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Highly diastereoselective nucleophilic additions using a novel myrtenal-derived oxathiane as a chiral auxiliary

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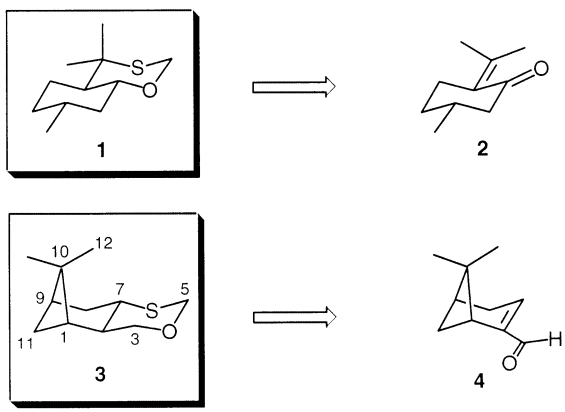
Abstract—The synthesis of novel oxathiane **3** and its acetyl derivative **12**, from commercially available (–)-myrtenal **4**, is described. The addition of several nucleophilic reagents to **12** furnished the corresponding tertiary carbinols in highly diastereomeric excess. The hydrolysis of **11a**, **b** yielded the expected α-hydroxycarbonyl compounds in excellent enantiomeric excess.

1. Introduction

Chiral 1,3-oxathiane derivatives have been widely used in the synthesis of chiral α-hydroxycarbonyl compounds[1a,b,c,d] with high enantiomeric excess (e.e.). Particularly, 1,3-oxathiane **1**, which was prepared[2a,b] from (*R*)-(+)-pulegone **2**, has proven to be a good chiral auxiliary for the enantioselective preparation of α-hydroxycarbonyl compounds[3a,b,c,d,e,f] and a useful chromatographic auxiliary in the synthesis of a prostaglandin precursor.[4] In addition, it has been used in the resolution of α-alkylcyclopentanones[5,6] and in the enantioselective synthesis of β-lactams[7] and β-amino alcohols.[8] Recently, a similar camphor-derived 1,3-oxathiane has been used in the enantioselective preparation of epoxides.[9] Interested in the potential of the 1,3-oxathiane ring to induce asymmetric nucleophilic additions, we decided to prepare oxathiane **3**, a structural analogue of compound **1**, starting from commercially available (–)-myrtenal **4**.



2. Results and discussion

The synthesis of oxathiane **3** was explored using a procedure similar to that described for the synthesis of oxathiane **1**.[2b] Thus, treatment of (–)-myrtenal **4** with benzylmercaptane and 10% aqueous NaOH in THF at room temperature gave adduct **5** (92% yield and 96% d.e.) after 18 h. Both hydrogenolysis of the benzylmercaptan and reduction of the carbonyl group to the corresponding mercaptoalcohol were initially attempted under Birch conditions with Na and liquid ammonia in anhydrous THF. While the carbonyl group was indeed reduced, 1,2-elimination of benzylmercaptan took place, giving myrtenol **6**. To overcome this problem, the aldehyde group in **5** was reduced to the corresponding alcohol with $LiAlH_4$ in ethyl ether, giving **7** in 96% yield, which, in turn, was hydrogenolyzed to mercaptoalcohol **8** under Birch reduction conditions (Scheme 1).

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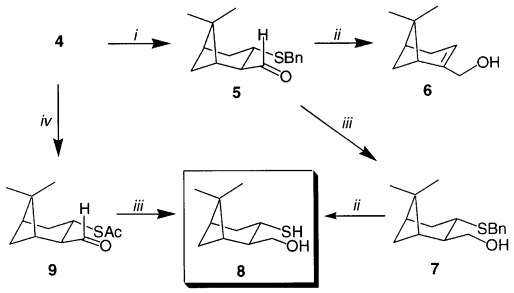
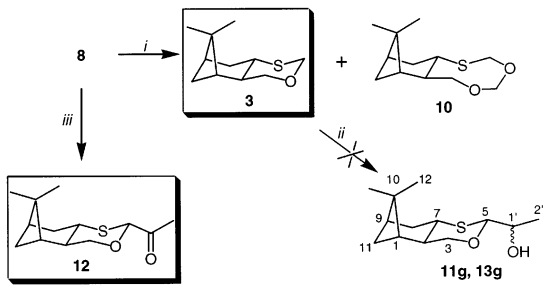


Scheme 1. (i) BnSH, THF, 10% aq. NaOH; (ii) NH_3, Na; (iii) $LiAlH_4$, Et_2O, −10°C; (iv) CH_3COSH, Py, 8°C, 10 h.

In some instances the hydrogenolysis reaction did not give satisfactory results, since small differences in reaction conditions drastically changed the course of the reaction, sometimes affording a complex mixture of uncharacterized compounds. In order to develop reproducible reaction conditions, thiolacetic acid was used as the nucleophile in the 1,4-addition to (−)-myrtenal **4** to give adduct **9** in 98% yield with >99% d.e. Compound **9** was subsequently treated with $LiAlH_4$ affording the hydroxythiol **8** in 95% yield. This procedure allowed us to carry out the reduction of the thioester group to the corresponding thiol using a one-pot procedure (instead of the complex C–S cleavage of the thiobenzyl group via hydrogenolysis) and the conversion of the aldehyde to the primary alcohol (Scheme 2).



Scheme 2. (i) $(HCHO)_n$, *p*-TsOH, C_6H_6; (ii) 1. *n*-BuLi, THF, 2. CH_3CHO; (iii) $CH_3COCH(OMe)_2$, *p*-TsOH, C_6H_6.

Hydroxythiol **8** was treated with paraformaldehyde in the presence of *p*-toluenesulfonic acid, to give oxathiane **3** and compound **10** in 35 and 6% yields, respectively. The latter was formed by condensation of two molecules of formaldehyde with hydroxythiol **8**. In order to verify the stereochemistry of the new stereogenic centers in oxathiane **3**, the vicinal coupling constant between H-2 and H-7 ($J = 10.2$ Hz) clearly reveals their relative *anti* relationship. In addition, a nOe difference experiment irradiating Me-12, produced enhancements of 10.5 and 2.5% for the H-7 and H-3*ax* signals, respectively, while H-2 remained unchanged. These data confirm that the absolute configuration is (*R*) at C(2) and (*S*) at C(7).

The condensation of acetaldehyde with the carbanion generated from oxathiane **3**, employing similar reaction conditions as described for oxathiane **1**,[2a] was attempted for the preparation of adduct **11g** and/or **13g**. This procedure failed, and all attempts to obtain deuterium exchange in the oxathiane methylene of **3** by quenching the expected carbanion with D_2O, gave a mixture of isotopically unexchanged starting material **3** and traces of decomposition products.

Since the preparation of **11g** and **13g** failed, a new synthetic strategy, starting from hydroxythiol **8**, was designed to obtain acetyloxathiane **12**. Thus, treatment of **8** with α,α-dimethoxyacetone gave oxathiane **12** in 32% yield, which was crystallized from chloroform–hexane yielding adequate crystals (mp 67–69°C) for X-ray crystallography.[10] The ORTEP drawing of oxathiane **3** (Fig. 1), clearly shows the *anti*-oriented relationship between H-2 and H-7 (H-2 and H-3 in Fig. 1) as a consequence of the *endo* approach of thiolacetic acid on myrtenal **4** because of the steric effect of Me-12 (Me-9 in Fig. 1). Another important structural feature in the solid state is the equatorial disposition of the acetyl group and the preferred *quasi*-coplanar conformation of the carbonyl group with sulfur atom, as revealed by the torsion angle S(1)–C(11)–C(12)–O(2) = 14.5(6)° (Fig. 1). The chair-like conformation of the oxathiane ring is also of note. In solution, the (*R*)-configuration at C(5) (C11 in Fig. 1) can also be determined by means

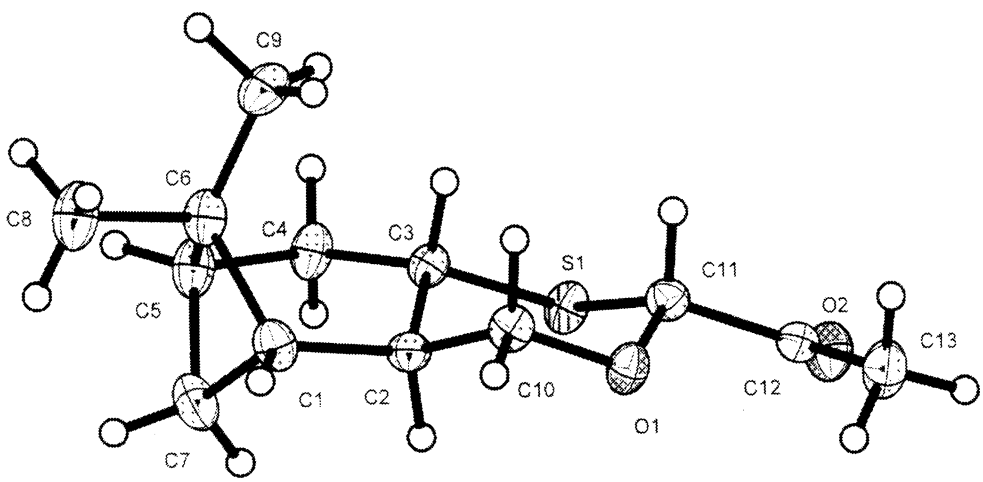
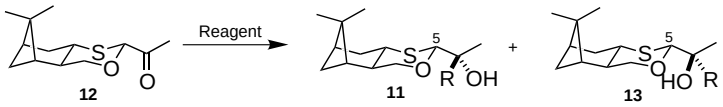


Figure 1. ORTEP drawing of acetyloxathiane **12**. The crystallographic numbering shown differs from the systematic numbering.

Table 1. Diastereoselective nucleophilic additions on acetyloxathiane **12**



Entry	Reagent	Comp. (%)	Ratio **11**:**13**[a]
1	PhMgBr	**11a** (92)	>99:<1
2	EtMgBr	**11b** (97)	>99:<1
3	*i*-PrMgBr	**11c** (93)	96:4
4	$PhCH_2MgBr$	**11d** (95)	95:5
5	*n*-BuLi	**11e** (60)	>99:<1
6	*sec*-BuLi	**11f** (53)	>99:<1
7	PhLi	**11a** (89)	>99:<1
8	LAH	**11g** (70)	71:29
9	DIBAL	**11g** (76)	80:20
10	LS-Selectride	**11g** (82)	>99:<1

[a] Determined by ^{1}H NMR integration of H-5, on the crude reaction mixture.

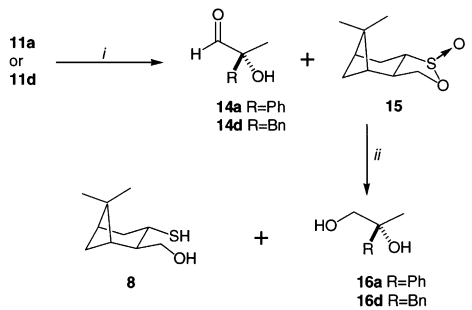
of a nOe difference experiment, since irradiation of H-5 gave signal enhancements of H-7 (6.4%) and H-3*ax* (3.6%).

1,2-Additions to acetyloxathiane **12** in THF with a number of nucleophiles, provided mainly oxathiane-carbinols **11** mixed with small amounts of **13**. The results, summarized in Table 1, show that in six of the ten cases[11] diastereoisomers **11** were formed almost exclusively.

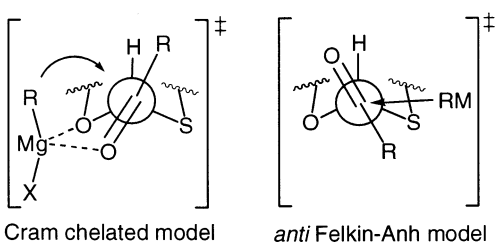
As can be seen, the addition of PhMgBr and PhLi gave the same diastereoisomer **11a** in alike d.r., and reduction with LS-Selectride produced the major diastereoisomer **11g** in higher d.r. than reactions using DIBAL-H and LAH. The major product obtained from the three hydride donors can be easily distinguished from the minor adduct by taking advantage of the coupling constant between H-5 and H-1′ (it being 3.3 and 6.9 Hz, respectively, in agreement with the predicted values derived from PCMODEL calculations).[12] The minimum energy found for both compounds is also in agreement with the corresponding hydrogen-bridged epimers, whose conformational analysis[13a,b] through H5-H1′ dihedral angles showed that the major compound is formed by hydride addition to the *Re* face of the carbonyl group.

In order to gain information about the approaching preference of the nucleophile to the carbonyl faces, cleavage of adducts **11a** and **11d** was undertaken to afford aldehydes **14a** and **14d** (R = Ph, $C_6H_5CH_2$, respectively), and presumably sultine **15**, since ^{1}H NMR spectra of the corresponding crude reaction mixture showed the aldehyde mixed with another compound displaying the characteristic spectral data expected for **15** (see Section 3). Because of the instability of the above aldehydes, the crude reaction mixtures were individually reduced with $LiAlH_4$ giving, after column chromatography, the corresponding diols (*R*)-(−)-**16a** (83%, >99% e.e.) and (*R*)-(−)-**16d** (74%, >99% e.e.), and unracemized hydroxythiol **8** (63–72%) (Scheme 3).

The absolute configuration of diols **16a** and **16d** indicates that the nucleophilic additions of Grignard and alkyllithium reagents proceed by attacking the *Re* face of the carbonyl group of acetyl oxathiane **12**. From these results, it could be concluded that the addition of Grignard reagents, and the reduction using LS-Selectride, can be rationalized in terms of the Cram chelation model, in a similar way as was explained for nucleophilic additions to oxathiane **1**.[14,15] It is assumed that the carbonyl–sulfur coplanarity observed in solid state (Fig. 1) is lost in solution in order to form the Cram chelated model when Grignard reagents and LS-Selectride are used. The major compounds obtained with the less chelating DIBAL, LAH and alkyllithium reagents, could in turn be rationalized via the *anti* Felkin-Anh model (L = O).[16] It is worth mentioning that the 2-acetyl derivative of **1** provides reversal in stereoselectivity by using DIBAL as compared with LS-Selectride and LAH, while in our case the three hydride donors gave the same stereoinduction. Small differences in steric requirements between the two chiral auxiliaries may account for these changes.[17]



Scheme 3. (i) $AgNO_3$, NCS, CH_3CN:H_2O 4:1; (ii) $LiAlH_4$, Et_2O.



3. Experimental

3.1. General

Melting points were determined on an Electrothermal capillary melting points apparatus and are uncorrected. Infrared spectra were recorded on a Perkin–Elmer 599B spectrometer. ^{1}H and ^{13}C NMR spectra were obtained on Varian Gemini and Mercury spectrometers at 300 and 75.4 MHz, respectively, using $CDCl_3$ as solvent and TMS as internal standard. ^{1}H and ^{13}C NMR data were assigned according to the numbering of compounds **5** (bicyclic series) and **11g** (tricyclic series) in Schemes 1 and 2, respectively. The mass spectra (MS) were recorded on a Hewlett–Packard 5971A GC/Selective Mass Detector at 70 eV. Microanalyses were performed by the M-H-W Laboratories, Phoenix, AZ, USA. Thin-layer chromatograms were carried out using precoated TLC sheets of silica gel 60 F_{254} (E. Merck). Flash chromatography was carried out using Merck silica gel (230–400 mesh). The purification of the oxathianecarbinols **11a–g** was performed on a Biotage Flash 40 apparatus using Flash 40S 4.0×7.0 cm prepacked cartridges. THF used in the nucleophilic additions was distilled from Na immediately prior to use and all other reagents were used without further purification. Optical rotations were measured at 589 nm using a 1 dm cell on a Jasco DIP–370 polarimeter. X-Ray data were collected on a Bruker AXS D8-APEX difractometer equipped with CCD. Molecular Modeling Calculations: minimum energy structures were generated using the MMX force-field as implemented in the PCMODEL molecular modeling program V6 (Serena Software, Box 3076, Bloomington, IN 47402-3076).

3.2. (1*S*,2*R*,3*S*)-2-Formyl-6,6-dimethyl-3-thiobenzyl-bicyclo[3.1.1]heptane 5

A mixture containing (−)-myrtenal **4** (4.96 g, 33 mmol), benzylmercaptan (8.6 mL, 8.18 g, 66 mmol) and 10% aq. NaOH (5 mL) in THF (5 mL), was stirred at room temperature under an N_2 atmosphere for 20 h. The reaction was extracted with cold EtOAc, washed successively with 15% aq. NaOH (5×40 mL) and water (3×40 mL), dried over anhydrous Na_2SO_4, and concentrated to dryness. The residue was subjected to fractional distillation on a Kugelrohr apparatus and the portion collected at 130–132°C/5 Torr gave **5** as a colorless oil (9.0 g, 92% yield, 96% d.e.). ^{1}H NMR ($CDCl_3$): δ 9.60 (s, 1H, H-10), 7.38–7.22 (m, 5H, Ar), 3.78 and 3.74 (AB system, 2H, J=13 Hz, H11a and H11b), 3.70 (ddd, 1H, J=10.1, 5.7, 5.4 Hz, H-3), 2.81 (dd, 1H, J=5.4, 2.8 Hz, H-2), 2.55 (m, 1H, H-1), 2.47 (m, 1H, H-4eq), 2.42 (m, 1H, H-7eq), 1.98 (m, 1H, H-4ax), 1.95 (m, 1H, H-5), 1.42 (d, 1H, J=10 Hz, H-7ax), 1.20 (s, 3H, Me-9), 0.65 (s, 3H, Me-8). ^{13}C NMR ($CDCl_3$): δ 203.0 (C-10), 138.1 (C-1′), 128.5 (C-6′ and C-2′), 128.5 (C-5′ and C-3′), 127.0 (C-4′), 62.0 (C-2), 42.4 (C-1), 41.1 (C-5), 38.3 (C-6), 36.6 (CH_2Ar), 35.5 (C-4), 30.8 (C-3), 30.1 (C-7), 26.5 (C-9), 23.0 (C-8). IR ($CHCl_3$) 3040, 2850, 1710, 1435, 1270, 840, 810 cm^{-1}.

3.3. (1*S*,2*R*,3*S*)-2-Hydroxymethyl-6,6-dimethyl-3-thiobenzyl-bicyclo[3.1.1]heptane 7

To a well-stirred suspension of $LiAlH_4$ (1.0 g, 26.3 mmol) in dry ethyl ether (15 mL) were added dropwise **5** (5 g, 18.2 mmol) in dry ethyl ether (25 mL) and the mixture stirred under reflux under an N_2 atmosphere for 40 min. The reaction mixture was cooled (0°C), diluted with ethyl ether (100 mL), quenched by careful addition of ethanol, ice and 10% aq. HCl, and stirred until formation of a white precipitate. After filtration, the organic layer was washed with brine (3×40 mL), dried over anhydrous Na_2SO_4 and evaporated to dryness. The residue was flash chromatographed using a mixture of hexane–EtOAc (19:1), giving **7** as a colorless oil (4.82 g, 96%). ^{1}H NMR ($CDCl_3$): δ 7.36–7.17 (m, 5H, Ar), 3.77 and 3.74 (AB system, J=13 Hz, 2H, CH_2-Ph), 3.58 (dd, 1H, J=9.1, 7.8 Hz, H-10a), 3.46 (t, 1H, J=9.1 Hz, H-10b), 2.78 (ddd, 1H, J=9.4, 7.6, 5.7 Hz, H-3), 2.45 (m, 1H, H-4eq), 2.41 (m, 1H, H-7eq), 2.25 (s, 1H, OH), 2.12 (m, 1H, H-4ax), 2.07 (m, 1H, H-1), 2.04 (m, 1H, H-2), 1.95 (m, 1H, H-5), 1.18 (s, 3H, Me-9), 1.09 (d, 1H, J=9.9 Hz, H-7ax), 0.85 (s, 3H, Me-8). ^{13}C NMR ($CDCl_3$): δ 139.2 (C-1′), 128.7(C-2′ and C-6′), 128.5 (C-3′ and C-5′), 127.0 (C-4′), 66.7 (C-10), 52.0 (C-2), 43.2 (C-1), 42.0 (C-5), 38.4 (C-6), 37.7 (C-4), 36.3 (C-3), 35.8 (CH_2-Ph), 33.0 (C-7), 27.5 (C-9), 23.3 (C-8). EM m/z (rel. int.): 276 (M^+, 8), 245 (1), 207 (7), 185 (14), 143 (8) 135 (9), 121 (7), 91 (100), 79 (20), 65 (20), 55(6).

3.4. (1*S*,2*R*,3*S*)-2-Hydroxymethyl-6,6-dimethyl-3-mercapto-bicyclo[3.1.1]heptane 8

Compound **8** was prepared by the following two procedures.

Method (a): A solution of **9** (23.6 g, 0.104 mol) in anhydrous ethyl ether (20 mL) was added dropwise to a well-stirred cooled (−5°C) suspension of $LiAlH_4$ (7.92 g, 0.208 mol) in dry ethyl ether (100 mL), and the resulting mixture was stirred for 1.5 h under an N_2 atmosphere. After dropwise addition of EtOH (2 mL), the reaction mixture was stirred for a further 20 min at the above temperature, then stirred in the presence of ice (5 g) and 7% aq. HCl (50 mL) at 5°C until formation of a white emulsion. The organic layer was separated, washed with water until pH 7, dried over anhydrous Na_2SO_4 and evaporated to dryness, yielding hydroxythiol **8** as white needles mp 46°C (18.5 g, 95%).

Method (b): According to the procedure described by Eliel et al.,[1c] a solution of **7** (1 g, 3.62 mmol) in anhydrous ethyl ether (4 mL) was treated with a solution of Na (260 mg, 11.39 mmol) and liquid NH_3 (7 mL). The oily residue obtained after workup was flash chromatographed using a mixture of hexane–EtOAc (19:1) as the eluent, giving **8** (490 mg, 72%) mp 46°C. $[\alpha]^{23}$=+76.5 (c=0.5, EtOH). ^{1}H NMR ($CDCl_3$): δ 3.75 (dd, 1H, J=10.6, 7.1 Hz, H-10a), 3.60 (dd, 1H, J=

10.6, 7.8 Hz, H-10b), 3.20 (dq, 1H, $J=8.4$, 7.3 Hz, H-3), 2.65 (br s, 1H, OH), 2.61 (m, 1H, H-4eq), 2.45 (m, 1H, H-7eq), 2.27 (dddd, 1H, $J=7.8$, 7.3, 7.1, 1.9 Hz, H-2), 2.25 (d, 1H, $J=7.1$ Hz, SH), 2.08 (td, 1H, $J=5.9$, 1.9 Hz, H-1), 1.96 (m, 1H, H-5), 1.93 (m, 1H, H-4ax), 1.22 (s, 3H, Me-9), 1.12 (d, 1H, $J=10.3$ Hz, H-7ax), 0.97 (s, 3H, Me-8). ^{13}C NMR ($CDCl_3$): δ 66.3 (C-10), 57.1 (C-2), 43.7 (C-1), 42.3 (C-5), 40.4 (C-4), 38.0 (C-6), 33.8 (C-7), 32.1 (C-3), 27.6 (C-9), 23.4 (C-8). IR ($CHCl_3$) 3486, 2922, 2574, 1074 cm^{-1}. MS m/z (rel. int.) 186 (M^+, 0.5), 171 (6), 155 (9), 145 (13), 121 (18), 99 (20), 85 (25), 82 (100), 67 (25), 55 (27). Anal. calcd for $C_{10}H_{18}OS$: C, 64.47; H, 9.74; S, 17.21. Found: C, 64.55; H, 9.49; S, 17.38%.

3.5. (1*S*,2*R*,3*S*)-2-Formyl-6,6-dimethyl-3-thioacetylbicyclo[3.1.1]heptane 9

A cold (−5°C) solution of (−)-myrtenal **4** (15.7 g, 0.1 mol) in thiolacetic acid (15.9 g, 0.21 mol) and pyridine (1 mL) was stirred for 5 h. The reaction mixture was diluted with CH_2Cl_2 (650 mL), washed successively with saturated aqueous $NaHCO_3$ (3×250 mL), 10% aq. HCl (3×250 mL) and brine (2×250 mL). The organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to leave pure **9** as a yellowish syrup (23.58 g, 98% yield, 99% d.e.). $[\alpha]^{23}=-4.4$ ($c=0.52$, EtOH). ^{1}H NMR ($CDCl_3$): δ 9.83 (s, 1H, H-10′), 4.43 (ddd, 1H, $J=10.3$, 5.3, 4.1 Hz, H-3), 2.80 (dd, 1H, $J=5.3$, 2.9 Hz, H-2), 2.70 (m, 1H, H-4eq), 2.56 (m, 1H, H-5), 2.45 (m, 1H, H-7eq), 2.31 (s, 3H, $COCH_3$), 1.98 (m, 1H, H-1), 1.95 (m, 1H, H-4ax), 1.28 (d, 1H, $J=10.3$ Hz, H-7ax), 1.22 (s, 3H, Me-9), 0.79 (s, 3H, Me-8). ^{13}C NMR ($CDCl_3$): δ 203.0 (C-10), 195.5 (C-11), 60.7 (C-2), 43.2 (C-5), 40.7 (C-1), 38.0 (C-6), 35.1 (C-4), 30.8 (C-3), 30.0 (C-7), 30.0 (C-12), 26.2 (C-9), 23.8 (C-8). IR ($CHCl_3$): 2938, 1723, 1683, 1457 cm^{-1}. MS m/z: 226 (M^+), 183, 151, 107, 95, 53. Anal. calcd for $C_{12}H_{18}O_2S$: C, 63.68; H, 8.02; S, 14.17. Found: C, 63.82; H, 7.92; S; 13.98%.

3.6. (1*S*,2*R*,7*S*)-10,10-Dimethyl-4-oxa-6-thia-tricyclo-[7.1.1.0^{2,7}]undecane 3

A solution containing **8** (1.0 g, 5.3 mmol), paraformaldehyde (186 mg, 6.2 mmol) and *p*-TsOH (6.5 mg, 0.0377 mmol) in toluene (2 mL) was heated under reflux under an N_2 atmosphere for 4 h in a round bottom flask equipped with a Dean–Stark trap. The solvent was eliminated under reduced pressure, the residue was diluted with hexane, washed with brine, dried over anhydrous Na_2SO_4 and evaporated to dryness. The residue was flash chromatographed using a mixture of hexane–EtOAc (19:1), giving initially **3** as a colorless oil (373 mg, 35%) ^{1}H NMR ($CDCl_3$): δ 4.96 and 4.94 (AB system, $J=12$ Hz, 2H, H-5a and H-5b), 3.96 (dd, 1H, $J=11.0$, 3.2 Hz, H-3eq), 3.73 (dt, 1H, $J=10.2$, 8.8 Hz, H-7), 3.60 (t, 1H, $J=11.0$ Hz, H-3ax), 2.60 (m, 1H, H-11eq), 2.51 (ddd, 1H, $J=11.0$, 10.2, 3.1 Hz, H-2), 2.36 (dddd, 1H, $J=13.3$, 8.8, 4.6, 2.0 Hz, H-8eq), 2.11 (qd, 1H, $J=6.0$, 1.5 Hz, H-9), 1.78 (t, 1H, $J=6.0$ Hz, H-1), 1.73 (ddd, 1H, $J=13.3$, 10.2, 1.5 Hz, H-8ax), 1.27 (s, 3H, Me-13), 1.17 (s, 3H, Me-12), 1.03 (d, 1H, $J=9.7$ Hz, H-11ax). ^{13}C NMR ($CDCl_3$): δ 76.6 (C-3), 74.0 (C-5), 52.5 (C-2), 46.2 (C-9), 43.5 (C-1), 42.1 (C-7), 39.6 (C-11), 39.1 (C-10), 33.6 (C-8), 29.6 (C-13), 24.5 (C-12). IR ($CHCl_3$): 2920, 1457, 1064, 835 cm^{-1}. MS m/z (rel. int.): 198 (M^+, 25), 183 (1), 168 (7), 142 (13), 129 (39), 111 (23), 99 (66), 91 (100), 79 (93), 67 (90), 53 (49).

3.7. (1*S*,2*R*,7*S*)-12,12-Dimethyl-4,6-dioxa-8-thia-tricyclo[9.1.1.0^{2,9}]tridecane 10

The latter fractions of the chromatography of the above product gave **10** (77 mg, 6%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 5.16 (d, 1H, $J=11.8$ Hz, OCHaS), 4.81 (d, 1H, $J=6.5$ Hz, OCHaO), 4.80 (d, 1H, $J=11.8$ Hz, OCHbS), 4.68 (d, 1H, $J=6.5$ Hz, OCHbO), 3.77 (t, 1H, $J=12.3$ Hz, H-3eq), 3.70 (dt, 1H, $J=10.5$, 5.5 Hz, H-7), 3.44 (dd, 1H, $J=12.3$, 6.7 Hz, H-3ax), 3.12 (dddd, 1H, $J=12.3$, 6.7, 5.5, 2.2 Hz, H-2), 2.54 (m, 1H, H-8eq), 2.34 (m, 1H, H-11eq), 1.95 (m, 1H, H-9), 1.74 (m, 1H, H-1), 1.70 (m, 1H, H-8ax), 1.20 (s, 3H, Me-13), 1.18 (d, 1H, $J=11.0$ Hz, H-11ax), 1.01 (s, 3H, Me-12). ^{13}C NMR ($CDCl_3$): δ 96.0 (O-$\underline{C}H_2$-O), 73.9 (C-3), 71.4 (O-$\underline{C}H_2$-S), 53.4 (C-2), 41.5 (C-9), 38.5 (C-11), 36.2 (C-10), 34.5 (C-6), 31.9 (C-8), 27.3 (C-13), 23.3 (C-12). MS m/z: 228 (M^+, 2), 198 (0.5), 183 (1), 168 (2), 152 (3), 134 (5), 129 (14), 113 (11), 99 (55), 82 (100), 67 (79), 53 (43).

3.8. (1*S*,2*R*,5*R*,7*S*)-5-Acetyl-10,10-dimethyl-4-oxa-6-thia-tricyclo[7.1.1.0^{2,7}]undecane 12

A solution of **8** (6.1 g, 32.8 mmol), α,α-dimethoxyacetone (4.1 g, 34.7 mmol) and *p*-TsOH 0.614 g, 3.22 mmol) in benzene (75 mL) was stirred at room temperature for 45 min. The reaction mixture was poured into cold saturated aqueous $NaHCO_3$, extracted with ethyl ether, washed with saturated aqueous $NaHCO_3$ (2×50 mL), dried over anhydrous Na_2SO_4 and evaporated to dryness. The residue was dissolved in toluene (100 mL) and *p*-TsOH (300 mg) were added. After heating the mixture under reflux for 10 min, the reaction mixture was cooled, diluted with ethyl ether (500 mL) and saturated aqueous $NaHCO_3$ (50 mL) were added. The organic layer was washed with a saturated soln of $NaHCO_3$ (2×200 mL), dried over anhydrous Na_2SO_4 and evaporated to dryness. The oily residue was purified through a Chromatoflash system using a mixture of hexane:EtOAc (10:1) as the eluent, obtaining the acetyloxathiane **12** as a white solid (2.5 g, 31%) (mp 41°C). $[\alpha]^{22}=+52.3$ ($c=0.2$, EtOH). ^{1}H NMR ($CDCl_3$): δ 5.49 (1H, s, H-5), 4.11 (dd, 1H, $J=12.0$, 3.1 Hz, H-3*eq*), 3.81 (q, 1H, $J=11.6$ Hz, H-7), 3.65 (t, 1H, $J=12.0$ Hz, H-3ax), 2.52 (m, 1H, H-11eq), 2. 48 (m, 1H, H-2), 2.33 (m, 1H, H-8eq), 2.28 (s, 3H, Me-2′), 2.14 (m, 1H, H-9), 1.85 (t, 1H, $J=6.0$ Hz, H-1), 1.77 (ddd, 1H, $J=11.6$, 2.7, 1.2 Hz, H-8ax), 1.28 (s, 3H, Me-13), 1.16 (s, 3H, Me-12), 1.02 (d, 1H, $J=9.5$ Hz, H-11ax). ^{13}C NMR ($CDCl_3$): δ 202.1 (C-1′), 88.7 (C-5), 76.0 (C-3), 51.0 (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), 29.5 (C-13), 25.7 (C-2′), 24.5 (C-12). IR ($CHCl_3$) 2993, 2922, 1722, 1455, 1357, 1226 cm^{-1}. MS m/z (rel. int.) 240 (M^+, 4), 197 (100),

135 (20), 107 (40), 93 (65), 79 (65), 69 (30), 55 (15). Anal. calcd for $C_{13}H_{20}O_2S$: C, 64.96; H, 8.39. Found: C, 64.96; H, 8.35%.

3.9. (1*S*,2*R*,5*R*,7*S*)-5-[(*R*)-1′-Hydroxy-1′-phenyl-1′-ethyl)]-10,10-dimethyl-4-oxa-6-thia-tricyclo[7.1.1.0^{2,7}]-undecane 11a

This compound was obtained using the following two procedures.

Method (a): To a well-stirred cooled (−78°C) solution of **12** (158.3 mg, 0.65 mmol) in anhydrous THF (10 mL) under an N_2 atmosphere, a solution of phenylmagnesium bromide (239.2 mg, 1.31 mmol) in diethyl ether (0.43 mL) was added dropwise. After stirring for 4 h at the same temperature, the reaction mixture was allowed to warm to room temperature and the mixture stirred for a further 1 h. The reaction mixture was quenched with saturated aqueous ammonium chloride (10 mL), the THF was evaporated and the remaining emulsion was extracted with ethyl ether. The organic layer was washed with saturated aqueous ammonium chloride, dried over anhydrous Na_2SO_4 and concentrated to dryness giving pure diastereoisomer **11a** as a colorless oil (193.5 mg, 92%).

Method (b): A well-stirred cooled (−78°C) solution of acetyloxathiane **12** (24 mg, 0.1 mmol) in anhydrous THF (2 mL) was treated with PhLi in cyclohexane (0.15 mmol) and stirred under an N_2 atmosphere for 2 h. The mixture was quenched with saturated soln of ammonium chloride (1 mL) and allowed to warm to room temperature. THF was evaporated and the residue extracted with ethyl ether (50 mL). The organic layer was washed with 5% aq. HCl (3×30 mL) and brine (1×30 mL), dried over anhydrous Na_2SO_4 and evaporated to dryness. The crude reaction outcome was purified through a Chromatotron system using a mixture of hexane:EtOAc (19:1) as the eluent to give **11a** as a colorless oil (28 mg, 89%). $[\alpha]^{21} = -58.9$ ($c = 0.34$, EtOH). ^{1}H NMR ($CDCl_3$): δ 7.48–7.21 (m, 5H, Ar-H), 5.01 (s, 1H, H-5), 3.98 (dd, 1H, $J = 10.6$, 2.8 Hz, H-3eq), 3.57 (q, 1H, $J = 11.0$ Hz, H-7), 3.55 (t, 1H, $J = 10.6$ Hz, H-3ax), 3.04 (br s, 1H, OH), 2.53 (m, 1H, H-11eq), 2.36 (td, 1H, $J = 10.6$, 3.4 Hz, H-2), 2.22 (m, 1H, H-8eq), 2.05 (dd, 1H, $J = 7.5$, 1.5 Hz, H-9), 1.77 (t, 1H, $J = 5.9$ Hz, H-1), 1.62 (m, 1H, H-8ax), 1.61 (s, 3H, Me-2′), 1.21 (s, 3H, Me-13), 1.08 (s, 3H, Me-12), 0.99 (d, 1H, $J = 9.7$ Hz, H-11ax). ^{13}C NMR ($CDCl_3$): δ 144.2 (C-*ipso*), 128.0 (2 C-*orto*), 127.4 (C-*para*), 125.7 (2 C-*meta*), 93.7 (C-5), 77.2 (C-1′), 75.9 (C-3), 51.4 (C-2), 45.6 (C-1), 43.4 (C-9), 41.1 (C-7), 39.4 (C-11), 39.0 (C-10), 33.4 (C-8), 29.6 (C-13), 24.7 (C-12), 24.4 (C-2′). IR ($CHCl_3$) 3953, 2921, 1449, 1369, 1057, 760, 699 cm^{-1}. MS m/z (rel. int.) 318 (M$^+$, 6), 303 (12), 241 (22), 197 (100), 135 (20), 107 (40), 93 (65), 79 (65), 69 (30), 55 (15). Anal. calcd for $C_{19}H_{26}O_2S$: C, 71.66; H, 8.23; S, 10.05. Found: C, 71.59; H, 7.95; S, 9.93%.

3.10. (1*S*,2*R*,5*R*,7*S*)-5-[(R)-2′-Hydroxy-2′-butyl)]-10,10-dimethyl-4-oxa-6-thiatricyclo[7.1.1.0^{2,7}]undecane 11b

Following the procedure (**a**) for the preparation of **11a**, compound **12** (169 mg, 0.7 mmol) in anhydrous THF (5 mL) was treated with ethylmagnesium bromide (187.7 mg, 1.4 mmol) in ethyl ether (0.47 mL). After workup pure **11b** was obtained as a single diastereoisomer (colorless oil; 184.4 mg, 97%). $[\alpha]^{23} = -12.6$ ($c = 0.45$, EtOH). ^{1}H NMR ($CDCl_3$): δ 4.82 (s, 1H, H-5), 4.06 (dd, 1H, $J = 10.9$, 3.2 Hz, H-3eq), 3.70 (td, 1H, $J = 10.4$, 8.6 Hz, H-7), 3.62 (t, 1H, $J = 10.9$ Hz, H-3*ax*), 2.58 (dddd, 1H, $J = 9.6$, 8.0, 6.2, 1.8 Hz, H-11eq), 2.40 (br s, 1H, OH), 2.39 (dddd, 1H, $J = 10.9$, 10.4, 8.1, 3.2 Hz, H-2), 2.35 (dddd, 1H $J = 10.5$, 9.2, 8.6, 1.8 Hz, H-8eq), 2.12 (ddd, 1H, $J = 10.5$, 6.2, 1.4 Hz, H-9), 1.82 (t, 1H, $J = 8.0$ Hz, H-1), 1.75 (ddd, 1H, $J = 10.4$, 9.2, 1.4 Hz, H-8ax), 1.60 (m, 2H, CH_2-3′), 1.27 (s, 3H, Me-13), 1.23 (s, 3H, Me-1′), 1.15 (s, 3H, Me-12), 1.02 (d, 1H, $J = 9.6$ Hz, H-11ax), 0.95 (t, 3H, $J = 7.5$ Hz, Me-4′). ^{13}C NMR ($CDCl_3$): δ 92.7 (C-5), 76.4 (C-3), 74.3 (C-2′), 51.7 (C-2), 45.7 (C-1), 43.3 (C-9), 41.1 (C-7), 39.5 (C-11), 39.0 (C-10), 33.6 (C-8), 31.3 (C-3′), 29.6 (C-13), 24.5 (C-12), 22.6 (C-1′), 7.7 (C-4′). IR (CH_2Cl_2): 3467, 2911, 1456, 1063, 1045, 733 cm^{-1}. MS m/z (rel. int.): 270 (M$^+$, 5), 255 (8), 241 (10), 197 (100), 135 (30), 107 (42), 93 (65), 79 (62), 69 (20), 55 (15). Anal. calcd for $C_{15}H_{26}O_2S$: C, 66.62; H, 9.69; S, 11.86. Found: C, 66.64; H, 9.54; S, 11.53%.

3.11. (1*S*,2*R*,5*R*,7*S*)-5-[(*R*)-2′-Hydroxy-3′-methyl-2′-butyl)]-10,10-dimethyl-4-oxa-6-thia-tricyclo[7.1.1.0^{2,7}]-undecane 11c

Following procedure (**a**) for the preparation of **11a**, compound **12** (109 mg (0.45 mmol) in anhydrous THF (4 mL) was treated with *iso*-propylmagnesium chloride (93.6 mg, 0.91 mmol) in ethyl ether (0.53 mL). After workup pure **11c** were obtained as a single diastereoisomer (colorless oil; 120 mg, 93%). $[\alpha]^{23} = -29.1$ ($c = 0.13$, EtOH). ^{1}H NMR ($CDCl_3$): δ 4.93 (s, 1H, H-5). 4.06 (dd, 1H, $J = 10.6$, 2.8 Hz, H-3eq), 3.57 (dd, 1H, $J = 10.6$, 8.6 Hz, H-7), 3.55 (t, 1H, $J = 10.6$ Hz, H-3ax), 2.60 (m, 1H, H-11eq), 2.36 (td, 1H, $J = 10.6$, 3.4 Hz, H-2), 2.18 (s, 1H, OH), 2.13 (m, 1H, H-9), 1.93 (hep, 1H, $J = 6.9$ Hz, H-3′), 1.81 (t, 1H, $J = 5.8$ Hz, H-1), 1.75 (m, 1H, H-8ax), 1.27 (s, 3H, Me-13), 1.17 (s, 3H, Me-1′), 1.15 (s, 3H, Me-12), 1.02 (d, 1H, $J = 9.7$ Hz, H-11ax), 0.98 (d, 3H, $J = 6.9$ Hz, Me-4′), 0.93 (d, 3H, $J = 6.9$ Hz, Me-5′). ^{13}C NMR ($CDCl_3$): δ 92.2 (C-5), 77.2 (C-3), 76.2 (C-2′), 51.9 (C-2), 45.9 (C-1) 43.5 (C-9), 41.1 (C-7), 39.5 (C-11), 39.1 (C-10), 33.9 (C-3′), 33.7 (C-8), 29.7 (C-13), 24.6 (C-1′), 19.6 (C-12), 17.5 and 16.7 (*i*-Pr Me's). IR (CH_2Cl_2) 3515, 2918, 1486, 1419, 1356, 1233, 1135, 1064, 735 cm^{-1}. MS m/z (rel. int.): 284 (M$^+$, 13), 269 (8), 241 (10), 197 (100), 135 (25), 93 (40), 79 (35), 55 (9). Anal. calcd for $C_{16}H_{28}O_2S$: C, 67.56; H, 9.92; S, 11.27. Found: C, 67.29; H, 9.94; S, 11.43.

3.12. (1*S*,2*R*,5*R*,7*S*)-5-[(*R*)-2′-Hydroxy-1′-phenyl-2′-propyl]-10,10-dimethyl-4-oxa-6-thia-tricyclo-[7.1.1.02,7]undecane 11d

Following procedure (**a**) for the preparation of **11a**, acetyloxathiane **12** (124 mg, 0.5 mmol) in THF (5 mL) was treated with benzylmagnesium chloride (233 mg, 1.5 mmol) in ethyl ether (1.54 mL). After usual workup and separation through a Chromatoflash system using a mixture of hexane:EtOAc (10:1) as the eluent were obtained **11d** (165 mg, 95%) and **13d** (9 mg, 5%) as colorless oils. Compound **11d** shows: $[\alpha]^{23}=-46.5$ ($c=0.6$, EtOH). ^{1}H NMR ($CDCl_3$): δ 7.25 (m, 5-H, Ar), 4.87 (s, 1H, H-5), 3.95 (dd, 1H, $J=10.6$, 3.5 Hz, H-3eq), 3.61 (dd, 1H, $J=10.5$, 8.6 Hz, H-7), 3.59 (t, 1H, $J=10.6$ Hz, H-3ax), 3.11 (s, 1H, OH), 2.91 and 2.85 (AB system, $J=13.5$ Hz, 2H, CH_2-1′), 2.6 (m, 1H, H-11eq), 2.4 (tdd, 1H, $J=10.6$, 5.9, 3.5 Hz, H-2), 2.29 (m, 1H, H-8eq), 2.01 (dd, 1H, $J=7.5$, 3.4 Hz, H-9), 1.78 (t, 1H, $J=5.9$ Hz, H-1), 1.66 (m, 1H, H-8ax), 1.59 (s, 3H, Me-3′), 1.26 (s, 3H, Me-13), 1.05 (s, 3H, Me-12), 0.95 (d, 1H, $J=9.5$ Hz, H-11ax). ^{13}C NMR ($CDCl_3$): δ 137.5 (C-*ipso*), 130.8 (C-*meta*), 128.0 (C-*para*), 126.3 (C-*orto*), 92.9 (C-5), 76.8 (C-3), 75.9 (C-2′), 51.4 (C-2), 45.6 (C-1), 43.4 (C-9), 41.1 (C-7), 39.4 (C-11), 39.1 (C-1′), 39.0 (C-10), 33.4 (C-8), 29.6 (C-13), 24.7 (C-12), 24.4 (C-3′). IR (CH_2Cl_2) 3952, 2920, 1648, 1449, 1369, 1056, 759, 699 cm^{-1}. MS m/z (rel. int.): 332 (M^+, 8), 317 (8), 241 (11), 197 (100), 135 (24), 115 (8), 93 (42), 79 (40), 55 (12). Anal. calcd for $C_{20}H_{28}O_2S$: C, 72.28; H, 8.43; S, 9.66. Found: C, 72.43; H, 8.49; S, 9.63%.

3.13. (1*S*,2*R*,5*R*,7*S*)-5-[(*R*)-2′-Hydroxy-3′-methyl-2′-pentyl)]-10,10-dimethyl-4-oxa-6-thia-tricyclo-[7.1.1.0^{2,7}]undecane 11e

Carbinol **11e** was obtained similarly as **11a**, following procedure **(b)** by addition of *n*-BuLi (66 mg, 1.02 mmol) in hexane to **12** (124 mg, 0.52 mmol) in anhydrous THF (5 mL). After separation by flash chromatography using hexane:EtOAc (99:5), **11e** was obtained as a colorless oil (92 mg, 60%). $[\alpha]^{23}=-4.8$ ($c=0.45$, EtOH). ^{1}H NMR ($CDCl_3$): δ 4.82 (s, 1H, H-5), 4.05 (dd, 1H, $J=10.9$, 3.2 Hz, H-3eq), 3.69 (td, 1H, $J=10.4$, 8.6 Hz, H-7), 3.62 (t, 1H, $J=10.9$ Hz, H-3ax), 2.59 (dddd, 1H, $J=9.6$, 8.0, 6.2, 1.8 Hz, H-11eq), 2.40 (dddd, 1H, $J=10.9$, 10.4, 8.1, 3.2 Hz, H-2), 2.34 (dddd, 1H, $J=10.5$, 9.2, 8.6, 1.8 Hz, H-8eq), 2.11 (ddd, 1H, $J=10.5$, 6.2, 1.4 Hz, H-9), 1.76 (t, 1H, $J=8.1$ Hz, H-1), 1.75 (ddd, 1H, $J=10.4$, 9.2, 1.4 Hz, H-8ax), 1.55 (m, 2H, CH_2-5′), 1.32 (m, 4H, CH_2's 3′ and 4′), 127 (s, 3H, Me-1′), 1.24 (s, 3H, Me-13), 1.15 (s, 3H, Me-12), 1.02 (d, 1H, $J=9.6$ Hz, H-11ax), 0.95 (t, 3H, $J=7.5$ Hz, Me-6′). ^{13}C NMR ($CDCl_3$): δ 92.7 (C-5), 76.3 (C-3), 74.5 (C-2′), 51.7 (C-2), 45.7 (C-1), 43.3 (C-9), 41.1 (C-7), 39.5 (C-9), 39.1 (C-10), 33.6 (C-3′), 31.3 (C-8), 29.6 (C-13), 24.5 (C-12), 23.1 and 23.1 (C-4′ and C-5′) 22.6 (Me-10), 7.7 (Me-6′). MS m/z (rel. int.): 283 (M^+-15, 2), 241 (8), 197 (100), 135 (24), 115 (8), 93 (42), 79 (40), 69 (18), 55 (12). Anal. calcd for $C_{17}H_{30}O_2S$: C, 68.41; H, 10.13; S, 10.74. Found: C, 68.57; H, 9.95; S, 10.66.

3.14. (1*S*,2*R*,5*R*,7*S*)-5-[(2′*R*,3′*S**)-2′-Hydroxy-3′-methyl-2′-pentyl)]-10,10-dimethyl-4-oxa-6-thia-tricyclo-[7.1.1.0^{2,7}]undecane 11f

Carbinol **11f** was obtained similarly as **11a** following procedure **(b)** by addition of *sec*-BuLi (53 mg, 0.82 mmol) in hexane (0.41 mL) to **12** (99 mg, 0.412 mmol) in anhydrous THF (5 mL). After separation by flash chromatography using hexane:EtOAc (19:1), **11e** was obtained as a colorless oil (66 mg, 53%). ^{1}H NMR ($CDCl_3$): δ 4.82 (s, 1H, H-5), 4.76 (s, 1H, H-5 *epimer*), 4.05 (dd, 2H, $J=10.9$, 3.2 Hz, H-3eq), 3.73 (td, 1H, $J=10.4$, 8.6 Hz, H-7), 3.65 (t, 1H, $J=10.9$ Hz, H-3ax), 2.62 (dddd, 1H, $J=9.6$, 8.0, 6.2, 1.8 Hz, H-11eq), 2.44 (dddd, 1H, $J=10.9$, 10.4, 8.1, 3.2 Hz, H-2), 2.36 (dddd, 1H $J=10.5$, 9.2, 8.6, 1.8 Hz, H-8eq), 2.14 (ddd, 1H, $J=10.5$, 6.2, 1.4 Hz, H-9), 1.82 (t, 1H, $J=8.1$ Hz, H-1), 1.78 (ddd, 1H, $J=10.4$, 9.2, 1.4 Hz, H-8ax), 1.51 (m, 1H, H-3′), 1.39 (m, 2H, CH_2-4′), 1.27 (s, 3H, Me-1′), 1.24 (s, 3H, Me-13), 1.22 (s, 3H, Me-12), 1.09 (d, 1H, $J=9.6$ Hz, H-11ax), 0.93 (m, 6H, Me-5′ and Me-6′). ^{13}C NMR: δ 92.7 (C-5), 91.6 (C-5 *epimer*), 76.3 (C-3), 74.5 (C-2′), 51.7 (C-2), 45.7 (C-1), 43.3 (C-9), 41.1 (C-7), 39.5 (C-11), 39.1 (C-10), 33.6 (C-3′), 31.3 (C-8), 29.6 (Me-13), 24.5 (Me-12), 23.2 and 23.1 (C-5′ and C-4′) 22.6 (Me-1′), 7.7 (Me-6′). MS m/z (rel. int.): 283 (M^+–15, 3), 241 (15), 197 (100), 169 (30), 135 (22), 115 (30), 93 (68), 79 (70), 55 (18). Anal. calcd for $C_{17}H_{30}O_2S$: C, 68.41; H, 10.13; S, 10.74. Found: C, 68.57; H, 9.95; S, 10.66.

3.15. (1*S*,2*R*,5*R*,7*S*)-5-[(*S*)-1′-Hydroxyethyl)]-10,10-dimethyl-4-oxa-6-thia-tricyclo-[7.1.1.0^{2,7}]undecane 11g

Three procedures were followed to obtain this compound.

Method (a): A solution of **12** (99 mg, 0.41 mmol) in dry ethyl ether (5 mL) was added to a stirred and cooled (−78°C) suspension of $LiAlH_4$ (31 mg, 0.82 mmol). The mixture was further stirred for 4 h and ethyl ether (50 mL) was added. The reaction was quenched by the slow successive addition of EtOH (0.1 mL) and cold water (0.2 g). The formed white precipitate was filtered and the organic layer was washed with brine (2×25 mL), dried over Na_2SO_4 and evaporated to dryness, yielding a mixture of **11g** and **13g** in a 71:29 ratio, respectively. The abundant diastereoisomer **11g** was obtained as a colorless oil (70 mg, 70%) after separation on a Chromatoflash system using hexane:EtOAc (19:1) as the eluent.

Method (b): A cold (−78°C) solution of **12** (24 mg, 0.1 mmol) in toluene (2 mL) was treated dropwise with DIBAL (24 mg, 0.17 mmol) in THF and stirred under an N_2 atmosphere for 2 h. The reaction mixture was quenched with saturated aqueous NH_4Cl (0.5 mL) at −78°C and allowed to warm to room temperature. Ethyl ether (15 mL) was added and the organic layer was washed with brine (2×5 mL), dried over anhydrous Na_2SO_4 and evaporated to dryness. The residue was flash chromatographed using a mixture of hex-

ane:EtOAc (19:1) as the eluent, giving **11g** as a colorless oil (18.4 mg, 76%).

Method (c): To a cold (−78°C) solution containing **12** (24 mg, 0.1 mmol) in toluene (2 mL) was added dropwise LS-Selectride (40 mg, 0.17 mmol) in THF (0.17 mL) and the mixture stirred under an N_2 atmosphere for 4 h. The reaction mixture was allowed to warm to room temperature and stirred overnight, cooled at −78°C and quenched with a saturated aqueous NH_4Cl. After reaching room temperature, the organic layer was dried over Na_2SO_4 and evaporated to dryness. The residue was treated with cold hexane (5 mL) and the formed white precipitate was filtered. The solvent was evaporated to dryness and the residue was flash chromatographed using a mixture of hexane–EtOAc (19:1) to give **11g** as a colorless oil (20 mg, 82%). Only adduct **11g** was fully characterized. $[\alpha]^{23}=-49.1$ ($c=0.23$, EtOH). ^{1}H NMR ($CDCl_3$): δ 4.95 (s, 1H, $J=3.3$ Hz, H-5), 4.04 (dd, 1H, $J=11.3$, 3.1 Hz, H-3eq), 3.99 (m, 1H, H-1′), 3.73 (dd, 1H, $J=12.2$, 8.7 Hz, H-7), 3.65 (t, 1H, $J=11.3$ Hz, H-3ax), 2.51 (m, 1H, H-11eq), 2.42 (dddd, 1H, $J=11.3$, 8.7, 5.8, 3.1 Hz, H-2) 2.36 (m, 1H, H-8eq), 2.22 (br s, 1H, OH), 2.10 (dd, 1H, $J=5.8$, 3.3 Hz, H-9), 1.81 (t, 1H, $J=5.8$ Hz, H-1) 1.79 (ddd, 1H, $J=12.2$, 10.9, 1.3 Hz, H-8ax), 1.27 (s, 3H, Me-13), 1.26 (d, 3H, $J=5.5$ Hz, Me-2′), 1.14 (s, 3H, Me-12), 1.02 (d, 1H, $J=9.7$ Hz, H-11ax). ^{13}C NMR ($CDCl_3$): δ 90.7 (C-5), 76.1 (C-3), 69.6 (C-1′), 51.7 (C-2), 45.8 C-1), 43.5 (C-5), 41.1 (C-7), 39.5 (C-11), 39.1 (C-10), 33.6 (C-8), 29.6 (C-13), 24.5 (C-12), 18.6 (C-2′). IR ($CHCl_3$) 3470, 2929, 1467, 1254, 1115, 1081, 839, 776 cm^{-1}. MS m/z (rel. int.): 242 (M^+, 12), 197 (100), 135 (20), 107 (25), 93 (42), 79 (45), 55 (8). Anal. calcd for $C_{13}H_{22}O_2S$: C, 64.42; H, 9.15; S, 13, 23. Found: C, 64.65; H, 9.45; S, 12.96.

3.16. (*S*)-2-Hydroxy-2-phenylpropanaldehyde 14a and (1*S*,2*R*,6*S*)-9,9-dimethyl-4-oxa-5-thia-tricyclo-[6.1.1.0^{2,6}]decane 5-oxide 15

Following the procedure described by Eliel et al.,[2a] carbinol **11a** (256 mg, 0.806 mmol) in CH_3CN (5 mL) were treated with NCS (274 mg, 1.61 mmol) and $AgNO_3$ (215 mg, 1.61 mmol) in CH_3CN–H_2O (4:1, 35 mL). After usual workup a yellowish oil was obtained (258 mg), whose ^{1}H NMR spectrum showed the presence of **15** and aldehyde **14a** (Scheme 3). Compound **14a**: ^{1}H NMR ($CDCl_3$): δ 9.47 (s, 1H, H-1), 7.48–7.26 (5H, Ar), 2.60 (br s, 1H, OH), 1.72 (s, 3H, CH_3-3). ^{13}C NMR ($CDCl_3$): δ 186.3 (C-1), 138.7 (C-1′), 129.0 (C-3′, C-5′), 128.3 (C-4′), 126.8 (C-2′, C-6′), 60.8 (C-2), 23.2 (C-3). Compound **13**: ^{1}H NMR ($CDCl_3$): δ 3.65–3.51 (m, 3H, H-3ax, H-3eq and H-6), 2.58 (m, 1H, H-10eq), 2.43 (m, 1H, H-2), 2.45–1.86 (3H, H-4eq, H-5 and H-1), 1.68 (m, 1H, H-7ax, 1.20 (s, 3H, CH_3-12), 1.03 (d, $J=9.70$ Hz, H-10ax), 0.92 (s, 3H, Me-11). ^{13}C NMR ($CDCl_3$): δ 65.3 (C-3), 53.1 (C-2), 42.9 (C-1), 42.2 (C-8), 41.5 (C-10), 38.9 (C-9), 36.0 (C-6), 33.2(C-7), 27.3 (C-12), 22.6 (C-11).

3.17. (*R*)-(+)-2-Phenyl-1,2-propanediol 16a

The above crude reaction mixture was treated with $LiAlH_4$ (42 mg 0.1 mmol) in ethyl ether (15 mL) at room temperature for 1 h the mixture was then treated successively with EtOH (1 mL), water (2 mL) and ethyl ether (15 mL). The organic layer was washed with brine (3×8 mL), dried over anhydrous Na_2SO_4, evaporated to dryness and the residue was purified through flash chromatography using hexane–EtOAc (4:1) as the eluent to give diol **16a** (102 mg, 83%) as a colorless oil. $[\alpha]^{23}=+5.9$ ($c=4.5$, EtOH) (lit.[18] +5.4). ^{1}H NMR ($CDCl_3$): δ 7.51–7.23 (5H, Ar), 3.80 (d, 1H, $J=11$ Hz, OCHa), 3.62 (d, 1H, $J=11$ Hz, OCHb), 2.70–2.30 (br s, 2H, 2 HO), 1.53 (s, 3H, CH_3-3). ^{13}C NMR δ 145 (C-1′), 128.4 (C-3′), 127.4 (C-4′), 125.0 (C-2′), 74.8 (C-2), 71.1 (C-1), 22.1 (C-3). These data are in agreement with those reported[2a] at 100 (^{1}H) and 25 (^{13}C) MHz.

3.18. (*R*)-(+)-2-Methyl-3-phenyl-1,2-propanediol 16d

The crude reaction mixture obtained from the hydrolysis of adduct **11d** was treated with $LiAlH_4$ as described in Section 3.17. After column chromatography hydroxythiol **8** (72%) and diol **16d** (82%) were obtained. $[\alpha]^{23}=+10.6$ ($c=1.8$, $CDCl_3$), lit.[19a] $[\alpha]^{23}=-24.0$ ($c=1.0$, H_2O and lit.[19c] $[\alpha]_D=-7.2$ ($c=2.5$, CH_2Cl_2)) for the (*S*)-enantiomer. ^{1}H NMR ($CDCl_3$): δ 7.19–7.26 (5H, Ar), 3.80 (d, 1H, $J=11$ Hz, OCHa), 3.62 (d, 1H, $J=12$ Hz, OCHb), 2.70–2.30 (br s, 2H, 2 HO), 1.16 (s, 3H, CH_3-3). ^{13}C NMR δ 145 (C-1′), 128.4 (C-3′), 127.4 (C-4′), 125.0 (C-2′), 74.8 (C-2), 71.1 (C-1), 22.1 (C-3). These data are in agreement with those reported[19b] at 100 (^{1}H) and 25 (^{13}C) MHz.

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