq, 1H, J = 9.5, 7.0 Hz, OCHb), 3.28 (dd, 1H, J = 9.9, 5.2 Hz, H-10a), 3.12 (t, 1H, J = 10.0 Hz, H-10b), 3.02 (s, 1H, OH), 2.40 (m, 1H, H-4eq), 2.33 (ddd, 1H, J = 10.0, 6.0, 6.0 Hz, H-7eq), 2.06 (m, 1H, H-4ax), 2.06 (m, 1H, H-5), 1.98 (m, 1H, H-3), 1.98 (m, 2H, H-3′), 1.86 (m, 1H, H-1), 1.86 (m, 1H, H-2), 1.20 (t, 3H, J = 7.0 Hz, CH_2CH_3), 1.13 (s, 3H, H-9), 0.98 (d, 1H, J = 10.0 Hz, H-7ax), 0.88 (s, 9H, *t*-Bu), 0.71 (t, 3H, J = 9.1 Hz, H-4′), 0.69 (s, 3H, H-8), 0.4 (s, 6H, $SiMe_2$). ^{13}C NMR ($CDCl_3$) δ 142.8 (C-*i*), 127.6 (C-*m*), 126.5 (C-*p*), 126.1 (C-*o*), 94.2 (C-1′), 79.2 (C-2′), 65.3 (C.10), 64.9 (OCH_2), 51.8 (C-2), 41.9 (C-1), 41.7 (C-5), 38.4 (C-6), 38.0 (C-4), 36.5 (C-3), 32.8 (C-7), 29.6 (C-3′), 27.4 (C-9), 25.9 (*t*-Bu), 22.9 (C-8), 18.2 (CSi), 14.5 (CH_2CH_3), 7.4 (C-4′), −5.2 (SiMe), −5.3 (SiMe). IR (film) ν_{max}: 3467, 3059, 2928, 2857, 1470, 1448, 1385, 1367, 1254, 1079, 837, 775, 701 cm^{-1}. EIMS (70 eV) *m*/*z* (rel. int): 447 (M^+−45), 135 (100), 357 (53), 107 (39), 193 (5). HREIMS calcd for $C_{28}H_{48}O_3SSi$+Na: 515.2991. Found: 515.3009.

4.6. General procedure for the hydrolysis of carbinols 4a–d, and 9–12

Following the procedure previously described,[10a–c] 1 equiv of carbinols **4a**–**d** and **9**–**12** in 5 mL of CH_3CN was treated with 2 equiv of NCS and $AgNO_3$ in 35 mL of CH_3CN–H_2O (4:1) at 0–4 °C for 1–5 min. The work-up was carried out by successively adding solutions of NaCl, Na_2SO_3 and $NaHCO_3$ (1 mL, each). The white precipitate was filtered, and the filtrate extracted with a mixture of hexane:CH_2Cl_2 (1:1). The organic layer was dried with anhydrous Na_2SO_4, filtered, and concentrated to dryness, to give a crude yellowish oil, whose ^{1}H NMR spectrum showed the presence of the respective aldehydes (*S*)-**15**, (*S*)-**16**, (*R*)-**15**, and (*R*)-**16**. Aldehydes (*S*)-**16** and (*R*)-**16** were purified by column chromatography using a mixture of hexane:EtOAc (19:1). All spectroscopic data of aldehydes (*S*)-**15**, (*S*)-**16**, (*R*)-**15**, and (*R*)-**16** were fully consistent with those described.[11a,b,12,17–19]

4.6.1. 2-Hydroxy-2-phenylbutanal (*S*)-(−)-16. Obtained in 63% yield and >95% ee as a colorless liquid $[\alpha]_D^{23}$ = −13.1 (*c* 0.23, EtOH), lit.[12] $[\alpha]_D^{23}$ = −13.4 (*c* 18.8, EtOH).

4.6.2. 2-Hydroxy-2-phenylbutanal (*R*)-(+)-16. Obtained in 72% yield and >95% ee as a colorless liquid $[\alpha]_D^{23}$ = +13.3 (*c* 0.23, EtOH).

4.6.3. Bis-[(1*S*,2*R*,3*S*,5*R*)-2-(*tert*-butyl-dimethyl-silanyl-oxymethyl)-6,6-dimethyl-bicyclo[3.1.1]heptane-3-thiol] 14. Obtained in 70% yield as a colorless syrup (R_f 0.87, hexane:EtOAc 19:1). $[\alpha]_D^{25}$ = +119.5 (*c* 0.48, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 3.77 (dd, 1H, J = 9.8, 4.8 Hz, H-10eq), 3.60 (t, 1H, J = 9.8 Hz, H-10ax), 3.00 (ddd, 1H, J = 9.8, 7.4, 5.9 Hz, H-3), 2.51 (1H, ddd, J = 13.0, 10.0, 2.7 Hz, H-4eq), 2.38 (m, 1H, H-7eq), 2.22 (dd, 1H, J=6.3, 6.0 Hz, H-1), 2.17 (m, 1H, H-2), 2.12 (m, 1H, H-4ax), 1.96 (m, 1H, H-5), 1.21 (s, 3H, Me-9), 1.11 (d, 1H, J = 9.7 Hz, H-7ax), 0.96 (s, 3H, Me-8), 0.89 (s, 9H, *t*-*Bu*Si), 0.05 (s, 6H, Me_2Si). ^{13}C NMR ($CDCl_3$) δ 65.6 (C-10), 52.6 (C-2), 43.1 (C-3), 42.1 (C-1), 41.9 (C-5), 38.6 (C-6), 36.6 (C-4), 32.5 (C-7), 27.5 (Me-9), 26.0 (*t*-Bu), 23.3 (Me-8), 18.4 (*C*Si), −5.2 (Me_2Si). IR (film) ν_{max}: 2928, 2857, 1470, 1448, 1385, 1363, 1255, 1112, 837 cm^{-1}. EIMS (70 eV) *m*/*z* (rel. int): 598 (1), 299 (3), 267 (16). HREIMS calcd for $C_{32}H_{62}O_2S_2Si_2$: 598.3730. Found: 598.3754.

4.7. General procedure for the preparation of α-hydroxyacids (*S*)-(+)-17, (*R*)-(−)-17, (*S*)-(+)-18, and (*R*)-(−)-18

Silver(I) oxide was freshly prepared as a brown dark semisolid according to the procedure described by Campaigne and LeSuer.[20] To the above resulting suspension containing 4 equiv of Ag_2O, cooled at −5 °C, were added 1 equiv of aldehydes (*S*)-**15**, (*S*)-**16**, (*R*)-**15**, and (*R*)-**16**, and the mixture was stirred during 15 min. The reaction outcome was filtered and the filtrate was washed with water and extracted with ethyl ether. The aqueous layer was treated with aq 10% HCl until pH = 4, and extracted with ethyl ether. The organic layer was dried over anhydrous Na_2SO_4 and evaporated to dryness to afford 40–58% yield of the corresponding α-hydroxyacids in 95–98% ee.

4.7.1. 2-Hydroxy-2-phenylpropanoic acid (*S*)-(+)-17. Obtained in 46% yield and >95% ee as a white solid mp 114–116 °C, $[\alpha]_D^{22}$ = +37.1 (*c* 0.50, EtOH); lit.[12] mp 114–116 °C, $[\alpha]^{23}$ = +35.5 (*c* 3.464, EtOH, ee 96%); lit.[16] mp 116–117 °C, $[\alpha]^{15}$ = +37.7 (*c* 3.5, EtOH).

4.7.2. 2-Hydroxy-2-phenylpropanoic acid (*R*)-(−)-17. Obtained in 40% yield and >95% ee as a white solid mp 114–116 °C, $[\alpha]_D^{22}$ = −36.8 (*c* 0.40, EtOH).

4.7.3. 2-Hydroxy-2-phenylbutanoic acid (*S*)-(+)-18. Obtained in 53% yield and >95% ee as a white solid mp 126–128 °C, $[\alpha]_D^{24}$ = +31.5 (*c* 0.6; EtOH); lit.[12] mp 127.5–128 °C, $[\alpha]^{24}$ = +31.53 (*c* 3.7, EtOH, 97% ee); lit.[16,17] mp 128–129 °C, $[\alpha]^{20}$ = +32.7 (*c* 4.0, EtOH).

4.7.4. 2-Hydroxy-2-phenylbutanoic acid (*R*)-(−)-18. Obtained in 58% yield and >95% ee as a white solid mp 127–129 °C, $[\alpha]^{24}$ = −31.4 (*c* 0.40, EtOH); lit.[12] mp 128–129 °C), $[\alpha]^{23}$ = −30.9 (*c* 3.680, EtOH, 94% ee).

Acknowledgements

L.G.Z. acknowledges CGPI/IPN (grant 20020683, 20030702, and 20040199) and CONACyT-Mexico (35013E, 44157-Q). M.E.V.D. and S.L.R. thank CONACyT-Mexico (92069 and 125225, respectively) and CGPI/IPN (PIFI) postgraduate fellowships. S.P.E. and P.V.P. thank Institutional Fellowship (CGPI/IPN).

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