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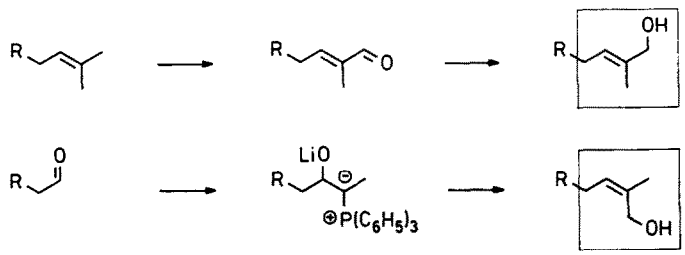
A Shortcut to α-Santalol

Manfred Schlosser * and Guo-fu Zhong

Institut de Chimie organique de l'Université
Rue de la Barre 2, CH-1005 Lausanne, Switzerland

Abstract : α-Santalol (Z-3) can be prepared from the readily available 8-bromotricyclene in a one-flask procedure under perfect regio- and stereocontrol.

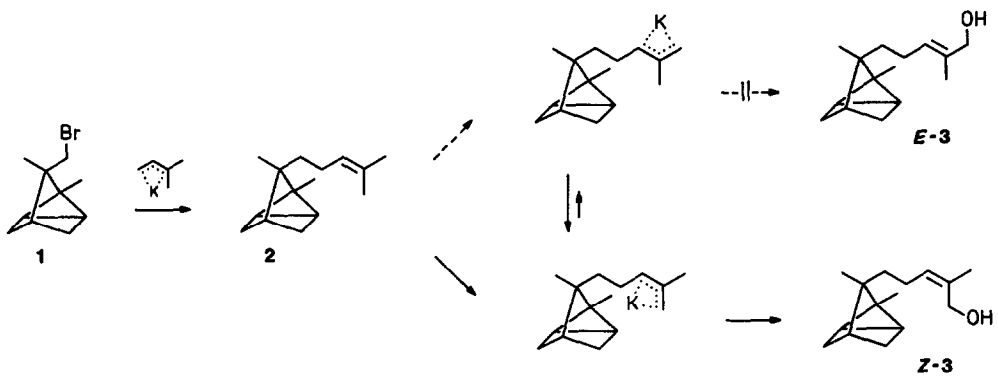
The site selective functionalization of isoprene units belongs to the inventory of classical synthetic challenges. If a *(E)*-2-methyl-2-butenyl structural motif is targeted, often a simple solution can be envisaged : selenium dioxide readily oxidizes 2-methyl-2-alkenes to afford *(E)*-2-methyl-2-alken-1-ols or *(E)*-2-methyl-2-alkenals, depending on the reaction conditions [1]. The allylsulfoxide/allylsulfinate isomerization with *in situ* reductive cleavage of the S,O linkage offers another expedient access to *(E)*-2-methyl-2-alken-1-ols [2]. In contrast, there appears to be no straightforward route leading to the corresponding *(Z)* isomers. Thus, fairly laborious multistep sequences had to be devised for their stereoselective construction [3, 4]. This situation was considerably improved when the "three-dimensional" Wittig reaction *via* betaine ylids ("SCOOPY" procedure) [5] was developed as a general method for the stereocontrolled assembly of branched and functionalized olefins having the *(Z)* configuration [5, 6]. It was indeed immediately applied to the synthesis of natural products including α-santalol [7, 8]. Nevertheless, also this method suffers from drawbacks, being very sensitive to deviations from the optimum temperature profile and producing invariably by-products when formaldehyde is employed as one of the two electrophilic components [9]. Moreover, it is not suitable for connecting isoprene C_5 units.



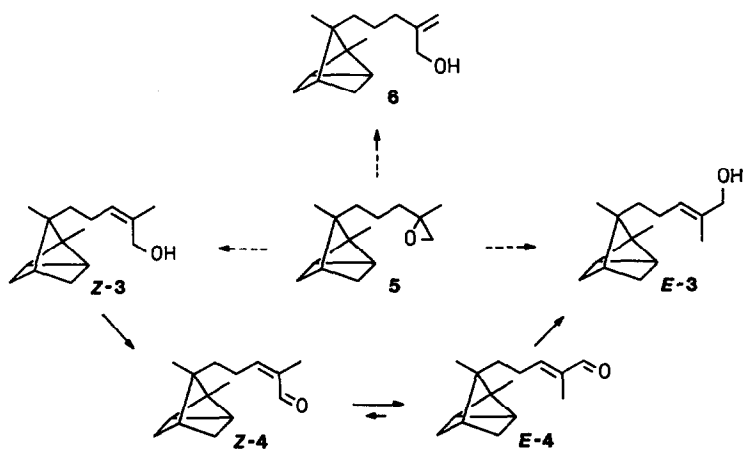
While systematically investigating the internal mobility of superbase generated allylpotassium species, we have discovered quite amazing conformational preferences [10]. Thus, 2-butenylpotassium was found to favor the *endo (Z)* over the *exo (E)* structure to the extent of 125 : 1. Replacement of the methyl by a longer straight-chain alkyl group diminishes the *endo/exo* equilibrium ratios to about 15 : 1. However, introduction of a bulky methyl

substituent at the 2-position increases again the discrimination against the *exo* structure and raises the thermodynamic *endo/exo* ratios to levels in the range of 50 : 1 to 250 : 1.

The torsional isomerization of allylsodium, -potassium or -cesium species allows one to achieve stereocontrol over the construction of unsaturated carbon backbones in a particularly convenient and efficient way. We wish to illustrate this principle by a new and extremely short synthesis of α-santalol. Starting with the readily accessible 3-bromomethyl-2,3-dimethyltricyclo[2.2.1.$0^{2,6}$]heptane (**1**; "8-bromotricyclene") [11], it requires three operational steps which may be contracted to a one-flask protocol : condensation with 3-methyl-2-butenylpotassium ("prenylpotassium") [12] to afford α-santalene (**2**), metalation with butyllithium in the presence of potassium *tert*-butoxide [10] and consecutive treatment with fluorodimethoxyboron [13] and hydrogen peroxide. The α-santalol *(Z-3)*, isolated with 35% over-all yield [14], was regio- and stereochemically pure (as evidenced by gas chromatographic analysis).



α-Santalol *(Z-3)* can be quantitatively converted into its unnatural *(E)* isomer *(E-3)* [15] by dehydrogenation with manganese dioxide, acid catalyzed stereoequilibration of the resulting *(Z)* enal *(Z-4)* and final reduction of the *(E)* unsaturated aldehyde *(E-4)* with sodium borohydride. On the other hand, the LIDA-KOR (lithium diisopropyl-



amide and potassium *tert*-butoxide) promoted ring opening of the epoxide (**5**) proved to proceed unselectively, as expected in such a case [16]. Besides 2-[3-(2,3-dimethyltricyclo[2.2.1.$0^{2,6}$]hept-3-yl)]prop-2-en-1-ol [17] (**6**, 29%); a mixture of *Z*-3 (12%) and *E-3* (47%) was obtained.

PRODUCTS AND PROCEDURES

(+)-α-Santalene (2) [18] : At -75 °C, precooled tetrahydrofuran (50 mL), 3-methyl-1-butene (5.6 mL, 3.5 g, 50 mmol) and potassium *tert*-butoxide (6.0 g, 54 mmol) are consecutively added to butyllithium (52 mmol) from which the commercial solvent (hexane) has been stripped off. The mixture is vigorously stirred at -50 °C until becoming homogeneous, then kept 30 min at -50 °C. At -75 °C, 3-bromomethyl-2,3-dimethyltricyclo[2.2.1.$0^{2,6}$]heptane [11] (10.8 g, 50 mmol) in tetrahydrofuran (10 mL) is added. After 30 min, the mixture is allowed to reach 25 °C. The solvent is evaporated and the residue is absorbed on silica gel (20 g). Elution with hexane from a column filled with fresh silica gel (150 g) followed by distillation affords α-santalene (2) as a colorless liquid; 64%; bp 116 - 118 °C/10 mmHg; n_D^{20} 1.4865; $[\alpha]_D^{20}$ +13 ($CHCl_3$; c = 0.10).

(+)-α-Santalol (Z-3) [7, 8] : At -75 °C, precooled tetrahydrofuran (40 mL), potassium *tert*-butoxide (2.2 g, 20 mmol) and α-santalene (4.1 g, 10 mmol) are added to solvent-free butyllithium (20 mmol). The mixture is vigorously stirred until it has reached -50 °C. At this temperature it is kept 2 h. At -75 °C, it is consecutively treated with fluorodimethoxyborane diethyl etherate (8.0 mL, 7.2 g, 42 mmol) and 30% aqueous hydrogen peroxide (5.1 mL, 5.6 g, 50 mmol). After 1 h of stirring at 25 °C, the aqueous phase is saturated with sodium chloride. The ethereal layer is decanted and absorbed on silica gel (15 g). The dry powder is poured on top of a column filled with fresh silica gel (150 g) and hexane. Elution with a 15 : 85 (v/v) mixture of ethyl acetate and hexane followed by distillation gives a colorless oil having a characteristic woody smell; 46%; bp 92 - 93 °C/0.1 mmHg; n_D^{20} 1:5022; $[\alpha]_D^{20}$ +17 ($CHCl_3$; c = 0.10). - ^{1}H-nmr : δ 5.31 (1 H, t, *J* 7.5), 4.14 (2 H, s), 1.97 (2 H, symm. m), 1.80 (3 H, q, *J* 1.3), 1.6 (3 H, t-like m), 1.2 (5 H, m), 1.06 (1 H, dd, *J* 10.0, 6.0), 1.00 (3 H, s), 0.84 (1 H, s), 0.83 (3 H, s). - Prior to purification, a sample of the crude mixture was withdrawn. According to gas chromatographic analysis, it did not contain even a trace of the (*E*) isomer (*E*-3).

(E)-*5-(2,3-Dimethyltricyclo[2.2.1.$0^{2,6}$]heptyl)-2-methylpent-2-en-1-ol* (*E*-3, santalol isomer) : α-Santalol (Z-3; 4.4 g, 20 mmol) is added to excess manganese dioxide (17 g, 0.20 mol) in hexane (50 mL). After 24 h of stirring at 25 °C, the aldehyde Z-4 (see below) is isolated and dissolved in chloroform (25 mL) containing benzoic acid (1.2 g, 10 mmol). The mixture is heated in a sealed tube 24 h to 100 °C. The isomeric aldehyde *E*-4 (15 mmol; see below) obtained is treated 6 h at 25 °C with sodium borohydride (0.61 g, 16 mmol) in ethanol (50 mL). Evaporation and chromatography give pure *E*-3; 88% (with respect to *E*-4; 80% with respect to *Z*-3); bp 98 - 99 °C/0.15 mmHg; n_D^{20} 1.5015; $[\alpha]_D^{20}$ +18 ($CHCl_3$, c = 0.90). - ^{1}H-nmr : δ 5.42 (1 H, thex, *J* 7.3, 1.4), 4.01 (2 H, d, *J* 4.8), 1.99 (2 H, symm. m), 1.72 (3 H, s), 1.61 (3 H, t-like m, *J* 9.4), 1.2 (5 H, m), 1.07 (1 H, dd, *J* 10.0, 6.5), 1.01 (3 H, s), 0.85 (3 H, s).

3-Iodomethyl-2,3-dimethyltricyclo[2.2.1.$0^{2,6}$]heptane [19] : From 1 (10 mmol) and sodium iodide (50 mmol) after 3 days at 110 °C in hexamethylphosphoric triamide (30 mL); 92%; bp 50 - 51 °C/0.1 mmHg; n_D^{20} 1.5444; $[\alpha]_D^{20}$ -26 ($CHCl_3$; c = 2.4).

(2,3-Dimethyltricyclo[2.2.1.$0^{2,6}$]hept-3-yl)methyl p-toluenesulfonate [8]: From (2,3-dimethyltricyclo[2.2.1.$0^{2,6}$]hept-3-yl)methanol (20 mmol), *p*-toluenesulfonyl chloride (20 mmol) and pyridine (20 mmol) after 15 h at 25 °C; 92%; mp 42 - 44 °C; $[\alpha]_D^{20}$ +20 ($CHCl_3$; c = 0.75).

(Z)-*5-(Dimethyltricyclo[2.2.1.$0^{2,6}$]hept-3-yl)-2-methylpent-2-enal* (Z-4) [15] : From α–santalol (10 mmol) and manganese dioxide (0.10 mol) after 24 h of stirring at 25 °C in hexane (50 mL); 96%; bp 126 - 127 °C/0.5 mmHg; n_D^{20} 1.4962; $[\alpha]_D^{20}$ +18 ($CHCl_3$; c = 0.80). - ^{1}H-nmr (250 MHz, $CDCl_3$) : δ 10.18 (1 H, s), 6.55 (1 H, tq, *J* 8.3, 1.4), 2.50 (2 H, q, *J* 8.4), 1.78 (3 H, q, *J* 0.8), 1.3 (4 H, m), 1.11 (1 H, dd, *J* 10.0, 4.5), 1.03 (3 H, s), 0.88 (3 H, s).

(E)-*5-(2,3-Dimethyltricyclo[2.2.1.$0^{2,6}$]hept-3-yl)-2-methylpent-2-enal* (*E*-4) [15] : From the *(Z)* isomer (Z-4, 10 mmol) by heating a chloroform (10 mL) solution of it, to which benzoic acid (1 mmol) had been added in a sealed tube 24 h to 100 °C; 95%; bp 121 - 122 °C/0.2 mmHg; n_D^{20} 1.4951; $[\alpha]_D^{20}$ +18 ($CHCl_3$; c = 0.80); ^{1}H-nmr (250 MHz, $CDCl_3$) : δ 9.40 (1 H, s), 6.52 (1 H, tq, *J* 7.5, 1.4), 2.3 (2 H, m), 1.78 (3 H, s), 1.63 (4 H, symm. m), 1.3 (4 H, m), 1.13 (1 H, dd, *J* 10.0, 4.3), 1.05 (3 H, s), 0.91 (3 H, s).

5-(2,3-Dimethyltricyclo[2.2.1.$0^{2,6}$]hept-3-yl)-2-methylpent-1-ene : From 2-(2,3-dimethyltricyclo[2.2.1.$0^{2,6}$]hept-3-yl)-ethyl *p*-toluenesulfonate (20 mmol), 2-methylallylmagnesium chloride (20 mmol) and dilithium trichlorocuprate [20] (0.5 mmol) in tetrahydrofuran (30 mL) after 1 h at -75 °C and warming up to 25 °C; 72%; bp 94 - 95 °C/3 mmHg; n_D^{20} 1.4752; $[\alpha]_D^{20}$ +9 ($CHCl_3$; c = 0.90).

5-(2,3-Dimethyltricyclo[2.2.1.$0^{2,6}$]hept-3-yl)propyl-2-methyloxirane (5) : From 5-(2,3-dimethyltricyclo[2.2.1.$0^{2,6}$]hept-3-yl)-2-methylpent-1-ene (30 mmol) and 3-chloroperbenzoic acid (50 mmol) after 24 h at 25 °C; 94%; bp 90 - 91°C/2 mmHg; n_D^{20} 1.4794; $[\alpha]_D^{20}$ +7 ($CHCl_3$; c = 0.90).

2-[3-(2,3-Dimethyltricyclo[2.2.1.$0^{2,6}$]hept-3-yl)propyl]prop-2-en-1-ol (6) : From oxirane 5 (20 mmol) by treatment with lithium diiso-propylamide and potassium *tert*-butoxide ("LIDA-KOR" mixture [16], 20 mmol) in tetrahydrofuran (0.10 L) during 12 h at -75 °C; 29% (after separation from Z-3 and *E*-3 by chromatography on silica gel); bp 122 - 124 °C/0.5 mmHg; n_D^{20} 1.5064; $[\alpha]_D^{20}$ +19 ($CHCl_3$, c = 0.80).

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14 Stepwise reactions : 64% of α-santalene (**2**; with respect to 8-bromotricyclene **1**) and 46% of α-santalol (**Z-3**; with respect to α-santalene **2**). The yield of α-santalene can be increased to 77% and 84% if the bromide **1** is replaced by the corresponding iodide or *p*-toluenesulfonate as the starting material.

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