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4'-Oxa-α-santalene and 4'-Oxa-α-santalol : An Olfactory Comparison with the Analogous Natural Sesquiterpenes

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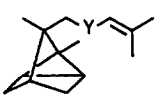
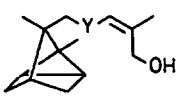
Abstract : Allyl type organometallic intermediates allow to prepare the 4'-oxa analogues of α-santalene and α-santalol (1 and Z-2) in a very convenient, regio- and stereocontrolled manner. The introduction of the heteroatom into the side chain of the natural fragrances changes the smelling properties profoundly.

Halogens are most suitable for the isosteric modification of a structural part located at the *periphery* of a molecule. Thus, hydrogen may be replaced by fluorine or methyl by trifluoromethyl, chlorine or bromine without affecting the space requirements to the extent that it would be recognized by enzymes of other biological receptors. Prominent examples are fluoroacetic acid [1], which leads to a "lethal synthesis" of fluorocitric acid when entering the Krebs cycle, 5-fluorouracil [2], an irreversible inhibitor of thymidylate synthetase, and deltamethrine [3], a mimic of the natural pyrethroids which block efficiently the sodium channels of insects.

Polyvalent elements such as nitrogen or sulfur have to be employed if the *backbone* of a hydrocarbon chain or ring is the target of an isosteric substitution. Typical cases are rare [4, 5]. We want to investigate systematically what effect the introduction of an isoperiodic [6] oxygen bridge into the aliphatic part of natural products has. A comparative neutron or X-ray diffraction study of the hydrocarbon model and its oxa analogue would, of course, provide the most objective description of the structural alteration caused by the hetero atom. We find it more intriguing, however, to monitor the variation of the physical and *organoleptic* properties within such isosteric series. As first examples we have synthesized the 4'-oxa analogues (1 and Z-2, respectively) of α-santalene and α-santalol, the latter being natural fragrances endowed with a characteristic woody scent.



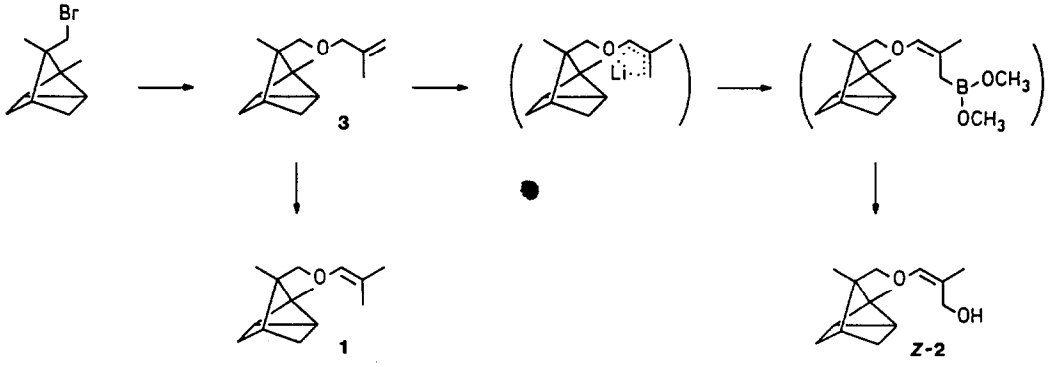
Y = CH_2 : α-santalene
Y = O : 1



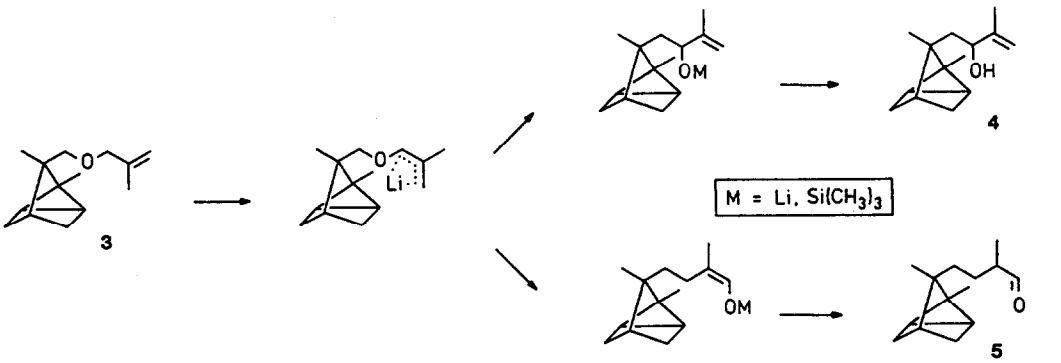
Y = CH_2 : α-santalol
Y = O : Z-2

The synthesis of 1 and Z-2 was straightforward. (*R*)-3-Bromomethyl-2,3-dimethyltricyclo[2.2.1.$0^{2,6}$]heptane ("8-bromotricyclene") [7] was treated with sodium 2-methyl-2-propenolate in tetrahydrofuran and in the presence of hexamethylphosphoric triamide (HMPT) to afford (*R*)-2,3-dimethyl-3-[(2-methyl-2-propenyloxy)methyl]tricyclo-

[2.2.1.$0^{2,6}$]heptane (**3**). Its base catalyzed isomerization [8] with sodium amide or sodium hydride gave directly the 4'-oxa-α-santalene (**1**). Deprotonation of the allyl ether **3** with *sec*-butyllithium in tetrahydrofuran at -75 °C generated a cherry-red colored alkoxyallyllithium species which immediately adopted the *endo* configuration [9]. It was converted into 4'-oxa-α-santalol (*Z*-**2**) by consecutive addition of fluorodimethoxyboron [10] and alkaline hydrogen peroxide. For comparison, the pure (*E*) isomer (*E*-**2**) was isolated by chromatographic separation of the (*Z*/*E*) mixture formed when the allyl ether **3** was oxidized with *m*-chloroperbenzoic acid and the resulting oxirane was treated with lithium diisopropylamide in the presence of potassium *tert*-butoxide [11].

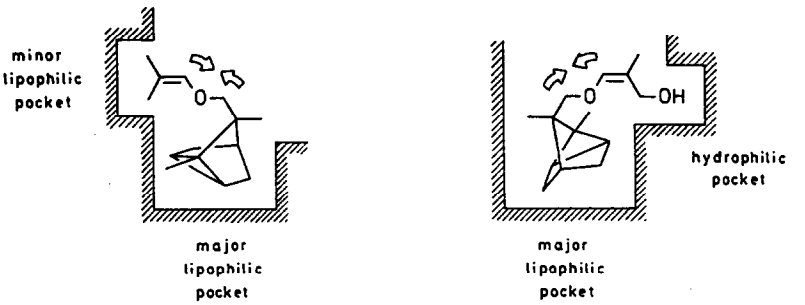


The intermediate obtained upon metalation of the allyl ether **3** can be intercepted only at low temperatures, of course. Upon warming to 0 °C, it underwent Wittig [1,2] and [3,2] rearrangements generating a lithium homoallyl alcoholate and a lithium enolate, respectively [12]. These species were trapped with chlorotrimethylsilane [12] before being hydrolyzed with dilute acid to afford the homoallyl alcohol **4** and the aldehyde **5**.



The olfactory characteristics of compounds **1** and **2** remarkably differ from those of the natural analogues α-santalene and α-santalol [13]. What kind of oxygen specific effects on the structure, and as a corollary, on the properties of such compounds do we expect ? In the case of the 4'-oxa-α-santalol (**2**) several possibilities have to be considered. First of all, the terminal hydroxy group may establish an intramolecular or intermolecular hydrogen bond to the ether oxygen donor center. In addition, the dipole moments associated with the two heteroatoms may impose a conformational change onto the side chain. However, the infrared and nuclear magnetic resonance spectra of 4'-oxa-α-santalol (*Z*-**2**) provide no evidence for either process. Such interactions cannot exist in the 4'-oxa-α-santalene (**1**) anyway, since it does not contain more than one hetero atom.

What is common to both model substances is the shrinking of the chain, typical C,C and C,O bond lengths being 1.54 Å and 1.41 Å, respectively. A slight compression of the C,O,C angle (107 - 112°) [14] compared to a C,C,C angle (112°) may cause an additional shortening of the distance between the tail of the side chain and the tricyclic head attached to its other end. The changes in geometry will inevitably affect the receptor-signal contact (see the schematic representation below).



REACTION CONDITIONS AND PRODUCT CHARACTERISTICS

(R)-(+)-2,3-Dimethyl-3-[(2-methylprop-2-enyloxy)methyl]tricyclo[2.2.1.0^{2,6}]heptane (3) [15] : Isolated by elution from silica gel with a 3 : 97 mixture of diethyl ether and hexane after heating 3-bromomethyl-2,3-dimethyltricyclo[2.2.1.0^{2,6}]heptane [16] and potassium 2-methyl-2-propen-1-olate, prepared from 2-methyl-2-propen-1-ol and potassium hydride, in a 1 : 1 mixture of tetrahydrofuran and HMPT 4 h to reflux; 85%; bp 48 - 49 °C/0.5 mmHg; n_D^{20} 1.4737; $[\alpha]_D^{20}$ +19 ($CHCl_3$; c = 2.3). - ^{1}H-nmr : δ 4.95 (1 H, s, fine str.), 4.87 (1 H, s, fine str.), 3.85 (2 H, s), 3.25 (1 H, d, *J* 9.3), 3.11 (1 H, d, *J* 9.3), 1.75 (1 H, s, fine str.), 1.74 (3 H, s, broad), 1.66 (1 H, s, fine str.), 1.61 (1 H, s, fine str.), 1.07 (2 H, dd, *J* 10.6, 4.3), 1.00 (3 H, s), 0.94 (3 H, s), 0.87 (1 H, dq, *J* 5.4, 1.0), 0.82 (1 H, dq, *J* 5.4, 1.3).

(R)-(+)-2,3-Dimethyl-3-[2-methylprop-1-enyloxy)methyl]tricyclo[2.2.1.0^{2,6}]heptane ("4'-oxa-α-santalene", 1) [15]: By treating the allyl ether 3 with sodium hydride (2 equiv.) 48 h in a refluxing 1 : 1 mixture of tetrahydrofuran and HMPT; 94%; bp 87 - 89 °C/mmHg; n_D^{20} 1.4785; $[\alpha]_D^{20}$ +15 ($CHCl_3$; c = 0.80). - ^{1}H-nmr : δ 5.80 (1 H, hept, *J* 1.4), 3.54 (1 H, d, *J* 9.6), 3.41 (1 H, d, *J* 9.6), 1.76 (1 H, s, broad), 1.67 (2 H, dm, *J* 10.7), 1.62 (3 H, symm. m), 1.54 (3 H, symm. m), 1.10 (2 H, d, *J* 10.7), 1.02 (3 H, s), 0.97 (3 H, s), 0.91 (1 H, dq, *J* 5.2, 1.0), 0.84 (1 H, dq, *J* 5.2, 1.0).

(R)-(+)-3-[((Z)-3-Hydroxy-2-methylprop-1-enyloxy)methyl]-2,3-dimethyltricyclo[2.2.1.0^{2,6}]heptane ("4'-oxa-α-santalol", Z-2) [15]: After treatment of the allyl ether 3 (1 equiv.) with a 1 M solution of *sec*-butyllithium in tetrahydrofuran for 1 h at -75 °C and subsequent addition of fluorodimethoxyborane [10] (2 equiv., at -75 °C) and 30% aqueous hydrogen peroxide (2 equiv., at 0 °C), then stirring 1 h at 25 °C) isolated by elution with a 15 : 85 (v/v) mixture of ethyl acetate and hexane from silica gel; 62%; mp -62 to -58 ° C; n_D^{20} 1.4936; $[\alpha]_D^{20}$ +6° ($CHCl_3$; c = 0.60). - ^{1}H-nmr : δ 5.90 (1 H, symm. m), 4.18 (2 H, d, *J* 5.6), 3.60 (1 H, d, *J* 9.6), 3.74 (1 H, d, *J* 9.6), 2.06 (1 H, t, *J* 5.6), 1.72 (1 H, s, broad), 1.66 (1 H, dq, *J* 7.3, 1.4), 1.62 (1 H, dq, *J* 7.3, 1.4), 1.58 (3 H, d, *J* 1.3), 1.10 (2 H, d, *J* 10.7), 1.01 (3 H, s), 0.93 (3 H, s), 0.91 (1 H, dq, *J* 5.2, 1.1), 0.85 (1 H, dq, *J* 5.2, 1.3). Upon irradiation of the olefinic hydrogen, the signal of the allylic methyl group (δ 1.58) is enhanced by 5% while no nuclear Overhauser effect is observed at the hydroxymethyl group.

(R)-(+)-3-[((E)-3-Hydroxy-2-methylprop-1-enyloxy)methyl]-2,3-dimethyltricyclo[2.2.1.0^{2,6}]heptane ("4'-oxa-α-santalol", E-3) [15]: Obtained by chromatographic separation (SiO_2, elution with ethyl acetate and hexane in a 15 : 85 v/v ratio) of the 2 : 1 *(Z/E)* mixture of 2 formed upon the LIDA-KOR [11] treatment of the diastereomeric oxiranes prepared by the oxidation of the allyl ether 3 with m-chloroper-benzoic acid; 28% *(E)*-isomer; mp -55 to -52 °C; n_D^{20} 1.4918; $[\alpha]_D^{20}$ +6 ($CHCl_3$; c = 1.2). - ^{1}H-nmr : δ 6.10 (1 H, symm. m), 3.95 (2 H, d, *J* 5.7), 3.63 (1 H, d, *J* 9.7), 3.51 (1 H, d, *J* 9.7), 1.74 (1 H, s, broad), 1.69 (3 H, d, *J* 1.2), 1.66 (2 H, tm, *J* 10.0), 1.10 (2 H, d-like m), 1.01 (3 H, s), 0.95 (3 H, s), 0.91 (1 H, d, *J* 5.3), 0.85 (1 H, d, *J* 5.3). Upon irradiation of the olefinic hydrogen, the signal of the allylic methylene group (δ 3.95) is enhanced by 9% while the allylic methyl group does not show any nuclear Overhauser effect.

1-(2,3-Dimethyltricyclo[2.2.1.0^{2,6}]hept-3-yl)-3-methylbut-3-en-2-ol (4) [15] : Separated from aldehyde 5 (see below) by chromatography (SiO_2, elution with a 15 : 85 mixture of ethyl acetate and hexane) after consecutive treatment of the allyl ether 3 with *sec*-butyllithium (1 equiv.) in neat tetrahydrofuran (1 h -75 °C, then 2 h +25 °C), chlorotrimethylsilane (1.2 equiv.) and hydrogen chloride (1.2 equiv.) in diethyl ether; 13%; bp 118 - 120 °C/0.1 mmHg; n_D^{20} 1.5013; $[\alpha]_D^{20}$ +17 ($CHCl_3$; c = 1.0). - According to ^{1}H-nmr a 1 : 1 diastereomeric mixture : δ 4.95 (1 H, symm. m), 4.78 (1 H, symm. m), 4.19 (1 H, symm. m), 1.75 (3 H, dd, *J* 1.3, 0.8), 1.5 (5 H, m), 1.09 (2 H, d, *J* 10.5), 1.02 (0.5 m × 3 H, s), 0.9 (2 H, m), 0.86 (0.5 m × 3 H, s), 0.85 (0.5 m × 3 H, s).

4-(2,3-Dimethyltricyclo[2.2.1.0^{2,6}]hept-3-yl)-2-methylbutanal (5) [15] : Isolated from the same reaction as alcohol 4 (see below); 54%; bp 104 - 105 °C/0.1 mmHg; n_D^{20} 1.4819; $[\alpha]_D^{20}$ +8 ($CHCl_3$; c = 1.0). - According to ^{1}H-nmr a 1 : 1 diastereomeric mixture : δ 9.7 (1 H, m), 2.26 (1 H, hex, *J* 6.7, 2.0), 1.6 (3 H, m), 1.5 (1 H, m), 1.1 (10 H, m), 1.09 (0.5 × 3 H, s), 1.06 (0.5 × 3 H, s), 0.82 (0.5 × 3 H, s), 0.80 (0.5 × 3 H, s).

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REFERENCES

1 R. Peters, in Carbon-Fluorine Compounds : *Chemistry, Biochemistry and Biological Activities* (K. Elliott, J. Birch, edts., on behalf of the Ciba Foundation), Elsevier, Amsterdam, 1972, p. 1 - 27, 55 - 70; V. Guarriera-Bobyleva, P. Buffa, *Biochem. J.* **113** (1969), 853; R.Z. Eanes, D.N. Skilleter, E. Kun, *Biochem. Biophys. Res. Commun.* **46** (1972), 1618; *Chem. Abstr.* **77** (1972), 29'527c; R.Z. Eanes, E. Kun, *Mol. Pharmacol.* **10** (1974), 130; *Chem. Abstr.* **80** (1974), 141'604 p.

2 C. Heidelberger, N.K. Chaudhuri, P. Danneberg, D. Mooren, L. Griesbach, R. Duschinsky, R.J. Schnitzler, E. Pleven, J. Scheiner, *Nature* **179** (1957), 663; R. Duschinsky, E. Pleven, C. Heidelberger, *J. Am. Chem. Soc.* **79** (1957), 4559.

3 M. Elliott, A.W. Farnham, N.F. Janes, P.H. Needham, D.A. Pulman, *Nature* **248** (1974), 710; M. Elliott, *Chem. Ind. (London)* **1979**, 757.

4 Natural products having an acetal or enether type oxygen in a ring position undergo rapid hydrolysis either under enzymatic catalysis or even merely at physiological *p*H. They become considerably more resistant if the heteroatom is replaced by a methylene unit. Prominent examples are the carbacyclines, *e.g.*, Cilaprost [W. Skuballa, E. Schillinger, C.S. Stürzebecher, H. Vorbrüggen, *J. Med. Chem.* **29** (1986), 313; W. Skuballa, M. Schäfer, *Nachr. Chem. Techn. Lab.* **37** (1989), 584], which are potent mimics of the thrombocyte aggregation inhibiting and hypotensive prostacycline PG-I_2, and *N*-3-(hydroxymethyl)cyclopentylguanine ("Carbovir") which exhibits a similar therapeutic activity against the human immunodeficiency virus as 3-azido-3-deoxythymidine ("AZT") but appears to be less toxic [S.M. Roberts, *Chem. Brit.* **27** (1991), 518].

5 Despite substantial differences in bond lengths, carbon can be exchanged against silicon without altering the overall behavior of the compounds too much. Thus, sila-analogous monoterpenes exhibit very similar organoleptic properties as the natural products do themselves [*e.g.*, D. Wrobel, U. Wannagat, *J. Organomet. Chem.* **225** (1982), 203; U. Wannagat, *Nachr. Chem. Techn. Lab.* **32** (1984), 717; U. Wannagat, V. Damrath, V. Huch, M. Veith. U. Harder, *J. Organomet. Chem.* **443** (1993), 153].

6 *Isosteric* = having similar bulk (*e.g.*, CH_3, CD_3, CF_3); *isoelectronic* = having identical electron configurations (*e.g.*, $\oplus$:CH_3, :NH_3, $\ominus$:OH_3); *isoperiodic* = belonging to the same row of the periodic table, carrying no charge and requiring an equal number of substituents to complete the octet shell (*e.g.*, CH_2, NH, O or SiH_3, PH_2, SH, Cl).

7 N. Nishimitsu, M. Nishikawa, M. Hagiwara, *Proc. Japan Acad.* **27** (1951), 285; *Chem. Abstr.* **46** (1952), 8263g; see also : E.J. Corey, S.W. Chow, R.A. Scherrer, *J. Am. Chem. Soc.* **79** (1957), 5773.

8 A.J. Hubert, H. Reimlinger, *Synthesis* **1969**, 97.

9 E. Moret, M. Schlosser, *Tetrahedron Lett.* **25** (1984), 4491, and work quoted therein.

10 G. Rauchschwalbe, M. Schlosser, *Helv. Chim. Acta* **58** (1975), 1094.

11 A. Mordini, E. Ben Rayana, C. Margot, M. Schlosser, *Tetrahedron* **46** (1990), 2401; A. Degl'Innocenti, A. Mordini, S. Pecchi, D. Pinzani, G. Reginato, A. Ricci, *Synlett* **1992**, 753 (≡ 803).

12 M. Schlosser, S. Strunk, *Tetrahedron* **45** (1989), 2649.

13 α-Santalene : fatty, oily, rancid; **1** : camphor, terpenes, carvacrol; α-santalol : woody, resinous, cedar; **Z-2** : earthy, musty, camphor (evaluation by courtesy of Dr. J.P. Calame, Givaudan-Roure, CH-8600 Dübendorf).

14 D. André, R. Fourme, K. Zechmeister, *Acta Crystallogr.* **B28** (1972), 2389; R.R. Rietz, A. Zalkin, D.H. Templeton, N.M. Edelstein, L.K. Templeton, *Inorg. Chem.* **17** (1978), 653; M.J. Bovill, D.J. Chadwick, I.O. Sutherland, D. Watkin,, *J. Chem. Soc., Perkin Trans. 2* **1980**, 1529; A.J. Blake, S. Cradock, E.A.V. Ebsworth, K.C. Franklin, *Angew. Chem.* **102** (1990), 87; *Angew. Chem. Int. Ed. Engl.* **29** (1990), 76.

15 The identity and purity of all new compounds was corroborated by correct elemental analyses and mass spectra.

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