

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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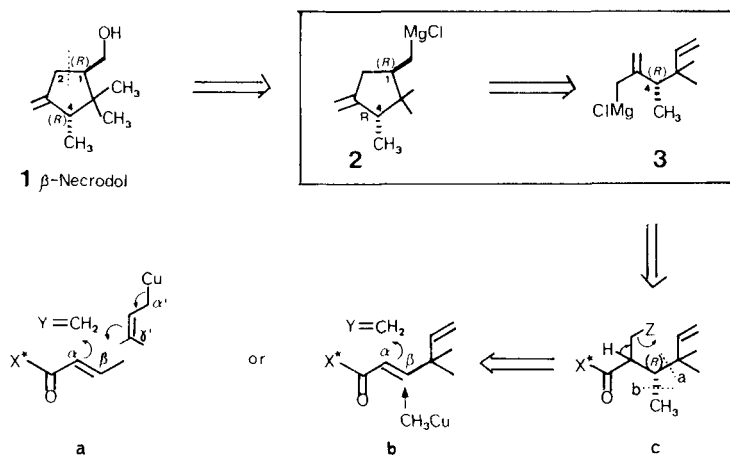
(8. IX. 86)

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 configuration¹⁾.

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



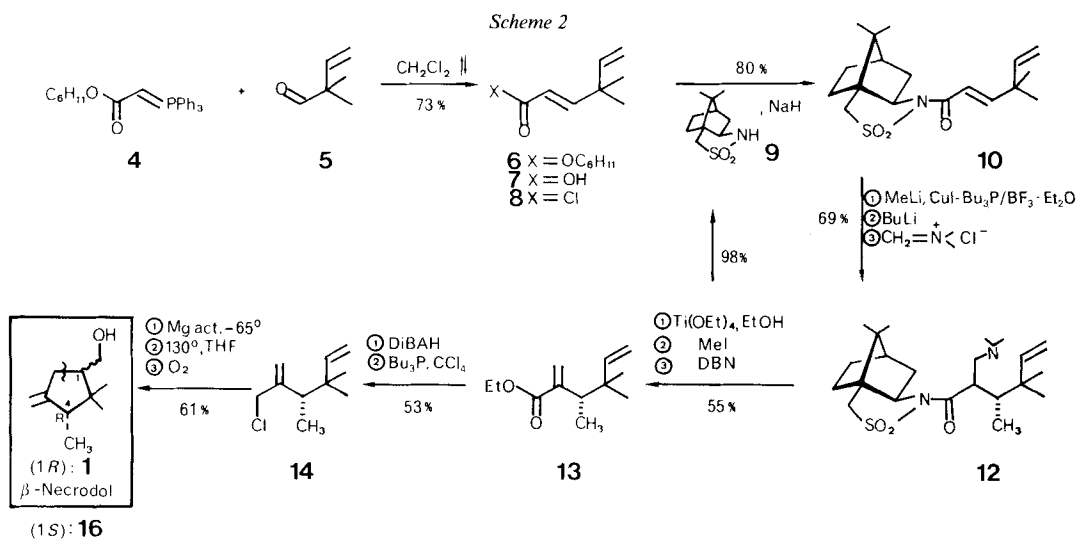
¹⁾ After termination of this work, we heard that β -necrodol has been assigned the (1*R*,4*R*)-configuration by Jacobs and Meinwald based on a synthesis starting from camphoric acid [1b].

Exploratory treatment of cyclohexyl crotonate (**a**, $X^* = C_6H_{11}O$)² with (1,1-dimethylallyl)lithium/CuCN/BF₃ · Et₂O 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 α' -(vs. γ')-attack of the allylic organocopper species. To avoid this complication, enoate **b** ($X^* = C_6H_{11}O$) was treated with MeLi/CuI-Bu₃P/BF₃ · Et₂O³ 1:1:1 (10 mol-equiv., Et₂O/THF 3:1, -78° → -40°, -40°, 6 h, followed by quenching with NH₄Cl 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 π -facial differentiation as observed in asymmetric *Diels-Alder* reactions [5].

Wittig reaction [6] of phosphorane **4** and aldehyde **5** [7] (CH₂Cl₂, reflux, 48 h; 73%) provided enoate **6**² which after saponification (2.5N NaOH, EtOH/H₂O 9:1, reflux, 5 h; 97%) and treatment of acid **7**² with oxalyl chloride (4 mol-equiv., C₆H₆, 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*)-enoylsultam² **10** (m.p. 153–154°; 80%).

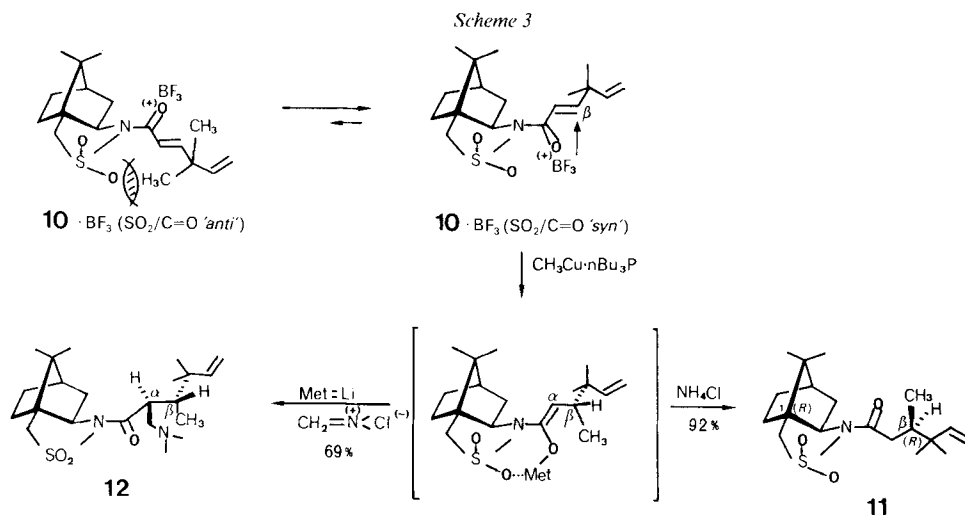
Addition of Bu₃P-stabilized MeCu · BF₃ to **10**, employing the same reaction conditions which had failed with the enoate **b** ($X^* = C_6H_{11}O$) furnished smoothly crystalline adduct **11**² (m.p. 132–133°) in 92% yield!

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-



²) All new compounds were characterized by chiroptic measurements, IR, ¹H-NMR (360 MHz), ¹³C-NMR, and MS. Observed [α]_D²⁰ values (CHCl₃, 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-Bu₃P complex: [4]. A solution of MeLi in Et₂O was freshly prepared from MeI and Li metal.



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 π -face differentiation. The depicted (3*R*)-configuration at C(β) 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 $\text{SO}_2/\text{C}=\text{O}$ thereby avoiding a steric repulsion between the SO_2 group and the substituents of the quaternary γ -C-atom⁴); addition of methylcopper to the less shielded β -*Re*-bottom face parallels the postulated topicity of asymmetric *Diels-Alder* reactions [5] and hydrogenations [12].

Pursuing the synthesis of β -necrodol, the required methylenide group at C(α) 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*-dimethylmethylenide ammonium chloride (25 mol-equiv.)⁵ to give, after chromatographic separation from the concomitantly formed **11** (20%), the crystalline *Mannich* product²) **12** (m.p. 121–122°, 69% from **10**). It appears that **12** is formed with high C(α)-stereoface selectivity in analogy to α -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 $\text{Ti}(\text{OEt})_4$ (1 mol-equiv., EtOH, 150°, 2 days) furnished pure sultam **9** (98%) and the corresponding ethyl ester²)

⁴) With sterically less hindered (β -silylenoyl)sultams, coordination with EtAlCl_2 (and not with $\text{BF}_3 \cdot \text{Et}_2\text{O}$) was needed to achieve similar π -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, C₆H₆, reflux, 2.5 h) afforded α -methylidene ester **13**²⁾ (78 %). Reduction of **13** with (i-Bu)₂AlH (2 mol-equiv. hexane, – 25°, 3 h, 65 %) and treatment of the resulting alcohol²⁾ with Bu₃P (1.5 mol-equiv.) in CCl₄ [14] (r.t., 24 h, 82 %) yielded allyl chloride²⁾ **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 O₂ (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 ([α]_D, IR, ¹H-NMR (360 MHz), ¹³C-NMR).

We thus conclude that naturally occurring β -necrodol (**1**) possesses the (1*R*,4*R*)-configuration¹⁾.

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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