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Stereospecific cyclodehydration of 1,4-sulfanylalcohols to thiolanes: mechanistic insights

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ABSTRACT

A series of thiolanes were prepared by cyclodehydration of sulfanylalcohols in the presence of catalytic amounts of *p*-toluenesulfonic acid or by using K10 clay. The sulfur heterocycles were synthesised in good to excellent yields using either a conventional Dean–Stark method or microwave irradiation under solvent-free conditions. The reaction could be performed regio- and stereoselectively and its mechanism was investigated by means of enantio- and diastereomerically enriched substrates. In contrast to previous studies, our results are consistent with an intramolecular S_N2-type mechanism as a general pathway.

1. Introduction

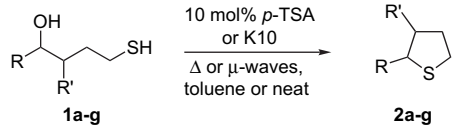
A large number of volatile organic sulfur compounds (VOSCs) is known to occur in plants, food and aroma extracts. In most cases, VOSCs have been described to provide a strong contribution to the organoleptic profile of these extracts due to their powerful olfactory properties.[1–3] Cyclic sulfides such as thiolanes (tetrahydrothiophenes) and thianes are found in abundance in crude oil distillates to which they are known to give malodour.[4–6] However, like many other sulfur heterocycles such as thiophenes, thiazoles and thiapyrans, they can exhibit interesting olfactory properties at low concentrations and thus contribute to the aromatic profile of exotic fruits,[7] wines[8] and meat.[9] In the frame of flavour and fragrance chemistry, we have been looking for new synthetic methodologies allowing the systematic preparation of sulfur heterocycles. In the last years, our work resulted in the development of novel routes to thiono-[10,11] and thiolactones,[12] thioethers,[13] thioesters[14] and sultines.[15]

According to the literature, thiolanes can be prepared by thiophene hydrogenation,[16] reaction of 1,4-dihalogenated compounds[17] or activated 1,4-diols[18–20] with sulfur reagents, or cycloisomerisation of olefinic thiols.[13] Our strategy was to prepare thiolanes from chiral 1,4-sulfanylalcohols[21,22] as their natural homologues—1,3-sulfanylalcohols—are known to be precursors of natural odourant sulfur heterocycles such as oxathianes[23] and sultines.[15]

Here, we report on the preparation of a series of thiolanes **2a**–**g** by cyclodehydration of 1,4-sulfanylalcohols **1a**–**g** previously obtained by reduction of thionolactones.[21] Although the cyclodehydration of compounds having the 1,4-thiol-alcohol pattern has already been described in the literature,[24–26] to the best of our knowledge, no previous study reported the synthesis of volatile thiolane derivatives under catalytic conditions.

2. Results and discussion

We found that 1,4-sulfanylalcohols **1a**–**g** provide direct access to thiolane derivatives **2a**–**g** upon treatment with catalytic amounts of *p*-toluenesulfonic acid (*p*-TSA) or Montmorillonite K10 (Scheme 1). Two activation methods were applied for these preparations: conventional oil-bath heating and solvent-free microwave irradiation. Our results are summarised in Table 1.



1a-g **2a-g**

Scheme 1. Cyclodehydration of 1,4-sulfanylalcohols **1** to thiolanes **2**.

We first investigated the cyclodehydration of 1,4-sulfanylalcohols **1a**–**d** to the corresponding thiolanes **2a**–**d** using a Dean–Stark trap over refluxing toluene in the presence of 10 mol % *p*-TSA. Under these conditions, a clean reaction took place, giving complete conversion of the substrates after ca. 5 h, affording the expected thiolanes in 80–94% yields with purities ≥98% as checked by GC (Table 1, entries 1–4). We further investigated the possibility to achieve this cyclodehydration in a microwave oven as previously used with some acid-promoted reactions.[27–29] Thus, a series of

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Table 1
Synthesis of thiolanes from 1,4-sulfanylalcohols

Entry	Sulfanylalcohols	R	R′	Activating method	Conditions	Thiolanes	Yield[a] (%)
1	**1a**	*n*-Pr	H	Δ	*p*-TSA, toluene, 5 h	**2a**	80
2	**1b**	*n*-Pent	H	Δ	*p*-TSA, toluene, 5 h	**2b**	84
3	**1c**	*n*-Hex	H	Δ	*p*-TSA, toluene, 5 h	**2c**	94
4	**1d**	*n*-Hept	H	Δ	*p*-TSA, toluene, 5 h	**2d**	89
5	**1a**	*n*-Pr	H	MW	*p*-TSA, 90 s	**2a**	74
6	**1b**	*n*-Pent	H	MW	*p*-TSA, 90 s	**2b**	84
7	**1e**	*n*-Bu	H	MW	*p*-TSA, 90 s	**2e**	92
8	**1a**	*n*-Pr	H	MW	K10 clay, 90 s	**2a**	65
9	**1c**	*n*-Hex	H	MW	K10 clay, 90 s	**2c**	88
10	**1f**	*n*-Oct	H	MW	K10 clay, 90 s	**2f**	90
11	**1g** (*syn*/*anti*, 4/6)	*n*-Bu	Me	MW	K10 clay, 90 s	**2g** (cis/trans 6/4)	88
12	*rac*-*syn*-**1g** (97% de)	*n*-Bu	Me	MW	K10 clay, 90 s	*rac*-*trans*-**2g** (87% de)[b]	84
13	*rac*-*anti*-**1g** (99% de)	*n*-Bu	Me	MW	K10 clay, 90 s	*rac*-*cis*-**2g** (82% de)[b]	85
14	(*R*)-**1c** (98% ee)	*n*-Hex	H	MW	K10 clay, 90 s	(*S*)-**2c** (80% ee)[c]	91
15	(*R*)-**1c** (98% ee)	*n*-Hex	H	Δ	*p*-TSA, toluene, 5 h	(*S*)-**2c** (98% ee)[c]	98
16	(*R*)-**1c** (98% ee)	*n*-Hex	H	MW	*p*-TSA, 90 s	(*S*)-**2c** (70% ee)[c]	91
17	(*R*)-**1c** (98% ee)	*n*-Hex	H	Δ	*p*-TSA, solvent free, 180 °C, 5 min	(*S*)-**2c** (86% ee)[c]+9% 2-hexyltetrahydrofuran	90[b]

[a] Determined after purification by silica gel column chromatography.
[b] Determined by GC.
[c] Determined by enantioselective GC after derivatisation of the thiolane into its corresponding thiolane-1-oxide (see Section 4 for details).

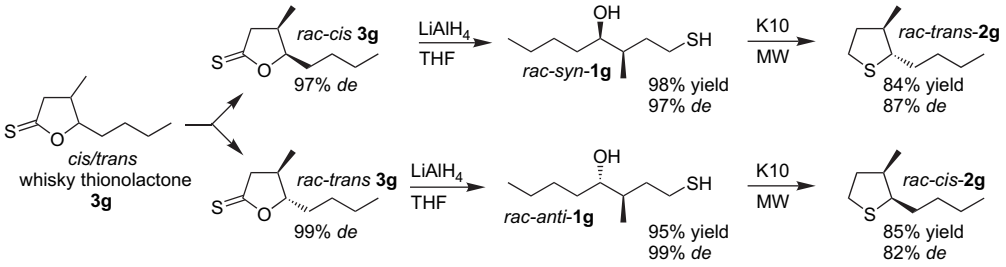
sulfanylalcohols **1** were directly submitted to solvent-free and microwave irradiation conditions with 10 mol % *p*-TSA in open glass tubes. In a typical experiment, the reaction mixture was irradiated for 90 s (3×30 s) at maximum power (850 W) until no water evolved from it. Purification was achieved by using a short silica gel column, and thiolanes **2** were obtained in good yields ranging from 74 to 92% (Table 1, entries 5–7). Comparing the results obtained for substrates **1a**–**b** (entries 1, 2, 5 and 6), both procedures were similar in terms of yield, but dramatically differed in terms of reaction time. Both procedures afforded selectively the expected thiolanes **2** with nearly no formation of the corresponding tetrahydrofurans as checked by GC (<1%). In further attempts, the reaction was carried out with Montmorillonite K10 instead of *p*-TSA, as this acidic clay has been described to efficiently promote various acid-catalysed reactions,[30] and reported to be particularly useful for solvent-free microwave procedures.

Thus, mixtures of sulfanylalcohol **1** and 1.5 wt equivalent of K10 clay were subsequently exposed to microwave irradiation for 90 s. The corresponding thiolanes **2a**, **c** and **f** were isolated by solvent extraction of the crude material in 65–90% yields (Table 1, entries 8–10). It is worth mentioning that, here again, the corresponding tetrahydrofurans were produced in only trace amounts.

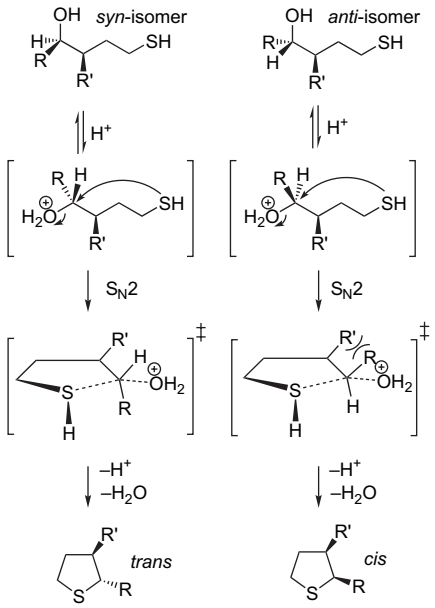
Conventional and microwave procedures using either *p*-TSA or Montmorillonite K10 afforded similar results in terms of selectivity. However, microwave procedures using open glass tubes offered less advantageous conditions for the synthesis of very volatile thiolanes, i.e., 2-propylthiolane **2a** was assumed to evaporate during irradiation, resulting in lower yields of 74 and 65% (entries 5 and 8).

As the reaction turned out to work well with each applied procedure, we were interested in getting more insights into its mechanism. Alcohol protonation in acidic media produces favourable conditions for a subsequent nucleophilic substitution. Usually, primary and tertiary alcohols are intended to proceed, respectively, through S_N2 and S_N1 mechanisms. In contrast, the reactivity of secondary alcohols is not so well defined and actually depends on several reaction parameters. To our knowledge, previous studies on thiolane preparation from cyclodehydration of 1,4-sulfanylalcohols reported the use of substrates having a tertiary alcohol.[24–26] Consequently, the reaction mechanism, when studied, was described to involve a carbocation as the reaction intermediate.[25,26]

When a 4/6 mixture of *syn*- and *anti*-isomers **1g** was submitted to cyclodehydration with *p*-TSA (entry 11), the reaction afforded **2g** as a mixture of diastereomers presenting the same 4/6 ratio, indicative of a specific mechanism during ring closure. In order to investigate this experimental observation, both *syn*- and *anti*-diastereomers of **1g** were independently synthesised from whisky thionolactone **3g**, previously obtained by thionation of whisky lactone.[10,31] The two diastereomers of **3g** were separated by silica gel column chromatography and further reduced with $LiAlH_4$ to *rac*-*syn*-**1g** (97% de) and *rac*-*anti*-**1g** (99% de),[22] as shown in Scheme 2. Submitting the isomer *rac*-*syn*-**1g** to cyclodehydration (under K10, MW, 90 s) afforded selectively *trans*-**2g** in 84% isolated yield and 87% de (entry 12). On the other hand, when the same reaction was run with *rac*-*anti*-**1g**, *rac*-*cis*-**2g** was isolated in 85% yield and presented 82% de (entry 13 and Scheme 2). The stereo- and regiospecificity observed in both cases clearly support a major intramolecular S_N2-type mechanism giving almost complete inversion of configuration during the formation of the thiolane ring. In the latter case, a higher steric hindrance in the transition state could explain a decrease of selectivity between S_N2 and S_N1, resulting in a higher racemisation (Scheme 3).



Scheme 2. Stereospecific synthesis of *cis*- and *trans*-whisky thiolanes **2g**.



Scheme 3. Stereospecific ring closure of 2,3-disubstituted thiolanes.

The possibility of considering a mechanism involving a first dehydration step with formation of a carbocationic intermediate (or an olefin) should therefore be considered as a minor pathway for these reactions.

To elucidate the reaction mechanism in more detail, we examined the cyclodehydration of (*R*)-**1c** enantiomerically enriched to 98% ee. (*R*)-**1c** was obtained from the reduction of (*R*)-γ-thionodecalactone **3c**, synthesised from commercial (*R*)-γ-decalactone **4c** (Scheme 4).[11] The cyclodehydration of (*R*)-**1c** in the presence of K10 under microwave irradiation produced the optically active thiolane (*S*)-**2c** ($[a]_D^{20}$ −59.8) isolated in 91% yield (entry 14, Scheme 4). In spite of the numerous chiral stationary phases tested, its enantiomeric excess failed to be determined by direct enantioselective GC analysis. Thus, (*S*)-**2c** was derivatised into its corresponding thiolane-1-oxide **5c** as a cis/trans mixture of diastereomers, which resulted in a baseline resolution on a Hydrodex-β-6tBDM capillary column (Macherey-Nagel, Germany). An 80% ee was determined for the major diastereomer (trans), indicating thus the same ee for (*S*)-**2c**.

In order to further examine the enantioselectivity of the reaction, we performed the cyclodehydration of (*R*)-**1c** using all the above-mentioned procedures. With 10 mol % *p*-TSA in refluxing toluene (entry 15), (*S*)-**2c** was obtained with 98% ee. On the other hand, when *p*-TSA was used under microwave irradiation and solvent-free conditions, (*S*)-**2c** showed a 70% ee, indicative of a partial racemisation (entry 16).

Exposing (*R*)-**1c** to microwave irradiation with *p*-TSA under solvent-free conditions (entry 15) resulted in a final temperature of 180±5 °C. As we wanted to determine a possible microwave effect on the reaction mechanism, (*R*)-**1c** was submitted to cyclodehydration with *p*-TSA using an oil-bath set to 180 °C. Despite a lower selectivity due to the formation of 2-hexyltetrahydrofuran (9%), (*S*)-**2c** was obtained with 86% ee (entry 17). As a consequence, the loss of enantioselectivity observed for both microwave procedures (entries 14 and 16) indicated that a carbocationic S_N1 mechanism participated in the reaction as a minor pathway, estimated to contribute in 7–15%. As previously mentioned for microwave-assisted synthesis, it is likely that carbocationic mechanisms having polar transition states may be favourably enhanced under microwave irradiation.[32]

Finally, these results confirmed a major S_N2 pathway involving the inversion of configuration during ring closure of 1,4-sulfanylalcohols containing secondary hydroxyl groups. Indeed, the type of mechanism involved in the cyclodehydration depends on the substitution pattern of the OH group, the nature and the strength of the acid used, and the activation method (conventional heating versus microwave irradiation).

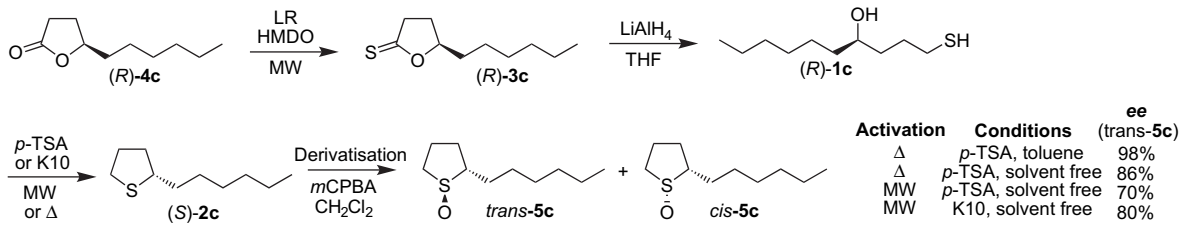
3. Conclusion

We described a new and efficient acid-catalysed regiospecific and stereoselective synthesis of thiolane derivatives from 1,4-sulfanylalcohols. The reaction can be performed either under conventional conditions (*p*-TSA, toluene, Dean–Stark) or more rapidly under microwave irradiation in the presence of Montmorillonite K10. The mechanism of ring formation has been examined and involves mainly an intramolecular S_N2 process with inversion of configuration during water displacement. The possibility to prepare enantio- and diastereomerically enriched sulfur heterocycles has been demonstrated.

4. Experimental

4.1. General

Solvents and chemicals were used as received otherwise indicated. *p*-TSA and Montmorillonite K10 were purchased from Sigma–Aldrich. *p*-TSA was dried according to the described procedure.[33] Toluene and THF were distilled over sodium/benzophenone prior to use in reaction. Sulfanylalcohols **1a–g** were prepared as described elsewhere.[21,22] The microwave oven used for this study was an unmodified household Samsung M181DN oven running at maximum power (850 W), so as to obtain the most homogeneous irradiation as possible. ^1H and ^{13}C NMR spectra were measured in $CDCl_3$ with Bruker AC200 and DRX 500 spectrometers locked on the solvent signal. EIMS was obtained from an Agilent 6890N/5973N GC/MS system operated at 70 eV as the strength of electron impact and with a 35–350 amu detection range. Optical rotation of thiolane (*S*)-**2c** was measured on an Ameria AA10 polarimeter using a 0.1 M dichloromethane solution in a thermostated room (20 °C). Elemental analyses were performed at the Institut de Chimie des Substances Naturelles (Gif-sur-Yvette, France), and at the Chemistry Department of the University of Nice (France) using a Thermo Electron microanalyser EA1112.



Scheme 4. Synthesis of (*S*)-2-hexylthiolane and its derivatisation for enantiomeric excess determination.

4.2. Dean–Stark procedure

In a 50 mL two-necked round-bottom flask equipped with a Dean–Stark trap, a mixture of sulfanylalcohol **1** (5 mmol) and *p*-TSA (0.5 mmol) was dissolved in 30 mL toluene. The reaction was run in refluxing toluene under magnetic stirring until no starting compound was detected in aliquots withdrawn from the reaction mixture and analysed by GC (about 5 h for complete conversion). The mixture was then washed with 0.1 N NaOH and the organic layer was dried over magnesium sulfate. After solvent evaporation, the crude product was purified by silica gel column chromatography using distilled *n*-hexane or petroleum ether (40–60 grade) as the eluting solvent. Thiolanes **2** were obtained as nearly colourless oils after solvent evaporation.

4.3. Microwave procedure

Sulfanylalcohols **1** (5 mmol) and *p*-TSA (0.5 mmol) or Montmorillonite K10 (1.5 equiv *w*/*w*) were placed in a Pyrex glass tube (160×15 mm i.d.). When K10 clay was used, both **1** and K10 were thoroughly mixed to obtain a powder material. The tube was then placed at the centre of the oven cavity and irradiated at 850 W for 90 s, using a sequential irradiation to check the evolution of water from the reaction mixture. In the case of *p*-TSA, the resulting mixture was dissolved in chloroform and treated as indicated above. In the case of Montmorillonite K10, the residue was triturated with hexane (2×10 mL) and directly filtered over Celite.

All compounds have been characterised by ^{1}H and ^{13}C NMR and EIMS. Partial spectral characterisation of starting sulfanylalcohols **1** has already been reported.[21] Thiolanes **2a**–**f** are known compounds (**2a**: CAS 1551-34-4; **2b**: CAS 3050-98-4; **2c**: CAS 876-37-9; **2d**: CAS 24767-96-2; **2e**: CAS 1613-49-6; **2f**: CAS 5143-23-7), however, only partial spectral data are given in the literature. New compounds *cis*-**2g** and *trans*-**2g** were characterised by NMR, EIMS and elemental analysis.

4.3.1. 1-Sulfanylheptan-4-ol ***1a***

See Ref. 21 for spectral characterisation.

4.3.2. 1-Sulfanyloctan-4-ol ***1e***

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.91 (m, 3H, C*H*$_3$), 1.37 (t, 1H, *J*=7.9 Hz, S*H*), 1.25–1.85 (m, 11H, 5×C*H*$_2$, O*H*), 2.56 (dt, 2H, *J*=6.8 Hz, *J*=7.9 Hz, C*H*$_2$SH), 3.60 ppm (m, 1H, C*H*OH). ^{13}C NMR ($CDCl_3$): δ 14.0 (C8), 22.7 (C7), 24.7 (C1), 27.8 (C6), 30.1 (C2), 36.0 (C3), 37.3 (C5), 71.4 ppm (C4). EIMS *m*/*z* (%): 39 (16.8), 41 (40.5), 43 (32.0), 43 (54.1), 57 (16.5), 60 (27.7), 69 (30.3), 71 (21.8), 87 (100), 101 (24.9), 162 ($M^{+\bullet}$, 0.1).

4.3.3. 1-Sulfanylnonan-4-ol ***1b***

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.90 (m, 3H, C*H*$_3$), 1.37 (t, 1H, *J*=7.8 Hz, S*H*), 1.20–1.90 (m, 13H, 6×C*H*$_2$, O*H*), 2.56 (dt, 2H, *J*=6.9 Hz, *J*=7.8 Hz, C*H*OH). ^{13}C NMR ($CDCl_3$): δ 14.1 (C9), 22.6 (C8), 24.8 (C1), 25.3 (C6), 30.1 (C2), 31.9 (C7), 36.0 (C3), 37.6 (C5), 71.5 ppm (C4). EIMS *m*/*z* (%): 41 (24.8), 43 (27.1), 55 (29.0), 60 (31.2), 71 (24.4), 83 (15.4), 87 (100), 101 (21.4), 115 (18.0), 129 (12.8), 176 ($M^{+\bullet}$, 0.1).

4.3.4. 1-Sulfanyldecan-4-ol ***1c***

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.88 (m, 3H, C*H*$_3$), 1.36 (t, 1H, *J*=7.8 Hz, S*H*), 1.20–1.90 (m, 15H, 7×C*H*$_2$, O*H*), 2.56 (dt, 2H, *J*=6.9 Hz, *J*=7.8 Hz, C*H*$_2$SH), 3.60 ppm (m, 1H, C*H*OH). ^{13}C NMR ($CDCl_3$): δ 14.1 (C10), 22.6 (C9), 24.8 (C1), 25.6 (C6), 29.3 (C7), 30.2 (C2), 31.8 (C8), 36.0 (C3), 37.6 (C5), 71.4 ppm (C4). EIMS *m*/*z* (%): 41 (29.2), 43 (30.0), 55 (35.0), 60 (37.5), 69 (13.9), 71 (24.7), 87 (100), 97 (11.1), 101 (19.5), 129 (23.3), 190 ($M^{+\bullet}$, 0.1). $[\alpha]_D^{20}$ −4.16 for (*R*)-1-sulfanyldecan-4-ol (99% ee).

4.3.5. 1-Sulfanylundecan-4-ol ***1d***

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.86 (m, 3H, C*H*$_3$), 1.33 (t, 1H, *J*=7.9 Hz, S*H*), 1.20–1.90 (m, 17H, 8×C*H*$_2$, O*H*), 2.56 (dt, 2H, *J*=7.0 Hz, *J*=7.8 Hz, C*H*$_2$SH), 3.60 ppm (m, 1H, C*H*OH). ^{13}C NMR (200 MHz, $CDCl_3$): δ 14.1 (C11), 22.7 (C10), 24.8 (C1), 25.7 (C6), 29.3 (C7), 29.7 (C8), 30.2 (C2), 31.9 (C9), 36.1 (C3), 37.7 (C5), 71.5 ppm (C4). MS (EI, 70 eV): *m*/*z* (%) 41 (33.8), 43 (35.2), 55 (26.9), 57 (15.8), 60 (41.0), 69 (29.6), 71 (20.2), 87 (100), 101 (23.7), 129 (14.3), 204 ($M^{+\bullet}$, 0.1).

4.3.6. 1-Sulfanyldodecan-4-ol ***1f***

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.88 (m, 3H, C*H*$_3$), 1.36 (t, 1H, *J*=7.8 Hz, S*H*), 1.20–1.90 (m, 19H, 9×C*H*$_2$, O*H*), 2.56 (dt, 2H, *J*=7.0 Hz, *J*=7.7 Hz, C*H*$_2$SH), 3.60 ppm (m, 1H, C*H*OH). ^{13}C NMR (200 MHz, $CDCl_3$): δ 14.1 (C12), 22.7 (C11), 24.7 (C1), 25.6 (C6), 29.3 (C8), 29.6 (C7), 29.7 (C9), 30.2 (C2), 31.9 (C10), 36.0 (C3), 37.6 (C5), 71.5 ppm (C4). MS (EI, 70 eV): *m*/*z* (%) 41 (30.0), 43 (32.7), 55 (26.8), 57 (16.7), 60 (42.0), 69 (23.8), 71 (18.6), 83 (12.7), 87 (100), 101 (23.9), 218 ($M^{+\bullet}$, 0.1).

4.3.7. syn-3-Methyl-1-sulfanyloctan-4-ol ***1g***

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.89 (d, 3H, *J*=6.8 Hz, CHC*H*$_3$), 0.93 (t, 3H, *J*=7.1 Hz, CH_2CH_3), 1.25–1.40 (m, 3H, $CH_3CH_2CH_2$), 1.35 (t, *J*=7.7 Hz, S*H*), 1.43–1.48 (m, 4H, $CH3CH_2CH_2CH_2$, O*H*), 1.56 (dtd, 1H, *J*=5.6 Hz, *J*=8.4 Hz, *J*=13.7 Hz, C*H*$_2$CH$_2$SH), 1.69 (m, 1H, $CH_2CH(OH)CH(CH_3)CH_2CH_2SH$), 1.76 (dddd, 1H, *J*=5.3 Hz, *J*=6.7 Hz, *J*=8.5 Hz, *J*=13.3 Hz, C*H*$_2$CH$_2$SH), 2.54 (dddd, 1H, *J*=6.8 Hz, *J*=7.5 Hz, *J*=8.5 Hz, *J*=12.9 Hz, C*H*$_2$SH), 2.65 (dddd, 1H, *J*=5.6 Hz, *J*=7.8 Hz, *J*=8.7 Hz, *J*=13.3 Hz, C*H*$_2$SH), 3.52 ppm (m, 1H, C*H*OH). ^{13}C NMR ($CDCl_3$): δ 13.3 (C9, CHC*H*$_3$), 14.2 (C8, C*H*$_2$CH$_3$), 22.8 (C1), 22.9 (C7), 28.6 (C6), 34.2 (C5), 37.1 (C3), 37.8 (C2), 74.8 ppm (C4). EIMS *m*/*z* (%): 41 (26.2), 55 (19.9), 56 (70.9), 57 (33.7), 69 (69.2), 81 (15.3), 85 (14.6), 87 (19.7), 90 (17.1), 101 (100), 176 ($M^{+\bullet}$, 0.1).

4.3.8. anti-3-Methyl-1-sulfanyloctan-4-ol ***1g***

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.92 (d, 3H, *J*=6.7 Hz, CHC*H*$_3$), 0.93 (t, 3H, *J*=6.9 Hz, CH_2CH_3), 1.25–1.58 (m, 9H, $CH_3CH_2CH_2CH_2CH(OH)CH(CH_3)CH_2$), 1.35 (t, *J*=7.6 Hz, S*H*), 1.69 (m, 1H, C*H*CH$_3$), 1.79 (dddd, 1H, *J*=3.8 Hz, *J*=7.2 Hz, *J*=9.1 Hz, *J*=13.2 Hz, C*H*$_2$CH$_2$SH), 2.50 (ddt, 1H, *J*=7.5 Hz, *J*=9.1 Hz, *J*=12.9 Hz, C*H*$_2$SH), 2.68 (dddd, 1H, *J*=5.1 Hz, *J*=7.8 Hz, *J*=9.0 Hz, *J*=12.9 Hz, C*H*$_2$SH), 3.52 ppm (ddd, 1H, *J*=2.7 Hz, *J*=5.1 Hz, *J*=8.6 Hz, C*H*OH). ^{13}C NMR ($CDCl_3$): δ 14.2 (C8, CH_2CH_3), 15.3 (C9, CHC*H*$_3$), 22.8 (C1 and C7), 28.3 (C6), 33.6 (C5), 36.5 (C2), 37.8 (C3), 75.9 ppm (C4). EIMS *m*/*z* (%): 41 (28.6), 43 (14.1), 55 (19.8), 56 (46.1), 57 (27.9), 69 (56.7), 81 (14.3), 87 (16.1), 90 (13.6), 101 (100), 176 ($M^{+\bullet}$, 0.1).

4.3.9. 2-Propylthiolane ***2a*** *(CAS: 1551-34-4)*

^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.85 (t, 3H, *J*=7.0 Hz, C*H*$_3$), 1.14–2.11 (m, 8H, H3 cycle, H4 cycle, C*H*$_2$-C*H*$_2$-CH$_3$), 2.79 (m, 2H, H5 cycle), 3.28 ppm (tt, 1H, *J*=5.8 Hz, *J*=7.7 Hz, H2 cycle). ^{13}C NMR ($CDCl_3$): δ 14.1 (*C*H$_3$), 22.4 (CH$_2$-*C*H$_2$-CH$_3$), 30.4 (C4 cycle), 32.2 (C5 cycle), 37.5 (C3 cycle), 40.1 (*C*H$_2$-CH$_2$-CH$_3$), 49.2 ppm (C2 cycle). EIMS *m*/*z* (%): 39 (4.1), 41 (5.1), 45 (6.0), 55 (4.0), 59 (4.3), 85 (4.6), 87 (100), 88 (5.9), 89 (4.6), 130 ($M^{+\bullet}$, 22.5).

4.3.10. 2-Butylthiolane ***2e*** *(CAS: 3050-98-4)*

^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.87 (m, 3H, C*H*$_3$), 1.19–2.15 (m, 10H, H3 cycle, H4 cycle, -C*H*$_2$-C*H*$_2$-C*H*$_2$-CH$_3$), 2.85 (m, 2H, H5 cycle), 3.32 ppm (tt, 1H, *J*=5.9 Hz, *J*=7.9 Hz, H2 cycle). ^{13}C NMR ($CDCl_3$): δ 14.2 (*C*H$_3$), 22.8 (CH$_2$-CH$_2$-*C*H$_2$-CH$_3$), 30.4 (C4 cycle), 31.5 (CH$_2$-*C*H$_2$-CH$_2$-CH$_3$), 32.2 (C5 cycle), 37.5 (C3 cycle), 37.6 (*C*H$_2$-CH$_2$-CH$_2$-CH$_3$), 49.6 ppm (C2 cycle). EIMS *m*/*z* (%): 41 (13.2), 45 (10.9), 53 (5.5), 55 (6.4), 59 (5.7), 87 (100), 88 (6.4), 89 (4.8), 101 (8.3), 144 ($M^{+\bullet}$, 21.3).

4.3.11. 2-Pentylthiolane ***2b*** *(CAS: 3050-98-4)*

^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.88 (m, 3H, C*H*$_3$), 1.20–2.17 (m, 12H, H3 cycle, H4 cycle, C*H*$_2$-C*H*$_2$-C*H*$_2$-C*H*$_2$-CH$_3$), 2.85 (m, 2H, H5 cycle), 3.33 ppm (tt, 1H, J=5.8 Hz, J=7.7 Hz, H2 cycle). ^{13}C NMR ($CDCl_3$): δ 14.1 (*C*H$_3$), 22.7 (CH$_2$-CH$_2$-CH$_2$-*C*H$_2$-CH$_3$), 29.0 (CH$_2$-*C*H$_2$-CH$_2$-CH$_2$-CH$_3$), 30.4 (C4 cycle), 31.9 (CH$_2$-CH$_2$-*C*H$_2$-CH$_2$-CH$_3$), 32.2 (C5 cycle), 37.5 (C3 cycle), 37.8 (*C*H$_2$-CH$_2$-CH$_2$-CH$_2$-CH$_3$), 49.5 ppm (C2 cycle). EIMS m/z (%): 39 (4.1), 41 (8.1), 45 (5.9), 55 (4.6), 87 (100), 88 (6.3), 89 (4.1), 115 (5.7), 129 (3.5), 158 ($M^{+\bullet}$, 12.6).

4.3.12. 2-Hexylthiolane ***2c*** *(CAS: 876-37-9)*

^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.88 (m, 3H, C*H*$_3$), 1.20–2.17 (m, 14H, H3 cycle, H4 cycle, -C*H*$_2$-C*H*$_2$-C*H*$_2$-C*H*$_2$-C*H*$_2$-CH$_3$), 2.85 (m, 2H, H5 cycle), 3.33 ppm (tt, 1H, J=5.8 Hz, J=7.7 Hz, H2 cycle). ^{13}C NMR ($CDCl_3$): δ 14.1 (*C*H$_3$), 22.7 (-CH$_2$-CH$_2$-CH$_2$-CH$_2$-*C*H$_2$-CH$_3$), 29.3 (-CH$_2$-*C*H$_2$-CH$_2$-CH$_2$-CH$_2$-CH$_3$), 29.3 (-CH$_2$-CH$_2$-*C*H$_2$-CH$_2$-CH$_2$-CH$_3$), 30.4 (C4 cycle), 31.9 (-CH$_2$-CH$_2$-CH$_2$-*C*H$_2$-CH$_2$-CH$_3$), 32.2 (C5 cycle), 37.5 (C3 cycle), 37.9 (-*C*H$_2$-CH$_2$-CH$_2$-CH$_2$-CH$_2$-CH$_3$), 49.5 ppm (C2 cycle). EIMS m/z (%): 39 (4.0), 41 (9.9), 45 (5.7), 55 (5.0), 67 (3.6), 87 (100), 88 (6.6), 89 (4.2), 129 (10.3), 172 ($M^{+\bullet}$, 10.6).

4.3.13. 2-Heptylthiolane ***2d*** *(CAS: 24767-96-2)*

^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.88 (m, 3H, C*H*$_3$), 1.20–2.17 (m, 16H, H3 cycle, H4 cycle, -C*H*$_2$-C*H*$_2$-C*H*$_2$-C*H*$_2$-C*H*$_2$-C*H*$_2$-CH$_3$), 2.85 (m, 2H, H5 cycle), 3.33 ppm (tt, 1H, J=5.8 Hz, J=7.7 Hz, H2 cycle). ^{13}C NMR ($CDCl_3$): δ 14.1 (*C*H$_3$), 22.8 (-CH$_2$-CH$_2$-CH$_2$-CH$_2$-CH$_2$-*C*H$_2$-CH$_3$), 29.3 (-CH$_2$-*C*H$_2$-CH$_2$-CH$_2$-CH$_2$-CH$_2$-CH$_3$), 29.5 (-CH$_2$-CH$_2$-CH$_2$-*C*H$_2$-CH$_2$-CH$_2$-CH$_3$), 29.6 (-CH$_2$-CH$_2$-*C*H$_2$-CH$_2$-CH$_2$-CH$_2$-CH$_3$), 30.5 (C4 cycle), 31.9 (-CH$_2$-CH$_2$-CH$_2$-CH$_2$-CH$_2$-CH$_2$-CH$_3$), 32.2 (C5 cycle), 37.5 (C3 cycle), 37.9 (-*C*H$_2$-CH$_2$-CH$_2$-CH$_2$-CH$_2$-CH$_2$-CH$_3$), 49.5 ppm (C2 cycle). EIMS m/z (%): 41 (7.6), 45 (3.8), 55 (4.6), 87 (100), 88 (6.9), 89 (4.3), 101 (4.0), 129 (7.0), 143 (7.1), 186 ($M^{+\bullet}$, 9.0).

4.3.14. 2-Octylthiolane ***2f*** *(CAS: 5143-23-7)*

^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.88 (m, 3H, C*H*$_3$), 1.20–2.17 (m, 18H, H3 cycle, H4 cycle, -C*H*$_2$-C*H*$_2$-C*H*$_2$-C*H*$_2$-C*H*$_2$-C*H*$_2$-C*H*$_2$-CH$_3$), 2.85 (m, 2H, H5 cycle), 3.33 ppm (tt, 1H, J=5.7 Hz, J=7.7 Hz, H2 cycle). ^{13}C NMR ($CDCl_3$): δ 14.1 (*C*H$_3$), 22.8 (-CH$_2$-CH$_2$-CH$_2$-CH$_2$-CH$_2$-CH$_2$-*C*H$_2$-CH$_3$), 29.3 (-CH$_2$-CH$_2$-CH$_2$-CH$_2$-CH$_2$-CH$_2$-CH$_2$-CH$_3$), 29.6 (-CH$_2$-CH$_2$-*C*H$_2$-CH$_2$-CH$_2$-CH$_2$-CH$_2$-CH$_3$), 29.7 (-CH$_2$-CH$_2$-CH$_2$-*C*H$_2$-CH$_2$-CH$_2$-CH$_2$-CH$_3$), 29.8 (-CH$_2$-CH$_2$-CH$_2$-CH$_2$-CH$_2$-CH$_2$-CH$_2$-CH$_3$), 30.5 (C4 cycle), 32.0 (-CH$_2$-CH$_2$-CH$_2$-CH$_2$-CH$_2$-CH$_2$-CH$_2$-CH$_3$), 32.2 (C5 cycle), 37.5 (C3 cycle), 37.9 (-*C*H$_2$-CH$_2$-CH$_2$-CH$_2$-CH$_2$-CH$_2$-CH$_2$-CH$_3$), 49.5 ppm (C2 cycle). EIMS m/z (%): 41 (8.3), 45 (3.6), 55 (5.3), 67 (3.3), 87 (100), 88 (7.3), 89 (4.3), 129 (7.2), 157 (5.5), 200 ($M^{+\bullet}$, 7.8).

4.3.15. Diastereoselective synthesis of 2-butyl-3-methylthiolane

cis- and *trans*-diastereomers of 3-methyl-4-butyl-γ-thionobutyrolactone (whisky thionolactone) were separated by silica gel column chromatography (Silica gel 60, 40–63 μm, Merck; 1 g of thionolactone/50 g of silica gel) by using a mixture of hexane/Et_2O (95/5 v/v) as eluent (elution order: *trans*- then *cis*-whisky thionolactone). Fractions of about 7 mL were collected and analysed by TLC. Each diastereomer was separately submitted to $LiAlH_4$ reduction to afford *syn*- and *anti*-3-methyl-1-sulfanyloctan-4-ol **1g**. *syn*- and *anti*-**1g** were submitted to cyclodehydration as described for the K10/microwave procedure to yield *trans*- and *cis*-**2g**.

cis-2-Butyl-3-methylthiolane **2g** (*cis*-whisky thiolane): ^{1}H NMR ($CDCl_3$): δ 0.92 (t, 3H, J=7.1 Hz, CH$_2$-C*H*$_3$), 0.97 (d, 3H, J=7.1 Hz, CH-C*H*$_3$), 1.25–1.45 (m, 5H, C*H*$_2$-C*H*$_2$-C*H*$_2$-CH$_3$), 1.65 (m, 1H, C*H*$_2$-CH$_2$-CH$_2$-CH$_3$), 1.82 (tdd, 1H, J=5.3 Hz, J=6.7 Hz, J=12.2 Hz, H4 cycle), 1.98 (dtd, 1H, J=5.1 Hz, J=7.7 Hz, J=12.6 Hz, H4′ cycle), 2.33 (m, 1H, H3 cycle), 2.84 (ddd, 1H, J=5.0 Hz, J=7.5 Hz, J=10.3 Hz, H5 cycle), 2.89 (ddd, 1H, J=6.8 Hz, J=8.0 Hz, J=10.2 Hz, H5′ cycle), 3.34 ppm (td, 1H, J=5.4 Hz, J=9.5 Hz, H2 cycle). ^{13}C NMR ($CDCl_3$): δ 13.4 (CH-*C*H$_3$), 14.2 (CH$_2$-*C*H$_3$), 22.9 (CH$_2$-CH$_2$-*C*H$_2$-CH$_3$), 29.7 (C5 cycle), 31.4 (CH$_2$-CH$_2$-CH$_2$-CH$_3$), 31.9 (*C*H$_2$-CH$_2$-CH$_2$-CH$_3$), 37.3 (C4 cycle), 40.3 (C3 cycle), 52.9 ppm (C2 cycle). EIMS m/z (%): 41 (5.0), 45 (3.1), 55 (5.0), 59 (6.2), 67 (7.6), 81 (3.0), 101 (100), 102 (7.2), 103 (4.5), 158 ($M^{+\bullet}$, 19.3). Anal. Calcd for $C_9H_{18}S$ (mixture of *cis*/*trans* **2g**): C, 68.28; H, 11.46; S, 20.26. Found: C, 68.29; H, 11.29; S, 20.10.

trans-2-Butyl-3-methylthiolane **2g** (*trans*-whisky thiolane): ^{1}H NMR ($CDCl_3$): δ 0.92 (t, 3H, J=7.0 Hz, CH$_2$-C*H*$_3$), 0.97 (d, 3H, J=6.6 Hz, CH-C*H*$_3$), 1.25–1.45 (m, 5H, C*H*$_2$-C*H*$_2$-C*H*$_2$-CH$_3$), 1.65 (dtd, 1H, J=7.6 Hz, J=9.5 Hz, J=12.2 Hz, H4 cycle), 1.78–1.82 (m, 2H, C*H*$_2$-CH$_2$-CH$_2$-CH$_3$ and H3 cycle), 2.18 (m, 1H, H4′ cycle), 2.80–2.89 ppm (m, 3H, H2 cycle and H5 cycle). ^{13}C NMR ($CDCl_3$): δ 14.2 (CH$_2$-*C*H$_3$), 17.6 (CH-*C*H$_3$), 22.9 (CH$_2$-CH$_2$-*C*H$_2$-CH$_3$), 29.9 (C5 cycle), 31.8 (CH$_2$-CH$_2$-CH$_2$-CH$_3$), 36.2 (*C*H$_2$-CH$_2$-CH$_2$-CH$_3$), 39.1 (C4 cycle), 44.6 (C3 cycle), 55.9 ppm (C2 cycle). EIMS m/z (%): 41 (5.3), 45 (2.8), 55 (6.3), 59 (7.7), 67 (9.5), 69 (2.6), 101 (100), 102 (7.7), 103 (4.5), 158 ($M^{+\bullet}$, 15.7).

Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.07.088.

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