

Stereocontrolled Total Synthesis of (\pm)- β -Necrodol

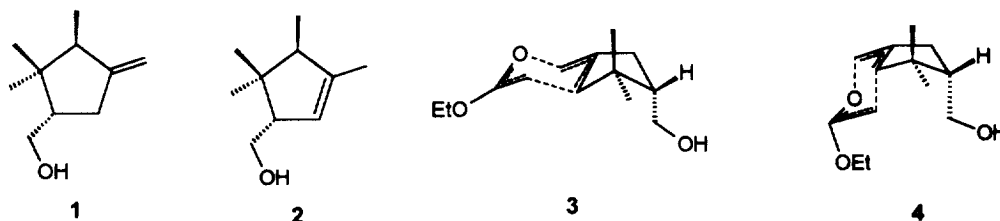
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Received 26 February 1999; accepted 12 April 1999

Abstract : A total synthesis of racemic β -necrodol is described using an ortho-ester Claisen rearrangement as the key step to dictate a high level of trans-1,3-diaxialeselection on a cyclopentane derivative.
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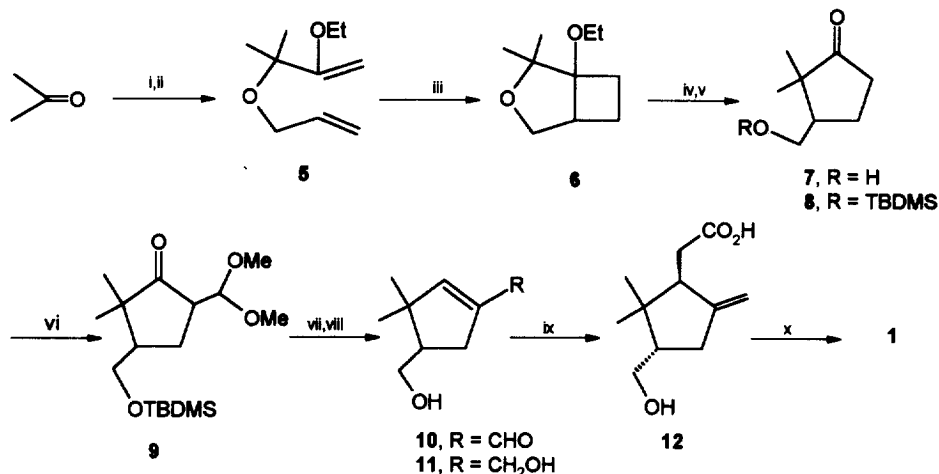
β -Necrodol **1**, a structurally novel monoterpene, has been isolated¹ from the defensive spray of the red-lined carrion beetle, *Necrodes surinamensis*, along with α -necrodol **2**. Because of their fascinating structures and anti-insectant activity, these compounds continue to be targets of synthetic investigations.² Necrodols pose a considerable synthetic challenge with construction of the sterically congested cyclopentane nucleus and generation of the thermodynamically unfavourable trans geometry between the 1- and 3- substituents being most important. While the necrodane nucleus has been successfully constructed, total diastereoselection has not been achieved with mixtures of trans- and cis-necrodane structures in ratios between 5:1 to 1:3 being obtained. We here report a total synthesis of β -necrodol in which a high level of 1,3-diaxialeselectivity has been achieved.



The key step in our approach was an ortho-ester Claisen rearrangement which establishes the trans geometry of the 1,3-substituents with simultaneous generation of the exo methylene unit. We reasoned that during the Claisen rearrangement, reaction would prefer to take place on the face opposite³ to the hydroxymethyl group through the transition state **3**. The alternative transition state **4** possesses an unfavourable 1,3-diaxial interaction. The allyl alcohol **11**, the precursor for the Claisen rearrangement, was prepared from the cyclopentanone derivative **7** (Scheme - 1). The cyclopentanone derivative **7** was obtained through a novel four-step sequence developed in our laboratory for the synthesis of vicinally substituted cyclopentanones⁴ and spirocyclopentanones.⁵ Reaction of acetone with ethoxyvinyl lithium followed by allylation of the resulting carbinol afforded the diene **5**. The diene **5** underwent smooth CuOTf catalysed [2+2] photocycloaddition to form the cyclobutane derivative **6** which on acid treatment afforded the cyclopentanone derivative **7**.⁶

For the transformation of the ketone **7** to the Claisen precursor **11**, the hydroxyl group in **7** was protected as a silyl ether to afford the ketone **8**.⁷ The ketone **8** was transformed to the unsaturated aldehyde **10** through the β -keto acetal

9 in excellent overall yield following Ghatak's protocol.⁸ The aldehyde **10** was then reduced with NaBH₄ to afford the diol **11** in 62% yield. The Claisen rearrangement was accomplished by heating a mixture of the alcohol **11**, triethylorthoacetate, mercuric acetate and propionic acid in a sealed tube at 200°C for 6 hrs. The product was directly hydrolysed to produce the hydroxy acid **12** along with its cis-epimer in a 10:1 ratio in a 42% overall yield for the two steps. Irradiation of a benzene solution of this hydroxy acid mixture in presence of quinoline and t-butyl mercaptan with pyrex filtered light led to smooth decarboxylation⁹ to afford β-necrodol **1** and epi-β-necrodol in the same ratio (10:1) in 61% yield. ¹H and ¹³C NMR spectral data¹⁰ of β-necrodol **1**, obtained in this way were closely comparable with those reported.^{2a}



Scheme - 1. Reagents and conditions: i) ethyl vinyl ether, ^tBuLi, THF, 81%. ii) NaH, THF, allyl bromide, HMPA, 73%. iii) hv CuOTf, Et₂O, 88%. iv) CH₂Cl₂, TfOH, 84%. v) TBDMSCl, Et₃N, DMAP, Imidazole, CH₂Cl₂, 73%. vi) CH(OMe)₃, BF₃·Et₂O, Et₃NPr₂, 79%. vii) NaBH₄, MeOH, then 6N HCl, 87%. viii) NaBH₄, MeOH, 62%. ix) CH₃C(OEt)₃, Hg(OAc)₂, propionic acid, 200°C, 6h then 5% NaOH, MeOH, H₂O, reflux, 2h, 42%. x) hv, quinoline, ^tBuSH, C₆H₆, 61%.

Acknowledgement : Financial supports from DST and CSIR, New Delhi are gratefully acknowledged. S.S thanks the CSIR for a Senior Research Fellowship.

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- ¹H NMR (300 MHz) δ (CDCl₃) 0.82 (3H, s), 0.934 (3H, d, J = 7 Hz), 0.935 (3H, s), 1.85 (1H, m), 2.15 (1H, m), 2.27 (1H, m), 2.59 (1H, m), 3.46 (1H, dd, J = 8.6, 10.3 Hz), 3.77 (1H, dd, J = 5.4, 10.3 Hz), 4.79 (1H, dddd, J = 2.2, 2.2, 2.2, 2.3), 4.85 (1H, dddd, J = 2.2, 2.2, 2.2, 2.3 Hz) and ¹³C (75 MHz) δ (CDCl₃) 13.5 (CH₃), 23.5 (CH₃), 24.2 (CH₃), 34.2 (CH₂), 42.6, 48.8 (CH), 49.3 (CH), 64.8 (CH₂), 105.5 (CH₂), 156.5.