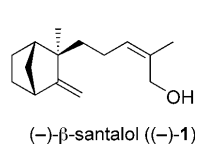


Rearrangement Reactions

Enantioselective Synthesis of (–)-β-Santalol by a Copper-Catalyzed Enynol Cyclization–Fragmentation Reaction**

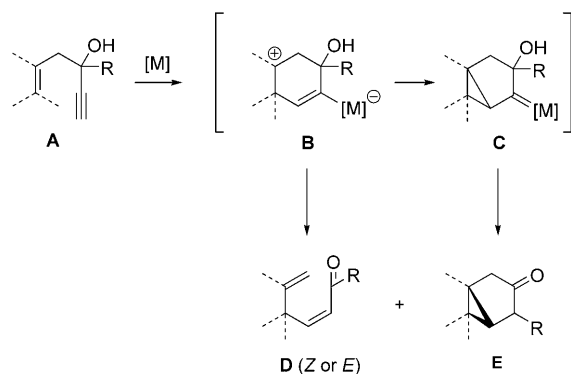
Charles Fehr,* Iris Magpantay, Jeremy Arpagaus, Xavier Marquet, and Magali Vuagnoux



We report herein the first enantioselective, direct synthesis of the highly prized natural sandalwood odorant (–)-β-santalol ((–)-1).^[1] The key step in the synthesis is an efficient copper-catalyzed rearrangement of an enynol.

The increasing scarcity of East Indian sandalwood oil^[2] has motivated research chemists over the last 40 years to develop a synthesis of the most valuable component, (–)-β-santalol ((–)-1), which makes up 20–25% of the composition of the oil, or its racemate.^[1] Despite extensive efforts, this excellent fragrance ingredient is still not commercially available.

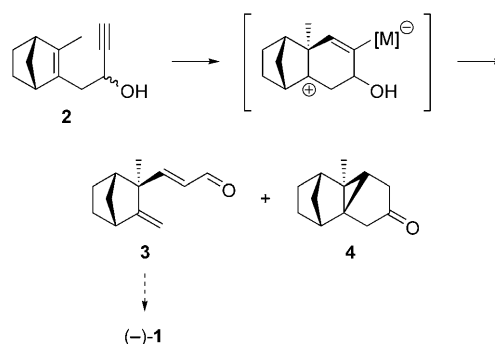
Recently, we reported the cost-efficient copper-catalyzed cycloisomerization of 5-en-1-yn-3-ols (cyclopropanation/1,2-alkyl shift; Scheme 1, **A**→**E**)^[3] and related enynol esters.^[4]



Scheme 1. Enynol cycloisomerization pathways.

These cyclopropanation reactions,^[5] which lead selectively to complex polycyclic compounds, are generally catalyzed by platinum^[6] or gold.^[7] During further studies on enynols of type **A**, we discovered that a cyclization–fragmentation pathway (Scheme 1, **A**→**D**) could compete with the cyclopropanation, and that [Cu(CH₃CN)₄]BF₄ was the reagent of choice for promoting this rearrangement, as opposed to Ag,^[8] Au,^[7b] or Pt catalysts.^[9] These results prompted us to devise a

new synthesis of (–)-β-santalol ((–)-1). If enynol **2** could be induced to preferentially undergo the cyclization–fragmentation to afford **3** (*E* or *Z*) with an *exo*-oriented enal side chain, at the expense of the cyclopropanation product **4**, this transformation would open a new direct route to (–)-1 (Scheme 2).



Scheme 2. Projected cyclization–fragmentation reaction en route to (–)-1.

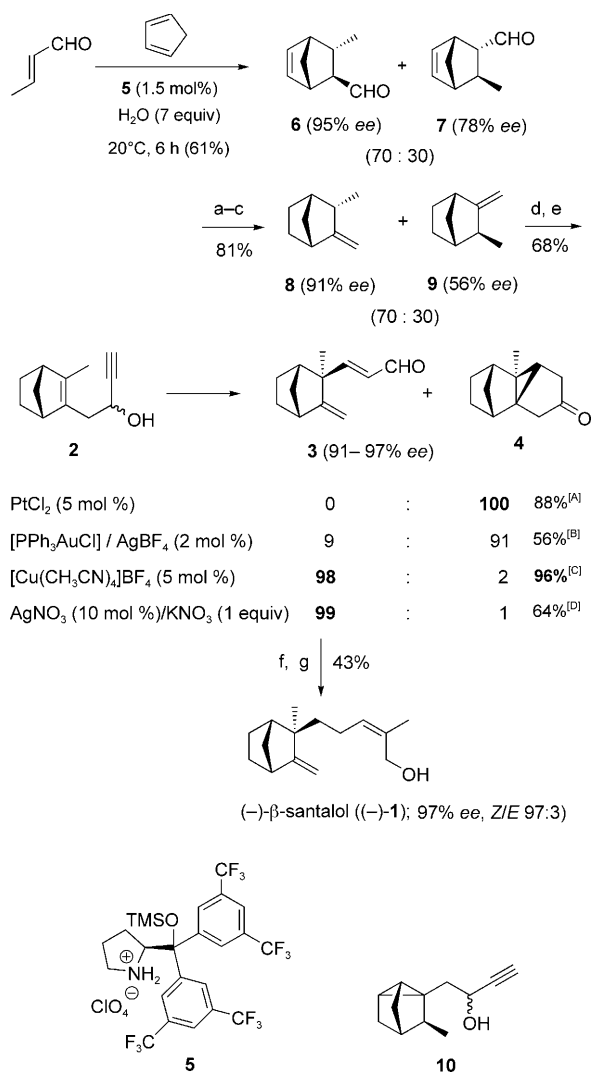
The successful realization of this synthetic plan began with a highly enantioselective and *exo*-selective Diels–Alder reaction between cyclopentadiene and crotonaldehyde (Scheme 3). Chiral amines have been employed as efficient catalysts for enantioselective Diels–Alder reactions through the reversible formation of a dienophilic iminium salt.^[10] The most impressive results in terms of enantioselectivity and *exo* selectivity for the formation of **6** were reported by the research groups of MacMillan,^[10a] Maruoka,^[10b] and Hayashi.^[10c] The system described by Hayashi et al.,^[10c] a concentrated two-phase system in water at 20°C, is by far the most practical. Hayashi et al. used catalyst **5** (5 mol %) and a threefold excess of cyclopentadiene and obtained **6** (99% *ee*) and **7** (99% *ee*) in a 72:28 ratio in 72% combined yield. When we carried out the reaction under the same conditions, we obtained **6** (96% *ee*) and **7** (77% *ee*) in a 72:28 ratio and 55% combined yield. We were able to optimize this reaction by using equimolar amounts of cyclopentadiene and crotonaldehyde and only 1.5 mol % of catalyst **5** (**6**+**7**: 61% yield; **6** (95% *ee*)/**7** (78% *ee*) 70:30).^[11] The use of just 1 mol % of **5** still led to the formation of **6** (94% *ee*) and **7** (80% *ee*) in a 69:31 ratio.

The cycloadducts **6** and **7** were hydrogenated as a mixture to give the corresponding saturated alcohols, which were converted into methyl carbonates and pyrolyzed to afford hydrocarbons **8** and **9** in high overall yield.^[12,13] Upon treatment with trimethylsilylpropynal,^[14] **8** underwent the expected ene reaction to afford **2** after desilylation. However,

[*] Dr. C. Fehr, I. Magpantay, J. Arpagaus, X. Marquet, Dr. M. Vuagnoux^[4]
Firmenich SA, Corporate R&D Division
P. O. Box 239, 1211 Geneva 8 (Switzerland)
Fax: (+41) 22-780-3334
E-mail: charles.fehr@firmenich.com

[†] Postdoctoral fellow at Firmenich SA (July 2007–June 2008).

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Scheme 3. Reagents and conditions: a) Raney Ni (2%), 20 bar, 80°C, 24 h (100%); b) ClCO₂Me (2 equiv), pyridine, toluene, 0°C→RT, 1 h (90%); c) pyrolysis (415°C; quartz tube, 3 m; N₂ stream; 90%); d) TMSCHCHO (1.0 equiv with respect to **8**), Me₂AlCl (1.0 equiv), CH₂Cl₂, -20°C (72%); e) K₂CO₃ (10 equiv), MeOH (89%); f) H₂, 5% Pd/CaCO₃ (5%), MeOH/H₂O (96:4), 4 h (85%); g) EtPPh₃I (1.1 equiv), BuLi (1.1 equiv), THF, -78°C; then BuLi (1.2 equiv), -78°C→0°C; then paraformaldehyde (6 equiv), 0°C→RT, 1 h (50%). [A] toluene, 70°C, 1 h; [B] CH₂Cl₂, -10°C, 2 h; [C] ClCH₂CH₂Cl, 50°C, 140 min; [D] THF, H₂O, 70°C, 8 h (87% conversion). TMS=trimethylsilyl.

9, which has a less accessible α hydrogen atom, underwent a “homoeene reaction” exclusively to afford **10** after desilylation.^[15] The formation of **10** could be prevented completely by adapting the amount of trimethylsilylpropynal used to that of **8**.

We tested Pt, Au, and Cu catalysis for the key cycloisomerization reaction of enynol **2**, which existed as one major and one minor diastereomer. PtCl₂ catalysis led exclusively to the undesired cyclopropane **4** in 88% yield. In the presence of catalytic amounts of [PPh₃AuCl] and AgSbF₆, the cycloisomerization leading to **4** was again favored (**4/3** 91:9). Evidently, the AgCl formed in situ does not influence the reaction course. In sharp contrast, [Cu(CH₃CN)₄]BF₄

(5 mol%) efficiently promoted the desired cyclization–fragmentation reaction to afford the desired aldehyde **3**^[16] in high yield with excellent chemoselectivity and face selectivity (**3/4** 98:2).^[17] The use of AgNO₃ (10 mol%) and KNO₃ (1 equiv)^[8] also led to a selective reaction (**3/4** 99:1); however, the reaction was slower (87% conversion after 8 h) and the yield lower (64%).

The ee value of **3** could be increased to 97% through one low-temperature crystallization (pentane). Finally, site-selective hydrogenation with Pd/CaCO₃, followed by a Wittig reaction under the modified conditions described by Corey and Yamamoto with hydroxyalkylation of the intermediate betaine^[18] afforded the target (–)-**1** (Z/E 97:3; 43% (2 steps)),^[19] the sandalwood odor of which was excellent.

In conclusion, we have developed an efficient enantioselective synthesis of (–)-β-santalol. The key step in the synthesis consists of a highly selective copper-catalyzed cyclization–fragmentation of an enynol. The scope and generality of this novel methodology will be reported in due course.

Experimental Section

6 and 7: A mixture of catalyst **5** (314 mg, 0.45 mmol), water (3.78 mL, 210 mmol), toluene (0.24 mL; internal standard), and crotonaldehyde (95% *trans*; distilled and stored in the freezer; 2.10 g (2.46 mL), 30.0 mmol) was stirred at 20°C for 5 min and then treated with freshly prepared cyclopentadiene monomer (stored in a dewar containing dry ice; 1.98 g (2.44 mL), 30.0 mmol). The two-phase system was stirred at 23°C for 6 h, then cooled to 10°C, treated with saturated aqueous NaHCO₃ solution (2.5 mL) and solid NaCl (100 mg), and stirred for 15 min. The two-phase system was separated, and the aqueous phase was washed with pentane (3 mL). Concentration (0°C, 50 mbar) and bulb-to-bulb distillation (oven temperature 100°C, 4 mbar) afforded a mixture of **6** and **7** (70:30; 2.07 g, 61%) with 88% purity. This material, which contained traces of toluene, dicyclopentadiene, and two unidentified products that may have originated from *cis*-crotonaldehyde, was used for the ensuing hydrogenation.

(–)-**3**: [Cu(CH₃CN)₄]BF₄ (0.294 g, 0.93 mmol) was added to a solution of **2** (3.24 g, 18.4 mmol) in 1,2-dichloroethane (100 mL) at room temperature under nitrogen, and the resulting mixture was stirred at 50°C for 140 min. The dark-gray mixture was then cooled to room temperature, filtered through a short pad of silica gel, and concentrated under vacuum to give an orange oil (3.87 g). Bulb-to-bulb distillation of this oil (oven temperature 100°C, 0.08 mbar) afforded (–)-**3** (3.12 g, 94%, 92% ee) with 98% purity (the impurity corresponding to the remaining 2% was **4**). Crystallization once from pentane at –78°C afforded (–)-**3** (2.79 g) with 97% ee. $[\alpha]_D^{20} = -267.4 \text{ deg cm}^3 \text{ g}^{-1} \text{ dm}^{-1}$ (CHCl₃, $c = 1.06 \times 10^{-2} \text{ g cm}^{-3}$).

¹H NMR (400 MHz, CDCl₃): δ = 9.52 (d, $J = 7.8 \text{ Hz}$, 1H), 6.77 (d, $J = 15.7 \text{ Hz}$, 1H), 6.09 (dd, $J = 15.7, 7.8 \text{ Hz}$, 1H), 5.01 (s, 1H), 4.58 (s, 1H), 2.76 (br s, 1H), 2.18 (br s, 1H), 1.69–1.80 (m, 2H), 1.52–1.58 (m, 2H), 1.30–1.37 (m, 1H), 1.24–1.27 (m, 1H), 1.23 ppm (s, 3H).

¹³C NMR (100 MHz, CDCl₃): δ = 194.5 (d), 165.4 (d), 160.4 (s), 130.1 (d), 104.1 (t), 49.7 (s), 46.5 (d), 46.3 (d), 37.1 (t), 29.8 (t), 23.0 (t), 22.7 ppm (q).

MS: m/z (%): 176 [M^+] (23), 161 (71), 147 (63), 133 (75), 119 (62), 105 (100), 91 (99), 79 (58), 77 (58), 39 (34).

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