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Synthesis of acyldodecaheterocycles derived from (1*R*)-(−)-myrtenal and evaluation as chiral auxiliaries

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ABSTRACT

New (1*R*)-(−)-myrtenal-derived macrocycles **5a** and **5b** were efficiently used as chiral auxiliaries in the diastereoselective nucleophilic addition of several nucleophiles (RMgX, RLi, $LiAlH_4$, and $NaBH_4$). We observed that the diastereoselectivity depended on the nucleophile, with the stereoselectivity order being RMgX (>99:1 dr) > RLi (7:3 dr) > $AlLiH_4 \geqslant NaBH_4$ (6:4 dr). The absolute configuration of the resulting carbinols was established by X-ray diffraction of adducts **9a** and **9b**, and through chemical correlation of carbinols **9b** and **9c** with diols of known absolute configuration.

1. Introduction

The formation of carbon–carbon bonds via nucleophilic addition of organometallic reagents onto substrates bearing a carbonyl group has in recent years shown a significant progress to control chirality. Such transformations are mainly performed by using chiral coadjuvants[1] (auxiliaries and/or chiral ligands), which are often the key tools in the synthesis of a wide variety of chiral biologically active molecules. At present, the search for new chiral auxiliaries is still a central target of great importance in asymmetric synthesis. Among these, particular emphasis on chiral auxiliaries possessing C_2 symmetry has been made since they usually promote higher levels of stereochemical control.[2–4]

We have already described[5a–f] the synthesis of several (1*R*)-(−)-myrtenal-derived chiral auxiliaries bearing an acyl group, which showed 8:2 to >99:1 diastereomeric ratios (dr) under nucleophilic additions wherein a Cram-chelated transition state determined RMgX > RLi > $LiAlH_4$ as the preferred order of diastereoselectivity. Among these chiral auxiliaries are acyloxathianes **1**,[5a,b] acyldioxanes **2**,[5c] acyl-*S*,*O*-thioacetals **3**,[5d,e] and acyldioxadithiadodecaheterocycles **4**[5f] (Fig. 1). The latter compounds showed high stereoselectivity (>99:1 dr) regardless of the chemical features of the nucleophile used, representing a new diastereoselectivity order not previously observed in structurally similar chiral auxiliaries prepared from (1*R*)-(−)-myrtenal[5a–e] or pulegone.[6] It was assumed that this stereoselectivity order is essentially due to steric effects, rather than to chelation effects.[5f] In continuation of this work, we were encouraged to prepare macrocycles **5a** and **5b** in order to evaluate their chiral auxiliary capabilities in the context of (1*R*)-(−)-myrtenal **6** derived chiral auxiliaries, particularly with regard to its structural analogue **4**.[5f]

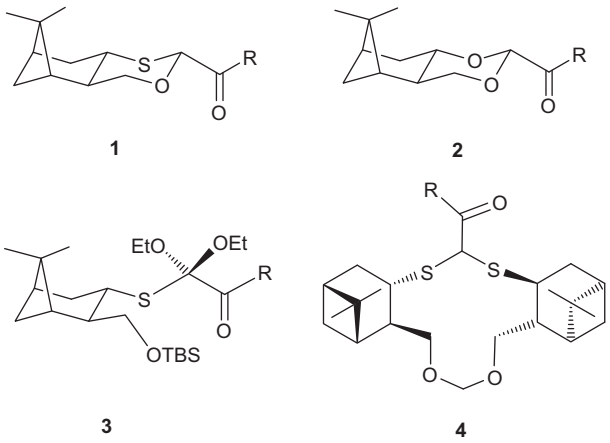

Figure 1. (1*R*)-(−)-Myrtenal derived chiral auxiliaries (R = alkyl or aryl group).

2. Results and discussion

The reaction sequence to obtain the title compounds is shown in Scheme 1. Treatment of (1*R*)-(−)-myrtenal **6** with thiolacetic

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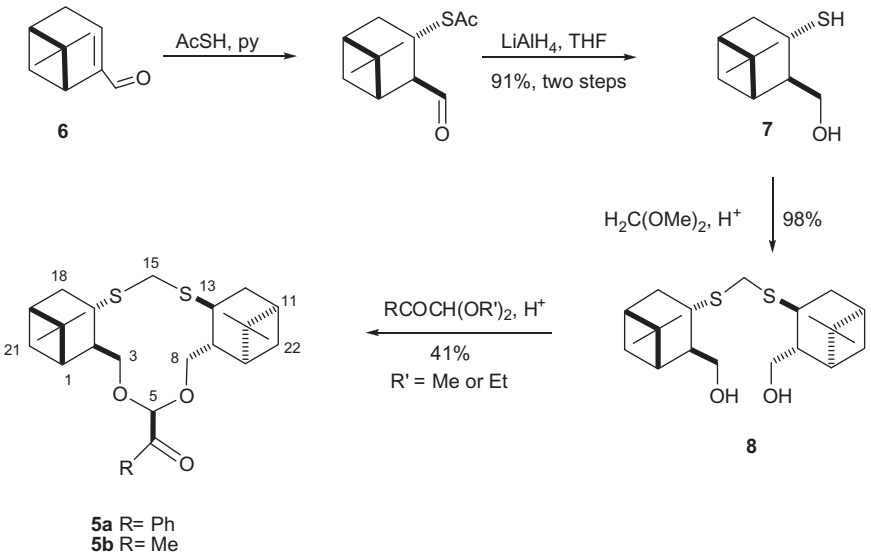


Scheme 1. Preparation of macroheterocycles **5a**,**b**.

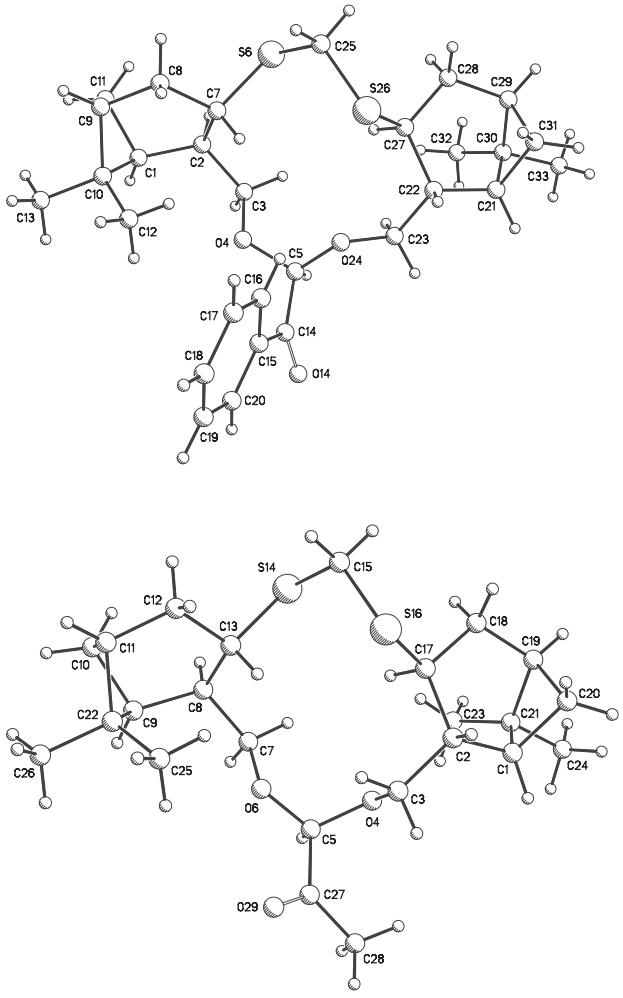


Figure 2. X-Ray structures of macroheterocycles **5a** (top) and **5b** (bottom).

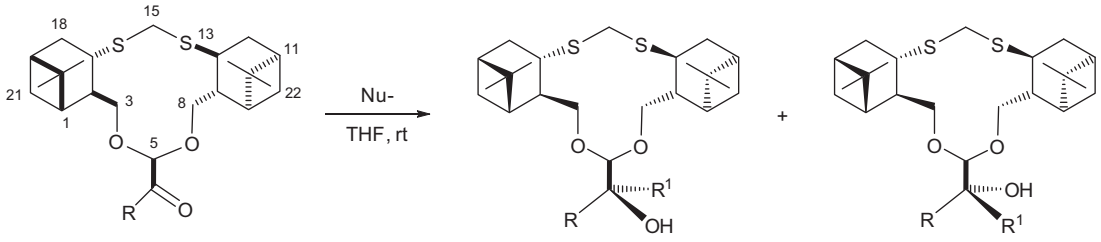
acid and successive reduction of the corresponding Michael adduct with $LiAlH_4$ afforded hydroxythiol **7** in 91% overall yield. Compound **7**, in a benzene solution, was reacted with dimethoxymethane in the presence of a catalytic amount of *p*-TsOH to give diol **8** in 98% yield. Macrocyclization was achieved through a transacetalization reaction of diol **8** with the corresponding α-ketoacetal to afford, after column chromatography, acyldioxadithiadodecacycles **5a**,**b** in 41% yields. The low yield was due to side reactions resulting from the hydrolysis of the thioacetal group to afford hydroxythiol **7** and the concomitant formation of the corresponding acyloxathiane 1.[5a,b]

The structural characterization of compounds **5a**,**b** was carried out by NMR measurements and single crystal X-ray diffraction analysis. Projections of the X-ray structures of **5a**,**b** are depicted in Figure 2, which show that both compounds differ in the conformation of the acyl group in the solid state, since in **5a**, the carbonyl group of the benzoyl moiety is almost coplanar with H-5, whereas in compound **5b** the carbonyl group of the acetyl moiety is coplanar with O4. It is worth noting that in both compounds, C-5 is a pseudostereogenic center, so α or β projection of this center represents the same structure for either compound. This structural feature confers compounds **5a** and **5b** similar properties to those of chiral auxiliaries with C_2 symmetry.

The results obtained after diastereoselective addition of several organometallic reagents on the *pro*-stereogenic center of compounds **5a**,**b** to yield carbinols **9a**–**h** and **10a**–**h** are summarized in Table 1. In contrast to the results observed for compound **4**,[5f] in which all of the nucleophilic reagents showed very similar stereoselectivities, the diastereoselectivity of the nucleophilic additions on to compounds **5a**,**b** depends on the nature of the nucleophile. For instance, Grignard reagents showed excellent yields and diastereoselectivities (entries 1–6, 11 and 12), whereas lithium alkylides and hydrides ($LiAlH_4$ and $NaBH_4$) showed significantly lower diastereoselectivities (entries 7–10). The above diastereoselectivity is in close agreement with that shown by acyloxathianes,[5a,b] acyldioxanes,[5c] and acyl-*S*,*O*-thioacetals[5d,e] in which the stereoselectivity was explained by means of a Cram chelated transition state.[7]

The facial diastereoselectivity was evidenced by X-ray diffraction of carbinols **9a**,**b** and chemical correlation of carbinols **9b**,**c** with diols of known absolute configuration.[8] Thus, the X-ray structure of adducts **9a** and **9b** showed an (*S*)-absolute configuration at the new stereogenic center (Fig. 3), revealing that the nucleophilic attack took place from the *re*-face of the carbonyl group. In turn, the absolute configuration of the new stereogenic center of

Table 1
Diastereoselective nucleophilic additions to macroheterocycles **5a,b**



5a R = Ph
5b R = Me

9 **10**

Entry	R	Nucleophile	R^1	Major adduct	Yield (%)	**9**:**10** (dr)*
1	Ph	MeMgBr	Me	**9a**	98	>99:1
2	Ph	EtMgBr	Et	**9b**	98	>99:1
3	Ph	BnMgBr	Bn	**9c**	98	>99:1
4	Ph	PhC≡CMgBr	PhC≡C–	**9d**	92	>99:1
5	Ph	CH≡CMgBr	CH≡C–	**9e**	90	>99:1
6	Ph	CH_2=CHMgBr	CH_2=CH–	**9f**	90	>99:1
7	Ph	MeLi	Me	**9a**	55	7:3
8	Ph	EtLi	Et	**9b**	60	7:3
9	Ph	$LiAlH_4$	H	**9g**	99	>7:3
10	Ph	$NaBH_4$	H	**9g**	99	>6:4
11	CH_3	PhMgBr	Ph	**10a****	95	1:>99
12	CH_3	BnMgBr	Bn	**9h**	95	9:1

*Diastereomeric ratio obtained by ^{1}H NMR integration of H-5 signals in the crude reaction mixture. **Major adduct **10a** in entry 11 corresponds to minor adduct obtained in entry 1 (R = Ph; R_1 = CH_3).

carbinol **10a** should be (*R*) (entry 11) since in this case the acyl group (CH_3CO–) and the incoming nucleophile (PhMgBr) are opposite to those shown in entry 1. As mentioned above, the stereofacial preference of the nucleophilic addition onto **5a** was also confirmed by chemical correlation with diols **11a** and **11b** of known absolute configuration.[8] Oxidative hydrolysis of carbinols **9b** and **9c**, followed by reduction of the intermediate α-hydroxyaldehydes with $NaBH_4$, afforded the corresponding tertiary carbinols **11a** and **11b** with excellent enantiomeric excesses (Scheme 2), while enantiopure chiral auxiliary diol **8** was recovered.

Furthermore, Table 1 shows that the addition of MeLi and EtLi (entries 7 and 8) onto compound **5a** afforded the same products (carbinols **9a** and **9b**, respectively), when this compound was treated with MeMgBr and EtMgBr (entries 1 and 2). Treatment of **5a** with hydrides ($LiAlH_4$ and $NaBH_4$, entries 9 and 10) also gave carbinol **9g**. Accordingly, it was possible to propose that all nucleophilic additions take place preferably on the same face of the carbonyl group.

According to the observed nucleophilic order RMgX > RLi > $LiAlH_4 \geqslant NaBH_4$, it is feasible to propose that the preferred product is generated through a rigid Cram chelated model[7] in which the diastereoselectivity depends on the coordinating capability of the metal belonging to the nucleophilic reagent; this is in agreement with the same mechanism as observed for previously described structural analogues.[5a–e] In this context, despite conformations of the acyl group and the macrocycle differing in compounds **5a** and **5b** in the solid state, it can be inferred that the coordinating site of the nucleophilic reagent must be the same in both compounds, since the X-ray structures of carbinols **9a** and **9b** and the chemical correlation of **9b** and **9c** strongly support the idea that the addition of the nucleophile takes place from the *re*-face. Furthermore, the inverse protocol followed for the nucleophilic addition on both compounds afforded epimeric products at the carbinol center (entries 1, 11, 3 and 12). This implies that the resulting chelated complex formed between the C=O groups of the acetyl and benzoyl moieties with the nucleophilic reagent must be similar in the corresponding transition state. Under this premise, transition states **5a.1** and **5a.2** were proposed taking into account the resulting Cram chelated model[7] by coordinating the C=O group of the acyl moiety and O4 or O6, respectively, with the nucleophilic reagent, as shown in Figure 4. In model **5a.1**, which shows a similar conformation to compound **5b** in the solid state (Fig. 2), a strong steric interaction between the nucleophile and the geminal methyl groups of the pinane system can be observed. In contrast, model **5a.2** yields a more stable chelated complex since the coordinating nucleophile lacks significant steric interactions. Such a transition state will allow a free nucleophile approach onto the *re*-face of the C=O group, which is in close agreement with the absolute configuration shown at the carbinol stereogenic center of the addition products.

3. Conclusion

Compounds **5a**,**b** provide a new structural feature in the series of chiral auxiliaries prepared from (1*R*)-(−)-myrtenal **6**. Although the observed diastereoselectivities of lithium alkylides and hydrides were lower when compared to those obtained with acylmacroheterocycle **4**, the addition of Grignard reagents is still highly diastereoselective, affording the antipode of diols obtained with **4**[5f] after completion of the present protocol. In addition, the hydrolysis of the resulting carbinols can be achieved under milder conditions as compared to those employed when acylmacroheterocyle **4** was used.[5f] A mechanism for the nucleophilic addition onto compounds **5a**,**b** has been proposed, in which transition state **5a.2**, where chelation takes place between the carbonyl group oxygen atom and O6, satisfactorily explains the observed *re*-facial stereoselectivity.

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

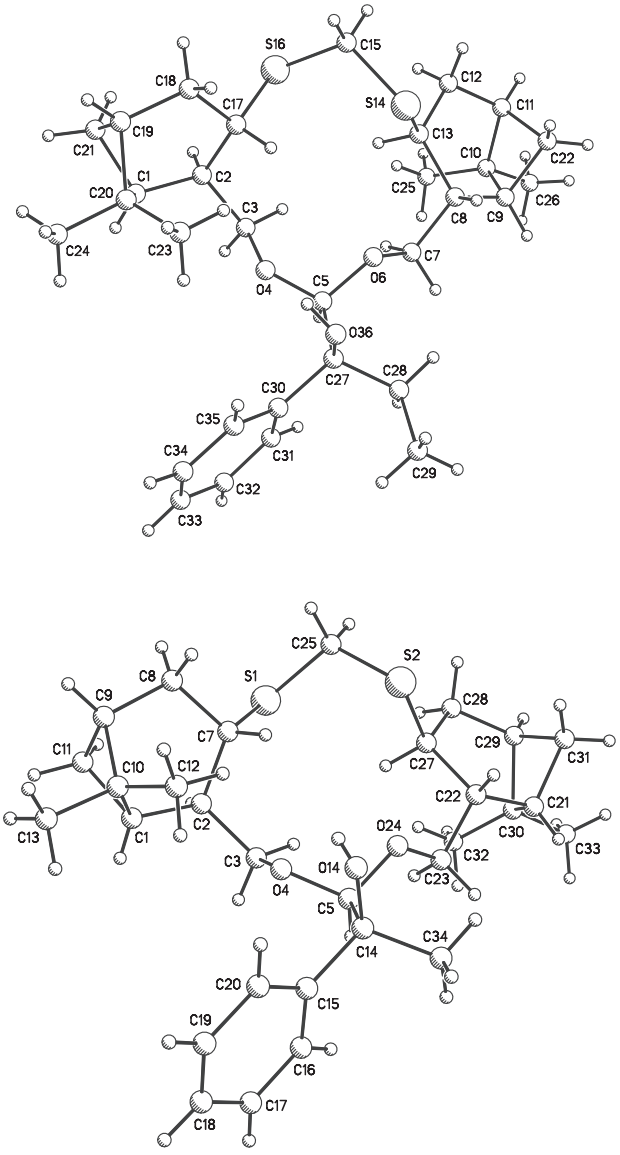


Figure 3. X-Ray structures of carbinols **9a** (top) and **9b** (bottom).

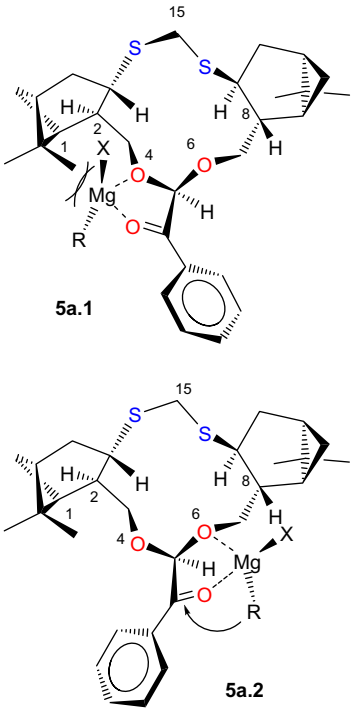


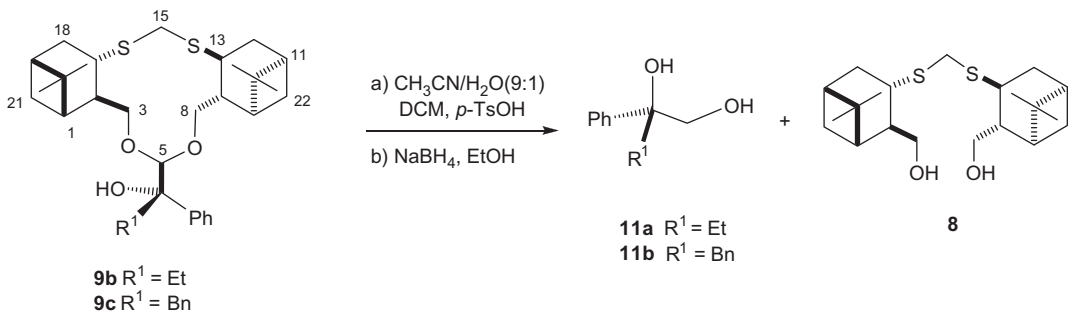
Figure 4. Non-preferred **5a.1** (top) and preferred **5a.2** (bottom) transition states for the diastereoselective nucleophilic addition on acylmacrocycles **5a,b**.

polarimeter. Infrared spectra were recorded on a Perkin-Elmer Spectrum 2000 spectrophotometer. ^{1}H and ^{13}C NMR spectra were obtained on a Varian Mercury spectrometer at 300 and 75.4 MHz, respectively, or 500 and 125 MHz on a Varian System as specified, using $CDCl_3$ as the solvent and TMS as the internal standard. The high-resolution fast atomic bombardment mass spectra (HRFABMS) were recorded on a VG 7070 high-resolution mass spectrometer at the UCR Mass Spectrometry Facility, University of California, Riverside, CA. High resolution electronic impact mass spectra (HREIMS) were determined using a JEOL GCmate spectrometer. Thin layer chromatograms were performed on precoated TLC sheets of silica gel 60 F_{254} (E. Merck). Flash chromatography was carried out using silica gel (Merck 230–400 mesh). The 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. Preparation of macroheterocycles 5a,b

4.2.1. (1*S*,2*R*,8*R*,9*S*,13*S*,17*S*)-4,6-Dioxa-14,16-dithia-5-benzoyl-10,10,20,20-tetramethylpentacyclo-[17.1.1.1^{9,11}.0^{2,17}.0^{8,13}]-docosane 5a

A well-stirred solution of 500 mg (1.3 mmol) of diol **8**, 406 mg (1.95 mmol) of 2,2-diethoxyacetophenone, and 50 mg of *p*-TsOH in 8 mL of benzene was stirred at 60 °C for 3 h. The reaction mixture was poured into a cold saturated solution of $NaHCO_3$, extracted with DCM, washed with a saturated solution of $NaHCO_3$



Scheme 2. Hydrolysis of adducts **9b** and **9c**.

(2 × 50 mL), dried over anhydrous Na_2SO_4, and concentrated to dryness. The residue was flash chromatographed using a mixture of hexane/EtOAc (9:1) as the eluent, affording 260 mg (41%) of dodecaheterocycle **5a** as a white solid, mp 166–167 °C, $[\alpha]_D^{25} = +294.5$ (*c* 0.49, $CHCl_3$). IR (cm^{-1}) ν_{max}: 2909, 1467, 1057, 689. ^1H NMR (500 MHz, $CDCl_3$): δ 8.15 (dd, 2H, *J* = 8.4, 1.3 Hz, H-*o*), 7.55 (tt, 1H, *J* = 7.5, 1.3 Hz, H-*p*), 7.43 (bt, 2H, *J* = 8.4 Hz, H-*m*), 5.25 (s, 1H, H-5), 4.01 (dd, 1H, *J* = 9.9, 3.8 Hz, H-3a), 3.90 (dd, 1H, *J* = 9.9, 3.3 Hz, H-3b), 3.86 (d, 1H, *J* = 14.2 Hz, H-15a), 3.85 (dd, 1H, *J* = 9.4, 3.3 Hz, H-17), 3.82 (d, 1H, *J* = 14.2 Hz, H-15b), 3.75–3.67 (m, 3H, H-7a, H-7b, H-13), 2.60–2.52 (m, 2H, H-12*eq*, H-18*eq*), 2.47 (m, 1H, H-21*eq*), 2.41 (m, 1H, H-22*eq*), 2.28 (m, 1H, H-8), 2.13–1.90 (m, 7H, H-2, H-1, H-12*ax*, H18*ax*, H-19, H-9, H-11), 1.20 (s, 3H, Me-26), 1.15 (d, 1H, *J* = 9.7 Hz, H-22*ax*), 1.10 (s, 3H, Me-24), 1.05 (d, 1H, *J* = 9.7 Hz, H-21*ax*), 1.04 (s, 3H, Me-25), 0.87 (s, 3H, Me-23). ^{13}C NMR (125 MHz, $CDCl_3$): δ 194.0 (CO), 134.1 (C-*i*), 133.4 (C-*p*), 129.6 (C-*m*), 128.2 (C-*o*), 102.3 (C-5), 70.9 (C-7), 70.8 (C-3), 49.7 (C-2), 48.9 (C-8), 46.9 (C-1), 45.4 (C-9), 42.4 (C-19), 41.9 (C-11), 38.8 (C-20), 38.5 (C-10), 37.5 (2C, C-18 and C-12), 35.7 (C-21), 34.6 (C-15), 34.1 (C-13), 33.7 (C-17), 33.4 (C-22), 27.8 (C-24), 27.7 (C-26), 24.9 (C-23), 24.4 (C-25). HREIMS Calcd for $C_{29}H_{40}S_2O_3$ (M+1): 501.2497. Found: 501.2501.

4.2.2. (1*S*,2*R*,8*R*,9*S*,13*S*,17*S*)-4,6-Dioxa-14,16-dithia-5-acetyl-10,10,20,20-tetramethypentacyclo-[17.4.1.1.1^{9,11}.0^{2,17}.0^{8,13}]-docosane 5b

A well-stirred solution of 500 mg (1.3 mmol) of diol **8**, 230 mg (1.95 mmol) of pyruvic aldehyde dimethyl acetal, and 50 mg of *p*-TsOH in 8 mL of benzene was refluxed for 3 h. The reaction mixture was poured into a cold saturated solution of $NaHCO_3$, extracted with DCM, washed with a saturated solution of $NaHCO_3$ (2 × 50 mL), dried over anhydrous Na_2SO_4, and concentrated to dryness. The residue was flash chromatographed using a mixture of hexane/EtOAc (19:1) as the eluent, affording 228 mg (41%) of dodecaheterocycle **5b** as a white solid, mp 103–105 °C, $[\alpha]_D^{25} = +324.9$ (*c* 0.40, $CHCl_3$). IR (cm^{-1}) ν_{max}: 3425, 2910, 1469, 1061.5, 668.5. ^1H NMR (500 MHz, $CDCl_3$): δ 4.39 (s, 1H, H-5), 3.93–3.79 (m, 5H, H-3a, H-3b, H-15a, H-15b, H-17), 3.65 (t, 1H, *J* = 9.0 Hz, H-7a), 3.64 (m, 1H, H-13), 3.51 (dd, 1H, *J* = 9.0, 4.2 Hz, H-7b), 2.63–2.46 (m, 3H, H-12*eq*, H-18*eq*, H-22*eq*), 2.41 (m, 1H, H-21*eq*), 2.29 (m, 1H, H-8), 2.19 (s, 3H, Me-28), 2.16–1.87 (m, 7H, H-1, H-2, H-11, H-12*ax*, H-18*ax*, H-19, H-9), 1.23 (s, 3H, Me-26), 1.24 (d, 1H, *J* = 9.8 Hz, H-22*ax*), 1.20 (s, 3H, Me-24), 1.07 (s, 3H, Me-25), 1.05 (d, 1H, *J* = 9.8 Hz, H-21*ax*), 0.97 (s, 3H, Me-23). ^{13}C NMR (125 MHz, $CDCl_3$): δ 204.6 (CO), 104.1 (C-5), 72.2 (C-7), 71.3 (C-3), 49.8 (C-2), 48.8 (C-8), 47.2 (C-1), 44.7 (C-9), 42.4 (C-11), 41.8 (C-19), 38.9 (C-10), 38.4 (C-20), 37.6 (C-12), 37.4 (C-18), 36.0 (C-21), 34.7 (C-15), 33.9 (C-13), 33.2 (C-17), 32.4 (C-22), 28.2 (C-26), 27.4 (C-24), 25.4 (C-25), 25.1 (C-28), 24.1 (C-23). HRFABMS Calcd for $C_{29}H_{40}S_2O_3$+Na: 461.2160. Found: 461.2160.

4.3. General procedure for the addition of Grignard reagents to dodecaheterocycle

To a solution of 200 mg of dodecaheterocycle **5a** or **5b** in anhydrous THF was added the Grignard reagent (1.5–4.0 equiv) at −78 °C under a nitrogen atmosphere. After stirring for 2 h at the same temperature, the reaction mixture was allowed to warm to room temperature and stirred for a further 2 h. The reaction mixture was quenched with 100 mL of a saturated solution of NH_4Cl, after which the THF was eliminated by evaporation and the remaining emulsion was extracted with ethyl ether. The organic layer was washed with a saturated solution of NH_4Cl, dried over anhydrous Na_2SO_4, and evaporated to dryness, giving the corresponding pure diastereoisomer **9a**–**f** or **10a**–**f** as a colorless oil or a white solid, as specified.

4.3.1. (1*S*,2*R*,8*R*,9*S*,13*S*,17*S*)-4,6-Dioxa-14,16-dithia-5-[(*S*)-1-phenyleth-1-yl-1-ol]-10,10,20,20-tetramethylpentacyclo-[17.1.1.1^{9,11}.0^{2,17}.0^{8,13}]-docosane 9a

To a solution of 300 mg (0.6 mmol) of macroheterocycle **5a** in 5 mL of anhydrous THF was added 0.3 mL (0.9 mmol) of MeMgBr (3.0 M) under a nitrogen atmosphere. After the usual work-up, 303 mg (98%) of carbinol **9a** was obtained as a white solid mp 167–168 °C, $[\alpha]_D^{25} = +163$ (*c* 0.20, $CHCl_3$). IR (cm^{-1}) ν_{max}: 3733, 2915, 1448, 1385, 1050, 1027, 757. ^1H NMR (300 MHz, $CDCl_3$): δ 7.49 (dd, 2H, *J* = 8.5, 1.5 Hz, H-*o*), 7.33 (t, 2H, *J* = 8.5 Hz, H-*m*), 7.26 (t, 1H, *J* = 8.5 Hz, H-*p*), 4.35 (s, 1H, H-5), 3.87–3.60 (m, 6H, H-3a, H-3b, H-7a, H-15a, H-15b, H-17), 3.46 (m, 1H, H-13), 3.13 (dd, 1H, *J* = 8.8, 4.3 Hz, H-7b), 2.75 (bs, 1H, OH), 2.63–2.33 (m, 4H, H-12*eq*, H-18*eq*, H-21*eq*, H-22*eq*), 2.26 (m, 1H, H-8), 2.08–1.82 (m, 7H, H-1, H-2, H-9, H-11, H-12*ax*, H-18*ax*, H-19), 1.57 (s, 3H, Me-28), 1.19 (s, 3H, Me-26), 1.16 (d, 1H, *J* = 9.9 Hz, H-22*ax*), 1.15 (s, 3H, Me-24), 1.07 (s, 3H, Me-25), 0.97 (d, 1H, *J* = 9.9 Hz, H-21*ax*), 0.84 (s, 3H, Me-23). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 144.2 (C*i*), 127.8 (C-*m*), 126.9 (C-*p*), 125.8 (C-*o*), 106.8 (C-5), 76.1 (C-27), 75.9 (C-7), 69.9 (C-3), 50.3 (C-2), 49.5 (C-8), 46.6 (C-1), 45.1 (C-9), 42.2 (C-19), 41.5 (C-11), 38.3 (C-10), 37.9 (C-20), 37.6 (C-18), 37.1 (C-12), 35.8 (C-21), 35.5 (C-13), 35.3 (C-15), 34.0 (C-17), 32.4 (C-22), 28.0 (C-26), 27.2 (C-24), 25.2 (C-25), 25.0 (C-28), 23.6 (C-23). HREIMS Calcd for $C_{30}H_{44}S_2O_3$: (M+1): 517.2810. Found: 517.2794.

4.3.2. (1*S*,2*R*,8*R*,9*S*,13*S*,17*S*)-4,6-Dioxa-14,16-dithia-5-[(*S*)-1-phenylpro-1-yl-1-ol]-10,10,20,20-tetramethylpentacyclo-[17.1.1.1^{9,11}.0^{2,17}.0^{8,13}]-docosane 9b

To a solution of 300 mg (0.6 mmol) of macroheterocycle **5a** in 5 mL of anhydrous THF was added 0.3 mL (0.9 mmol) of EtMgBr (3.0 M) under a nitrogen atmosphere. After the usual work-up, 311 mg (98%) of carbinol **9b** was obtained as a white solid mp 162–163 °C, $[\alpha]_D^{25} = +242$ (*c* 0.10, $CHCl_3$). IR (cm^{-1}) ν_{max}: 3563, 2908, 1449, 1385, 1061, 756. ^1H NMR (500 MHz, $CDCl_3$): δ 7.43 (d, 2H, *J* = 7.8 Hz, H-*o*), 7.34 (t, 2H, *J* = 7.8 Hz, H-*m*), 7.23 (t, 1H, *J* = 7.8 Hz, H-*p*), 4.41 (s, 1H, H-5), 3.86–3.75 (m, 4H, H-3a, H-7a, H-15a, H-15b), 3.62–3.56 (m, 2H, H-3b, H-13), 3.44–3.40 (m, 2H, H-7b, H-17), 2.62 (bs, 1H, OH), 2.57 (m, 2H, H-12*eq*, H-18*eq*), 2.42–2.38 (m, 2H, H-21*eq*, H-22*eq*), 2.30 (bq, 1H, *J* = 4.9 Hz, H-8), 2.04–1.87 (m, 8H, H-2, H-1, H-11, H-12*ax*, H-18*ax*, H19, H-28a,b), 1.73 (t, 1H, *J* = 5.8 Hz, H-9), 1.19 (s, 3H, Me-26), 1.16 (d, 1H, *J* = 9.8 Hz, H-22*ax*), 1.13 (s, 3H, Me-24), 1.02 (s, 3H, Me-25), 0.91 (d, 1H, *J* = 9.8 Hz, H-21*ax*), 0.90 (s, 3H, Me-23), 0.70 (t, 1H, *J* = 7.8 Hz, H-29). ^{13}C NMR (125 MHz, $CDCl_3$): δ 142.2 (C-*i*), 127.7 (C-*m*), 126.5 (C-*p*), 126.1 (C-*o*), 106.1 (C-5), 79.1 (C-27), 75.2 (C-7), 69.6 (C-3), 50.5 (C-2), 49.9 (C-8), 46.4 (C-1), 45.3 (C-9), 42.1 (C-19), 41.6 (C-11), 38.3 (C-20), 38.1 (C-10), 37.6 (C-18), 37.2 (C-12), 35.9 (C-13), 35.6 (C-21), 35.5 (C-15), 34.4 (C-17), 32.8 (C-22), 28.8 (C-28), 27.9 (C-24), 27.3 (C-26), 24.9 (C-25), 23.7 (C-23), 7.0 (C-29). HREIMS Calcd for $C_{31}H_{46}S_2O_3$ (M+1): 531.2961. Found: 531.2956.

4.3.3. (1*S*,2*R*,8*R*,9*S*,13*S*,17*S*)-4,6-Dioxa-14,16-dithia-5[(*S*)-1,2-diphenyleth-1-yl-1-ol]-10,10,20,20-tetramethylpentacyclo-[17.1.1.1^{9,11}.0^{2,17}.0^{8,13}]-docosane 9c

To a solution of 300 mg (0.6 mmol) of macroheterocycle **5a** in 5 mL of anhydrous THF was added 0.2 mL (0.9 mmol) of $PhCH_2MgBr$ (3.0 M) under a nitrogen atmosphere. After the usual work-up, 347 mg (98%) of carbinol **9c** was obtained as a white solid mp 124–125 °C, $[\alpha]_D^{25} = +196$ (*c* 0.20, $CHCl_3$). IR (cm^{-1}) ν_{max}: 3560, 2911, 1440, 1380, 1164, 710, ^1H NMR (300 MHz, $CDCl_3$): δ 7.36 (dd, 2H, *J* = 8.2, 2.2 Hz, H-*o*), 7.28–7.19 (m, 3H, H-*o*′, *H-p*′), 7.12–7.07 (m, 3H, H-*p*,*m*), 6.95–6.92 (m, 2H, H-*m*′), 4.6 (s, 1H, H-5), 3.95 (dd, 1H, *J* = 9.1, 6.0 Hz, H-3a), 3.87–3.75 (m, 3H, H-7a, H-15a, H-15b), 3.62–3.53 (m, 3H, H-3b, H-7b, H-17), 3.44 (m, 1H, H-13), 3.25 (d, 1H,

J = 13.8 Hz, H-28a), 3.17(d, 1H, *J* = 13.8 Hz, H-28b), 2.84 (bs, 1H, OH), 2.58–2.29 (m, 5H, H-8, H-12*eq*, H-18*eq*, H-21*eq*, H-22*eq*), 2.06–1.88 (m, 6H, H-2, H-9, H-11, H-12*ax*, H-18*ax*, H-19), 1.69 (td, 1H, *J* = 6.0, 1.3 Hz, H-9), 1.23 (s, 3H, Me-26), 1.16 (d, 1H, *J* = 9.9 Hz, H-22*ax*), 1.08 (s, 3H, Me-24), 0.98 (s, 3H, Me-25), 0.95 (s, 3H, Me-23), 0.92 (d, 1H, *J* = 9.9 Hz, H-21*ax*). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 142.3 (C-*i*), 136.6 (C-*i*′), 130.7 (C-*m*′), 127.5 (C-o′,*p*), 126.6 (C-*o*), 126.3 (C-*p*′), 126.0 (C-*m*), 104.7 (C-5), 78.9 (C-27), 74.1 (C-7), 69.6 (C-3), 50.5 (C-2), 50.0 (C-8), 46.4 (C-1), 45.5 (C-9), 43.5 (C-28), 42.0 (C-19), 41.7 (C-11), 38.3 (C-10), 38.2 (C-20), 37.5 (C-18), 37.3 (C-12), 35.9 (C-21), 35.5 (C-13, C-15), 34.5 (C-17), 33.2 (C-22), 27.9 (C-24), 27.5 (C-26), 24.8 (C-25), 23.9 (C-23). HRFABMS Calcd for $C_{36}H_{48}S_2O_3$+Na: 615.2942. Found: 615.2953.

4.3.4. (1*S*,2*R*,8*R*,9*S*,13*S*,17*S*)-4,6-Dioxa-14,16-dithia-5-[(*S*)-1,2-diphenyl-2-propyn-1-yl-1-ol]-10,10,20,20-tetramethylpentacyclo-[17.1.1.1^{9,11}.0^{2,17}.0^{8,13}]-docosane 9d

To a solution of 300 mg (0.6 mmol) of macroheterocycle **5a** in 5 mL of anhydrous THF was added 0.9 mL (0.9 mmol) of PhCΞCMgBr (1.0 M) under a nitrogen atmosphere. After the usual work-up, 324 mg (90%) of carbinol **9d** was obtained as a white solid mp 90–91 °C. $[\alpha]_D^{25} = +247$ (*c* 0.23, $CHCl_3$). IR (cm^{-1}) ν_{max}: 3558, 2917, 1450, 1366, 1131, 1065, 757. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.72 (dd, 2H, *J* = 8.8, 2.2 Hz, H-*o*), 7.48 (dd, 2H, *J* = 7.1, 2.2 Hz, H-*o*′), 7.40–7.29 (m, 6H, H-*p*,*p*′, *m*,*m*′), 4.46 (s, 1H, H-5), 3.92 (dd, 1H, *J* = 10.0, 3.1 Hz, H-3a), 3.90 (d, 1H, *J* = 13.9 Hz, H-15a), 3.80 (d, 1H, *J* = 13.9 Hz, H-15b), 3.79–3.66 (m, 3H, H-3b, H-7a, H-17), 3.56 (m, 1H, H-13), 3.40 (bs, 1H, OH), 3.31 (dd, 1H, *J* = 8.8, 3.7 Hz, H-7b), 2.60–2.42 (m, 4H, H-12*eq*, H-18*eq*, H-21*eq*, H-22*eq*), 2.36 (m, 1H, H-8), 2.06–1.91 (m, 6H, H-2, H-1, H-11, H-12*ax*, H-18*ax*, H-19), 1.78 (td, 1H, = 6.1, 2.2 Hz, H-9), 1.23 (d, 1H, *J* = 9.8 Hz, H-22*ax*), 1.19 (s, 3H, Me-26), 1.12 (s, 3H, Me-24), 1.10 (s, 3H, Me-25), 0.97 (d, 1H, *J* = 9.8 Hz, H-21*ax*), 0.83 (s, 3H, Me-23). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 140.2 (C-*i*), 132.0 (C-*o*′), 128.5 (C-*p*), 128.4 (C-*m*,*m*′), 128.2 (C-*p*′), 126.9 (C-*o*), 122.9 (C-*i*′), 106.5 (C-5), 89.9 (C-28), 86.1 (C-29), 76.9 (C-27), 75.2 (C-7), 69.7 (C-3), 50.5 (C-2), 49.4 (C-8), 46.7 (C-1), 45.2 (C-9), 42.3 (C-19), 41.5 (C-11), 38.5 (C-20), 37.9 (C-10), 37.7 (C-18), 37.1 (C-12), 35.9 (C-21), 35.2 (C-15), 35.1 (C-13), 34.5 (C-17), 32.0 (C-22), 28.1 (C-26), 27.2 (C-24), 25.1 (C-25), 23.7 (C-23). HRFABMS Calcd for $C_{37}H_{46}S_2O_3$+Na: 625.2786. Found: 625.2761.

4.3.5. (1*S*,2*R*,8*R*,9*S*,13*S*,17*S*)-4,6-Dioxa-14,16-dithia-5-[(*S*)-1-phenyl-2-propyn-1-yl-1-ol]-10,10,20,20-tetramethylpentacyclo-[17.1.1.1^{9,11}.0^{2,17}.0^{8,13}]-docosane 9e

To a solution of 300 mg (0.6 mmol) of macroheterocycle **5a** in 5 mL of anhydrous THF was added 1.8 mL (0.9 mmol) of HCΞCMgBr (0.5 M) under a nitrogen atmosphere. After the usual work-up, 309 mg (98%) of carbinol **9e** was obtained as a white solid mp 135–136 °C, $[\alpha]_D^{25} = +180.3$ (*c* 0.35, $CHCl_3$). IR (cm^{-1}) ν_{max}: 3306, 2910, 1450, 1386, 1163, 1063, 755. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.67 (dd, 2H, *J* = 8.2, 1.6 Hz, H-*o*), 7.44–7.22 (m, 3H, H-*m*,*p*), 4.41 (s, 1H, H-5), 3.92–3.65 (m, 5H, H-3a, H-7a, H-3b, H-15a, H-15b), 3.59 (m, 1H, H-17), 3.44 (m, 1H, H-13), 3.37 (bs, 1H, OH), 3.27 (dd, 1H, *J* = 8.8, 3.9 Hz, H-7b), 2.68–2.24 (m, 2H, H-12*eq*, H-29), 2.52–2.40 (m, 2H, H-18*eq*, H-21*eq*), 2.39–2.26 (m, 2H, H-8, H-22*eq*), 2.10–1.88 (m, 6H, H-2, H-1, H-11, H-12*ax*, H-18*ax*, H-19), 1.82 (m, 1H, H-9), 1.20 (d, 1H, *J* = 9.9 Hz, H-22*ax*), 1.20 (s, 3H, Me-26), 1.14 (s, 3H, Me-24), 1.08 (s, 3H, Me-25), 0.96 (d, 1H, *J* = 9.9 Hz, H-21*ax*), 0.79 (s, 3H, Me-23). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 139.8 (C-*i*), 128.3 (C-*p*), 128.1 (C-*m*), 126.8 (C-*o*), 106.4 (C-5), 84.6 (C-28), 76.7 (C-27), 74.9 (C-7), 74.6 (C-29), 69.8 (C-3), 50.6 (C-2), 49.6 (C-8), 46.5 (C-1), 45.3 (C-9), 42.4 (C-19), 41.6 (C-11), 38.8 (C-20), 38.1 (C-10), 37.9 (C-18), 37.1 (C-12), 35.9 (C-21), 35.7 (C-13), 35.5 (C-15), 35.1 (C-17), 32.0 (C-22), 28.2 (C-26), 27.3 (C-24), 25.2 (C-25), 23.8 (C-23). HRFABMS Calcd for $C_{31}H_{42}S_2O_3$+Na: 549.2484. Found: 549.2575.

4.3.6. (1*S*,2*R*,8*R*,9*S*,13*S*,17*S*)-4,6-Dioxa-14,16-dithia-5-[(*S*)-1-phenyl-2-propyn-1-yl-1-ol]-10,10,20,20-tetramethylpentacyclo-[17.1.1.1^{9,11}.0^{2,17}.0^{8,13}]-docosane 9f

To a solution of 300 mg (0.6 mmol) of macroheterocycle **5a** in 5 mL of anhydrous THF was added 1.8 mL (0.9 mmol) of CH_2=CHMgBr (0.5 M) under a nitrogen atmosphere. After the usual work-up, 284 mg (90%) of **9f** was obtained as a white solid, mp 151–152 °C. $[\alpha]_D^{25} = +236$ (*c* 0.50, $CHCl_3$). IR (cm^{-1}) ν_{max}: 3434, 2909, 1449, 1366, 1127, 1053, 754. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.49 (dd, 2H, *J* = 7.9, 1.3 Hz, H-*o*), 7.31 (t, 2H, *J* = 7.9 Hz, H-*m*), 7.23 (bt, 1H, *J* = 7.9 Hz, H-*p*), 6.52 (dd, 1H, *J* = 17.3, 10.8 Hz, H-28), 5.46 (dd, 1H, *J* = 17.3, 1.6 Hz, H-29a), 5.25 (dd, 1H, *J* = 10.8, 1.6 Hz, H-29b), 4.46 (s, 1H, H-5), 3.83 (dd, 1H, *J* = 10.1, 4.7 Hz, H-3a), 3.82 (d, 1H, *J* = 14.1 Hz, H-15a), 3.78 (d, 1H, *J* = 14.1 Hz, H-15b), 3.71 (dd, 1H, *J* = 10.1, 2.5 Hz, H-3b), 3.68 (t, 1H, *J* = 8.7, H-7a), 3.60 (m, 1H, H-17), 3.50 (m, 1H, H-13), 3.11 (dd, 1H, *J* = 8.7, 3.9 Hz, H-7b), 2.84 (bs, 1H, OH), 2.57 (m, 1H, H-12*eq*), 2.52–2.40 (m, 2H, H-18*eq*, H-21*eq*), 2.36 (m, 1H, H-22*eq*), 2.26 (m, 1H, H-8), 2.08–1.87 (m, 6H, H-2, H-1, H-11, H-12*ax*, H-18*ax*, H-19), 1.79 (td, 1H, *J* = 6.1, 2.2 Hz, H-9), 1.16 (d, 1H, *J* = 9.8 Hz, H-22*ax*), 1.15 (s, 6H, Me-26, Me-24), 0.96 (d, 1H, *J* = 9.8 Hz, H-21*ax*), 0.95 (s, 3H, Me-25), 0.84 (s, 3H, Me-23). ^{13}C NMR (125 MHz, $CDCl_3$): δ 142.6 (C-*i*), 140.1 (C-28), 127.9 (C-*m*), 127.1 (C-*p*), 126.9 (C-*o*), 115.1 (C-29), 106.5 (C-5), 78.2 (C-27), 76.7 (C-7), 69.6 (C-3), 50.5 (C-2), 49.2 (C-8), 46.5 (C-1), 45.1 (C-9), 42.2 (C-19), 41.5 (C-11), 38.4 (C-20), 37.9 (C-10), 37.7 (C-18), 37.2 (C-12), 35.7 (C-21), 35.4 (C-15), 35.3 (C-13), 34.3 (C-17), 32.2 (C-22), 27.9 (C-26), 27.2 (C-24), 25.4 (C-25), 23.7 (C-23). HREIMS Calcd for $C_{31}H_{44}S_2O_3$ (M+1): 529.2805. Found: 529.2796.

4.3.7. (1*S*,2*R*,8*R*,9*S*,13*S*,17*S*)-4,6-Dioxa-14,16-dithia-5-[(*R*)-1-phenyleth-1-yl-ol]-10,10,20,20-tetramethylpentacyclo-[17.1.1.1^{9,11}.0^{2,17}.0^{8,13}]-docosane 10a

To a solution of 300 mg (0.68 mmol) of macroheterocycle **5b** in 5 mL of anhydrous THF was added 0.9 mL (0.9 mmol) of PhMgBr (1.0 M) under a nitrogen atmosphere. After the usual work-up, 311 mg (98%) of carbinol **10a** was obtained as a white solid mp = 103–105 °C, $[\alpha]_D^{25} = +333$ (*c* 0.33, $CHCl_3$). IR (cm^{-1}) ν_{max}: 3432, 2909, 1452, 1387, 1165, 754. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.51 (d, 2H, *J* = 7.8 Hz, H-*o*), 7.32 (t, 1H, *J* = 7.8 Hz, H-*m*), 7.23 (t, 1H, *J* = 7.8 Hz, H-*p*), 4.37 (s, 1H, H-5), 3.91–3.61 (m, 5H, H-3a, H-7a, H-15a, H-15b, H-17), 3.56 (dd, 1H, *J* = 10.1, 2.5 Hz, H-3b), 3.43 (m, 1H, H-13), 3.14 (dd, 1H, *J* = 8.9, 4.6 Hz, H-7b), 2.73 (bs, 1H, OH), 2.64–2.41 (m, 3H, H-12*eq*, H-18*eq*, H-21*eq*), 2.34 (m, 1H, H-8), 2.20–2.17 (m, 1H, H-22*eq*), 2.10–1.88 (m, 6H, H-2, H-1, H-11, H-12*ax*, H-18*ax*, H-19), 1.72 (m, 1H, H-9), 1.53 (s, 3H, Me-28), 1.24 (s, 3H, Me-26), 1.13 (s, 3H, Me-24), 1.12 (d, 1H, *J* = 9.8 Hz, H-22*ax*), 1.05 (s, 3H, Me-25), 0.99 (d, 1H, *J* = 9.8 Hz, H-21*ax*), 0.86 (s, 3H, Me-23). ^{13}C NMR (75.4 MHz, $CDCl_3$): 144.6 (C-*i*), 127.8 (C-*m*), 126.8 (C-*p*), 125.7 (C-*o*), 106.8 (C-5), 76.2 (C-7), 75.0 (C-27), 70.4 (C-3), 50.0 (C-2), 49.5 (C-8), 46.9 (C-9), 44.8 (C-1), 42.2 (C-11), 41.5 (C-19), 38.6 (C-20), 38.0 (C-10), 37.4 (C-12), 37.3 (C-18), 36.0 (C-21), 35.3 (C-13), 35.11 (C-15), 33.5 (C-17), 32.5 (C-22), 28.2 (C-26), 27.2 (C-24), 25.0 (C-25), 24.9 (C-28), 23.6 (C-23). HREIMS Calcd for $C_{30}H_{44}S_2O_3$ (M+1): 517.2810. Found: 517.2794.

4.3.8. (1*S*,2*R*,8*R*,9*S*,13*S*,17*S*)-4,6-Dioxa-14,16-dithia-5[(*R*)-1-phenylprop-2-yl-2-ol]-10,10,20,20-tetramethylpentacyclo-[17.1.1.1^{9,11}.0^{2,17}.0^{8,13}]-docosane 9h

To a solution of 300 mg (0.68 mmol) of macroheterocycle **5b** in 5 mL of anhydrous THF was added 2.7 mL (1.36 mmol) of $PhCH_2MgBr$ (3.0 M) under a nitrogen atmosphere. After the usual

work-up, 254 mg (70%) of carbinol **9h** was obtained as colorless oil, $[\alpha]_D^{25} = +269.7$ (*c* 0.28, $CHCl_3$). IR (cm^{-1}) ν_{max}: 3530, 2900, 1453, 1385, 1170, 765. ^1H NMR (300 MHz, $CDCl_3$): δ 7.35–7.20 (m, 5H, H-*Ar*), 4.08 (s, 1H, H-5), 3.95 (dd, *J* = 10.1, 3.95 Hz, 1H, H-3a), 3.92–3.55 (m, 6H, H-7a, H-3b, H-7b, H-15a, H-15b, H-17), 3.55 (m, 1H, H-13), 2.84 (d, *J* = 13.5 Hz, 1H, H-28a), 2.79 (d, *J* = 13.5 Hz, 1H, H-28b), 2.62–2.49 (m, 3H, H-8, H-18*eq*, H-22*eq*), 2.41 (m, 1H, H-12*eq*), 2.31 (m, 1H, H-21*eq*), 2.25–1.85 (m, 6H, H-1, H-2, H-11, 12*ax*, H-18*ax*, H-19), 1.70 (bt, 1H, *J* = 6.2 Hz, H-9), 1.25 (s, 3H, H-26), 1.21 (s, 3H, H-24), 1.20 (d, 1H, *J* = 9.9 Hz, H-22*ax*), 1.13 (s, 3H, Me-25), 1.10 (s, 3H, H-23), 1.03 (d, 1H, *J* = 9.9 Hz, H-21*ax*), 0.97 (s, 3H, Me-29). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 137.3 (C-*i*), 130.7 (C-*m*), 127.9 (C-*o*), 126.2 (C-*p*), 105.9 (C-5), 75.6 (C-27), 74.4 (C-7), 67.2 (C-3), 50.4 (C-2), 49.8 (C-8), 47.3 (C-1), 45.2 (C-9), 43.9 (C-28), 42.3 (C-11), 41.7 (C-19), 38.6 (C-20), 38.2 (C-10), 37.6 (C-12,18), 37.4 (C-21), 36.1 (C-13), 35.1 (C-15), 33.6 (C-17), 32.8 (C-22), 28.2 (C-26), 27.4 (C-24), 25.5 (C-23), 23.9 (C-29), 22.2 (C-25). HREIMS Calcd for $C_{31}H_{46}O_3S_2$ (M+1): 531.2967. Found: 531.2972.

4.3.9. (1*S*,2*R*,8*R*,9*S*,13*S*,17*S*)-4,6-Dioxa-14,16-dithia-5-[(*S*)-phenylmethanol]-10,10,20,20-tetramethylpentacyclo-[17.1.1.1^{9,11}.0^{2,17}.0^{8,13}]-docosane 9g

Method 1. A solution of 300 mg (0.60 mmol) of dodecaheterocycle **5a** in 5 mL of dry THF, cooled to −78 °C, was added to a well-stirred suspension of 90.8 mg (2.4 mmol) of $LiAlH_4$. The mixture was stirred for a further 4 h after which 50 mL of ethyl ether was added. The reaction was quenched by the slow addition small of pieces of ice and 1 mL of cold water. The organic layer was washed with brine (2 × 25 mL), dried over Na_2SO_4, and evaporated to dryness, giving 295 mg (86%) of a 73:27 mixture of **9g** and **10g** as a colorless oil. ^1H NMR data for **9g** (300 MHz, $CDCl_3$): δ 7.45–7.29 (m, 5H, H-*Ar*), 4.67 (*d*, 1H, *J* = 5.7 Hz, H-5), 4.61 (d, *J* = 5.7 Hz, 1H, H-27), 3.94–3.41 (m, 7H, H-3a, H-3b, H-7a, H-7b, H-15a, H-15b, H-17), 2.90–2.86 (m, 1H, H-13), 2.73 (s, 1H, OH), 2.73–2.44 (m, 4H, H-12*eq*, H-18*eq*, 21*eq*, H-22*eq*), 2.29–2.1.99 (m, 7H, H-1, H-2, H-9, H-11, H-12ax, H-18ax, H-19), 1.25 (s, 3H, Me-26), 1.19 (d, 2H, *J* = 9.9 Hz, H-22*ax*), 1.13 (s, 3H, Me-24), 1.10 (s, 3H, Me-25), 1.04 (d, 1H, *J* = 9.9 Hz, H-21*ax*), 1.02 (s, 3H, Me-23). HREIMS *m*/*z* Calcd for $C_{29}H_{42}O_3S_2$ (M+1): 503.2654. Found: 503.2662. ^1H NMR data for **10g** (300 MHz, $CDCl_3$): δ 7.45–7.29 (m, 10H, H-*Ar*), 4.38 (d, 1H, *J* = 6.5 Hz, H-5), 4.28 (d, *J* = 6.5 Hz, 1H, H-27), 3.94–3.41 (m, 7H, H-3a, H-3b, H-7a, H-7b H-15a, H-15b, H-17), 2.90–2.86 (m, 1H, H-13), 2.73 (s, 1H, OH), 2.73–2.44 (m, 4H, H-12*eq*, H-18*eq*, 21*eq*, H-22*eq*), 2.29–2.1.99 (m, 7H, H-1, H-2, H-9, H-11, H-12ax, H-18ax, H-19), 1.25 (s, 3H, Me-26), 1.19 (d, 1H, *J* = 9.9 Hz, H-22*ax*), 1.13 (s, 3H, Me-24), 1.10 (s, 3H, Me-25), 1.04 (d, 1H, *J* = 9.9 Hz, H-21*ax*), 1.02 (s, 3H, Me-23). HREIMS *m*/*z* Calcd for $C_{29}H_{42}O_3S_2$ (M+1): 503.2654. Found: 503.2662.

Method 2. A solution of 100 mg (0.20 mmol) of dodecaheterocycle **5a** in 5 mL of ethanol was treated with $NaBH_4$ (0.40 mmol). The reaction mixture was stirred for 1 h, after which it was quenched by the slow addition of small pieces of ice and 1 mL of cold water. The organic layer was washed with brine (2 × 25 mL), dried over Na_2SO_4, and evaporated to dryness, giving 108 mg (95%) of a 6:4 mixture of **9g** and **10g** as a colorless oil.

4.4. General procedure for the addition of lithium reagents to dodecaheterocycle 5a

To a solution of 200 mg (0.40 mmol) of dodecaheterocycle **5a** in anhydrous THF was added an organolithium reagent (1.5 equiv) at −78 °C under a nitrogen atmosphere. After stirring for 2 h at the same temperature, the reaction mixture was allowed to warm to room temperature and stirred for 2 h. The reaction mixture was quenched with 100 mL of a saturated solution of NH_4Cl. The THF was eliminated by evaporation and the remaining emulsion was extracted with ethyl ether. The organic layer was washed with a saturated solution of NH_4Cl, dried over anhydrous Na_2SO_4, and concentrated to dryness, giving the corresponding diasteoisomer **9a** or **9b** as a colorless oil or a white solid, as specified.

4.4.1. (1*S*,2*R*,8*R*,9*S*,13*S*,17*S*)-4,6-Dioxa-14,16-dithia-5-[1-phenyleth-1-yl-ol]-10,10,20,20-tetramethylpentacyclo-[17.1.1.1^{9,11}.0^{2,17}.0^{8,13}]-docosane 9a

To a solution of 300 mg (0.6 mmol) of macroheterocycle **5a** in 5 mL of anhydrous THF was added 0.3 mL (0.9 mmol) of MeLi (3.0 M) under a nitrogen atmosphere. After the usual work-up, 92 mg (30%) of a mixture of carbinols **9a**:**10a** (7:3) was obtained as a colorless oil.

4.4.2. (1*S*,2*R*,8*R*,9*S*,13*S*,17*S*)-4,6-Dioxa-14,16-dithia-5-[1-phenylpro-1-yl-ol]-10,10,20,20-tetramethylpentacyclo-[17.1.1.1^{9,11}.0^{2,17}.0^{8,13}]-docosane 9b

To a solution of 300 mg (0.6 mmol) of macroheterocycle **5a** in 5 mL of anhydrous THF was added 1.8 mL (0.9 mmol) of EtLi 0.5 M under a nitrogen atmosphere, giving 63 mg (20%) of a mixture of carbinols **9b**:**10b** (7:3) as a colorless oil.

4.5. General procedure for the hydrolysis of carbinols 9b and 9c and successive reduction of the corresponding aldehydes to obtain 1,2-propanodiols 11a and 11b

Carbinols **9b** or **9c** (1 equiv) were treated with a 10% solution of *p*-TsOH in 5 mL of CH_3CN:H_2O:DCM (8:1:1) at 50 °C for 3 h. The work-up was carried out by adding 1 mL of water. The white precipitate was filtered, and the filtrate was extracted with a mixture of hexane/DCM (1:1). The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated to dryness, giving a crude yellowish oil, whose ^1H NMR spectrum showed the presence of aldehydes. This mixture was stirred with $NaBH_4$ in ethanol at room temperature for 2 h, after which 10 mL of hot water was added, and stirring was continued for 20 min after which the mixture was extracted with ethyl ether. The organic layer was dried over anhydrous Na_2SO_4, evaporated to dryness and the yellowish oil residue was flash chromatographed using a mixture of hexane/ethyl acetate (9:1) as the eluent, giving diol **8** and the corresponding diols **11a** or **11b**.

4.5.1. (*S*)-2-Phenyl-3-butene-1,2-diol 11a

A 200 mg portion of the crude reaction mixture obtained after hydrolysis of adduct **9b** was treated with $NaBH_4$ as described above. Column chromatography gave 50 mg (80%) of diol **11a** as a colorless oil. $[\alpha]_D^{22} = +6.7$ (*c* 0.30, EtOH) >90% ee, Lit.[8] $[\alpha]_D^{25} = +7.3$ (*c* 0.70, EtOH) >98% ee. ^1H NMR (300 MHz, $CDCl_3$): δ 7.42–7.35 (m, 3H, H-Ar), 7.28–7.25 (m, 2H, H-Ar), 3.82 (d, 1H, *J* = 11.2 Hz, H-1a), 3.69 (d, 1H, *J* = 11.2 Hz, H-1b), 2.59 (bs, 1H, OH), 1.90–1.78 (m, 2H, H-3a,b), 1.25 (bs, 1H, OH), 0.77 (t, 3H, *J* = 7.3 Hz, H-4).

4.5.2. (*S*)-2,3-Diphenylpropane-1,2-diol 11b

A 200 mg portion of the crude reaction mixture obtained after hydrolysis of adduct **9c** was treated with $NaBH_4$ as described above. After purification by column chromatography 53 mg (70%) of diol **11b** was obtained as a colorless oil. $[\alpha]_D^{21} = +56.7$ (*c* 0.18, EtOH) >90% ee, Lit.[8] $[\alpha]_D^{25} = +59.5$ (*c* 0.25, EtOH) >95% ee. ^1H NMR (300 MHz, $CDCl_3$): δ 7.38–6.98 (m, 10H, H-2Ar), 3.85 (d, 2H, *J* = 12.4 Hz, H-1a), 3.77 (d, 2H, *J* = 12.4 Hz, H-1b), 3.18 (d, 2H, *J* = 13.5 Hz, H-3a), 3.14 (d, 2H, *J* = 13.5 Hz, H-3b), 2.52 (bs, 1H, OH), 1.25 (bs, 1H, OH).

Table 2
Single crystal X-ray data collection, processing, and refinement parameters

	5a	5b	9a	9b
Empirical formula	$C_{29}H_{40}O_3S_2$	$C_{24}H_{38}O_3S_2$	$C_{31}H_{46}O_3S_2$	$C_{30}H_{44}O_3S_2$
Formula weight	500.73	438.66	530.80	516.77
Crystal size (mm)	0.30 × 0.2 × 0.22	0.50 × 0.47 × 0.43	0.57 × 0.55 × 0.38	0.38 × 0.30 × 0.30
Wavelength (Å)	0.71073	0.71073	0.71073	1.54184
Crystal system	Monoclinic	Monoclinic	Monoclinic	Monoclinic
Space group	$P2_1$	$P2_1$	$P2_1$	$P2_1$
Cell *a* (Å)	9.9640(7)	11.8571(2)	10.2452(3)	10.227(1)
b (Å)	11.0740(9)	6.9562(1)	11.3977(3)	11.209(2)
c (Å)	13.429(1)	14.8009(3)	12.9552(3)	12.864(2)
β (deg)	110.665(2)	98.301(2)	105.216(3)	105.81(2)
Volume (Å^3)	1386.4(2)	1207.99(4)	1459.77(7)	1418.9(3)
Z	2	2	2	2
ρ Calc (mg/mm^3)	1.199	1.206	1.208	1.210
μ (mm^{-1})	0.219	0.242	0.212	1.914
F(000)	540	476	576	560
Theta range (deg)	1.62–26.00	2.78–32.42	2.73–32.55	4.49–59.96
Limiting indices	$-12 \leqslant h \leqslant 11$ $-13 \leqslant k \leqslant 13$ $0 \leqslant l \leqslant 16$	$-17 \leqslant h \leqslant 17$ $-8 \leqslant k \leqslant 10$ $0 \leqslant l \leqslant 22$	$-15 \leqslant h<14$ $-16 \leqslant k \leqslant 16$ $0 \leqslant l \leqslant 19$	$-11 \leqslant h \leqslant 11$ $0 \leqslant k \leqslant 12$ $0 \leqslant l \leqslant 14$
Reflections collected	9278	11178	14736	2417
Reflections unique	5095	6656	8618	2231
Data/parameters	3196/315	5368/268	6058/341	2208/357
Goodness-of-fit	0.884	1.044	0.975	1.068
Final R1 (%)	3.9	3.5	3.9	2.7
wR2 (%)	9.0	7.4	9.9	7.4
Residual e$^-$ (e.Å^3)	0.256/−0.284	0.156/−0.217	0.269/−0.167	0.137/−0.121
CCDC deposition No.	*,906776	*,906777	*,906778	*,906779

4.6. Single crystal X-ray structure determination

Data collection for **5a** was carried out on a Bruker Smart 6000 CCD diffractometer using MoKα radiation (*λ* = 0.7073 Å). A total of 1321 frames were collected at a scan width of 0.3° and exposure times of 10 s/frame. The data were processed with the SAINT software package, provided by the diffractometer manufacturer, by using a narrow-frame integration algorithm. Data for **5b** and **9a** were collected on an Oxford XCalibur S diffractometer using MoKα radiation (*λ* = 0.7073 Å). Data for **9b** were collected on a Bruker-Nonius CAD4 diffractometer using CuKα radiation (*λ* = 1.54184 Å). Specific information for each crystal studied is given in Table 2. The structures for **5a** and **9b** were solved by direct methods using the SIR2002 program while the structures **5b** and **9a** were solved using the SIR92 software. All structural refinements were carried out by full-matrix least squares on F^2 using the SHELX97 program. The non-hydrogen atoms were treated anisotropically, and the hydrogen atoms, included in the structure factor calculation, were refined isotropically. Atomic coordinates, bond lengths, bond angles, and anisotropic thermal parameters have been deposited at the Cambridge Crystallographic Data Center.

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