Asymmetric Synthesis of (−)-(*E*)-5-Hydroxy-5-isopropyl-3-hepten-2-one, A Cembrane-Derived Compound from Greek Tobacco

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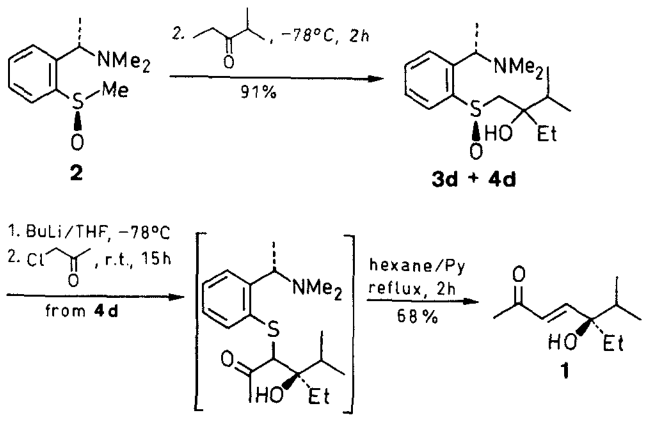
The lithiation of (+)-*N*,*N*-dimethyl-1-(2-methylsulfinylphenyl)-ethylamine (**2**) with butyllithium followed by reaction with unsymmetrical ketones gave the corresponding *tert*-alcohols with high diastereoselectivity. By following this procedure, (*R*)-(*E*)-5-hydroxy-5-isopropyl-3-hepten-2-one (**1**), isolated from the extract of Greek tobacco, was synthesized and the absolute configuration on the asymmetric carbon determined.

In 1990, six new cembrane-derived compounds including (−)-(*E*)-5-hydroxy-5-isopropyl-3-hepten-2-one (**1**), were isolated from Greek tobacco and their structures were identified spectroscopically.[1] However, the absolute configuration of **1** was not determined and remained unknown. We report here the asymmetric synthesis of **1** and contributing at the same time the absolute configuration of **1** as (−)-(*E*)-5-hydroxy-5-isopropyl-3-hepten-2-one. The synthetic strategy is shown in Scheme 1.

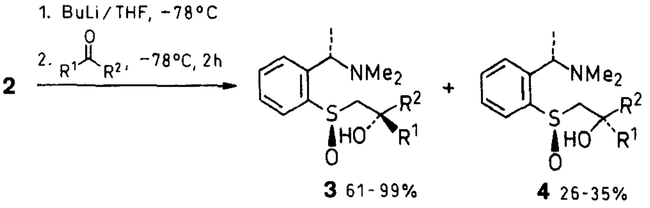


Scheme 1

Recently, we presented the synthesis of chiral *N*,*N*-dimethyl-1-(2-methylsulfinylphenyl)ethylamine (**2**) by the diastereoselective oxidation of the corresponding sulfide with sodium perborate.[2] Two sulfoxides obtained by this oxidation can be easily separated from each other and **2** was obtained in 100% optical purity. The starting material for **2** is 1-phenylethylamine which is a very cheap chiral amine and hence the use of **2** is economical in organic syntheses.

First the lithiation of **2** with butyllithium and followed by the reaction with various ketones were examined and the results are shown in Table 1. The reaction of several chiral α-sulfinylcarbanions have already been reported.[3] However, we could separate the resulting sulfoxides **3a–d** and **4a–d**[4] from each other by column chromatography on silica gel to afford optically pure aryl alkyl sulfoxides. The diastereomer excess values were better than the previous reports.[3,5] The obtained data suggest that the functional group substituted at the ortho-position contributes to a chelation control for the stereoselective reaction.

The structures of **3b** and **4b** were determined with an NOE experiment of their ^1H NMR spectra as shown in the Figure. The assignment of two signals for the α-protons to the arylsulfinyl group was done based on literature data.[6] The chemical shift values of the methyl groups corresponding to the R-groups of **3b** and **4b** in their ^1H NMR spectra were different from each other, and the value of **3b** was larger than **4b**. This seems to result from the anisotropic effect of the sulfinyl group. An NOE experiment of **3d** and **4d** which might be starting materials for the synthesis of **1** could not be accomplished because the target signals for the irradiation gave an overlap with other signals in their ^1H NMR spectra. However, their structures could be estimated by the order of elution in the column chromatography and on the chemical shift value of the ethyl groups corresponding to their R-groups on the ^1H NMR spectra.



3,4	R^1	R^2
a	Me	*i*-Pr
b	Me	*i*-Bu
c	Me	*t*-Bu
d	Et	*i*-Pr

Scheme 2

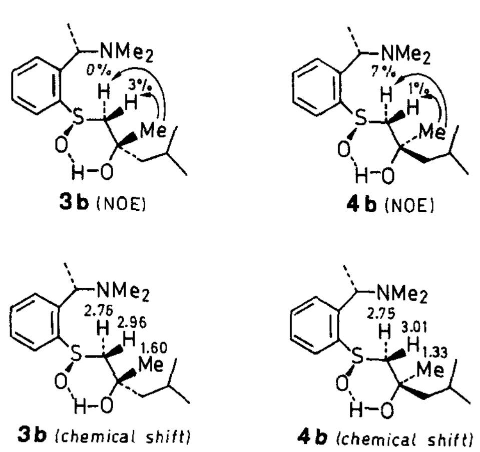


Figure. NOE Experiments and Chemical Shift Data (δ) of **3b** and **4b**

The optical rotation values of **3d** and **4d** were positive, and the value of **3d** was larger than **4d**. Naturally occurring **1** has a negative optical rotation and it was

Table. Compounds **3** and **4** Prepared

Product[a]	Yield (%)	de	Molecular Formula[b]	$[\alpha]_D$[c]	^{1}H NMR ($CDCl_3$/TMS) δ, J (Hz)	MS (DCI) (m/z) ($M^+ + 1$)
3a	99	100	$C_{16}H_{27}NO_2S$ (297.5)	+118°	0.90 (d, 3H, J = 6.9), 0.92 (d, 3H, J = 6.9), 1.32 (d, 3H, J = 6.8), 1.45 (s, 3H), 1.69–1.80 (m, 1H), 2.09 (s, 6H), 2.62 (d, 1H, J = 12.9), 2.78–2.90 (q, 1H, J = 6.8), 3.08 (d, 1H, J = 12.9), 7.28 (d, 1H, J = 8.0), 7.44 (t, 1H, J = 8.0), 7.53 (t, 1H, J = 8.0), 8.16 (d, 1H, J = 8.0)	298
3b	70	46	$C_{17}H_{29}NO_2S$ (311.5)	+112°	0.96 (d, 6H, J = 6.9), 1.47 (d, 2H, J = 6.9), 1.49 (d, 3H, J = 6.9), 1.60 (s, 3H), 1.79–1.86 (m, 1H), 2.18 (s, 6H), 2.76 (d, 1H, J = 13.1), 2.96 (d, 1H, J = 13.0), 3.30 (q, 1H, J = 6.9), 7.30 (d, 1H, J = 8.0), 7.40 (t, 1H, J = 8.0), 7.50 (t, 1H, J = 8.0), 8.18 (d, 1H, J = 8.0)	312
3c	96	100	$C_{17}H_{29}NO_2S$ (311.5)	+124°	0.92 (s, 9H), 1.48 (d, 3H, J = 6.9), 1.60 (s, 3H), 2.18 (s, 6H), 2.75 (d, 1H, J = 13.0), 3.08 (d, 1H, J = 13.0), 3.30 (q, 1H, J = 6.9), 7.29 (d, 1H, J = 8.0), 7.42 (t, 1H, J = 8.0), 7.53 (t, 1H, J = 8.0), 8.20 (d, 1H, J = 8.0)	312
3d	61	27	$C_{17}H_{29}NO_2S$ (311.5)	+141°	0.84 (d, 3H, J = 6.9), 0.95 (d, 3H, J = 6.9), 1.04 (t, 3H, J = 6.9), 1.48 (d, 3H, J = 6.9), 1.87–1.96 (m, 3H), 2.15 (s, 6H), 2.76 (d, 1H, J = 13.1), 2.94 (d, 1H, J = 13.1), 3.28 (q, 1H, J = 6.9), 7.29 (d, 1H, J = 8.0), 7.41 (t, 1H, J = 8.0), 7.51 (t, 1H, J = 8.0), 8.19 (d, 1H, J = 8.0)	312
4b	26	46	$C_{17}H_{29}NO_2S$ (311.5)	+98°	1.03 (d, 3H, J = 6.9), 1.06 (d, 3H, J = 6.9), 1.33 (s, 3H), 1.47 (d, 2H, J = 6.9), 1.48 (d, 3H, J = 6.9), 1.82–1.94 (m, 1H), 2.15 (s, 6H), 2.75 (d, 1H, J = 13.1), 3.01 (d, 1H, J = 13.1), 3.29 (q, 1H, J = 6.9), 7.30 (d, 1H, J = 8.0), 7.40 (t, 1H, J = 8.0), 7.50 (t, 1H, J = 8.0), 8.18 (d, 1H, J = 8.0)	312
4d	35	27	$C_{17}H_{29}NO_2S$ (311.5)	+122°	0.92 (t, 3H, J = 7.5), 1.02 (d, 3H, J = 6.7), 1.03 (d, 3H, J = 6.7), 1.49 (d, 3H, J = 6.8), 1.68–1.80 (m, 3H), 2.15 (s, 6H), 2.77 (d, 1H, J = 13.1), 3.02 (d, 1H, J = 13.1), 3.26 (q, 3H, J = 6.8), 7.30 (d, 1H, J = 8.0), 7.41 (t, 1H, J = 8.0), 7.52 (t, 1H, J = 8.0), 8.20 (d, 1H, J = 8.0)	312

[a] All products are thermally unstable colorless viscous oils.
[b] Satisfactory HRMS values obtained: ± 0.003 amu.
[c] Optical rotation measured in $CHCl_3$ ($c = 1.0$) at 22 °C.

estimated that the configuration on the asymmetric carbon of **1** constitutes (*R*)-form. Consequently, **4d** was selected as the starting material for the synthesis of (−)-**1**. Compound **4d** was alkylated with chloroacetone at the α-position to the phenylsulfinyl group in the presence of butyllithium (2 equivalents). The tertiary alcohol formed was dehydrated by refluxing in hexane containing pyridine to give **1** in 68 % yield. The optical rotation of the product was − 4.5° and compared well with the literature value (Lit.[1] $[\alpha]_D$ − 4.1°) donating the *R*-configuration for (−)-**1**.

(+)-*N*,*N*-Dimethyl-1-(2-methylsulfinylphenyl)ethylamine was prepared from commercial (−)-1-phenylethylamine purchased from Tokyo Kasei Kogyo Co., Ltd. according to the reported procedure.[2] The other reagents were of commercial quality. A 1.6 M solution of BuLi in hexane and ethyl isopropyl ketone were purchased from Aldrich Chemical Co. Methyl butyl ketone, methyl isopropyl ketone, methyl *tert*-butyl ketone and chloroacetone were purchased from Tokyo Kasei Kogyo Co., Ltd. THF was dried over a mixture of Na and benzophenone and distilled. The other reagent quality solvents were used without further purification. Mass spectra were obtained using a Hitachi M-80B spectrometer. ^{1}H NMR spectra were recorded on a Bruker AM-400 using TMS as the internal standard. The NOE experiment was carried out with the same apparatus. Optical rotations were measured at the Na-D line with a Japan Spectroscopic Co. DIP-360 polarimeter.

(*S*)- and (*R*)-*N*,*N*-Dimethyl-1-[2-(3-ethyl-2-hydroxy-2-methylbutylsulfinyl)phenyl]ethylamines (3d and 4d); Typical Procedure:

To a solution of (*S*)-**2** (1.05 g, 5 mmol) dissolved in anhydrous THF (25 mL) was added BuLi (1.6 M solution in hexane, 3 mL, 5 mmol) at − 78 °C under an Ar atmosphere. The mixture was stirred for 30 min at − 78 °C and ethyl isopropyl ketone (1.00 g, 10 mmol) was added. After stirring for 2 h, the mixture was poured into 5 % HCl (200 mL) and the aqueous solution was washed with Et_2O (3 × 50 mL), neutralized with K_2CO_3 and extracted with Et_2O. After drying (Na_2SO_4), Et_2O was removed by distillation and the residue applied to a silica gel column (silica gel 60, 240–400 mesh, 30 g). When EtOAc was used as the developing solvent, **3d** was eluted first; yield: 945 mg (61 %) followed by **4d**; yield: 549 mg (35 %).

(−)-(*E*)-5-Hydroxy-5-isopropyl-3-hepten-2-one (1):

To a solution of **4d** (311 mg, 1 mmol) in anhydrous THF (5 mL) was added BuLi (1.6 M solution in hexane, 1.3 mL, 2 mmol) at − 78 °C under an Ar atmosphere. The mixture was stirred for 30 min at − 78 °C and chloroacetone (140 mg, 1.5 mmol) was added. After stirring for 15 h at r.t., the mixture was poured into water (50 mL) and the aqueous solution was extracted with Et_2O (3 × 20 mL). The Et_2O solution was dried (Na_2SO_4) and concentrated in a water bath. Hexane (20 mL) and pyridine (1 mL) were added to the residue and the mixture was refluxed for 2 h with vigorous stirring. The mixture was washed with 5 % HCl (3 × 10 mL) and dried (Na_2SO_4). The solvent was removed by distillation in vacuo to afford a pale yellow oil, which was purified by distillation to give (−)-**1** as a colorless oil. Yield: 116 mg (68 %); oil (Lit.[1] oil); $[\alpha]_D^{20}$ − 4.5° (c = 0.50, $CHCl_3$) [Lit.[1] $[\alpha]_D$ − 4.1° (c = 0.41, $CHCl_3$)]. The spectroscopic data are in agreement with the reported data for naturally occurring **1**.[1]

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