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# The Synthesis of 4'-Thia-α-Santalene and 4'-Thia-α-Santalol Through an Organometallic Approach

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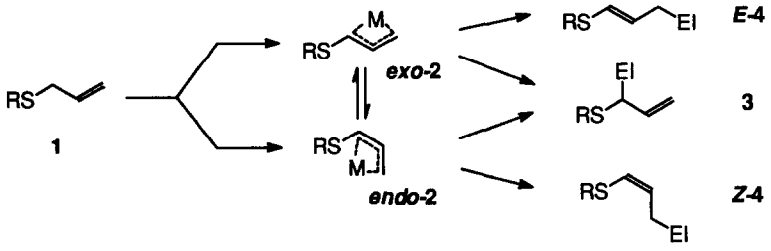
**Abstract**: The 4'-thia analogues of α-santalene and α-santalol are prepared in a very convenient, regio- and stereocontrolled manner by using allyl type organometallic intermediates.

The mobility of the allylic hydrogen atoms in allyl sulfides is high enough [1] to allow their deprotonation with simple organolithium reagents such as butyllithium [2 - 4], *sec*-butyllithium [5 - 8] or alkyllithium reagents activated by complexing agents such as 1,4-diazabicyclo[2.2.2]octane (DABCO) [3, 9] or *N,N,N',N'*-tetramethylethylenediamine (TMEDA) [9 - 10].



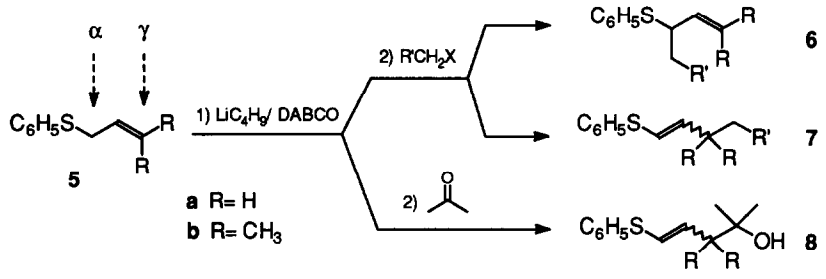

Metalation of allyl sulfides **1** is therefore easy to achieve leading to the corresponding α-thioallyl metallic compounds **2** which may then react with a wide variety of electrophiles to afford either the α-substituted allyl sulfides **3** or the γ-substituted vinyl sulfides **4**, the latter existing in two stereoisomeric forms (***Z*-4** and ***E*-4**).

## Regioselectivity of thioallyl "anions": a survey

Regio- and stereocontrol is the main problem to deal with when one wishes to generate thioallyl "carbanions" and to functionalize them with electrophilic reagents. The proportions of the three isomers (**3**, ***Z*-4** and ***E*-4**) are dictated by many factors such as the nature of the electrophile used, the metal and hence the organometallic base employed, the unreactive alkyl or aryl group bonded to sulfur, the substitution pattern of the allylic moiety and detailed reaction conditions such as temperature and solvent. The lithio derivative of allyl phenyl sulfide **5a**, generated by metalation with butyllithium/DABCO in tetrahydrofuran at -30 °C, reacts with

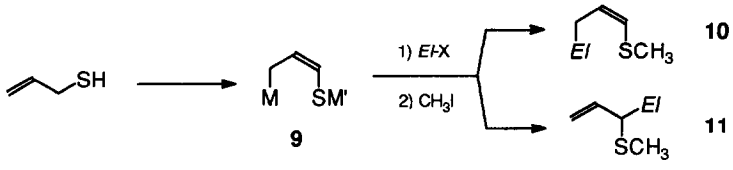
primary alkyl halides ($R'CH_2X$) leading to a mixture of α and γ regioisomers (**6a** and **7a** respectively) in a 76 : 24 ratio when R' = H and 68 : 32 when R' = $CH_2$=CH [9].

The α-selectivity increases when the allylic moiety is substituted at the γ-position. Thus, the 3,3-dimethylallyl phenyl sulfide **5b** is alkylated exclusively in the α-position with a very good yield of the allyl sulfide **6b**. Carbonyl compounds exhibit a different regioselectivity giving preferentially γ-attack: the 3,3-dimethylallyl phenyl sulfide **5b**, after metalation with butyllithium in the presence of DABCO in THF at -20 °C and reaction with acetone, gives, with quantitative yield, exclusively the product deriving from γ-attack **8b** [11].



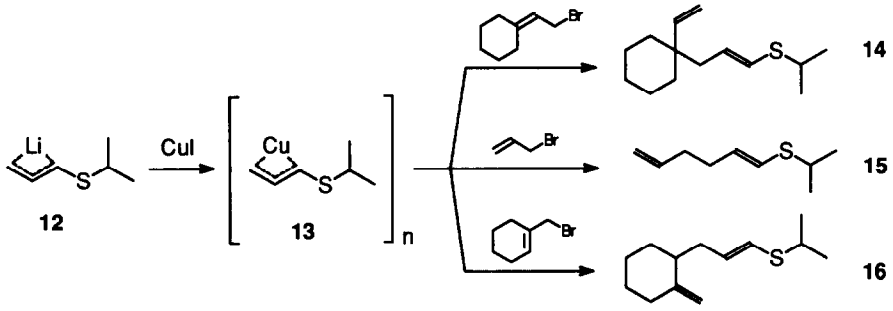

Both the use of solvating additives in the metalation step [11] and the presence on the substrate of substituents capable of chelating the metal [12 - 14], play an important role in driving the regiocontrol of the reaction of thioallyl "anions" with electrophiles. Thus acetone reacts essentially at the γ center (α: γ = 25 : 75) if the metalation is performed with butyllithium in tetrahydrofuran alone, whereas after addition of cryptand[2.2.2], the reaction occurs only at the α-center. The alkylation of thioallyl "anions" occurs with the highest percentage of α-attack when the reaction is conducted in tetrahydrofuran with *sec*-butyllithium (α : γ = 95 : 5) but the regioselectivity drops down (α : γ = 70 : 30) if an additive such as DABCO is employed together with butyllithium [2, 7].

In order to achieve mainly γ-reactivity a thioallylic "dianion" might be used [15]. The metalation of allyl thiol with two equivalents of butyllithium and TMEDA in tetrahydrofuran gives the dilithio derivative **9** (M = M' = Li) which reacts with different electrophiles to afford mainly the γ-substituted thioether **10**, the α : γ ratio varying from 35 : 65 for alkyl halides to 30 : 70 for carbonyl compounds. The γ-preference further increases when hexamethylphosphoric triamide (HMPA; 12%) and potassium *tert*-butoxide (1 eq.) are added to the reaction mixture.




The most thoroughly investigated factor is the effect of the metal counterion. Thus the the γ-isomer **10** is obtained almost exclusively when the thioallyl "dianion" **9** is consecutively treated with chlorotriisopropoxytitanium [16] and a carbonyl compound. The α-isomer **11** is alternatively the main product when magnesium bromide [17] is used instead.

Addition of tetraisopropoxytitanium to the lithium derivatives of allyl sulfides is indeed an useful method in order to control both the regio- and stereoselectivity of reactions with carbonyl electrophiles. The thioallyltitanium reagents react with a very high α-selectivity giving β-hydroxy sulfides in a highly stereoselective manner too, the *anti* alcohol being formed predominantly [18, 19]. The addition of copper (I) iodide to the lithium derivative of isopropyl allyl thioether **12** leads to the organocopper species **13** which reacts with electrophiles with a selectivity opposite to that of the lithio reagent [5]. Alkylation with allylic halides affords the γ-alkylated products **14** - **16** with inversion of the allyl unit while reaction with acetone yields mainly the α-adduct.

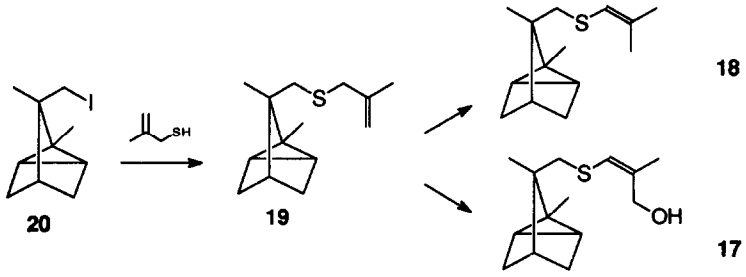



It is well known [20] that allylpotassium compounds, easily generated by the superbase [21] metalation of alkenes, show a high selectivity in their reaction with electrophiles. Their behaviour has been studied [22] in the metalation of allyl sulfides. Allyl phenyl sulfide, when treated with butyllithium/potassium *tert*-butoxide and then with methyl iodide, gives a mixture of the two possible α and γ regioisomers, which is oriented towards the α when tetrahydrofuran is used as solvent and, at a lower extent, towards the γ with petroleum ether. The use of the superbasic mixture allows control of the stereochemistry of the γ-product: the (*Z*)-enethioether is obtained as the major isomer with (*Z*) : (*E*) ratios ranging from 1.8 to 3.7 when the reaction is performed in hexane.

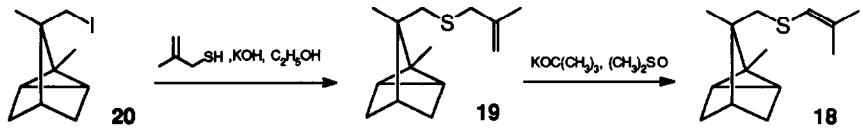
**Trimethylsilylation of thioallyl "anions"**

As a part of an ongoing program based on the synthesis of thia-analogues of naturally occurring compounds, we had to find an easy and selective method to prepare the (*Z*)-4-thia-2-methyl-2-alken-1-ol moiety which is isosteric [23] to the (*Z*)-2-methyl-2-alken-1-ol widely found in natural products.

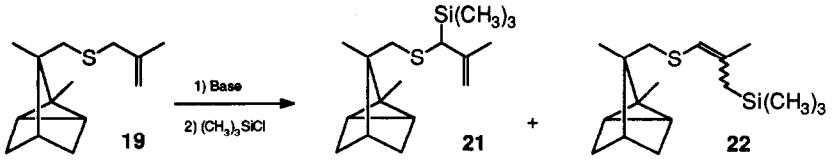

An organometallic approach, via metalation of an allyl sulfide, looked suitable for our purpose. As a first target we selected the 4'-thia-α-santalol **17**. A straightforward synthetic sequence, shown below, relies on (*R*)-1,7-dimethyl-7-(2-methyl-1-propenyl-thiomethyl)tricyclo[2.2.1.$0^{2,6}$]heptane **19** as a possible intermediate which can be derived from (*R*)-7-iodomethyl-1,7-dimethyltricyclo[2.2.1.$0^{2,6}$]heptane ("8-iodotricyclene" [24]) **20** and 2-methyl-1-propene-3-thiol. The allyl sulfide **19** is also a precursor of 4'-thia-α-santalene **18**; compounds **17** and **18** are isosteres of α-santalol and α-santalene respectively, which are two of the main constituents of Sandalwood oil [25], a highly prized fragrance.




Iodide **20** was prepared from the corresponding bromo derivative [26] with sodium iodide in HMPA. The 2-methyl-1-propene-3-thiol was easily obtained [27] by treatment of 3-chloro-2-methyl-1-propene with thiourea in aqueous sodium hydroxide. Condensation of iodide **20** and methallyl thiol, in the presence of potassium hydroxyde, gave 78% of allyl sulfide **19** which was then isomerized with potassium *tert*-butoxide in dimethylsulfoxide [28], to afford 65% of the thermodynamically more stable 4'-thia-α-santalene **18**.



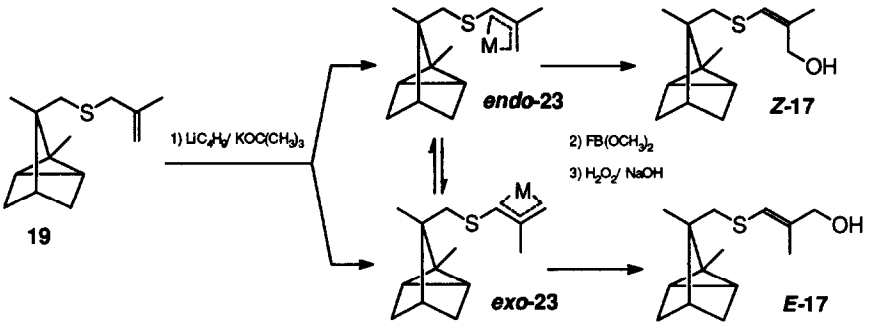

Allyl sulfide **19** was then submitted to metalation and was trapped with electrophiles in order to evaluate the regio- and stereochemical outcome of the reaction. Thus, trimethylsilylation of the thioallyl "anion" has revealed a strong effect of the organometallic base. When allyl sulfide **19** was consecutively treated with *sec*-butyllithium in tetrahydrofuran at -50 °C and trimethylchlorosilane, a 52 : 48 mixture of α and γ regioisomers (**21** and **22**) was obtained, the latter with a *Z* : *E* ratio of 81 : 19. When *sec*-butyllithium was replaced by Schlosser's base, the selectivity increased considerably. ***Z*-22** was obtained in a 75% yield as almost the unique product (α : γ = 4 : 96) in both tetrahydrofuran solution at -50 °C or pentane suspension at 25 °C.




**Boronate mediated hydroxylation of thioallyl "anions"**

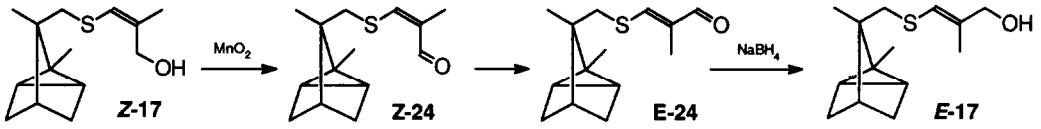
The borylation/ oxidation sequence [29] was employed to convert allyl sulfide **19** into 4'-thia-α-santalol, the same method having recently been used for the synthesis of α-santalol [30] and 4'-oxa-α-santalol [31]. Allyl sulfide **19** was treated with the superbasic mixture butyllithium/potassium *tert*-butoxide in pentane at 25 °C to afford the brown red-coloured allylpotassium species **23** (M = K) which was then oxidized to 4'-thia-α-santalol (**17**) by consecutive addition of fluorodimethoxyboron and alkaline hydrogen peroxide. Metalation at 25 °C afforded 60% of a mixture of *Z* and *E* isomers in a 66 : 34 ratio after 1 h, which increased to 90 : 10 (62% global yield) when the time was prolonged to 16 h. When the metalation reaction was performed in tetrahydrofuran at -50 °C,

a mixture of (*Z*)- and (*E*)-**17** was obtained in a 80 : 20 ratio irrespective of the reaction time in a 64% global yield.




The two isomers were separated by chromatography and analyzed by $^1$H nmr. Irradiation of the olefinic hydrogen caused an Overhauser enhancement of the signal assigned to the allylic methyl group of ***Z*-17** and to the allylic methylene group of ***E*-17**. No other nuclear Overhauser effect was observed, the assumed structures being thus confirmed. The use of the Schlosser's base proved to be of fundamental importance once again; *sec*-butyllithium alone in tetrahydrofuran did deprotonate allyl sulfide **19** but the allyllithium species **23** (M = Li), thus formed, gave a mixture of all possible regio- and stereoisomeric alcohols after the borylation/oxidation sequence. In pentane suspension, the metalation reaction with *sec*-butyllithium did not occur; after 24 h at 25 °C almost all of the starting material was recovered.

(*Z*)-4'-Thia-α-santalol (***Z*-17**) can be easily converted into its stereoisomer ***E*-17**. The (*Z*)/(*E*) mixture isolated was treated with manganese dioxide in refluxing hexane for 30 h resulting in the formation of pure (*E*) enal (**24**) which was then reduced to ***E*-17** with sodium borohydride in a 78% yield. In contrast to the isomerization [30] of α-santalol, the (*Z*) to (*E*) equilibration of aldehyde **24** occurred spontaneously, without requiring acid catalysis.




The method here described represents an easy access to thia-analogues of natural products containing an alkenol structural unit. The replacement of a methylene group with a sulfur atom may lead to an intriguing modification of biological properties such as odor or pharmaceutical activity. Therefore we would like to evaluate the effect of the isosteric substitution and to extend this kind of comparison to other natural products.

## Experimental part

*1. General remarks*

*Starting materials* are commercially available unless otherwise stated. Commercial reagents were used without further purification except HMPA which was distilled from calcium hydride. *Air and moisture sensitive compounds* were stored in Schlenk tubes or burettes. They were protected by and handled under an atmosphere of 99.99% pure nitrogen. *Tetrahydrofuran* was obtained anhydrous by distillation from sodium wire after the characteristic blue colour of in situ generated sodium diphenylketyl [32] was found to persist. *Pentane* was distilled and stored over lithium aluminum hydride. *Ethereal extracts were dried* with sodium sulfate.

The temperature of dry ice/ ethanol baths is consistently indicated as -78°C and that of ice baths as 0°C. If no reduced pressure is specified, *boiling ranges* were determined under ordinary atmospheric conditions (720 ± 35 mmHg). If no melting points are given it means that all attempts to crystallize the liquid product failed even at temperatures as low as -75°C.

Purifications by *flash column chromatography* were performed using glass columns (10-50 mm wide); silica gel 230-400 mesh was chosen as stationary phase (15 cm high), with an elution rate of 5 cm/ min [33].

*Nuclear magnetic resonance spectra* of hydrogen nuclei were recorded at 200 MHz. Chemical shifts were determined relative to the residual solvent peak ($CHCl_3$ : 7.26 ppm). Coupling constants (*J*) are measured in Hz. Coupling patterns are described by abbreviations: s (singlet), d (doublet), t (triplet), hept (heptuplet), dd (doublet of a doublet), m (multiplet); bs (broad singlet). Nuclear magnetic resonance spectra of carbon-13 nuclei were recorded at 50.3 MHz. Chemical shifts were determined relative to the residual solvent peak ($CHCl_3$: 77.0 ppm). *Mass spectra* were obtained at a 70 eV ionization potential.

*2. Preparation of (R)-7-iodomethyl-1,7-dimethyltricyclo[2.2.1.0$^{2,6}$]heptane* (**20**)

22.9 g (0.100 mol) of (*R*)-7-bromomethyl-1,7-dimethyltricyclo[2.2.2.0$^{2,6}$]heptane and 59.7 g (0.400 mol) of sodium iodide are mixed in HMPA (80 mL) and kept at 130 °C while stirring for 3 days. The mixture is then cooled to 25 °C, added with water (30 mL), extracted with diethylether (3x 90 mL). The ethereal solution is washed with water (3x 100 mL) and dried. After evaporation of the solvent, the residue is distilled through a Vigreux column (20 cm) affording 24.6 g (94%) of **20**, bp 50 - 51°C/ 0.1 mmHg, $n_D^{20}$ 1.5444, $[\alpha]_D^{20}$ -25.9° (c = 2.37, $CHCl_3$). - $^1$H-NMR ($CDCl_3$): 3.17 (1 H, d, *J* 10.0); 3.09 (1 H, d, *J* 10.0); 1.73 (1 H, bs); 1.67 (1 H, ddd, *J* 10.8, 2.0, 1.5); 1.58 (1 H, ddd, *J* 10.8, 2.5, 1.0); 1.1 (4 H, m); 1.04 (3 H, s); 0.98 (3 H, *s*).

*3. Preparation of 2-methyl-1-propene-3-thiol*

A mixture of 45.2 g (0.500 mol) of 3-chloro-2-methyl-1-propene and 38.0 g (0.500 mol) of thiourea in water (50 mL) is refluxed for 12 h. The solution is then cooled to 25 °C and a 10 N solution of NaOH (100 mL) is added. The mixture is refluxed for 30 min and then cooled to 25 °C. The solution is acidified at 0 °C with conc. $H_2SO_4$ to pH 1 and extracted with diethylether (3x 50 mL). The ethereal extracts are collected and dried. The solvent and the residue are distilled through a Vigreux column (20 cm) affording 28.6 g (65%) of the thiol, bp: 91 - 92°C (lit. [30] 93.5°C), $n_D^{20}$ 1,4794. - $^1$H-NMR ($CDCl_3$): 4.90 (1 H, m); 4.76 (1 H, m); 3.14 (2 H, dd, *J* 8.0, 0.9); 1.84 (3 H, m); 1.46 (1 H, t, *J* 8.0).

*4. Preparation of (R)-1,7-dimethyl-7-(2-methyl-1-propenylthiomethyl)tricyclo[2.2.1.0$^{2,6}$]heptane* (**19**)

26.2g (0.100 mol) of **20** and 8.8 g (0.100 mol) of 2-methyl-1-propene-3-thiol are added together to a solution of 5.6 g (0.100 mol) of KOH in ethanol (100 mL). The mixture is then refluxed for 12 h, cooled down to 25 °C and poured into water (100 mL). The mixture is extracted with diethylether (3x 150 mL), the ethereal solution is washed with water (4x 100 mL), brine (100 mL) and dried. The solvent is then evaporated and the residue distilled through a Vigreux column (10 cm) affording 17.3 g (78%) of **19**, bp 101 - 102°C/ 2 mmHg, $n_D^{20}$ 1.5135, $[\alpha]_D^{20}$ +41.1° (c = 1.14, $CHCl_3$). - $^1$H-NMR ($CDCl_3$): 4.82 (2 H, m); 3.08 (2 H, d, *J* 1.1); 2.40 (1 H, d, *J* 11.5); 2.28 (1 H, d, *J* 11.5); 1.82 (3 H, m); 1.75 (1 H, m); 1.65 (1 H, m); 1.60 (1 H, m); 1.11 (1 H, m); 1.08 (1 H, m); 1.02 (3 H, s); 0.93 (3 H, s); 0.88 (2 H, m). - $^{13}$C-NMR ($CDCl_3$): 141.65; 113.06; 46.97; 40.77; 38.79; 37.62; 31.31; 31.06; 27.24; 20.68; 19.80; 19.39; 17.61; 10.58. - MS: 222 (0.4%; $M^+$); 221 (1.1%); 167 (50%); 133 (29%), 121 (30%); 107 (22%); 105 (29%); 93 (100%); 91 (65%); 79 (44%); 77 (50%); 55 (89%); 53 (35%). Calc. for $C_{14}H_{22}S$ (222.39) C 75.61, H 9.97; found C 75.34, H 10.11.

*5. Synthesis of 4'-thia-α-santalene* (**18**)

In a Schlenk tube 2.8 g (25.0 mmol) of potassium *tert*-butoxide are dissolved in dimethyl sulfoxide (25 mL) and 5.6 g (25.0 mmol) of **19** are added. The mixture is kept at 25 °C for 2 h, then poured into water (25 mL) and diethylether (25 mL). The phases are separated, the water phase extracted with diethylether (3x 25 mL) and the ethereal solution dried. After evaporation of the solvent the residue is distilled through a Vigreux column (10 cm) affording 3.6 g (65%) of 4'-thia-α-santalene **18**, bp 86 88°C/ 0.8 mmHg, $n_D^{20}$ 1.5132, $[\alpha]_D^{20}$ +5.5° (c = 1.09, $CHCl_3$). - $^1$H-NMR ($CDCl_3$): 5.62 (1 H, hept., *J* 1.1); 2.70 (1 H, d, *J* 12.5); 2.50 (1 H, d, *J* 12.5); 1.78 (1 H, m); 1.74 (6 H, m); 1.66 (1 H, m);1.62 (1 H, m); 1.12 (1 H, m); 1.08 (1 H, m); 1.02 (3 H, s); 0.94 (3 H, s); 0.90 (2 H, m). - $^{13}$C-NMR ($CDCl_3$): 132.64; 119.69; 47.54; 40.73; 38.59; 31.25; 31.11; 27.08; 25.19; 19.86; 19.46; 19.30; 17.37; 10.56. - MS: 222 (14%; $M^+$); 167 (1.4%); 121 (29%); 107 (44%); 93 (100%); 91 (60%); 79 (39%); 77 (43%); 65 (22%); 55 (39%); 53 (36%). Calc. for $C_{14}H_{22}S$ (222.39) C 75.61, H 9.97; found C 75.56, H 10.39.

*6. Synthesis of (R)-1,7-dimethyl-7-(2-methyl-3-trimethylsilyl-1-propenylthiomethyl)tricyclo[2.2.1.0$^{2,6}$]heptane* (*21*)

7.1 mL of 1.4 M solution of *sec*-butyllithium (10.0 mmol; from which the original cyclohexane solvent has been stripped off) and 2.22 g (10.0 mmol) of **19** in tetrahydrofuran (20 mL) are kept 10 h at -50 °C. After addition of 1.1 g of chlorotrimethylsilane (10.0 mmol) the solution is slowly warmed up to 25 °C, then poured into water (20 mL) and extracted with diethylether (3x 40 mL). The organic extracts are collected, washed with brine (60 mL) and dried. After evaporation of the solvent, the residue is distilled affording a 52 : 48 mixture of **21** and **22**; 2.1 g (70%), bp 125-128 °C/ 0.07 mmHg. **21** was obtained as a 60 : 40 mixture of diasteroisomers by chromatography on silica gel column (eluant pentane). Major diasteroisomer: $^1$H-NMR ($CDCl_3$): 4.76 (1 H, m);

4.71 (1 H, m); 2.65 (1 H, s); 2.31 (2 H, s); 1.76 (4 H, m); 1.64 (1 H, m); 1.59 (1 H, m); 1.10 (1 H, m); 1.05 (1 H, m); 0.99 (3 H, s); 0.90 (3 H, s); 0.85 (2 H, s); 0.09 (9 H, s). - $^{13}$C-NMR ($CDCl_3$): 144.46; 111.11; 47.21; 43.34; 38.71; 38.46; 31.33; 31.21; 27.36; 20.78; 19.53; 19.37; 17.44; 10.64; -2.08; MS: 294 (20%; $M^+$); 160 (21%); 159 (100%); 107 (42%); 105 (11%); 93 (70%); 91 (27%); 79 (15%); 77 (17%); 73 (99%); 55 (12%). Minor diasteroisomer: $^1$H-NMR ($CDCl_3$): 4.76 (1 H, m); 4.71 (1 H, m); 2.65 (1 H, s); 2.41 (1 H, d, *J* 11.2); 2.20 (1 H, d, *J* 11.2); 1.76 (4 H, m); 1.70 (1 H, m); 1.64 (1 H, m); 1.10 (1 H, m); 1.05 (1 H, m); 1.00 (3 H, s); 0.94 (3 H, s); 0.85 (2 H, s); 0.09 (9 H, s). - $^{13}$C-NMR ($CDCl_3$): 144.51; 111.11; 47.14; 43.49; 38.77; 38.46; 31.28; 30.99; 27.13; 20.78; 19.94; 19.46; 17.77; 10.64; -2.08; MS: 294 (10%; $M^+$); 160 (16%); 159 (77%); 107 (39%); 105 (10%); 93 (65%); 91 (26%); 79 (15%); 77 (17%); 73 (100%); 55 (12%). Calc. for $C_{17}H_{30}SSi$ (294.58) C 69.31, H 10.27; found C 69.49, H 10.23.

*7. Synthesis of (R)-1,7-dimethyl-7-(2-methyl-1-trimethylsilyl-2-propenylthiomethyl)tricyclo[2.2.1.0$^{2,6}$]heptane (22)*

6.8 mL of 1.5 M solution of butyllithium (10.0 mmol; from which the hexane solvent has been stripped off) and 1.12 g (10.0 mmol ) of potassium *tert*-butoxide are mixed in tetrahydrofuran (20 mL) and stirred at -78 °C for 30 min. Then 2.22 g (10.0 mmol) of **19** are added and the solution kept 10 h at -50 °C. After addition of 1.1 g of chlorotrimethylsilane (10.0 mmol) the solution is warmed up to 25 °C, then poured into water (20 mL) and extracted with diethylether (3x 40 mL). The organic extracts are collected, washed with brine (60 mL) and dried. After evaporation of the solvent, the residue is distilled affording **22**; 2.3 g (78%), bp 125-126 °C/ 0.07 mmHg; $n_D^{20}$ 1.5156, $[\alpha]_D^{20}$ -5.2° (c = 1.00, $CHCl_3$). - $^1$H-NMR ($CDCl_3$): 5.50 (1 H, m); 2.64 (2 H, d, *J* 12.4); 2.45 (1 H, d, *J* 12.4); 1.77 (1 H, m); 1.73 (3 H, d, *J* 1.2); 1.70 (2 H, s); 1.66 (1 H, m); 1. 61 (1 H, m); 1.11 (1 H, m); 1.05 (1 H, m); 1.01 (3 H, s); 0.94 (3 H, s); 0.88 (2 H, s); 0.05 (9 H, s). - $^{13}$C-NMR ($CDCl_3$): 135.58; 116.56; 47.57; 40.97; 38.59; 31.25; 31.14; 25.59; 25.32; 19.88; 19.30; 17.40; 10.58; -0.59. - MS: 294 (34%; $M^+$); 160 (27%); 159 (100%); 121 (15%); 107 (50%); 105 (14%); 93 (87%); 91 (32%); 79 (17%); 77 (19%); 73 (93%); 55 (14%). Calc. for $C_{17}H_{30}SSi$ (294.58) C 69.31, H 10.27; found C 69.45, H 10.34.

*8. Synthesis of (Z)-4'-thia-α-santalol (Z-17)*

6.8 mL of 1.5 M butyllithium solution in hexane (10.0 mmol) are placed in a Schlenk tube and then pentane (30 mL) and 1.12 g (10.0 mmol ) of potassium *tert*-butoxide are added. The heterogeneous mixture is stirred 10 min at 25 °C, then 2.22 g (10.0 mmol ) of **19** are added, after cooling to 0 °C. The reaction mixture is kept at 25 °C under vigorous stirring for 20 h, then cooled to -78 °C, treated with fluorodimethoxyboron (1.2 mL of 8.5 M solution in diethylether, 10.0 mmol) and allowed to reach 25 °C. After cooling to 0 °C, 1.2 mL of 34% hydrogen peroxide solution (12.0 mmol) are added slowly, immediately followed by 3.4 mL of 3N aq. NaOH (10.0 mmol). The temperature is again allowed to rise to 25 °C, then the reaction mixture is poured into water (20 mL) and extracted with diethylether (3x 40 mL). The organic extracts are collected, washed with brine (80 mL) and dried. After evaporation of the solvent the residue is purified by chromatography on silica gel column (eluant diethylether/ hexane 1:1). Two main fractions are collected which are the (*Z*)-4'-thia-α-santalol **Z-17** (1.34 g; 56%) and the (*E*)-4'-thia-α-santalol ***E*-17** (0.14 g; 6%). *(Z)-4'-thia-α-santalol* (**Z-17**): $n_D^{20}$ 1.5391, $[\alpha]_D^{20}$ +1.6° (c = 1.02, $CHCl_3$). - $^1$H-NMR ($CDCl_3$) 5.81 (1 H, m); 4.24 (2 H, d, *J* 6.2); 2.71 (1 H, d, *J* 12.5); 2.52 (1 H, d, *J* 12.5); 1.83 (3 H, d, *J* 1.3); 1.74 (1 H, m); 1.65 (1 H, m); 1.6 (2 H, m); 1.13 (1 H, m); 1.07 (1 H, m); 1.02 (3 H, s); 0.94 (3 H, s); 0.90 (2 H, m). - $^{13}$C-NMR ($CDCl_3$): 134.78; 123.15; 62.97; 47.56; 41.37; 38.62; 31.27; 31.11; 27.10; 20.90; 19.88; 19.27; 17.39; 10.55. - MS: 238 (40%; $M^+$); 221 (73%); 134 (26%); 121 (59%); 107 (57%); 93 (100%); 91 (59%); 79 (32%); 77 (32%). Calc. for $C_{14}H_{22}OS$ (238.39) C 70.54, H 9.30; found C 70.78, H 9.65.

*9. Synthesis of (E)-4'-thia-α-santalol (E-17)*

2.38 g (10.0 mmol) of **Z-17** are added to excess manganese dioxide (8.7 g, 100 mmol) in hexane (25 mL) and the mixture stirred at reflux for 30 h. After filtering off the manganese dioxide and evaporating the solvent under reduced pressure, the crude aldehyde **23** is dissolved in ethanol and treated with 0.38 g (10.0 mmol) of sodium borohydride. After 4 h at 25 °C, ethanol is evaporated under reduced pressure and the crude is purified by chromatography on a silica-gel column (eluant diethylether/ hexane 1:1). 1.86 g (78%) of ***E*-17** are obtained, $n_D^{20}$ 1.5358, $[\alpha]_D^{20}$ + 0.5° (c = 1.00, $CHCl_3$). - $^1$H-NMR ($CDCl_3$): 5.97 (1 H, m); 4.02 (2 H, d, *J* 6.4 ); 2.74 (1 H, d, *J* 12.6); 2.56 (1 H, d, *J* 12.6); 1.75 (4 H, m); 1.65 (1 H, m); 1.61 (1 H, m); 1.42 (1 H, t, *J* 6.4 ); 1.13 (1 H, m); 1.07 (1 H, m); 1.02 (3 H, s); 0.94 (3 H, s); 0.90 (2 H, m). - $^{13}$C-NMR ($CDCl_3$):133.08; 123.53; 68.05; 47.55; 40.73; 38.59; 31.25; 31.12; 27.08; 19.88; 19.26; 17.35; 15.38; 10.54. - MS: 238 (25%; $M^+$); 134 (42%); 121 (54%); 107 (58%); 105 (29%); 93 (100%); 91 (63%); 79 (42%); 77 (37%); 55 (25%). Calc. for $C_{14}H_{22}OS$ (238.39) C 70.54, H 9.30; found C 70.68, H 9.45.

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## References and notes

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