

Synthesis of Polysantol® and related sandalwood-type odorants using magnesium α -bromoketone enolates

Juan M. Castro, Pablo J. Linares-Palomino, Sofía Salido, Joaquín Altarejos,*
Manuel Nogueras and Adolfo Sánchez

Departamento de Química Inorgánica y Orgánica, Facultad de Ciencias Experimentales, Universidad de Jaén, 23071 Jaén, Spain

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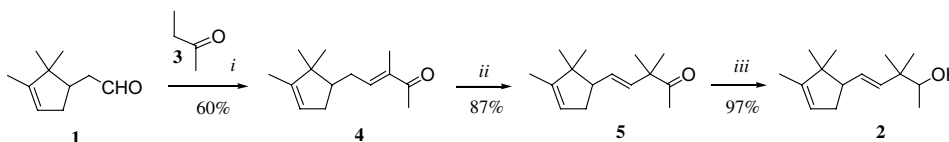
Abstract—The syntheses of the commercial sandalwood-type odorant Polysantol® and several structurally related compounds are described. The methodology followed is based on a selective and efficient magnesium-mediated aldol reaction of the starting material, α -campholenic aldehyde and different α -bromoketones. Dehydration of the resulting secondary alcohol and reduction of the carbonyl group allowed the completion of the syntheses of the target molecules in 30–56% overall yields.

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The East Indian sandalwood oil, obtained by steam distillation of the heartwood and roots of *Santalum album* L., is one of the oldest and most valuable perfumery raw materials, and it has been used extensively in perfumery because of its non-varying composition, fixative properties, and sweet, warm, spicy and tenacious fragrance.¹ Due to a general widespread shortage and a steep rise in the price of this natural oil, great efforts have been made during the last decades to develop cheap synthetic substitutes.² Among these, two classes of compounds have been commercially successful: the terpenyl cyclohexanols and the derivatives of α -campholenic aldehyde **1**.² Within the latter group, Polysantol® **2** is the most expensive and appreciated by perfumers and its synthesis has been achieved through aldol condensation of **1** with ethyl methyl ketone **3**, deconjugative α -methylation of the enone **4** and reduction of **5** (Scheme 1).³ This straightforward process seems to have in the first step a certain drawback as

compound **4** is usually accompanied by the other aldol condensation product resulting from the reaction of **3** through the terminal carbon C-1.

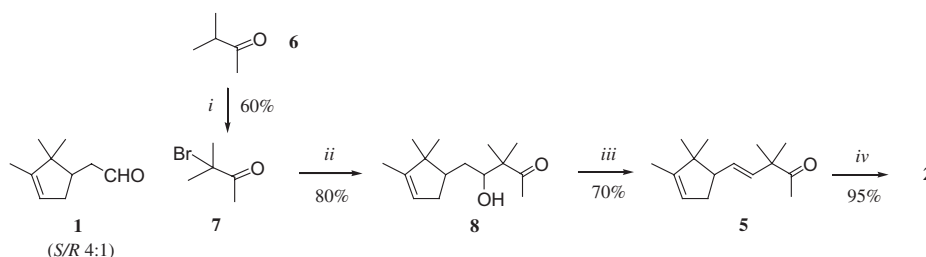
As a continuation of our previous studies on the synthesis of odorants,⁴ we were interested on this occasion in the synthesis of Polysantol® **2** and structurally related compounds. In order to minimize the presence of the undesired aldol condensation product mentioned above we envisaged the direct coupling of α -campholenic aldehyde **1** with the α -bromoketone **7** (Scheme 2)⁵ by a magnesium-mediated aldol-type reaction.⁶ Introducing a bromine atom⁷ at the more substituted carbon of 3-methyl-2-butanone **6** should favour the reaction of compound **7** with **1** preferentially through carbon C-3.^{5b} In fact, the reaction of **7** with magnesium in refluxing diethyl ether to generate the corresponding bromo-magnesium enolate and subsequent coupling to **1**, under experimental conditions similar to the classical Grignard



Scheme 1. Synthesis of Polysantol® **2** from α -campholenic aldehyde **1**.³ (i) KOH, MeOH–H₂O, –5 °C; H₂SO₄. (ii) NaOH, hexadecyltrimethylammonium bromide, toluene; MeCl. (iii) NaBH₄, EtOH.

Keywords: Polysantol®; α -Campholenic aldehyde; α -Bromoketones; Magnesium enolates; Aldol reaction; Sandalwood; Odorants.

* Corresponding author. Tel.: +34-953-002743; fax: +34-953-012141; e-mail: jaltare@ujaen.es



Scheme 2. Synthesis of Polysantol® **2** from **1** using the magnesium enolate of **7**.^{5a} (i) Br₂, AcOH, CCl₄.^{7a} (ii) Mg, Et₂O, Δ. ^{7b} (iii) MsCl, Py, 0 °C; LiBr, Li₂CO₃, DMF, 150 °C.^{8a} (iv) NaBH₄, MeOH, –10 to 0 °C.

reaction,^{6,7b} gave the β-hydroxyketone **8** in 80% yield (Scheme 2). In this manner, the isomer of **8**, formed by reacting **1** and **7** through the terminal carbon C-1, was only detected by GC as a minor by-product (2–4%). This demonstrates that the aldol-type reaction between **1** and the magnesium enolate of **7** occurs in a more regioselective manner than the direct aldol condensation between **1** and **3** described in the literature.³ In addition, it is not necessary now to introduce a methyl group by a further deconjugative α-methylation step as both methyl groups are present in the starting ketone **6**. However, this a priori advantage turned out to be troublesome as a consequence of the difficulties encountered in the dehydration of **8**. This compound did not eliminate water easily to give **5** as readily as the corresponding analogue of **8** (when **1** and **3** reacted to give **4**, Scheme 1). After using different systems we finally obtained **5** in reasonable yield (70%) by treating **8** with methanesulfonyl chloride followed by eliminating the resulting mesylate with lithium bromide and lithium carbonate in *N,N*-dimethylformamide (Scheme 2).^{8a,9} Finally, ketone **5** was reduced with sodium borohydride to give **2** (95%),^{5a} which means that the synthesis of Polysantol® **2** has

efficiently been accomplished from α-campholenic aldehyde **1** in 53% overall yield (Scheme 2).

Taking into account that the reaction of **1** with the enolate of **7** was conducted in a selective and effective way we were also interested in extending this methodology to other α-bromoketones in order to determine the scope of the reaction and prepare several Polysantol® structurally related compounds. Thus, α-bromoketones **9–12** were reacted with magnesium^{7b} to give the corresponding bromomagnesium enolates, which were reacted in situ with α-campholenic aldehyde **1** to afford compounds **17–20** in 54–76% yields (Table 1). According to these data it was evident that the reaction is convenient in terms of yield and regioselectivity and needed shorter reaction times when compared with the direct aldol reactions between aldehyde **1** and ketones **3**, **6** and **13–15**. This magnesium-mediated aldol reaction works better when the starting ketone has both primary and tertiary carbon atoms on α positions, as for **13** (Table 1) and **6** (Scheme 2). It is worth noting that longer reaction times led to a general decrease in the regioselectivity of the reaction, possibly due to the existence of an inter-

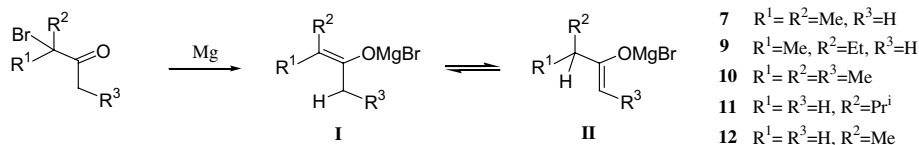
Table 1. Reaction of α-bromoketones **9–12** with α-campholenic aldehyde **1** in the presence of magnesium^a

Starting material ^b	Product	Yield (%) ^c
 13 → 9	 17	76 (8)
 14 → 10	 18	54 (18)
 15 → 11	 19	61 (5)
 3 → 12	 20	75 (70)

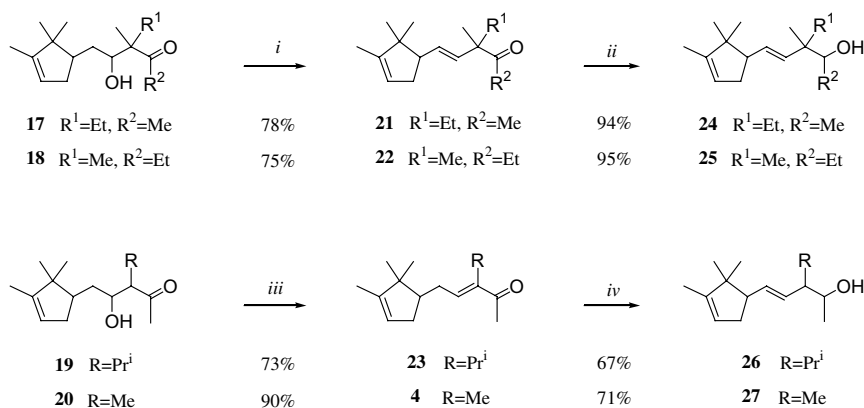
^a See general procedure.^{7b}

^b Compounds **9–12** were prepared from the corresponding ketones **13–15** and **3** following the general procedure.^{7a}

^c Percentages after column chromatography. Numbers in bracket refer to yields of **17–20** (deduced from the GC analysis of the crude reactions) in the direct aldol reactions of ketones **3** and **13–15** with **1**.



Scheme 3.



Scheme 4. Synthesis of Polysantol[®] analogues following the magnesium-mediated aldol-type approach. (i) MsCl, Py, 0 °C; LiBr, Li₂CO₃, DMF, 150 °C.^{8a} (ii) NaBH₄, MeOH, 0 °C. (iii) *p*-TsOH, toluene, Δ.^{8b} (iv) (a) KBu^tO, DMF; AcOH, 0 °C. (b) NaBH₄, MeOH, 0 °C.

molecular equilibration of the initially formed enolate **I** and its isomer **II** (Scheme 3), through which undesired products progressively appeared. Furthermore, this equilibrium could also be responsible for the lower regioselectivity observed for bromoketone **10** (Table 1) as the corresponding trisubstituted enolate **II** (R¹ = R² = R³ = Me, Scheme 3) should be comparatively more stable than the disubstituted enolates **I** resulting from bromoketones **7**, **9**, **11** and **12**. Continuing with the synthesis of Polysantol[®] analogues, the β-hydroxyketones **17–20** were dehydrated⁸ to enones **21–23** and **4**, which were reduced with sodium borohydride (**23** and **4** were deconjugated prior to reduction),¹⁰ to finally give the target alcohols **24–27** (Scheme 4).^{5a} These final compounds revealed interesting olfactory properties. In addition to the well known commercially available Ebanol[®] **27**, compound **24** showed a woody note with strong sandalwood odour, terpenic and a faint aroma of burning, compound **25** showed a woody note with a sweet tonality and leather-spicy aspects, and compound **26** was similar to **24** with a clear cedarwood-like note.

In conclusion, the magnesium enolates of several α-bromoketones were employed to achieve selective and effective aldol reactions on α-campholenic aldehyde, which opened a modified route to the synthesis of the sandalwood-type odorant Polysantol[®] and closely related compounds in reasonable yields. To our knowledge this is the first time that bromomagnesium enolates have been used for synthetic purposes since Fellmann and Dubois studied the aldol condensation of ethanal with the magnesium enolate prepared from 2-bromo-2,5,5-trimethyl-cyclopentanone.^{6,11} Furthermore, the use herein of ketones with enolisable hydrogens in both α substituents allowed us to study the regioselectivity

aspects of this synthetically useful reaction. Finally, because of the potential interest of the alcohols prepared we are currently working on the characterization of pure isomers and subsequent sensory analysis in order to further study the structure–activity relationships.

Acknowledgements

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- (a) The starting material **1** used in this work had a specific rotation of -2.2 , which corresponds to an optical purity of ca. 60% ((*S*)-**1**/(*R*)-**1** 4:1). This means that all compounds obtained from **1** in this work are nonracemic mixtures of stereoisomers on which studies to determine configurations have not been carried out; (b) The direct conventional aldol reaction of α -campholenic aldehyde **1** and 3-methyl-2-butanone **6** was previously carried out yielding the β -hydroxyketone **8** in 32% yield, along with important amounts of unreacted starting material and other compounds resulting from the alternative aldol reaction attack of **6** (C-1) to **1**.
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 - (a) Bromination of ketones **3**, **6** and **13–15**. General procedure: A solution of bromine (12 mmol) in CCl_4 (5 mL) was slowly added to a stirred solution of the ketone (12 mmol) in AcOH (1 mL) at room temperature. After 1–2 h, Et_2O was added and the organic layer washed with 40% aq NaHCO_3 , saturated aq NaHCO_3 and brine, and dried over anhydrous Na_2SO_4 . After removing the solvent on a rotary evaporator the residue was purified by reduced pressure distillation to yield the corresponding α -bromoketone; (b) Reaction of α -bromoketones **7** and **9–12** with **1**. General procedure: A solution of the α -bromoketone (20.0 mmol) in Et_2O (15 mL) was added dropwise to a stirred mixture of Mg (20.5 mmol) and Et_2O (6 mL) under argon. Then, the mixture was refluxed for 30 min and a solution of **1** (10.0 mmol, *S/R* 4:1) in Et_2O (15 mL) was added dropwise. After refluxing for 10 min the mixture was poured onto 0.5 M HCl (100 mL) and extracted with Et_2O . The organic layer was washed with saturated aq NaHCO_3 and brine, and dried over anhydrous Na_2SO_4 . After removing the solvent on a rotary evaporator the residue was purified by silica gel column chromatography to yield the corresponding β -hydroxyketone. For compounds **19** and **20**, an α -bromoketone/**1** ratio of 6:5 and more concentrated solutions were used in order to achieve better results.
 - (a) Dehydration of β -hydroxyketones **8**, **17** and **18**. General procedure: To a stirred solution of the β -hydroxyketone (0.2 mmol) in pyridine (2 mL) was added MsCl (0.3 mmol) at 0°C . The mixture was allowed to warm to room temperature and stirred for 1 h. Then, 2 M HCl (15 mL) was added and the mixture extracted with Et_2O . The organic layer was washed with 2 M HCl , saturated aq NaHCO_3 and brine, and dried over anhydrous Na_2SO_4 . After removing the solvent on a rotary evaporator the residue was dissolved in dry DMF (15 mL) and LiBr (1.0 mmol) and Li_2CO_3 (1.2 mmol) were added. The stirred mixture was heated to 150°C for 1 h under argon. The mixture was cooled and diluted with Et_2O , and the organic layer washed with 2 M HCl , saturated aq NaHCO_3 and brine, and dried over anhydrous Na_2SO_4 . Evaporation of the solvent on a rotary evaporator yielded the corresponding enone; (b) Dehydration of β -hydroxyketones **19** and **20**. General procedure: To a stirred solution of the β -hydroxyketone (8.5 mmol) in toluene (15 mL) was added *p*- TsOH (0.15 mmol). A Dean–Stark trap device was fitted and the reaction mixture refluxed for 1 h. Then, the mixture was washed with saturated aq NaHCO_3 and brine, and dried over anhydrous Na_2SO_4 . Evaporation of the solvent on a rotary evaporator yielded the corresponding enone.
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