# 193. Enantioselective Synthesis of β-Necrodol and of 1-Epi-β-necrodol *via* Asymmetric 1,4-Addition and Magnesium-Ene Cyclization

Preliminary Communication

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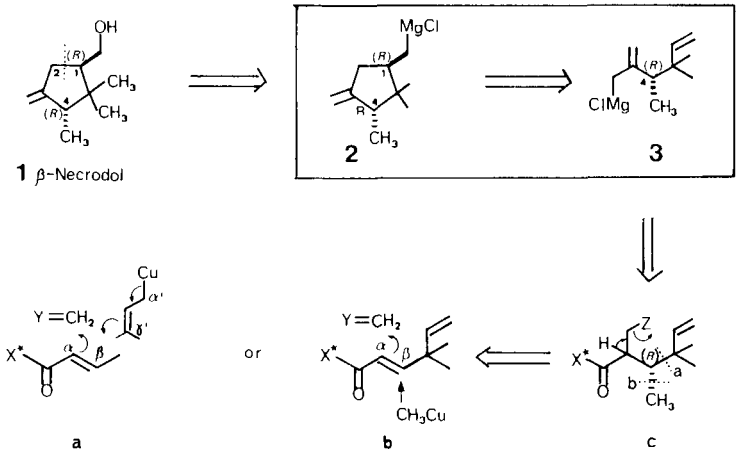
Enantiomerically pure β-necrodol (**1**) and its 1-epimer **16** have been synthesized starting from aldehyde **5**. The two key steps are an asymmetric conjugate addition/*Mannich* reaction tandem (**10**→**12**) and a type-II-magnesium-ene cyclization/oxidation sequence (**14**→**1** + **16**).

β-Necrodol, isolated from the defensive secretion of a carrion beetle has been assigned constitution and relative configuration **1** [1a]. In conjunction with our interest in asymmetric 1,4-additions [2] as well as Magnesium-ene-type reactions [3], we present here an enantioselective synthesis of **1**, thereby establishing its absolute configuration[1]).

Disconnective analysis *(Scheme 1)* shows the crucial type-II-magnesium-ene cyclization **3**→**2**, where center C(4) should control the generation of center C(1). The pre-existing (4*R*)-configuration in **3** was supposed to derive from the π-face-selective conjugate additions **a**→**c** or, alternatively, **b**→**c**.

*Scheme 1*




[1]) After termination of this work, we heard that β-necrodol has been assigned the (1*R*,4*R*)-configuration by *Jacobs* and *Meinwald* based on a synthesis starting from camphoric acid [1b].

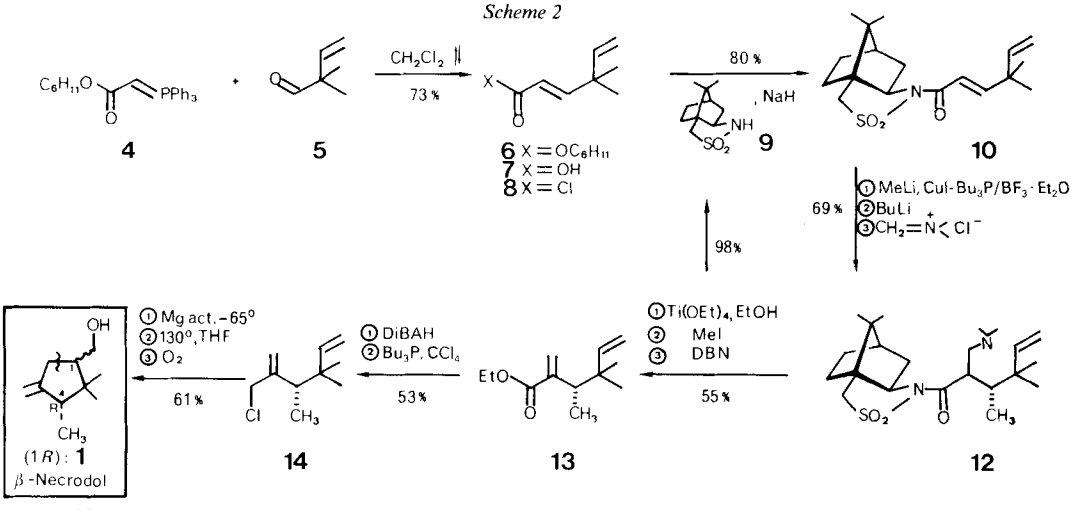
Exploratory treatment of cyclohexyl crotonate (**a**, X* = $C_6H_{11}O$)[2]) with (1,1-dimethylallyl)lithium/CuCN/$BF_3 \cdot Et_2O$ gave in 76% yield a 3:1 mixture of regioisomeric 1,4-adducts in favor of the 'undesired' 3,6-dimethyl-5-heptenoate. This reflects predominant $\alpha'$-(*vs.* $\gamma'$-)attack of the allylic organocopper species. To avoid this complication, enoate **b** (X* = $C_6H_{11}O$) was treated with MeLi/CuI-$Bu_3P$/$BF_3 \cdot Et_2O$[3]) 1:1:1 (10 mol-equiv., $Et_2O$/THF 3:1, $-78° \rightarrow -40°$, $-40°$, 6 h, followed by quenching with $NH_4Cl$ and oxidation of the phosphine with *m*-chloroperbenzoic acid) [2c]; however, only unchanged enoate **b** could be isolated, presumably due to the steric congestion in **b**. Accordingly, we abandoned the prospect of using chiral ester auxiliaries [2a–c] and explored methylcopper additions to a camphor-derived enoyl sultam **b**. It was expected that the electron-withdrawing sultam group X* would accelerate this process and confer good $\pi$-facial differentiation as observed in asymmetric *Diels-Alder* reactions [5].

*Wittig* reaction [6] of phosphorane **4** and aldehyde **5** [7] ($CH_2Cl_2$, reflux, 48 h; 73%) provided enoate **6**[2]) which after saponification (2.5N NaOH, EtOH/$H_2O$ 9:1, reflux, 5 h; 97%) and treatment of acid **7**[2]) with oxalyl chloride (4 mol-equiv., $C_6H_6$, reflux, 75 min; 90%) gave acyl chloride **8**[2]). Acylation of the deprotonated camphor-derived sultam **9** (NaH, toluene, r.t.) by **8** (r.t., 14 h), yielded crystalline (*E*)-enoylsultam[2]) **10** (m.p. 153–154°; 80%).

Addition of $Bu_3P$-stabilized MeCu · $BF_3$ to **10**, employing the same reaction conditions which had failed with the enoate **b** (X* = $C_6H_{11}O$) furnished smoothly crystalline adduct **11**[2]) (m.p. 132–133°) in 92% yield!

Direct GC analysis of the crude product showed a diastereoisomeric excess of 98% which was confirmed by hydrolysis (LiOH, aq. THF, r.t., 3 days), amidation (propyl-

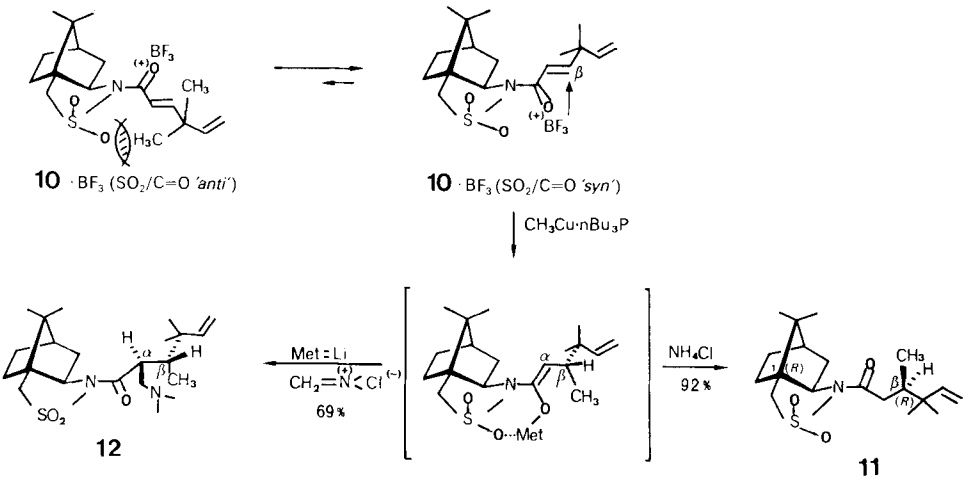
*Scheme 2*




[2]) All new compounds were characterized by chiroptic measurements, IR, $^1$H-NMR (360 MHz), $^{13}$C-NMR, and MS. Observed $[\alpha]_D^{20}$ values ($CHCl_3$, *c* [g/100 ml]): **10**: 80.2° (*c* = 1.27); **11**: −47.0° (*c* = 1.13); **12**: −30.8° (*c* = 1.10); **13**: +27.1° (*c* = 1.18); **14**: +52.7° (*c* = 1.48); **1**: −10.74° (*c* = 0.65); **16**: +37.4° (*c* = 0.72).

[3]) Preparation of the CuI-$Bu_3P$ complex: [4]. A solution of MeLi in $Et_2O$ was freshly prepared from MeI and Li metal.

*Scheme 3*




phosphonic anhydride/*N*-ethylmorpholine [8] followed by (−)-(*S*)-1-[(1-naphthyl)ethyl]-amine) and GC as well as HPLC analyses of the *Pirkle* derivatives [9]. It thus follows that the addition **10**→**11** has proceeded efficiently *and* with excellent $\pi$-face differentiation. The depicted (3*R*)-configuration at C($\beta$) of **11** was readily determined by means of an X-ray diffraction analysis [10a] accounting for the known chirality of the camphor-derived sultam moiety as well as for a least-squares refinement of the absolute-structure parameter $x$ [11]. To rationalize the observed asymmetric induction, we assume that the $BF_3$-coordinated sultam **10** prefers a *'syn'*-conformation for $SO_2$/C=O thereby avoiding a steric repulsion between the $SO_2$ group and the substituents of the quaternary $\gamma$-C-atom[4]); addition of methylcopper to the less shielded $\beta$-*Re*-bottom face parallels the postulated topicity of asymmetric *Diels-Alder* reactions [5] and hydrogenations [12].

Pursuing the synthesis of $\beta$-necrodol, the required methylidene group at C($\alpha$) could be (and actually was) introduced after removal of the auxiliary. More directly and interestingly, the transient enolate formed from **10** was trapped by consecutive additions of BuLi (9 mol-equiv.) and *N,N*-dimethylmethylidene ammonium chloride (25 mol-equiv.)[5]) to give, after chromatographic separation from the concomitantly formed **11** (20%), the crystalline *Mannich* product[2]) **12** (m.p. 121–122°, 69% from **10**). It appears that **12** is formed with high C($\alpha$)-stereoface selectivity in analogy to $\alpha$-methylations and -protonations of enolates resulting from hydride/enoylsultam additions [2e]. The expected (2*S*,3*R*)-topicity of **12** was also confirmed by an X-ray diffraction analysis [10b]. Although not relevant for our synthesis of **1**, this constitutes, to our knowledge, the first asymmetric *Mannich* reaction.

Non-destructive cleavage of the auxiliary by heating **12** with $Ti(OEt)_4$ (1 mol-equiv., EtOH, 150°, 2 days) furnished pure sultam **9** (98%) and the corresponding ethyl ester[2])

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[4]) With sterically less hindered ($\beta$-silylenoyl)sultams, coordination with $EtAlCl_2$ (and not with $BF_3 \cdot Et_2O$) was needed to achieve similar $\pi$-facial stereodifferentiation on conjugate additions of organocopper reagents [2d].

[5]) Cu/Li-transmetalation proved to be essential since the initial enolate-type adduct *(Scheme 3)* did not react with various electrophiles (except with $H^+$).

(71%) which on *N*-methylation (12 mol-equiv. of MeI, MeOH, r.t., 4 days) and base-induced elimination [13] (2.2 mol-equiv. of DBN, $C_6H_6$, reflux, 2.5 h) afforded α-methylidene ester **13**[2]) (78%). Reduction of **13** with $(i\text{-}Bu)_2AlH$ (2 mol-equiv. hexane, $-25°$, 3 h, 65%) and treatment of the resulting alcohol[2]) with $Bu_3P$ (1.5 mol-equiv.) in $CCl_4$ [14] (r.t., 24 h, 82%) yielded allyl chloride[2]) **14**.

In the subsequent key step, **14** was added over 1.5 h at $-65°$ to a stirred slurry of precondensed Mg [15] (7 mol-equiv.) in THF: heating of the solution in a *Carius* tube at 130° for 23 h followed by oxidation with $O_2$ (15 min, 0°) gave, after workup, a 1:1 mixture (61%) of the desired β-necrodol (**1**)[2]) and its 1-epimer **16**[2]) which were separated by chromatography and identified by comparison with authentic samples ($[\alpha]_D$, IR, $^1$H-NMR (360 MHz), $^{13}$C-NMR).

We thus conclude that naturally ocurring β-necrodol (**1**) possesses the (1*R*,4*R*)-configuration[1]).

The topological control of the magnesium-ene process **3**→**2** as well as the described sultam-derived asymmetric α- and β-inductions are subjects of further studies in our laboratory.

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