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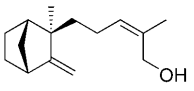
Enantioselective Synthesis of (−)-β-Santalol by a Copper-Catalyzed Enynol Cyclization–Fragmentation Reaction**

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

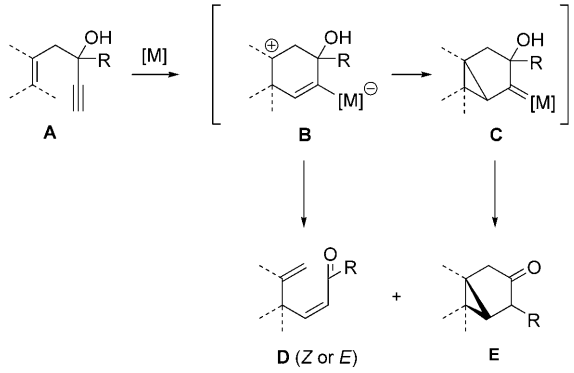


(−)-β-santalol ((−)-**1**)

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.

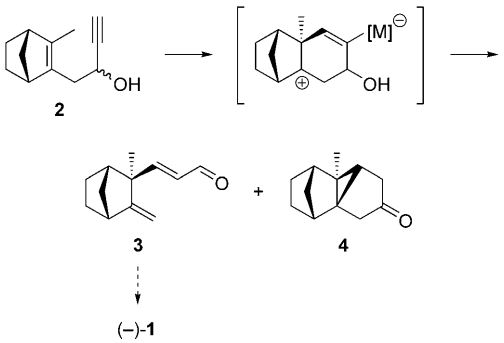
The increasing scarcity of East Indian sandalwood oil[2] has motivated research chemists over the last 40 years to develop a synthesis of the most valuable component, (−)-β-santalol (−)-**1**, which makes up 20–25% of the composition of the oil, or its racemate.[1] Despite extensive efforts, this excellent 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 $[Cu(CH_3CN)_4]BF_4$ 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,

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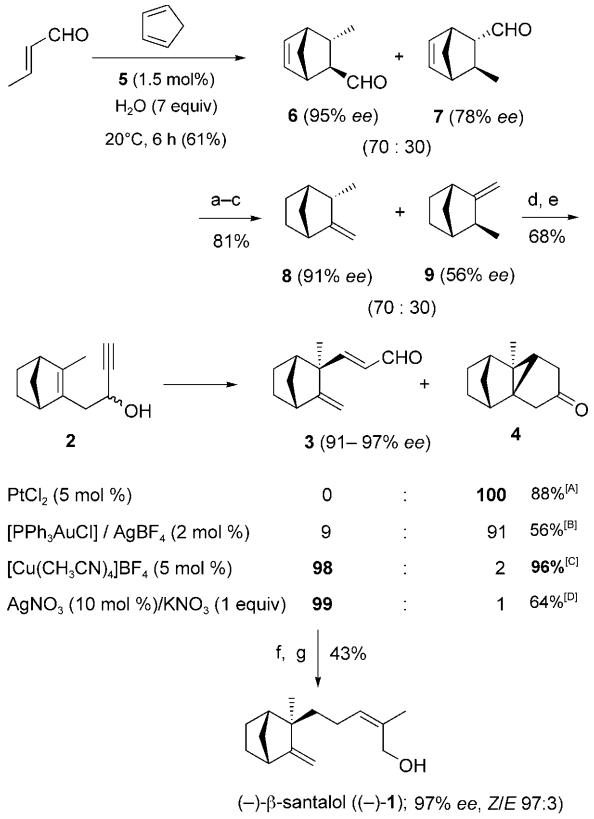

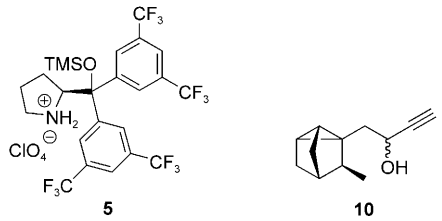

Scheme 3. Reagents and conditions: a) Raney Ni (2%), 20 bar, 80°C, 24 h (100%); b) $ClCO_2Me$ (2 equiv), pyridine, toluene, 0°C→RT, 1 h (90%); c) pyrolysis (415°C; quartz tube, 3 m; N_2 stream; 90%); d) TMSCCCHO (1.0 equiv with respect to **8**), Me_2AlCl (1.0 equiv), CH_2Cl_2, −20°C (72%); e) K_2CO_3 (10 equiv), MeOH (89%); f) H_2, 5% $Pd/CaCO_3$ (5%), MeOH/H_2O (96:4), 4 h (85%); g) $EtPPh_3I$ (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] CH_2Cl_2, −10°C, 2 h; [C] $ClCH_2CH_2Cl$, 50°C, 140 min; [D] THF, H_2O, 70°C, 8 h (87% conversion). TMS = trimethylsilyl.

9, which has a less accessible α hydrogen atom, underwent a "homoene 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. $PtCl_2$ catalysis led exclusively to the undesired cyclopropane **4** in 88% yield. In the presence of catalytic amounts of $[PPh_3AuCl]$ and $AgSbF_6$, 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, $[Cu(CH_3CN)_4]BF_4$ (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 $AgNO_3$ (10 mol%) and KNO_3 (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 $Pd/CaCO_3$, 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 $NaHCO_3$ 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**: $[Cu(CH_3CN)_4]BF_4$ (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*. $[\alpha]_D^{20} = -267.4\ deg\,cm^3\,g^{-1}\,dm^{-1}$ ($CHCl_3$, $c = 1.06 \times 10^{-2}\ g\,cm^{-3}$).

^1H NMR (400 MHz, $CDCl_3$): $\delta = 9.52$ (d, $J = 7.8$ Hz, 1H), 6.77 (d, $J = 15.7$ Hz, 1H), 6.09 (dd, $J = 15.7$, 7.8 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).

^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 194.5$ (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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Keywords: copper · cyclopropanes · enantioselectivity · fragrances · rearrangement

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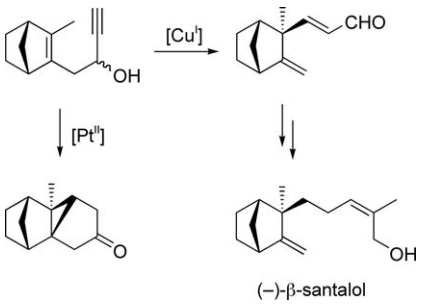
Communications

Rearrangement Reactions

C. Fehr,* I. Magpantay, J. Arpagaus, X. Marquet, M. Vuagnoux — ■■■■–■■■■

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



The right cat for the desired odor: The key step in an enantioselective synthesis of the prized fragrance (−)-β-santalol was a highly selective copper-catalyzed cyclization–fragmentation reaction of an enynol (see scheme). When a platinum catalyst was used for the cyclization step, the desired fragmentation did not take place; instead, a product containing a cyclopropane ring was formed with 100% selectivity.