Synthesis of (+)-13-Stemarene and (+)-18-Deoxystemarin: Expeditious Preparation of the Key 6-*exo*-Hydroxybicyclo[2.2.2]octan-2-one[1]) Ethylene Dithioacetal

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Dedicated to the memory of Professor *Michael Lederer*[2])

An expeditious preparation of the 6-*exo*-hydroxybicyclo[2.2.2]octan-2-one ethylene dithioacetal **2b**, a key intermediate in the synthesis of (+)-13-stemarene (**4**) and (+)-18-deoxystemarin (**5**) is described. Compound **2b** was obtained as the major product by equilibrating the *endo* rich mixture of 6-hydroxybicyclo[2.2.2]octan-2-one ethylene dithioacetals **2** with TsOH in benzene at reflux, easily available from the corresponding hydroxy ketones **9**. The model experiments which preceeded the above transformation, not previously described in the literature, are also presented.

Introduction. – The 6-*exo*-hydroxybicyclo[2.2.2]octan-2-one ethylene dithioacetals **1** and **2b** are key intermediates in the synthesis of the stemarane diterpenoids (±)-stemarin (**3**) [1][2], (+)-13-stemarene (**4**) [3][4] and (+)-18-deoxystemarin (**5**) [3][5], respectively.

By *Raney*-Ni desulfurization, hydroxydithioacetals **1** and **2b** were in fact transformed into bicyclo[2.2.2]octan-2-ols **6** and **7**, and the latter rearranged[3]) to the stemarane system (*Scheme 1*).

Compounds **1** and **2b** were efficiently prepared from the corresponding 6-*exo*-hydroxybicyclo[2.2.2]octan-2-ones **8** and **9b** by thioacetalization with 1,2-ethanedithiol in the presence of $BF_3 \cdot Et_2O$ [2][6]. Given that 6-*exo*-hydroxybicyclo[2.2.2]octan-2-ones of the type of **8** and **9b** are the minor products (*endo*/*exo* 85:15) of the intramolecular aldol condensation of a 3-oxocyclohexaneacetaldehyde [7][8] (*Scheme 2*), the efficiency of the synthesis of stemarane diterpenoids, by this approach,

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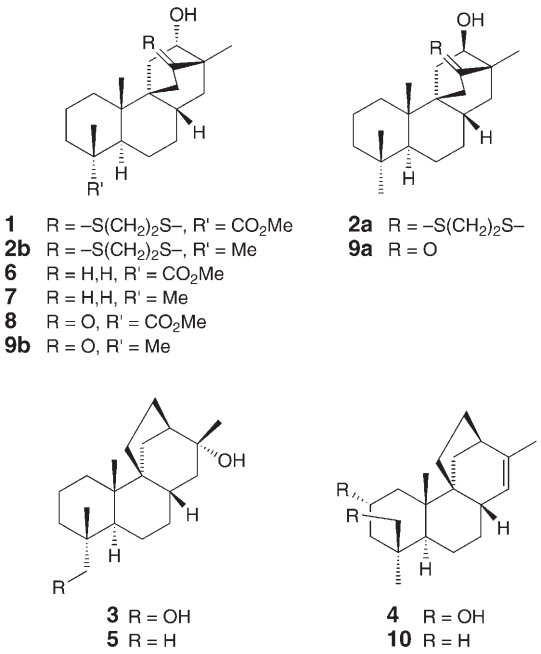
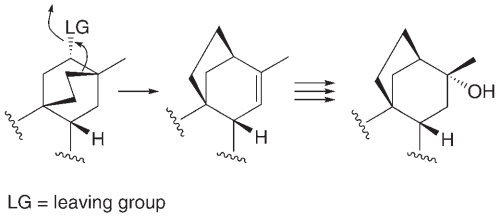
[1]) The numbering refers to the bicyclo[2.2.2]octane moiety and will be used throughout the text.

[2]) Professor *Michael Lederer* (1924–2006), a well known scientist in the field of chromatography, was the founding Editor of the *Journal of Chromatography*. Since 1960, for *ca.* 20 years, he was also the Director of the Laboratorio di Cromatografia del CNR, based for many years in the Chemistry Department of Università degli Studi 'La Sapienza' in Rome. He moved then to the Institute of Inorganic and Analytical Chemistry of the University of Lausanne. One of us (*R. M. B.*) recalls him as one of his first chemistry teachers.

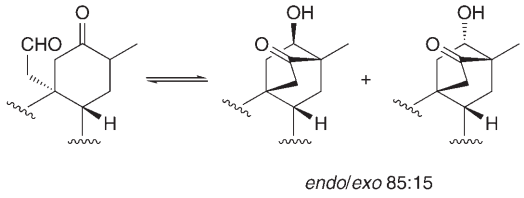
[3]) In the case of the synthesis of **3**, the rearrangement was performed on the tosyl derivative of **6**.



Scheme 1. *Rearrangement of Bicyclo[2.2.2]octane Intermediate to the Stemarane System*



Scheme 2. *Intramolecular Aldol Condensation of 3-Oxocyclohexaneacetaldehydes*



is heavily handicapped if only the minor epimer is required, as it was the case for the synthesis of **3** [2].

A correctional step, based on the conversion of 6-*endo*-hydroxybicyclo[2.2.2]octan-2-ones into the epimeric 6-*exo*-2-oxobicyclo[2.2.2]octane-carboxylates, was, therefore, worked out and applied to the synthesis of (+)-**4** and (+)-**5** [3][5][6].

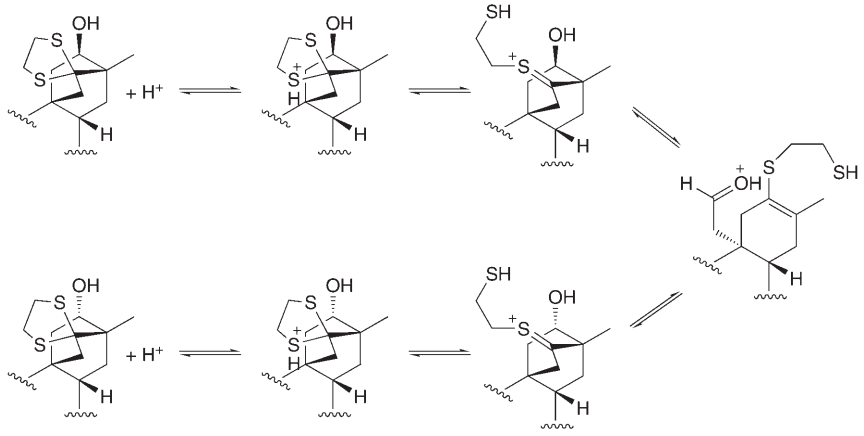
Aiming to bring the process for the synthesis of stemarane diterpenoids to a 'maximum correlation between the individual synthetic operations' [9], a necessary standard to make the synthesis of complex molecules practical, we decided to investigate whether, under suitable conditions, 6-hydroxybicyclo[2.2.2]octan-2-one ethylene dithioacetals of the type described above could equilibrate. If the equilibrium distribution would be in favor of the *exo* epimer, it should be possible to submit the 6-hydroxybicyclo[2.2.2]octan-2-one diastereoisomeric mixture to the thioacetalization reaction, and to obtain, after equilibration, a diastereoisomeric mixture of the dithioacetal, in which the major epimer has the OH group oriented towards the α (*exo*) face.

This plan might have worked provided that the epimerization at C–OH occurs and that the *exo* epimer is more stable than the *endo* one. In this case, an undoubted simplification of the whole process could have been achieved.

Results and Discussion. – The thioacetalization method selected by us to this end implies heating to reflux with azeotropic distillation (*Dean–Stark* apparatus) a solution of the 6-hydroxybicyclo[2.2.2]octan-2-one in benzene in the presence of 1,2-ethanedithiol and TsOH as catalyst. This methodology has been applied for the preparation of steroidal hemithioacetals in the past [10]. Nevertheless, to the best of our knowledge, applications of this protocol to the preparation of hydroxy dithioacetals of the type of **1** and **2b** have not been described yet.

Under these experimental conditions, the 6-hydroxybicyclo[2.2.2]octan-2-one ethylene dithioacetal system might have undergone opening/closure of both the dithiane ring and bicyclo[2.2.2]octane system (*Scheme 3*)[4]) and, owing to the bulkiness of the dithiane ring on the *endo* side, the OH group might have adopted the *exo* configuration.

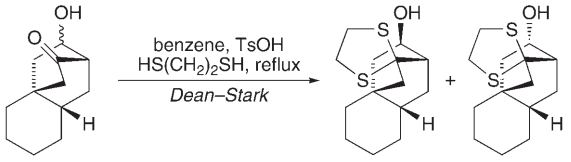
Scheme 3. *Hypothesized Mechanism for the Epimerization of Hydroxybicyclo[2.2.2]octan-2-one Ethylene Dithioacetals*



[4]) The same transformation could also have proceeded under these conditions *via* other processes.

Preliminary tests were performed with the known 6-*endo*-hydroxybicyclo[2.2.2]octan-2-one (**11a**) [3][11]. Gratifyingly, an *endo*/*exo* equilibrium ratio of *ca.* 2:8 was recorded (*Table 1*, *Entry 1*). The same *endo*/*exo* ratio was obtained starting from **11b** [3] (*Entry 2*). This ratio is almost opposite to the equilibrium distribution at the starting hydroxybicyclo[2.2.2]octan-2-ones (*Scheme 2*).

Table 1. *Diastereoisomeric Distribution at Various Times and at 1:30 Substrate/Dithiol Ratio*[a]) *in the Thioacetalization with Ethane-1,2-dithiol and TsOH in Refluxing Benzene with Azeotropic H_2O Removal* (*Dean–Stark* apparatus)



11a *endo*-OH
11b *exo*-OH
12a **12b**

Entry	Starting hydroxy ketone	Time [h]	Yield [%]	**12a**/**12b** Ratio
1	**11a**	24	65	3.3:6.7
		48		2.2:7.8
		72		2.2:7.8
2	**11b**	24	71	2.2:7.8

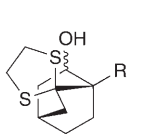
[a]) Similar results were obtained starting from **11a** at 1:6 and 1:300 substrate/ethane-1,2-dithiol ratios.

The diastereoisomeric ratios could be established by ^{1}H-NMR spectroscopy, after workup and column chromatography to remove ethane-1,2-dithiol, by virtue of the rather large H–C(OH) chemical shift difference and absence of other signals in that ppm range [12]. In the *exo* epimer, the H–C(OH) resonates at lower field (*ca.* 4.40 ppm) than in the *endo* epimer (*ca.* 3.80 ppm). The *endo*/*exo* ratios were confirmed by HPLC. Pure samples of **12a** and **12b** were prepared from the corresponding 6-hydroxybicyclo[2.2.2]octan-2-ones with 1,2-ethanedithiol in the presence of $BF_3 \cdot Et_2O$. Under these conditions, epimerization at C–OH was not observed [2][6][13].

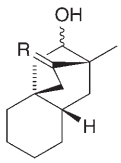
Considering the harsh reaction conditions necessary to bring about the thioacetalization and the following equilibration, and the fact, that under these experimental conditions by-products might be formed [14], we decided to perform the equilibration in benzene with TsOH on the preformed thioacetals obtained at r.t. in few minutes by the '1,2-ethanedithiol/$BF_3 \cdot Et_2O$ protocol'.

Thus, a number of 6-hydroxybicyclo[2.2.2]octan-2-one ethylene dithioacetals (**12**–**15**) were submitted to equilibration in benzene in the presence of a catalytic amount of TsOH. Sampling at various times allowed HPLC evaluation of the *endo*/*exo* ratios.

Apart from the lower yields recorded in the case of compounds **13** and **14**, the results reported in *Table 2* (*Entries 1–8*) are comparable to those obtained by the 'one pot' procedure (*Table 1*) confirming, therefore, that the previously recorded diastereoisomeric distribution is the result of an equilibration process rather than a preferential thioacetalization of the less hindered *exo*-hydroxybicyclo[2.2.2]octan-2-one CO-group.



13a R = H, *endo*-OH
13b R = H, *exo*-OH
14a R = Me, *endo*-OH
14b R = Me, *exo*-OH



15a R = –S(CH$_2$)$_2$S–, *endo*-OH
15b R = –S(CH$_2$)$_2$S–, *exo*-OH
16a R = O, *endo*-OH
16b R = O, *exo*-OH

Table 2. endo/exo *Distribution of Hydroxy Dithioacetals* **12**–**15** *and* **2** *at Various Times in Boiling Benzene and in the Presence of TsOH*

Entry	Starting hydroxy dithioacetal	Time [h]	Yield [%][a])	*endo*/*exo* Ratio[b])
1	**13a**	24	40	7.0 : 3.0
		48		2.4 : 7.6
		72		2.4 : 7.6
2	**13b**	24	35	2.4 : 7.6
		48		2.4 : 7.6
		72		–
3	**14a**	24	36	6.4 : 3.6
		48		2.9 : 7.1
		72		2.9 : 7.1
4	**14b**	24	41	1.6 : 8.4
		48		2.4 : 7.6
		66		2.9 : 7.1
		72		2.9 : 7.1
5	**12a**	24	60	3.3 : 6.7
		48		2.2 : 7.8
		72		2.2 : 7.8
6	**12b**	24	80	1.3 : 8.6
		48		1.7 : 8.3
		72		2.2 : 7.8
7	**15a**	24	77	5.1 : 4.9
		48		4.0 : 5.6
		69		3.4 : 6.6
		74		3.4 : 6.6
8	**15b**	24	82	3.4 : 6.6
		48		3.4 : 6.6
		72		–
9	**2**	3	83	5.0 : 5.0
		18		4.0 : 6.0
		24		4.0 : 6.0
		48		4.0 : 6.0

[a]) Yields refer to the isolated *endo*/*exo* mixture. [b]) Evaluated by HPLC.

It can also be observed that the presence of the bridgehead Me group slightly lowers the de value in favor of the *exo* epimer, probably owing to a conformational change which reduces the stability difference between the epimers.

We then submitted a 7:3 *endo*/*exo* mixture of hydroxydithioacetals **2**, prepared from **9**[5]) by the action of 1,2-ethanedithiol in the presence of $BF_3 \cdot Et_2O$ to equilibration with TsOH in benzene at various times. In this case, the *endo*/*exo* equilibrium ratio was 4:6 (*Table 2*, *Entry 9*). It appears, therefore, that in the case of **2** the stability difference between the two epimers is further reduced by the presence of the *A*/*B* ring system. Hydroxy dithioacetals **2a** [13] and **2b** [6] could be separated by HPLC. Though the *endo*/*exo* ratio is less favorable than expected, by repeating three times the equilibration/separation cycle, practically all the material (94%) can be converted into the desired *exo* epimer **2b** which, as pointed out above, had been previously transformed into (+)-**4** and (+)-**5**.

In conclusion, we have shown that 6-hydroxybicyclo[2.2.2]octan-2-one ethylene dithioacetals might be equilibrated under suitable experimental conditions. In some cases, the recorded equilibrium *endo*/*exo* ratio is about the opposite to that of the corresponding 6-hydroxybicyclo[2.2.2]octan-2-ones.

The results described above further simplify the syntheses of (+)-**4** and (+)-**5**, as it can be appreciated by comparing this solution to the problem with those developed over the years by us to this end [3][5][6] (*Scheme 4*). These studies are also potentially useful for the synthesis of stemarin (**3**) and oryzalexin S (**10**) [15], a phytoalexin produced from *Oryza sativa* when attacked from *Pyricularia Oryzae*.

Finally, this equilibration, which to the best of our knowledge has not been described before, could be adopted as a methodology for reversing the configuration of the hydroxy group of 6-*endo*-hydroxybicyclo[2.2.2]octan-2-ones, in the presence of acid stable groups, when the previously described procedures [3][5][6] cannot be applied.

Experimental Part

General. All solvents were of anal. grade. TsOH used in the reactions was monohydrate. TLC: *Merck* silica gel (SiO_2) *60* F_{254}. Column Chromatography (CC): SiO_2 *60*, (70–230 mesh, *ASTM*). HPLC Analysis: *Shimadzu LC-10AD*; RID detector; flow rate of 0.8 ml/min; t_R in min. M.p.: *Mettler FP-61* apparatus (uncorrected). IR Spectra: *Shimadzu 470* scanning IR spectrophotometer; in cm^{-1}. ^1H- and ^{13}C-NMR: *Bruker AC-300* at 300.13 and 75.48 MHz, resp.; δ in ppm relative to the residual solvent peak of C_6D_6 at 7.15 and 128.02 ppm and $CDCl_3$ at 7.26 and 77.0 ppm for ^1H and ^{13}C, resp.; *J* in Hz.

*Preparation of (±)-(1′*RS*,6′*SR*,8′*SR*,12′*RS*)-Spiro[1,3-dithiolane-2,9′-tricyclo[6.2.2.0^{1,6}]dodecan]-12′-ol* (**12a**) *from* **11a** *with Ethane-1,2-dithiol in the Presence of* $BF_3 \cdot Et_2O$. To a soln. of **11a** (214.9 mg, 1.11 mmol) in ethane-1,2-dithiol (2.15 ml, 25.59 mmol), cooled to 0°, $BF_3 \cdot Et_2O$ (0.84 ml, 6.66 mmol) was added while stirring. The reaction was completed after 10 min (TLC with petroleum ether (40–70°)/Et_2O 4:6; R_f(**11a**) < R_f(**12a**)). The mixture was poured into a separatory funnel, diluted with CH_2Cl_2 (1 ml) and washed with 2N NaOH (3 × 1 ml). The org. phase was washed with H_2O until neutral and finally with brine. It was dried (Na_2SO_4) and evaporated to dryness. The crude mixture was purified by CC (hexane/Et_2O 8:2) to give **12a** (288.1 mg, 96%) as a white solid. M.p. 86.2–87.8° (Et_2O/hexane). HPLC (*250/4 Nucleosil 100-5* column (*Macherey-Nagel*), hexane/AcOEt 9:1): t_R 15.0. IR (CCl_4): 3495, 2930, 2850, 1455, 1273, 1070. ^1H-NMR (C_6D_6): 3.93–3.82 (*m*, 1 H); 3.23 (*d*, *J* = 6, 1 H); 2.93–2.63 (*m*, $-SCH_2CH_2S-$); 2.47–2.18 (*m*, 3 H); 2.10–1.94 (*m*, 2 H); 1.63–0.50 (*m*, 11 H). ^{13}C-NMR (C_6D_6): 70.4; 67.0; 56.8; 45.6; 39.6; 37.0; 36.9; 36.4; 35.6; 34.0; 33.5; 31.2; 26.5; 21.8. EI-MS: 270 (98, M^+), 242 (30), 223 (11), 209 (86), 198 (47), 191 (21), 177 (18), 166 (62), 159 (15), 151 (19), 133 (47), 118 (22), 105 (40), 91

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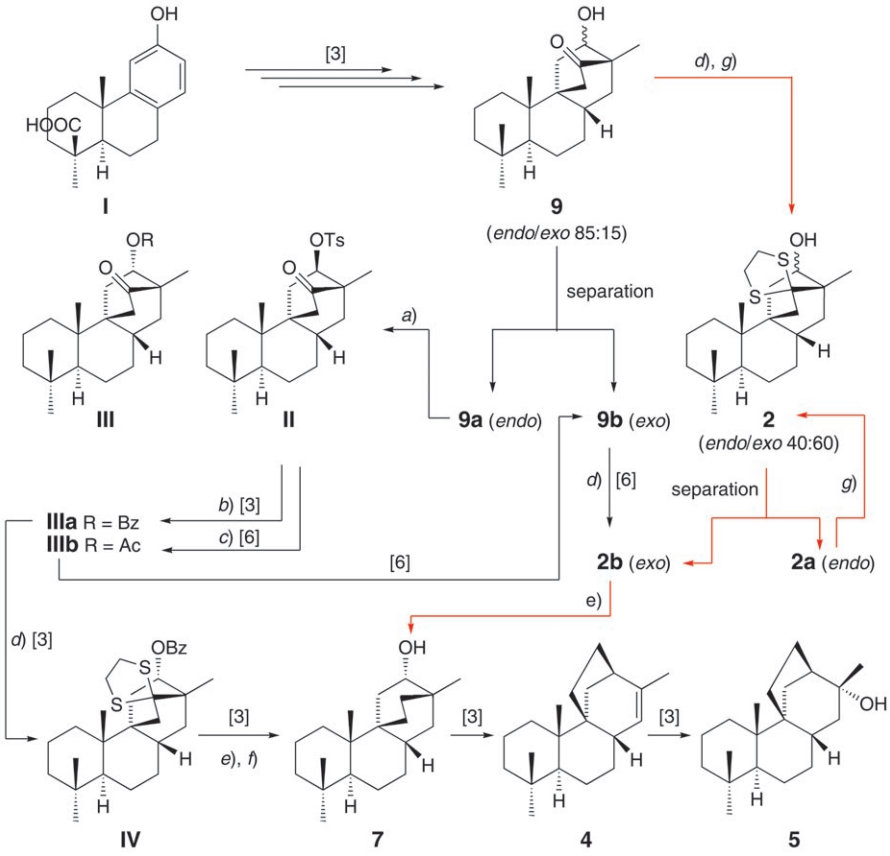
5) *endo*/*exo* Epimeric mixture.

Scheme 4. *Evolution of the Strategy* (present work in red) *for the Obtaining of* **7**, *a Key Intermediate in the Synthesis of (+)-13-Stemarene* (**4**) *and (+)-18-Deoxystemarin* (**5**) *from (+)-Podocarpic Acid*



a) TsCl, Py, r.t. *b*) Et_4NOBz, acetone, reflux, 22 h. *c*) Bu_4NOAc, benzene, reflux, 40 min. *d*) 1,2-Ethanedithiol, $BF_3 \cdot Et_2O$, r.t. *e*) *Raney*-Ni, EtOH, reflux, 2 h. *f*) 1% KOH (MeOH), r.t. *g*) TsOH, benzene, reflux. *h*) MeONa/$La(OTf)_3$/MeOH, r.t., 6 d.

(100), 79 (42), 67 (38), 61 (45), 55 (46), 45 (46), 41 (91). Anal. calc. for $C_{14}H_{22}OS_2$ (270.46): C 62.17, H 8.20, S 23.71; found: C 62.37, H 8.30, S 24.06.

*Preparation of (±)-(1′*RS,*6′*SR,*8′*SR,*12′*SR)-Spiro[1,3-dithiolane-2,9′-tricyclo[6.2.2.0^{1,6}]dodecan]-12′-ol* (**12b**) *from* **11b** *with Ethane-1,2-dithiol in the Presence of* $BF_3 \cdot Et_2O$. Compound **12b** was prepared from **11b** (37.2 mg, 0.19 mmol) as described for the preparation of **12a** from **11a**. The reaction was completed after 10 min (TLC: petroleum ether (40–70°)/Et_2O 4:6; R_f(**11b**) < R_f(**12b**)). The mixture was poured into a separatory funnel, diluted with CH_2Cl_2 (1 ml) and washed with 2N NaOH (3 × 1 ml). The org. phase was washed with H_2O until neutral and finally with brine. It was dried (Na_2SO_4) and evaporated to dryness. The crude mixture was then purified by CC (hexane/Et_2O 7.5:2.5) to give **12b** (44.2 mg, 86%) as a white solid. M.p. 131.0–133.0° (Et_2O/hexane). HPLC (*250/4 Nucleosil 100-5* column (*Macherey–Nagel*), hexane/AcOEt 9:1): t_R 15.8. IR (CCl_4): 3620, 2935, 2860, 1455, 1234, 1004. ^{1}H-NMR (C_6D_6): 4.56–4.35 (*m*, 1 H); 3.02–2.68 (*m*, –SCH_2CH_2S–); 2.35–2.20 (*m*, 1 H); 2.09 (*A* of *AB*, J_{AB} = 14.59, 1 H); 2.01 (*B* of *ABX*, J_{AB} = 14.59, J_{BX} = 3.01, 1 H); 1.91–1.85 (*m*, 1 H); 1.75–0.78 (*m*, 13 H). ^{13}C-NMR

(C_6D_6): 69.2; 68.3; 56.0; 48.0; 39.1; 39.0; 37.8; 36.0; 35.8; 34.9; 30.5; 27.1; 26.3; 21.9. EI-MS: 270 (77, M^+), 209 (65), 198 (22), 177 (37), 166 (36), 151 (93), 140 (43), 133 (52), 119 (25), 105 (41), 91 (92), 79 (50), 66 (45), 61 (67), 55 (40), 45 (52), 41 (100). Anal. calc. for $C_{14}H_{22}OS_2$ (270.46): C 62.17, H 8.20, S 23.71; found: C 62.15, H 8.39, S 23.43.

Preparation of **12** *with Ethane-1,2-dithiol in Benzene at Reflux and in the Presence of TsOH.* A soln. of **11a** (40.7 mg, 0.21 mmol), ethane-1,2-dithiol (0.53 ml, 6.3 mmol), and TsOH (1.95 mg, 0.10 mmol) in anh. benzene (10 ml) was placed into a two-neck flask fitted with a *Dean–Stark* apparatus, a condenser, and a $CaCl_2$ tube. The mixture was then heated to reflux for various times (24 h, 48 h, 144 h). Before starting, the *Dean–Stark* trap was filled with anh. benzene. After cooling, the mixture was poured into a separatory funnel, diluted with Et_2O (1 ml) and washed with 2N NaOH (3 × 1 ml). The org. soln. was washed with H_2O until neutral and finally with brine. It was dried (Na_2SO_4) and evaporated to dryness. The crude mixture was separated from excess ethane-1,2-dithiol by CC. Due to the very close R_f value (TLC with petroleum ether (40–70°)/Et_2O 6:4; R_f(**12a**) < R_f(**12b**)) of **12a** and **12b**, the *endo*/*exo* ratio was evaluated by HPLC (*Table 1*, *Entry 1*) and ^{1}H-NMR.

Equilibration of **12a** *with TsOH in Benzene at Reflux.* A soln. of **12a** (139.5 mg, 0.52 mmol) and TsOH (4.9 mg, 0.026 mmol) in anh. benzene (5 ml) was placed into a two-neck flask fitted with a condenser and a $CaCl_2$ tube. The mixture was refluxed for 72 h monitoring the *endo*/*exo* ratio by HPLC. After cooling to r.t., the mixture was poured into a separatory funnel, diluted with Et_2O (1 ml), and washed with 2N NaOH (3 × 1 ml). The org. soln. was washed with H_2O until neutral and finally with brine. It was then dried (Na_2SO_4) and evaporated to dryness. The crude diastereoisomeric mixture was purified by CC (hexane/AcOEt 9:1) to give **12** (84.4 mg, 60%); the *endo*/*exo* ratio was evaluated by HPLC (*Table 2*, *Entry 5*) and ^{1}H-NMR.

Equilibration of **12b** *with TsOH in Benzene at Reflux.* The equilibration of **12b** (20.9 mg, 0.08 mmol) was carried out as described for **12a**. The crude diastereoisomeric mixture was purified by CC (hexane/AcOEt 9:1) to give **12** (17.3 mg, 80%); the *endo*/*exo* ratio was evaluated by HPLC (*Table 2*, *Entry 6*) and ^{1}H-NMR.

*Preparation of (±)-(1′*RS*,6′*SR*,8′*SR*,12′*RS*)-8′-Methylspiro[1,3-dithiolane-2,9′-tricyclo[6.2.2.0^{1,6}]dodecan]-12′-ol* (**15a**) *with Ethane-1,2-dithiol in the Presence of $BF_3 \cdot Et_2O$.* Compound **15a** was prepared from *(±)-(2*RS*,4a*SR*,8a*RS*,10*SR*)-10-hydroxy-2-methylhexahydro-2*H*-2,4a-ethanonaphthalen-3(4*H*)-one* (**16a**)[6]) (35 mg, 0.17 mmol) as described for the preparation of **12a** from **11a**. The crude mixture was purified by CC (hexane/AcOEt 9.5:0.5; R_f(**16a**) < R_f(**15a**)) to give **15a** (38.7, 80%) as a white solid. M.p. 93.5–95.1° (hexane). HPLC (*250/4 Nucleosil 100-5 C18* (*Macherey–Nagel*), H_2O/MeCN 3:7): t_R 11.7. IR (CCl_4): 3610, 2930, 2850, 1456, 1265, 1044. ^{1}H-NMR (C_6D_6): 3.55 (*pseudo d*, *J* = 9.30, 1 H); 2.62–2.99 (*m*, $-SCH_2CH_2S-$); 2.49 (*d*, *J* = 14.13, 1 H); 1.96–2.41 (*m*, 4 H); 0.66–1.80 (*m*, 13 H); 0.51 (*dd*, *J* = 14.19, 7.39, 1 H). ^{13}C-NMR (C_6D_6): 75.2; 72.4; 61.1; 42.0; 41.2; 40.9; 37.5; 37.3; 37.1; 36.3; 34.0; 30.9; 26.3; 21.9; 20.6. EI-MS: 284 (32, M^+), 240 (11), 224 (31), 180 (34), 165 (29), 119 (25), 105 (64), 91 (46), 85 (21), 81 (19), 79 (38), 67 (30), 61 (35), 55 (36), 45 (47), 41 (100). Anal. calc. for $C_{15}H_{24}OS_2$ (284.48): C 63.33, H 8.50, S 22.54; found: C 63.02, H 8.76, S 22.15.

*Preparation of (±)-(1′*RS*,6′*SR*,8′*SR*,12′*SR*)-8′-Methylspiro[1,3-dithiolane-2,9′-tricyclo[6.2.2.0^{1,6}]dodecan]-12′-ol* (**15b**) *with Ethane-1,2-dithiol in the Presence of $BF_3 \cdot Et_2O$.* Compound **15b** was prepared

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[6]) White solid. M.p. 92.5–93.3° (hexane/Et_2O). HPLC (*250/4 Nucleosil 100-5* column (*Macherey-Nagel*), hexane/AcOEt 7:3): t_R 8.2. IR (CCl_4): 3623, 2929, 2854, 1720, 1450, 1050. ^{1}H-NMR ($CDCl_3$): 3.80 (*d*, *J* = 8.30, 1 H); 2.78–2.52 (*m*, 1 H); 2.12 (*pseudo d*, *J* = 18.58, 1 H); 2.13–0.95 (*m*, 17 H). ^{13}C-NMR ($CDCl_3$): 215.5; 74.1; 52.2; 49.6; 37.5; 37.4; 36.4; 35.8; 35.3; 30.6; 25.9; 21.2; 16.4. EI-MS: 208 (2, M^+), 164 (10), 148 (100), 133 (15), 121 (11), 106 (44), 91 (22), 80 (21), 67 (22), 55 (21), 43 (30), 39 (32). Anal. calc. for $C_{13}H_{20}O_2$ (208.30): C 74.96, H 9.68; found: C 75.23, H 9.87.

[7]) White solid. M.p. 65.9–67.1° (hexane). HPLC (*250/4 Nucleosil 100-5* column (*Macherey–Nagel*), hexane/AcOEt 7:3): t_R 7.1. IR (CCl_4): 3640, 2930, 2850, 1720, 1456, 1235, 1036. ^{1}H-NMR ($CDCl_3$): 3.91–3.60 (*m*, 1 H); 1.03–2.27 (*m*, 16 H); 0.94 (*s*, 3 H). ^{13}C-NMR ($CDCl_3$): 216.4; 70.0; 52.2; 50.0; 38.0; 36.6; 36.2; 34.5; 31.7; 29.9; 26.0; 21.0; 15.5. EI-MS: 208 (7, M^+), 164 (34), 148 (87), 133 (11), 121 (30), 106 (25), 91 (20), 79 (25), 69 (42), 55 (27), 43 (36), 41 (100). Anal. calc. for $C_{13}H_{20}O_2$ (208.30): C 74.96, H 9.68; found: C 74.78, H 9.39.

from *(±)-(2*RS*,4a*SR*,8a*RS*,10*RS*)-10-hydroxy-2-methylhexahydro-2*H*-2,4a-ethanonaphthalen-3(4*H*)-one* (**16b**)[7]) (17 mg, 0.08 mmol) as described for the preparation of **12b** from **11b**. The crude mixture was purified by CC (hexane/AcOEt 9.5:0.5; R_f(**16a**) < R_f(**15a**)) to give **15b** (21.6 mg, 95%) as an oil. HPLC (*250/4 Nucleosil 100-5 C18* (*Macherey–Nagel*), H_2O/MeCN 3:7): t_R 10.9. IR (CCl_4): 3640, 2930, 2850, 1455, 1233, 1035. ^{1}H-NMR (C_6D_6): 4.14–3.88 (*m*, H–C(11)); 3.00–2.60 (*m*, $-SCH_2CH_2S-$); 2.42–2.22 (*m*, 2 H); 1.86 (*ddd*, *J* = 13.36, 9.56, 2.18, 1 H); 1.73 (*ddd*, *J* = 13.85, 4.70, 2.90, 1 H); 1.67–0.72 (*m*, 15 H). ^{13}C-NMR (C_6D_6): 74.3; 72.4; 61.2; 43.9; 40.2; 39.6; 37.8; 37.5; 37.1; 34.5; 34.3; 30.4; 26.4; 22.0; 18.7. EI-MS: 284 (53, M^+), 224 (15), 191 (19), 180 (23), 165 (100), 148 (35), 121 (22), 105 (64), 91 (33), 85 (17), 79 (29), 67 (26), 61 (31), 55 (29), 45 (33), 41 (74). Anal. calc. for $C_{15}H_{24}OS_2$ (284.48): C 63.33, H 8.50, S 22.54; found: C 63.70, H 8.29, S 22.94.

Equilibration of **15a**, **15b**, **13a**, **13b**, **14a**, *and* **14b** *with TsOH in Benzene at Reflux.* The equilibration of **15a**, **15b**, **13a**, **13b**, **14a**, and **14b** [12] was carried out as described for **12a**. See *Table 2* for the yields; the *endo*/*exo* ratio was evaluated by HPLC (*Table 2*) and ^{1}H-NMR.

Preparation of Spiro[9β-13β-ethanopodocarpane-12,2′-[1,3]dithiolan]-13-methyl-16α-ol (*=(±)-(1′*RS*,2′*RS*,7′*RS*,10′*RS*,12′*RS*,16′*RS*)-2′,6′,6′,12′-Tetramethylspiro[1,3-dithiolane-2,13′-tetracyclo[10.2.2.0^{1,10}.0^{2,7}]hexadecan]-16′-ol*; **2b**) *with Ethane-1,2-dithiol in the Presence of* $BF_3 \cdot Et_2O$. Compound **2b** was prepared from **9b** (78 mg, 0.26 mmol) as described for the preparation of **12a** from **11a**. The crude mixture was purified by CC (hexane/AcOEt 9:1; R_f(**9b**) < R_f(**2b**)) to give **2b** (79 mg, 80%) as a white solid. M.p. 152.4–153.8° (hexane). HPLC (*250/4 Nucleosil 100-5* column (*Macherey–Nagel*), hexane/AcOEt 9:1): t_R 8.5. IR (CCl_4): 3645, 2935, 2855, 1468, 1375, 1094. ^{1}H-NMR (C_6D_6): 3.99–3.78 (*m*, H–C(12)); 2.92–2.65 (*m*, $-SCH_2CH_2S-$); 2.54 (*A* of *ABX*, J_{AB} = 14.50, J_{AX} = 3.44, 1 H); 2.25 (*B* of *AB*, J_{AB} = 14.50, 1 H); 2.07–1.82 (*m*, 3 H); 1.69–0.97 (*m*, 17 H); 0.86 (*s*, 3 H); 0.83 (*s*, 3 H); 0.79 (*s*, 3 H). ^{13}C-NMR (C_6D_6): 75.0; 72.5; 51.6; 46.2; 42.8; 42.3; 42.0; 40.2; 39.6; 38.7; 35.0; 34.3; 33.6; 33.3; 32.8; 32.3; 31.6; 22.5; 22.4; 19.0; 18.8; 16.2. EI-MS: 380 (50, M^+), 336 (29), 276 (13), 261 (7), 200 (23), 168 (10), 161 (14), 151 (11), 145 (34), 137 (23), 119 (27), 105 (100), 95 (24), 81 (29), 69 (42), 61 (29), 55 (50), 41 (71). Anal. calc. for $C_{22}H_{36}OS_2$ (380.65): C 69.42, H 9.53, S 16.85; found: C 69.12, H 9.62, S 16,47.

Equilibration of **2** *with TsOH in Benzene at Reflux.* The equilibration of **2** (**2a**/**2b** 7:3, 24.5 mg, 0.06 mmol) was carried out as described for **12a**. The *endo*/*exo* ratio was evaluated by HPLC (*Table 2*, *Entry 9*). The crude mixture was purified by CC (hexane/Et_2O 9:1) to give **2** (19.0 mg, 83%); **2a** and **2b** could be separated by HPLC (*250/4 Nucleosil 100-5* column (*Macherey–Nagel*), hexane/AcOEt 9:1, t_R(**2a**) 7.7, t_R(**2b**) 8.5).

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