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Diastereoselective schenck ene reaction of singlet oxygen with chiral allylic alcohols; access to enantiomerically enriched 1,2,4-trioxanes

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ABSTRACT

A series of antimalarial chiral 1,2,4-trioxanes (**1**–**8**) were synthesised in high enantiomeric purities. Enantioselective addition of R_2Zn reagent to 3-methyl-2-butenal catalysed by (+)-MIB or (−)-MIB yielded both the enantiomers of the chiral allylic alcohols **9**–**11** (90–98% ee), which were subjected to diastereoselective photooxygenation in the presence of tetraphenylporphine (TPP) to obtain (*R*,*R*)-*threo*- or (*S*,*S*)-*threo*-β-hydroperoxy alcohols (**12**–**14**). Reaction of β-hydroperoxy alcohols (**12**–**14**) with different cyclic ketones produced optically active trioxanes **1**–**8**.

1. Introduction

Many of the commonly used drugs against malaria are not very effective due to the development of resistance by the *Plasmodium* parasite.[1] More than 85% of malarial infections are caused by *Plasmodium falciparum*, which is also responsible for majority of fatal malarial infections.[2] Currently artemisinin-based combination therapies (ACTs) are considered to be the best treatment for falciparum malaria.[3] Artemisinin is an enantiomerically pure natural sesquiterpene lactone occurring in plant *Artemesia annua* and was first isolated by Chinese researchers in 1972.[4] Artemisinin and its semi-synthetic derivatives have limited availability, as the plant *A. annua* can only be cultivated in some parts of the world. As recognised by Klayman the pharmacophoric peroxide bond in artemisinin is essential for antimalarial activity.[4] Since then many synthetic peroxidic antimalrials have been synthesised.[5] Synthetic 1,2,4-trioxanes retain the trioxane pharmacophore of artemisinin and are effective as antimalarials and it is widely accepted that the peroxidic antimalarials interact with Fe(II) to form carbon-centred free radicals, which are the parasiticidal species.[6] Recent research indicates that the parasiticidal activity of artemisinins may arise from the inhibition of the malaria parasite sarco-/endoplasmic reticulum Ca^{2+} (SERCA) ATPase (PfATP6).[7–9] Since thapsigargin and artemisinin are both naturally occurring sesquiterpene lactones (Fig. 1), Eckstein-Ludwig et al. hypothesised that artemisinins like thapsigargin should inhibit PfATP6ase.[7–9] They also demonstrated that artemisinin and thapsigargin antagonise each other's activity.[7–9] Since PfATP6 is an enzyme, we hypothesised that it should interact differently with mirror image enantiomers of chiral 1,2,4-trioxanes. In our previous published work we reported the synthesis and antimalarial activities of some enantiomerically pure 1,2,4-trioxanes and demonstrated that the in vitro antimalarial activities of the individual enantiomers were similar.[10,11]

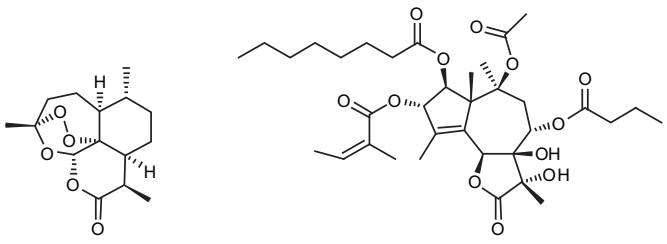

Figure 1.

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2. Results and discussion

Previously, Griesbeck et al. synthesised racemic trioxanes similar to trioxanes **1**–**6** and reported excellent in vitro antimalarial activities against the K1 strain of *P. falciparum*.[12–14] Given the promising profile of some of these endoperoxides we were interested in developing a general asymmetric route to 1,2,4-trioxanes in this class and here we wish to report the synthesis of spirocyclic 1,2,4-trioxanes **1**–**8** in high enantiomeric purities (Fig. 2).

In order to prepare the target trioxanes **1**–**8** with high enantiomeric excesses we decided to use enantiomerically pure allylic alcohols as the starting material. Lurain et al. used (−)-3-*exo*-morpholinoisoborneol [(−)-MIB] as a catalyst in enantioselective alkyl addition of dialkylzinc reagents to α,β-unsaturated aldehydes to obtain (*R*)-(−)-**9b** and other allylic alcohols in high optical purities.[15] Use of MIB as a catalyst in the enantioselective addition of organozinc reagents to aldehydes was first described by Nugent.[16,17] (−)-MIB is commercially available but (+)-MIB was synthesised following the procedure described by Nugent.[16,17] We used (+)-MIB as a catalyst in the addition reaction of R_2Zn with 3-methyl-2-butenal to obtain (*R*)-(+)-enantiomers of **9a**, **10a** and **11a** with 90–98% ees (Scheme 1).

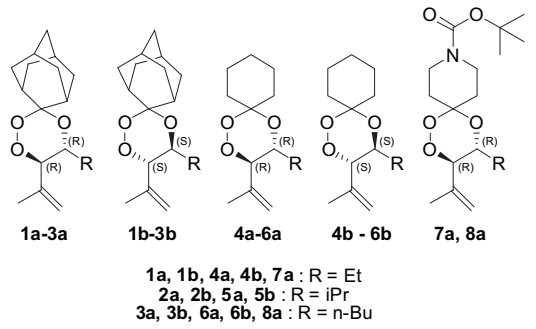
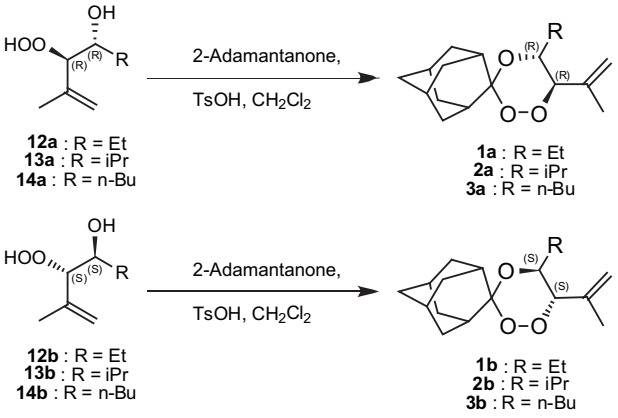
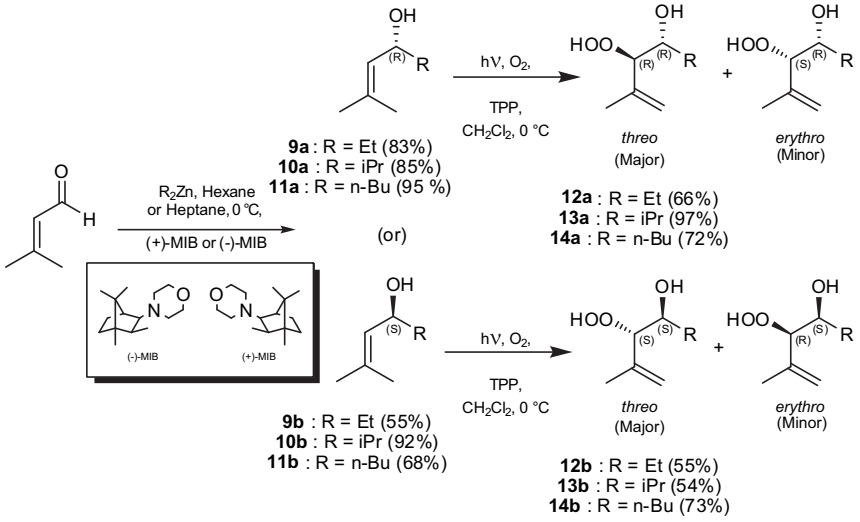


Figure 2. Enantiomerically enriched antimalarial 1,2,4-trioxanes synthesised.

hydroperoxides, was first discovered by Adam et al.[26] Griesbeck et al. utilised this diastereoselective photooxygenation to synthesise racemic *threo*-β-hydroperoxy alcohols that were in turn used to synthesise diastereomerically pure racemic chiral 1,2,4-trioxanes similar to trioxanes **1**–**8**.[12–14,20,28] Dye-sensitised photooxygenation of achiral allylic alcohols has been used by Chandan Singh to obtain β-hydroperoxy alcohols, which were then used to synthesise 1,2,4-trioxanes.[29] To our knowledge no one has ever reported the synthesis of enantiomerically enriched chiral 1,2,4-trioxanes **1**–**8** described in Figure 2. Enantiomerically enriched chiral allylic alcohols **9a**–**11a** and **9b**–**11b** were subjected to photooxygenations to obtain enantiomerically enriched *threo*-β-hydroperoxy alcohols **12**–**14** (Scheme 1) following procedures previously published.[19,27] Diastereoselectivities (*threo*/*erythro*) were in the range of 91:9 to 92:8, which were similar to the previously reported data for similar alcohols.[12,19,20,22,24–27] It was difficult to separate the major diastereomers of β-hydroperoxy alcohols **12**–**14**, so they were used in the next step after purification by liquid chromatography (EtOAc/*n*-Hex).



Scheme 2. Synthesis of enantiomerically enriched spirobicylcic adamantane 1,2,4-trioxanes **1**–**3**.



Scheme 1. Enantioselective addition of dialkyl zincs to 3-methyl-2-butenal and photooxygenation of enantiomerically enriched chiral allylic alcohols **9**–**11**.

(−)-MIB was used in a similar procedure to obtain (*S*)-(−)-enantiomers of **9b**, **10b** and **11b** with similar ee (Scheme 1). Singlet oxygen ene reaction of alkenes to yield allylic hydroperoxides has been widely used since it was first described by Schenck in 1948.[18–22] The diastereoselectivity of singlet oxygen photooxygenation of chiral allylic alcohols in non-polar solvents yields *threo*-β-hydroperoxy alcohols as the major product.[19–27] The hydroxy-directed regio and diastereoselective photooxygenation of chiral alcohols, to yield allylic

Using catalytic amount of *p*-toluenesulfonic acid (TsOH) according to a procedure previously described, [30,31] (*R*,*R*)-*threo*- or (*S*,*S*)-*threo*-β-hydroperoxy alcohols were reacted with 2-adamantanone (see Scheme 2) or with corresponding cyclic ketones (see Table 1) to yield enantioenriched 1,2,4-trioxanes **1**–**8**. The major diastereomers of enantiomerically enriched 1,2,4-trioxanes **1**–**8** were separated from the minor diastereomers using liquid chromatography (EtOAc/*n*-Hex). Trioxanes **1**–**6** were

Table 1
Enantiomerically enriched spirobicyclic trioxanes

Entry	β-Hydroperoxy alcohol (*threo*)	Cyclic ketone	Enantioenriched trioxane & configuration	Yield (%)
1	**12a**	2-Adamantanone	**1a** (*R*,*R*)	74
2	**12b**	2-Adamantanone	**1b** (*S*,*S*)	55
3	**13a**	2-Adamantanone	**2a** (*R*,*R*)	61
4	**13b**	2-Adamantanone	**2b** (*S*,*S*)	57
5	**14a**	2-Adamantanone	**3a** (*R*,*R*)	78
6	**14b**	2-Adamantanone	**3b** (*S*,*S*)	65
7	**12a**	Cyclohexanone	**4a** (*R*,*R*)	76
8	**12b**	Cyclohexanone	**4b** (*S*,*S*)	66
9	**13a**	Cyclohexanone	**5a** (*R*,*R*)	44
10	**13b**	Cyclohexanone	**5b** (*S*,*S*)	61
11	**14a**	Cyclohexanone	**6a** (*R*,*R*)	78
12	**14b**	Cyclohexanone	**6b** (*S*,*S*)	73
13	**12a**	*N*-Boc-4-piperidone	**7a** (*R*,*R*)	16
14	**14a**	*N*-Boc-4-piperidone	**8a** (*R*,*R*)	18

obtained in good yields but the yields of trioxanes **7a** and **8a** were low. The single crystal X-ray analysis of **1a** and **8a** (Fig. 3) confirmed the chirality and *syn* position of the oxygen atoms in the molecule.

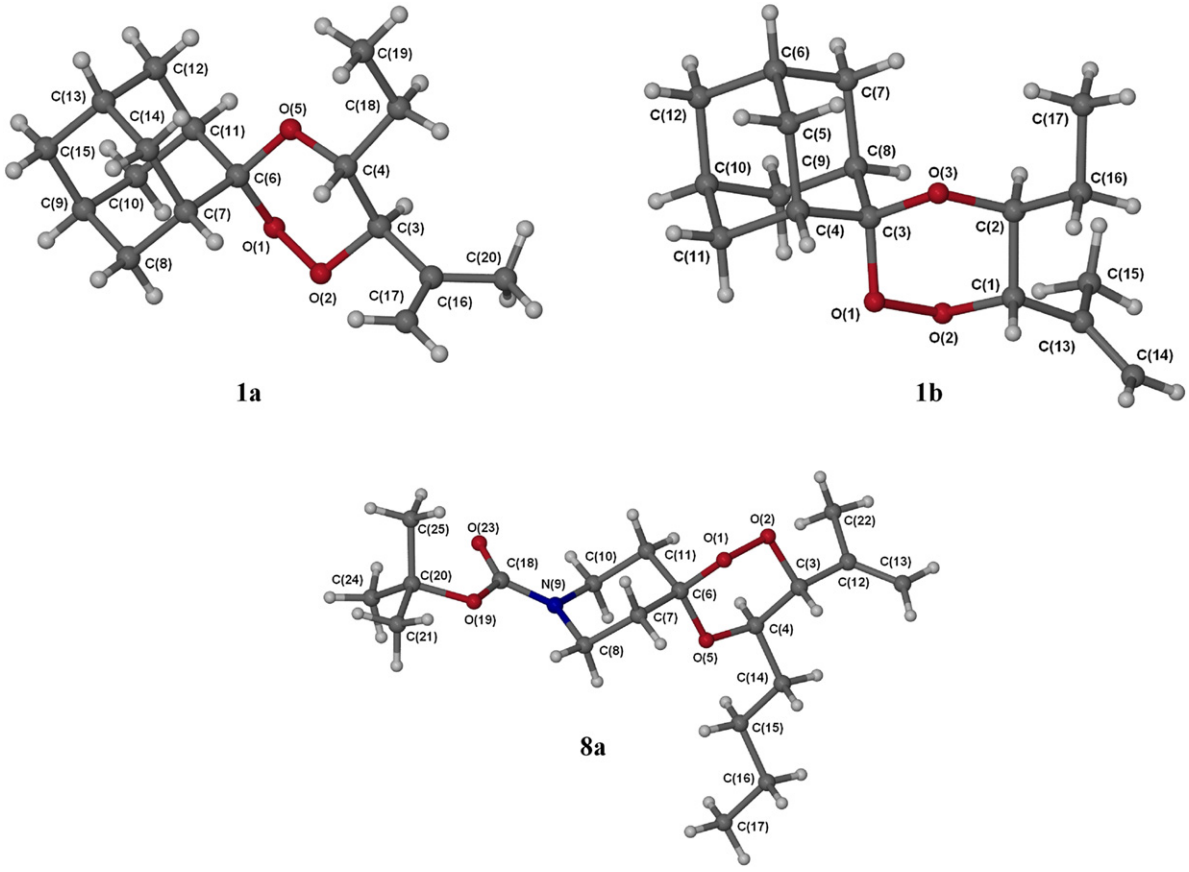


Figure 3. X-ray structures of enantioenriched 1,2,4-trioxanes **1a**, **1b** and **8a**.

3. Conclusions

The comparatively high efficiency of this synthetic approach may lend itself to a cost effective synthesis of chiral 1,2,4-trioxanes with high enantiomeric purity. Currently we are investigating the potential differences in the antimalarial activities of mirror image pairs of enantiomers of trioxanes **1**–**8**.

4. Experimental

4.1. General

The glassware was dried overnight in a hot air oven at 140 °C and the reactions were performed under a nitrogen atmosphere unless otherwise specified. Anhydrous dichloromethane was obtained by distillation using calcium hydride as a drying agent and anhydrous *n*-heptane and *n*-hexane used in the chemical syntheses were purchased from Sigma Aldrich. Thin layer chromatography (TLC) was carried out on pre-coated silica gel plates (Merck 60 F_{254}) and visualised using iodine or anisaldehyde solution. Preparative liquid chromatography (LC) was performed on silica gel (BDH 60 230–400 mesh) employing various solvent mixtures and using an air line to apply pressure. (−)-MIB was obtained from Sigma Aldrich and (+)-MIB was synthesised following the procedure described by Nugent.[16,17] Diastereomeric ratios (dr) of β-hydroperoxy alcohols **12**–**14** were determined by ^{1}H NMR of the crude products. NMR spectra were recorded on a Brucker AMX 400 (^{1}H, 400 MHz; ^{13}C, 100 MHz) spectrometer. Microanalyses were performed in the University of Liverpool Microanalysis Laboratory. Mass spectra were recorded on a VG analytical 7070E machine and Fisons TRIO spectrometers using electron ionisation (EI) and chemical ionisation (CI). Solids and liquids were used directly without any further treatment to record IR spectra using a JASCO FT/IR-4100 spectrometer. Enantiomeric excesses of compounds **9**–**11** were determined using GC Varian 3800GC (Supelco β-Dex-120 column, 30 m×0.25 mm; He, 5 bar; air, 4 bar); GC Varian CP-3380 (Chromapack Chirasil Dex CB column, 25 m×0.25 mm; He, 5 bar) and Shimadzu GC-14B (Supelco α-Dex-120 column, 30 m×0.25×0.25 μm; He, 50 KPa). Optical rotations

were determined using a Perkin–Elmer polarimeter 343 plus instrument. Absolute configurations of enantiomerically enriched allylic alcohols **9**–**11** were determined by comparison of the optical rotations with the published optical rotations. X-ray analyses were carried out at the University of Liverpool.

4.2. (*R*)-(+)-5-Methylhex-4-en-3-ol (9a). Enantioselective addition of dialkyl zincs to 3-methyl-2-butenal: general procedure-A

(+)-MIB (0.299 g, 1.25 mmol) in 31.2 mL anhydrous hexane was cooled to 0 °C and Et_2Zn in hexane solution (1.0 M, 62.4 mL, 62.4 mmol) was added dropwise. A mixture of freshly distilled 3-methyl-2-butenal (2.63 g, 31.2 mmol) was added and the reaction mixture was stirred at 0 °C under N_2 atmosphere. After 4.0 h, satd aq NH_4Cl was added to the reaction mixture and the organic layer was separated from the aqueous layer. The aqueous layer was extracted twice with hexane and once with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), filtered and then concentrated under reduced pressure to give the crude product, which was purified by flash chromatography (using a gradient of EtOAc in *n*-hexane as eluant) to give **9a** as a light yellowish to colourless oil (2.97 g, 83% yield, 94% ee). $[\alpha]_D^{20}$ +1.3 (*c* 1.0, $CHCl_3$). The absolute configuration was determined by comparing the optical rotation of **9a** with the published optical rotation of the mirror image enantiomer.[15] ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.15 (1H, dsept, *J*=8.7 and 1.3 Hz), 4.25 (1H, dt, *J*=8.7 and 6.6 Hz), 1.79 (1H, br s), 1.73 (3H, d, *J*=1.3 Hz), 1.68 (3H, d, *J*=1.3 Hz), 1.54–1.65 (1H, m), 1.39–1.50 (1H, m), 0.88 (3H, t, *J*=7.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.26, 128.47, 70.38, 30.92, 26.08, 18.54, 10.06; IR (neat, cm^{-1}) 3334, 2966, 2927, 2875, 2360, 1446, 1376, 1088, 1003, 958; *m*/*z* (CI, +ve, NH_3), 114 ($[M+NH_4-H_2O]^+$, 100%); HRMS: Found $[M+NH_4-H_2O]^+$, 114.12800, $C_7H_{16}N$ requires 114.12830.

4.3. (*S*)-(−)-5-Methylhex-4-en-3-ol (9b)

This product was prepared by enantioselective addition of Et_2Zn (1.0 M in dry *n*-hexane, 62.4 mL, 62.4 mmol) to 3-methyl-2-butenal (2.625 g, 31.2 mmol) following General procedure-A and using (−)-MIB (299 mg, 1.25 mmol) as the catalyst to give **9b** as a colourless oil (1.97 g, 55% yield, 94% ee). $[\alpha]_D^{20}$ −1.7 (*c* 1.0, $CHCl_3$) {Lit.[15] $[\alpha]_D^{20}$ −10.5 (*c* 0.002, CHCl3, 95% ee)}. NMR and other analytical data were similar to that of **9a**.

4.4. (*R*)-(−)-2,5-Dimethylhex-4-en-3-ol (10a)

This product was prepared by General procedure-A using 16.0 mL *i*-Pr_2Zn in toluene (1.0 M, 16 mmol), 76.59 mg (+)-MIB (0.32 mmol), 3-methyl-2-butenal (673 mg, 8.0 mmol) and 8.0 mL anhydrous toluene. The purified product **10a** was obtained as a light yellowish to colourless oil (0.87 g, 85% yield, 98% ee). $[\alpha]_D^{20}$ −13.8 (*c* 1.0, $CHCl_3$). The absolute configuration was determined by comparing the optical rotation of **10a** with the published optical rotation of the mirror image enantiomer.[32] ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.18 (1H, dsept, *J*=9.0 and 1.3 Hz), 4.04 (1H, dd, *J*=9.0 and 6.8 Hz), 1.74 (3H, d, *J*=1.3 Hz), 1.70 (1H, br s), 1.68 (3H, d, *J*=1.3 Hz), 1.61–1.71 (1H, m), 0.95 (3H, d, *J*=6.7 Hz), 0.85 (3H, d, *J*=6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.77, 126.86, 74.02, 34.79, 26.26, 18.73, 18.71, 18.44; IR (neat, cm^{-1}) 3354, 2958, 2925, 2873, 2360, 2337, 1448, 1379, 1259, 1097, 1012; *m*/*z* (CI, +ve, NH_3), 128 ($[M+NH_4-H_2O]^+$, 12.34%); HRMS: Found $[M+NH_4-H_2O]^+$, 128.14405, $C_8H_{18}N$ requires 128.14392.

4.5. (*S*)-(+)-2,5-Dimethylhex-4-en-3-ol (10b)

This product was prepared by enantioselective addition of *i*-Pr_2Zn (1.0 M in toluene, 18.0 mL, 18.0 mmol) to 3-methyl-2-butenal (760 mg, 9.0 mmol) in dry toluene following General procedure-A and using (−)-MIB (86.45 mg, 0.36 mmol) as the catalyst to give **10b** as a colourless oil (1.066 g, 92% yield, 98% ee). $[\alpha]_D^{20}$ +16.97 (*c* 1.0, $CHCl_3$) {Lit.[32] $[\alpha]_D$ +8.8 (*c* 1.0, $CHCl_3$)} (Note: The configuration of this allylic alcohol was wrongly assigned in the literature).[32] NMR and other analytical data were similar to that of **10a**.

4.6. (*R*)-(+)-2-Methyloct-2-en-4-ol (11a)

The product was prepared by General procedure-A using 41.6 mL *n*-Bu_2Zn in *n*-heptane (1.0 M, 41.6 mmol), 0.199 g (+)-MIB (0.832 mmol), 1.75 g 3-methyl-2-butenal (20.8 mmol) and 20.8 mL anhydrous *n*-heptane. The purified product was obtained as a colourless oil **11a** (2.796 g, 95% yield, 90% ee). $[\alpha]_D^{20}$ +15.43 (*c* 1.0, $CHCl_3$). The absolute configuration was determined by comparing the optical rotation of **11a** with the published optical rotations for series of similar alcohols and the fact that (+)-MIB has the same selectivity.[15,16] ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.16 (1H, dsept, *J*=8.8 and 1.3 Hz), 4.33 (1H, dt, *J*=8.8 and 6.6 Hz), 1.73 (3H, d, *J*=1.3 Hz), 1.68 (3H, d, *J*=1.3 Hz), 1.21–1.62 (6H, m), 0.90 (3H, t, *J*=7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) 135.09, 128.79, 69.04, 37.83, 28.03, 26.14, 23.09, 18.57, 14.44; IR (neat, cm^{-1}) 3334, 2958, 2927, 2860, 2339, 1676, 1448, 1377, 1047, 1005; *m*/*z* (CI, +ve, NH_3), 142 ($[M+NH_4-H_2O]^+$, 75%); HRMS: Found $[M+NH_4-H_2O]^+$, 142.15980, $C_9H_{20}N$ requires 142.15960.

4.7. (*S*)-(−)-2-Methyloct-2-en-4-ol (11b)

This product was prepared by enantioselective addition of *n*-Bu_2Zn (1.0 M in *n*-heptane, 50 mL, 50 mmol) to 3-methyl-2-butenal (2.1 g, 25 mmol) in anhydrous *n*-hexane following General procedure-A and using (−)-MIB (240 mg, 1.0 mmol) as the catalyst to give **11b** as a colourless oil (2.42 g, 68% yield, 90% ee). $[\alpha]_D^{20}$ −15.81 (*c* 1.0, $CHCl_3$). NMR and other analytical data were similar to that of **11a**.

4.8. (3*R*,4*R*)-4-Hydroperoxy-5-methylhex-5-en-3-ol (12a). Diastereoselective schenck ene reaction: general procedure-B

Dry oxygen was bubbled through a solution of 5.0 mg tetraphenylporphine (TPP) in 80 mL CH_2Cl_2 for 10 min. The flow rate was later reduced to obtain a slow and steady flow of O_2 and the reaction mixture was cooled to 0 °C. A solution of (*R*)-(+)-5-methylhex-4-en-3-ol **9a** (1.532 g, 13.42 mmol) in a small amount of CH_2Cl_2 was added to the reaction flask and then irradiated with three halogen floodlights (100/150 W). The ice bath was changed at regular intervals as the ice melted due to the heat produced by the lamps. The reaction mixture was continuously stirred at 0 °C for 8 h and then the solvent was evaporated under reduce pressure. The crude product was purified by flash chromatography. CH_2Cl_2 was used as the starting eluent to get rid of TPP and then 20% EtOAc in *n*-hexane or gradient EtOAc/*n*-hexane was used to obtain the pure product **12a** as colourless oil [1.287 g, 66% yield, dr 91:9 (*threo*/*erythro*)]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.80 (1H, br s), 5.06–5.08 (2H, m), 4.22 (1H, d, *J*=8.4 Hz), 3.64 (1H, dt, *J*=8.4 and 3.4 Hz), 3.35 (1H, br s), 1.75 (3H, t, *J*=1.2 Hz), 1.32–1.56 (2H, m), 0.98 (3H, t, *J*=7.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.82, 116.85, 93.74, 72.49, 25.99, 18.43, 9.99; IR (neat, cm^{-1}) 3329, 2970, 2935, 2881, 2360, 1712, 1649, 1456, 1377, 1234, 972, 903; *m*/*z* (CI, +ve, NH_3), 146 ($[M+NH_4-H_2O]^+$, 39%) and 164 ($[M+NH_4]^+$, 1.4%); HRMS: Found $[M+NH_4]^+$, 164.12886, $C_7H_{18}NO_3$ requires 164.12867.

4.9. (3*S*,4*S*)-4-Hydroperoxy-5-methylhex-5-en-3-ol (12b)

Photooxygenation of **9b** (1.54 g, 13.48 mmol) by General procedure-B gave **12b** as a pale yellow oil (1.079 g, 55% yield, dr 91:9 *threo*/*erythro*). NMR and other analytical data were similar to that of **12a**.

4.10. (3*R*,4*R*)-4-Hydroperoxy-2,5-dimethylhex-5-en-3-ol (13a)

Photooxygenation of **10a** (0.64 g, 4.99 mmol) by General procedure-B gave **13a** as a pale yellow oil [0.779 g, 97% yield, dr 92:8 (*threo*/*erythro*)]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.55 (1H, br s), 5.10–5.11 (2H, m), 4.34 (1H, d, J=8.4 Hz), 3.53–3.56 (1H, dd, J=8.4 and 2.8 Hz), 1.75 (3H, t, J=1.1 Hz), 1.69–1.73 (1H, m), 1.01 (3H, d, J=7.0 Hz), 0.91 (3H, d, J=6.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.65, 117.01, 92.34, 75.09, 29.56, 20.75, 18.35, 15.34; *m*/*z* (CI, +ve, NH_3), 160 ([M+NH_4−H_2O]$^+$), 10.77%; HRMS: Found [M+NH_4−H_2O]$^+$ 160.13412, $C_8H_{18}O_2N$ requires 160.13375.

4.11. (3*S*,4*S*)-4-Hydroperoxy-2,5-dimethylhex-5-en-3-ol (13b)

Photooxygenation of **10b** (0.96 g, 7.49 mmol) by General procedure-B gave **13b** as a pale yellow oil [0.642 g, 54% yield, dr 92:8 (*threo*/*erythro*)]. NMR and other analytical data were similar to that of **13a**.

4.12. (3*R*,4*R*)-3-Hydroperoxy-2-methyloct-1-en-4-ol (14a)

The product was prepared by General procedure-B using 5 mg TPP, 80 mL CH_2Cl_2 and 1.91 g (13.42 mmol) of **11a** to obtain **14a** as light yellowish to colourless oil [1.67 g, 72% yield, dr 92:8 (*threo*/*erythro*)]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.28 (1H, br s), 5.08–5.11 (2H, m), 4.21 (1H, d, J=8.4 Hz), 3.69 (1H, dt, J=8.4 and 3.2 Hz), 2.97 (1H, br s), 1.75 (3H, t, J=1.2 Hz), 1.24–1.52 (6H, m), 0.89 (3H, t, J=7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.65, 117.10, 94.11, 71.16, 32.68, 27.83, 22.96, 18.57, 14.40; IR (neat, cm^{-1}) 3336, 2954, 2931, 2864, 2360, 1709, 1649, 1454, 1376, 1082, 1001, 903; *m*/*z* (CI, +ve, NH_3), 174 ([M+NH_4−H_2O]$^+$, 65%) and 192 ([M+NH_4]$^+$, 9%); HRMS: Found [M+NH_4]$^+$, 192.15981, $C_9H_{22}NO_3$ requires 192.15997.

4.13. (3*S*,4*S*)-3-Hydroperoxy-2-methyloct-1-en-4-ol (14b)

Photooxygenation of **11b** (2.2 g, 15.47 mmol) by General procedure-B gave **14b** as a pale yellow oil [1.964 g, 73% yield, dr 92:8 (*threo*/*erythro*)]. NMR and other analytical data were similar to that of **14a**.

4.14. (5*R*,6*R*)-5-Ethyl-6-(prop-1-en-2-yl)spiro[1,2,4,trioxacyclohexane-3,2′-adamantane] (1a). Synthesis of enantiomerically enriched 1,2,4-trioxanes: general procedure-C

To a mixture of (3*R*,4*R*)-4-hydroperoxy-5-methylhex-5-en-3-ol **12a** (0.25 g, 1.71 mmol) and 2-adamantanone (0.405 g, 2.7 mmol) in anhydrous CH_2Cl_2 (23 mL) was added 0.036 g of *p*-toluenesulfonic acid monohydrate and the reaction mixture was stirred at room temperature for 4 h and then silica gel was added to the reaction mixture and the solvent was evaporated under reduced pressure to adsorb the crude product directly onto silica gel for purification by flash chromatography without any further workup. Alternatively the solvent from the crude reaction mixture was evaporated and the crude product was dissolved in small amount of *n*-hexane, which was purified by flash chromatography (SiO_2, 5% EtOAc in *n*-Hexane or gradient EtOAc in *n*-hexane) to give pure trioxane **1a** as thick colourless oil, which turned into a white solid on standing (0.35 g, 74% yield). $[\alpha]_D^{20}$ −86.4 (*c* 1.0, $CHCl_3$); mp 46–48 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.07–5.09 (2H, m), 4.27 (1H, d, J=9.6 Hz), 3.83 (1H, dt, J=9.6 and 2.8 Hz), 2.93 (1H, br s), 1.55–2.15 (13H, m), 1.76 (3H, t, J=1.3 Hz), 1.31–1.54 (2H, m), 1.0 (3H, t, J=7.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.88, 118.21, 105.23, 87.96, 70.45, 37.61, 37.10, 34.00, 33.79, 33.73, 33.38, 30.23, 27.68, 27.62, 24.43, 20.33, 10.19; IR (neat, cm^{-1}) 2904, 2856, 1649, 1448, 1377, 1319, 1221, 1092, 1070, 1024, 1001, 966, 920, 893; *m*/*z* (CI, +ve, NH_3), 279 ([M+H]$^+$, 14.25%); HRMS: Found [M+H]$^+$, 279.19664, $C_{17}H_{27}O_3$ requires 279.19602. Elemental analysis ($C_{17}H_{26}O_3$), C: 73.67, H: 9.52 (requires, C: 73.34, H: 9.41).

4.15. (5*S*,6*S*)-5-Ethyl-6-(prop-1-en-2-yl)spiro-[1,2,4,trioxacyclohexane-3,2′-adamantane] (1b)

Using **12b** (0.240 g, 1.642 mmol) and 2-adamantanone (0.39 g, 2.59 mmol) in General procedure-C gave **1b** (0.252 g, 55% yield). $[\alpha]_D^{20}$ +59.3 (*c* 1.0, $CHCl_3$). NMR and other analytical data were similar to that of **1a**.

4.16. (5*R*,6*R*)-5-Isopropyl-6-(prop-1-en-2-yl)spiro-[1,2,4,trioxacyclohexane-3,2′-adamantane] (2a)

Using **13a** (0.100 g, 0.62 mmol) and 2-adamantanone (0.103 g, 0.68 mmol) in General procedure-C gave **2a** (0.11 g, 61% yield). $[\alpha]_D^{20}$ −100.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.07–5.10 (2H, m), 4.46 (1H, d, J=9.9 Hz), 3.84 (1H, dd, J=9.9 and 2.6 Hz), 2.93 (1H, br s), 1.55–2.14 (14H, m), 1.77 (3H, t, J=1.2 Hz), 1.01 (3H, d, J=6.9 Hz), 0.93 (3H, d, J=6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.02, 118.24, 104.94, 85.95, 72.56, 37.66, 37.04, 34.04, 33.75, 33.38, 30.18, 28.58, 27.70, 27.66, 20.71, 20.21, 15.45; IR (neat, cm^{-1}) 2906, 2856, 1649, 1450, 1379, 1221, 1109, 1074, 1038, 908; *m*/*z* (CI, +ve, NH_3), 293 ([M+H]$^+$, 13.23%); HRMS: Found [M+H]$^+$, 293.21110, $C_{18}H_{29}O_3$ requires 293.21167. Elemental analysis ($C_{18}H_{28}O_3$), C: 74.83, H: 9.90 (requires, C: 73.93, H: 9.65).

4.17. (5*S*,6*S*)-5-Isopropyl-6-(prop-1-en-2-yl)spiro-[1,2,4,trioxacyclohexane-3,2′-adamantane] (2b)

Condensation of **13b** (0.228 g, 1.42 mmol) with 2-adamantanone (0.337 g, 2.24 mmol) by General procedure-C gave **2b** (0.238 g, 57% yield). $[\alpha]_D^{20}$ +100.1 (*c* 1.0, $CHCl_3$). NMR and other analytical data were similar to that of **2a**.

4.18. (5*R*,6*R*)-5-Butyl-6-(prop-1-en-2-yl)spiro-[1,2,4,trioxacyclohexane-3,2′-adamantane] (3a)

Condensation of **14a** (0.298 g, 1.71 mmol) with 2-adamantanone (0.405 g, 2.70 mmol) by General procedure-C gave **3a** as a thick colourless oil (0.407 g, 78% yield). $[\alpha]_D^{20}$ −57.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.07–5.08 (2H, m), 4.26 (1H, d, J=9.7 Hz), 3.91 (1H, dt, J=9.7 and 3.0 Hz), 2.93 (1H, br s), 1.51–2.14 (13H, m), 1.76 (3H, t, J=1.2 Hz), 1.25–1.44 (6H, m), 0.91 (3H, t, J=7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.84, 118.31, 105.21, 88.09, 69.05, 37.61, 37.08, 34.00, 33.78, 33.73, 33.45, 30.98, 30.24, 27.78, 27.67, 27.62, 23.00, 20.31, 14.46; IR (neat, cm^{-1}) 2910, 2856, 1649, 1450, 1379, 1221, 1107, 1093, 1072, 1024, 1005, 908; *m*/*z* (CI, +ve, NH_3), 307 ([M+H]$^+$, 26.94%); HRMS: Found [M+H]$^+$, 307.22600, $C_{19}H_{31}O_3$ requires 307.22732. Elemental analysis ($C_{19}H_{30}O_3$), C: 74.11, H: 9.94 (requires, C: 74.47, H: 9.87).

4.19. (5*S*,6*S*)-5-Butyl-6-(prop-1-en-2-yl)spiro-[1,2,4,trioxacyclohexane-3,2′-adamantane] (3b)

Condensation of **14b** (0.256 g, 1.504 mmol) with 2-adamantanone (0.358 g, 2.38 mmol) by General procedure-C gave **3b** as a pale yellow oil (0.30 g, 65% yield). $[\alpha]_D^{20}$ +89.5 (*c* 1.0, $CHCl_3$). NMR and other analytical data were similar to that of **3a**.

4.20. (3*R*,4*R*)-4-Ethyl-3-(prop-1-en-2-yl)-1,2,5-trioxaspiro-[5.5]undecane (4a)

Condensation of **12a** (0.252 g, 1.72 mmol) with cyclohexanone (0.267 g, 2.72 mmol) by General procedure-C gave **4a** as a light

yellowish to colourless oil (0.296 g, 76% yield). $[\alpha]_D^{20}$ −123.1 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 5.06–5.08 (2H, m), 4.27 (1H, d, *J*=9.5 Hz), 3.85 (1H, dt, *J*=9.3 and 2.9 Hz), 2.14–2.19 (1H, m), 1.99–2.07 (1H, m), 1.77 (3H, t, *J*=1.2 Hz), 1.29–1.64 (10H, m), 0.98 (3H, t, *J*=7.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) 139.85, 118.19, 103.26, 87.95, 70.91, 35.47, 29.88, 26.10, 24.43, 22.82, 22.70, 20.20, 9.95; IR (neat, cm^{-1}) 2935, 2858, 1649, 1450, 1365, 1273, 1240, 1159, 1142, 1092, 997, 912; *m*/*z* (CI, +ve, NH_3), 244 ($[M+NH_4]^+$, 28.06%); HRMS: Found $[M+NH_4]^+$, 244.19072, $C_{13}H_{26}NO_3$ requires 244.19127. Elemental analysis ($C_{13}H_{22}O_3$), C: 69.02, H: 9.84 (requires, C: 68.99, H: 9.80).

4.21. (3*S*,4*S*)-4-Ethyl-3-(prop-1-en-2-yl)-1,2,5-trioxaspiro[5.5]undecane (4b)

Condensation of **12b** (0.100 g, 0.68 mmol) with cyclohexanone (0.073 g, 0.75 mmol) by General procedure-C gave **4b** as a colouless oil (0.102 g, 66% yield). $[\alpha]_D^{20}$ +102.9 (*c* 1.0, $CHCl_3$). NMR and other analytical data were similar to that of **4a**.

4.22. (3*R*,4*R*)-4-Isopropyl-3-(prop-1-en-2-yl)-1,2,5-trioxaspiro[5.5]undecane (5a)

Condensation of **13a** (0.247 g, 1.54 mmol) with cyclohexanone (0.239 g, 2.43 mmol) by General procedure-C gave **5a** as a colourless oil (0.163 g, 44% yield). $[\alpha]_D^{20}$ −95.7 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 5.07–5.10 (2H, m), 4.46 (1H, d, *J*=9.9 Hz), 3.83 (1H, dd, *J*=9.9 and 2.6 Hz), 2.21–2.28 (1H, m), 1.91–1.97 (1H, m), 1.77 (3H, t, *J*=1.2 Hz), 1.71–1.75 (1H, m), 1.36–1.63 (8H, m), 1.0 (3H, d, *J*=7.0 Hz), 0.92 (3H, d, *J*=6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.01, 118.18, 103.03, 86.09, 73.13, 35.34, 29.78, 28.53, 26.13, 22.80, 22.69, 20.46, 20.06, 15.42; IR (neat, cm^{-1}) 2933, 2860, 1649, 1448, 1367, 1275, 1161, 1093, 1039, 1012, 908; *m*/*z* (CI, +ve, NH_3), 258 ($[M+NH_4]^+$, 51.36%); HRMS: Found $[M+NH_4]^+$, 258.20684, $C_{14}H_{28}NO_3$ requires 258.20692. Elemental analysis ($C_{14}H_{24}O_3$), C: 70.20, H: 10.11 (requires C: 69.96%, H: 10.07%).

4.23. (3*S*,4*S*)-4-Isopropyl-3-(prop-1-en-2-yl)-1,2,5-trioxaspiro[5.5]undecane (5b)

Condensation of **13b** (0.386 g, 2.41 mmol) with cyclohexanone (0.374 g, 3.81 mmol) by General procedure-C gave **5b** as a colourless oil (0.351 g, 61% yield). $[\alpha]_D^{20}$ +102.0 (*c* 1.0, $CHCl_3$). NMR and other analytical data were similar to that of **5a**.

4.24. (3*R*,4*R*)-4-Butyl-3-(prop-1-en-2-yl)-1,2,5-trioxaspiro[5.5]undecane (6a)

Condensation of **14a** (0.298 g, 1.71 mmol) with cyclohexanone (0.265 g, 2.70 mmol) by General procedure-C gave **6a** as light yellowish to colourless oil (0.337 g, 78% yield). $[\alpha]_D^{20}$ −102.6 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 5.07–5.08 (2H, m), 4.26 (1H, d, *J*=9.7 Hz), 3.92 (1H, dt, *J*=9.5 and 3.0 Hz), 2.14–2.20 (1H, m), 1.99–2.06 (1H, m), 1.77 (3H, t, *J*=1.2 Hz), 1.26–1.63 (14H, m), 0.90 (3H, t, *J*=7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.82, 118.25, 103.23, 88.16, 69.55, 35.47, 30.96, 29.86, 27.59, 26.09, 22.96, 22.85, 22.69, 20.17, 14.43; IR (neat, cm^{-1}) 2935, 2860, 1649, 1450, 1363, 1273, 1255, 1242, 1159, 1132, 1093, 1003, 966, 910; *m*/*z* (CI, +ve, NH_3), 272 ($[M+NH_4]^+$, 35.27%); HRMS: Found $[M+NH_4]^+$, 272.22155, $C_{15}H_{30}NO_3$ requires 272.22257. Elemental analysis ($C_{15}H_{26}O_3$), C: 70.90, H: 10.34 (requires, C: 70.83, H: 10.30).

4.25. (3*S*,4*S*)-4-Butyl-3-(prop-1-en-2-yl)-1,2,5-trioxaspiro[5.5]undecane (6b)

Condensation of **14b** (0.342 g, 1.96 mmol) with cyclohexanone (0.304 g, 3.1 mmol) by General procedure-C gave **6b** as a colourless oil (0.366 g, 73% yield). $[\alpha]_D^{20}$ +73.10 (*c* 1.0, $CHCl_3$). NMR and other analytical data were similar to that of **6a**.

4.26. (3*R*,4*R*)-*tert*-Butyl-4-ethyl-3-(prop-1-en-2-yl)-1,2,5-trioxa-9-azaspiro[5.5]undecane-9-carboxylate (7a)

Condensation of **12a** (0.25 g, 1.71 mmol) with *N*-Boc-4-piperidone (0.538 g, 2.7 mmol) by General procedure-C gave **7a** as colourless oil, which on standing crystallised (0.092 g, 16% yield). $[\alpha]_D^{20}$ −85.0 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 5.09–5.10 (2H, m), 4.32 (1H, d, *J*=9.7 Hz), 3.86 (1H, dt, *J*=9.3 and 2.8 Hz), 3.38–3.53 (4H, m), 2.13–2.25 ($2H_a$, m), 1.77 (3H, t, *J*=1.2 Hz), 1.63–1.73 ($2H_b$, m), 1.30–1.59 (2H, m), 1.46 (9H, s), 0.97 (3H, t, *J*=7.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.06, 139.44, 118.60, 101.74, 88.00, 80.08, 71.44, 35.07, 28.84, 24.35, 20.22, 17.82, 9.90; IR (neat, cm^{-1}) 2974, 2933, 1689, 1421, 1360, 1240, 1171, 1144, 1103, 1074, 947, 918, 862, 764; *m*/*z* (CI, +ve, NH_3), 328 ($[M+H]^+$, 26.47%); HRMS: Found $[M+H]^+$, 328.21234, $C_{17}H_{30}NO_5$ requires 328.21240. Elemental analysis ($C_{17}H_{29}NO_5$), C: 63.58, H: 9.35, N: 3.99 (requires, C: 62.36, H: 8.93, N: 4.28).

4.27. (3*R*,4*R*)-*tert*-Butyl-4-butyl-3-(prop-1-en-2-yl)-1,2,5-trioxa-9-azaspiro[5.5]undecane-9-carboxylate (8a)

Condensation of **14a** (0.298 g, 1.71 mmol) with *N*-Boc-4-piperidone (0.538 g, 2.7 mmol) by General procedure-C gave **8a** as colourless oil, which on standing crystallised (0.112 g, 18% yield). $[\alpha]_D^{20}$ −64.0 (*c* 0.3, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 5.08–5.10 (2H, m), 4.31 (1H, d, *J*=9.7 Hz), 3.93 (1H, dt, *J*=9.5 and 3.0 Hz), 3.37–3.52 (4H, m), 2.18–2.21 ($2H_a$, m), 1.76 (3H, t, *J*=1.1 Hz), 1.56–1.70 ($2H_b$, m), 1.26–1.51 (6H, m), 1.46 (9H, s), 0.9 (3H, t, *J*=7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.02, 139.41, 118.68, 101.71, 88.21, 80.07, 70.09, 35.09, 30.85, 28.83, 27.53, 22.93, 20.21, 17.81, 14.42; IR (neat, cm^{-1}) 2931, 2870, 1697, 1421, 1365, 1240, 1174, 1144, 1097, 1005, 910, 866, 800, 769; *m*/*z* (ES, +ve, solvent: CH_3OH), 378 ($[M+Na]^+$, 100%); HRMS: Found $[M+Na]^+$, 378.22380, $C_{19}H_{33}NO_5Na$ requires 378.22560. Elemental analysis ($C_{19}H_{33}NO_5$),C: 64.30, H: 9.42, N: 3.95 (requires, C: 64.20, H: 9.36, N: 3.94).

5. X-ray crystallography

Single crystal X-ray data were collected on a Bruker APEX D8 diffractometer at 100(2) K and Mo Kα radiation, λ=0.71073 Å. Multi-scan absorption corrections were carried out for compound **1a** and **1b** using the program SADABS (reference: Bruker. SADABS V2008-1, Bruker AXS.: Madison, WI, USA, 2008). The crystals of compound **8a** were twinned; twin boundaries could be observed under a polarising microscope. A multiple crystal of **8a** was indexed using cell_now (reference: Bruker. cell_now, Bruker AXS.: Madison, WI, USA, 2007). All the reflections could be fitted with a monoclinic cell and two twin components. Each component was scaled separately using singles in TWINABS (reference: Bruker. TWINABS, Bruker AXS.: Madison, WI, USA, 2008), and the resulting scale factors were then also used to scale the composite reflections. As the twin was interpenetrating, a large proportion of reflections were overlapping.

The structures were solved and refined with X-SEED (reference: Barbour, L. J. *J. Supramol. Chem.* **2001**, *1*, 189–191.), a graphical interface to SHELX (reference: Sheldrick, G. M. *Acta Cryst.* **2008**, A64, 112–122). Refinement of F^2 on all reflections; for **8a** merged data involving domains 1 and 2 only, as well as those involving both domains. The refined absolute structure parameter (reference: Flack, H. D. *Acta Cryst.* **1983**, *A39*, 876–881) is close to zero for structures **1a** and **1b**, indicating that the chirality has been determined correctly. The absolute configuration of **8a** could not be

determined unambiguously from the X-ray data due to the twinning, but the chiral atoms C3 and C4 are both R in this structure, and are the same as previously determined for structures **1a** and **1b** in this series for which absolute configuration was determined unambiguously. In the final cycles of refinement all non-hydrogen atoms were refined anisotropically, and the hydrogen atoms refined with either restraints or constraints.

5.1. Crystal data for 1a

$C_{17}H_{26}O_3$, M=278.38, colourless prism, 0.30×0.10×0.07 mm^3, orthorhombic, space group $P2_12_12_1$ (No. 19), a=7.3801(17), b=13.320(3), c=15.564(3) Å, V=1530.0(6) Å^3, Z=4, D_c=1.209 g/cm^3, F_{000}=608, Bruker D8 diffractometer with APEX detector, Mo Kα radiation, λ=0.71073 Å, T=173(2)K, $2\theta_{max}$=50.0°, 6139 reflections collected, 2571 unique (R_{int}=0.0396). Final *GooF*=1.142, *R*1=0.0654, *wR*2=0.1186, *R* indices based on 2091 reflections with *I*>2sigma(*I*) (refinement on F^2), 247 parameters, 37 restraints. Lp and absorption corrections applied, μ=0.081 mm^{-1}. Absolute structure parameter=1(2) (Flack, H. D. *Acta Cryst*. **1983**, *A39*, 876–881).

5.2. Crystal data for 1b

$C_{17}H_{26}O_3$, M=278.38, colourless block, 0.30×0.20×0.20 mm^3, monoclinic, space group $P2_1$ (No. 4), a=11.118(3), b=10.098(2), c=14.117(3) Å, β=104.322(4)°, V=1535.7(6) Å^3, Z=4, D_c=1.204 g/cm^3 F_{000}=608, Bruker D8 diffractometer with APEX detector, Mo Kα radiation, λ=0.71073 Å, T=100(2)K, $2\theta_{max}$=55.0°, 8040 reflections collected, 5369 unique (R_{int}=0.0342). Final *GooF*=0.948, *R*1=0.0621, *wR*2=0.1081, *R* indices based on 3128 reflections with *I*>2sigma(*I*) (refinement on F^2), 365 parameters, 1 restraint. Lp and absorption corrections applied, μ=0.081 mm^{-1}.

5.3. Crystal data for 8a

$C_{19}H_{33}NO_5$, M=355.46, colourless plate, 0.50×0.40×0.10 mm^3, monoclinic, space group $P2_1$ (No. 4), a=10.255(2), b=8.640(2), c=11.780(2) Å, β=103.46(3)°, V=1015.1(5) Å^3, Z=2, D_c=1.165 g/cm^3, F_{000}=388, Bruker D8 diffractometer with APEX detector, Mo Kα radiation, λ=0.71073 Å, T=120(2)K, $2\theta_{max}$=55.3°, 4449 reflections collected, 4449 unique (R_{int}=0.0374). Final *GooF*=1.071, *R*1=0.0660, *wR*2=0.1432, *R* indices based on 3328 reflections with *I*>2sigma(*I*) (refinement on F^2), 232 parameters, 1 restraint. Lp and absorption corrections applied, μ=0.083 mm^{-1}. Absolute structure parameter=1.5(16) (Flack, H. D. *Acta Cryst*. **1983**, *A39*, 876–881).

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