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Stereocontrolled Total Synthesis of (±)-β-Necrodol

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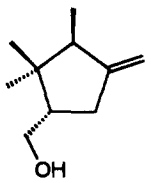
Abstract : A total synthesis of racemic β-necrodol is described using an ortho-ester Claisen rearrangement as the key step to dictate a high level of trans-1,3-diastereoselection on a cyclopentane derivative.

β-Necrodol **1**, a structurally novel monoterpene, has been isolated[1] 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-diastereoselectivity has been achieved.



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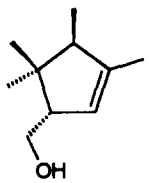

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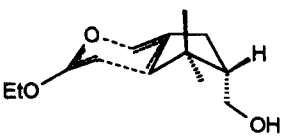

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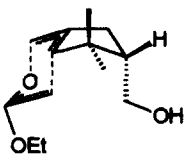

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The key step in our approach was an ortho-ester Claisen rearrangement which establishes the trans geometry of the 1,3-substituents with simultaneous generation of the exo methylene unit. We reasoned that during the Claisen rearrangement, reaction would prefer to take place on the face opposite[3] 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 cyclopentanones[4] 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

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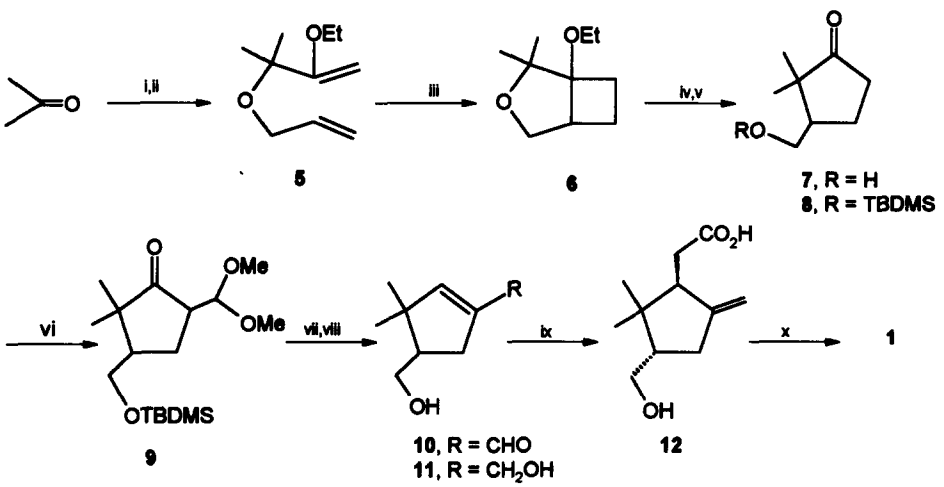
9 in excellent overall yield following Ghatak's protocol.[8] The aldehyde 10 was then reduced with $NaBH_4$ to afford the diol 11 in 62% yield. The Claisen rearrangement was accomplished by heating a mixture of the alcohol 11, triethylorthoacetate, mercuric acetate and propionic acid in a sealed tube 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 decarboxylation[9] to afford β-necrodol 1 and epi-β-necrodol in the same ratio (10:1) in 61% yield. ^1H and ^{13}C NMR spectral data[10] 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) hν CuOTf, Et_2O, 88%. iv) CH_2Cl_2, TfOH, 84 %. v) TBDMSCl, Et_3N, DMAP, Imidazole, CH_2Cl_2, 73%. vi) $CH(OMe)_3$, $BF_3.Et_2O$, $EtNPr^i_2$, 79%. vii) $NaBH_4$, MeOH, then 6N HCl, 87%. viii) $NaBH_4$, MeOH, 62%. ix) $CH_3C(OEt)_3$, $Hg(OAc)_2$, propionic acid, 200°C, 6h then 5% NaOH, MeOH, H_2O, reflux, 2h, 42%. x) hν, quinoline, ^tBuSH, C_6H_6, 61%.

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References and Notes

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10. ^1H NMR (300 MHz) δ ($CDCl_3$) 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 ^{13}C (75 MHz) δ ($CDCl_3$) 13.5 (CH_3), 23.5 (CH_3), 24.2 (CH_3), 34.2 (CH_2), 42.6, 48.8 (CH), 49.3 (CH), 64.8 (CH_2), 105.5 (CH_2), 156.5.