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A Synthesis of β-Necrodol Via A Palladium Catalyzed Reductive Enyne Cyclization

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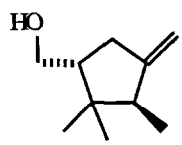
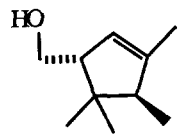
Summary: The Pd catalyzed reductive enyne cyclization provides an approach to control 1,3-diastereoselectivity and thereby provides a five step synthesis of β-necrodol, a key substituent of the defensive secretion of the red-lined carrion beetle.

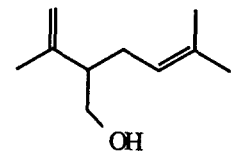
The defensive secretion of the red-lined carrion beetle consists of β-necrodol (1), α-necrodol (2), lavandulol (3), and several aliphatic acids[1]. The synthetic challenge represented by the necrodanes involves the novel 1,2,2,3,4-pentamethylcyclopentane skeleton



1
β-necrodol



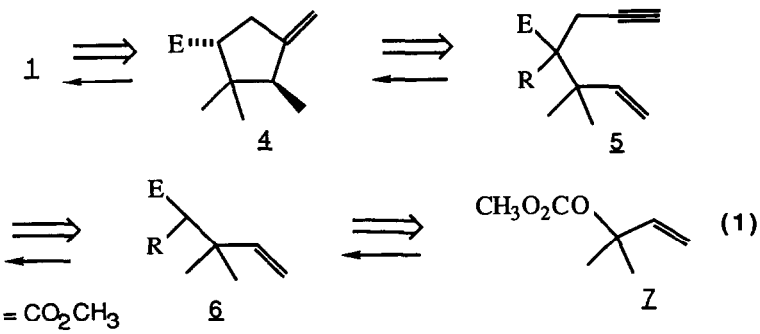
2
α-necrodol



3
lavandulol

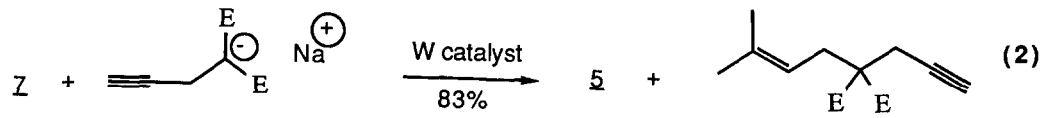
and the control of 1,3-stereochemistry. In developing a reductive cyclization of 1,6-enynes catalyzed by palladium[2], we were interested in the ability of such a process to control diastereoselectivity. These studies led to a very concise and diastereoselective synthesis of β-necrodol. In the two previous syntheses, 1,3-diastereoselectivity in the required direction was not observed[1,3].

Our proposed synthetic strategy is outlined in eq 1, where the



critical question relates to the diastereoselectivity of the reductive cyclization of enyne 5 (R=H). The availability of the acyclic precursor 5 (R=H) requires a regioselective alkylation of a prenyl substrate at the tertiary terminus (i.e., 7 -> 6).

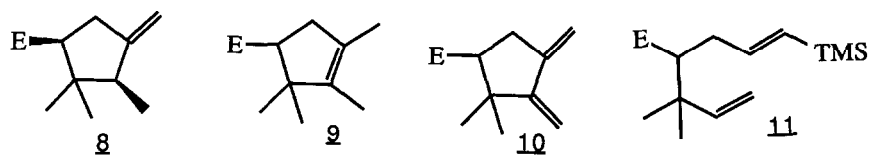
In an attempt to synthesize 5 ($R=CO_2CH_3$) directly, we performed the alkylation of dimethyl propargylmalonate with 7 catalyzed by 25 mol% $(C_2H_5CN)_3W(CO)_3$ [75 mol% propionitrile, 25 mol% bpy in THF, rt][4].



1.1 : 1

However, as illustrated in eq 2, a 1.1:1 mixture of regioisomers resulted. On the other hand, the molybdenum catalyzed allylic alkylation[5] [5 mol% Mo $(CO)_6$, BSA, $CH_2(CO_2CH_3)_2$, $PhCH_3$, 100°] of 7 gave an 83% yield of alkylation products in which capillary gc revealed a ratio of >20:1 in favor of the desired regioisomer 6[6,7]. Steric hindrance made direct propargylation of the malonate 6 ($R=CO_2CH_3$) impractical. Increasing the reactivity of the nucleophile by propargylating 6 (R=H), obtained in 60% yield by decarbomethoxylation [NaCN, H_2O, DMSO, 160°][8], gave a 66% yield of 5 (R=H)[6] [LDA, $HC{\equiv}CCH_2Br$, THF, -78°].

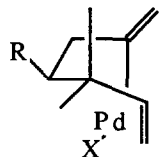
Subjecting the enyne to palladium catalyzed reductive cyclization could generate a variety of products including, in addition to the desired product 4, compounds 8 - 11. For



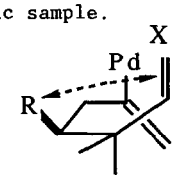
example, use of 2.5 mol% $(dba)_3Pd_2 \cdot CHCl_3$, 10 mol% $(o\text{-}C_7H_7)_3P$, and 200 mol% acetic acid as the catalytic system with PMHS[9] as the hydride source in benzene gave a 1.0:0.3:0.5 mixture of 4, 8, and 9. Using chloroform or THF as solvent gave a similar mixture of 4, 8, and 9, and, in addition, generated a small amount of the non-reduced cyclized product 10. The amount of this latter product increased substantially by switching the ligand from the phosphine to N,N[1]-dibenzylideneethylene diamine[10]. The genesis of the tetrasubstituted

olefin 9 was demonstrated to be by reduction of the initially produced diene 10 which is the normal product of non-reductive Pd catalyzed cyclization[11].

The occurence of 9 and 10 suggested that variation of the hydride source may preclude their formation. While switching to diphenylsilane did appear to minimize formation of 9 and 10, other unidentified by-products arose. The best hydride source appeared to be trimethylsilane which eliminated formation of 9 and 10 but did generate some of the direct hydrosilylation product 11. In this way, the desired cyclization occurred in 46% yield to give a 5:1 ratio of the two diastereomers 4[6] and 8. Proof of the stereochemistry of the major diastereomer as 4 was verified by LAH reduction to β-necrodol whose spectral properties were identical to those of an authentic sample.



12a



12b

The stereochemistry of the cyclization derives from the conformational bias in the intramolecular addition of a vinylpalladium species 12 formed by the hydropalladation of the acetylene[12]. The skew butane type interaction that arises between the substituent R and the vinyl group destabilizes cyclization via conformer 12b which leads to 8. The alternative conformer 12a, which generates the desired diastereomeric product 4, does not encounter such destabilizing interactions and is, therefore, favored. Thus, this approach to cyclization does appear to be a promising one for controlling non-adjacent stereogenic centers.

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6. All new compounds have been fully characterized spectroscopically, and elemental compositions have been established by either combustion analysis or high resolution mass spectroscopy.
7. Trost, B.M.; Schmuff, N.R.; Miller, M.J. *J. Am. Chem. Soc.*, **1980**, *102*, 5979.
8. Cf Guiard, B.; Furth, B.; Kossanyi, J. *Bull. Soc. Chim. France*, **1976**, 1552. Also see Trost, B.M.; Dietsche, T.J. *J. Am. Chem. Soc.*, **1973**, *95*, 8200; McMurry, J.E.; Wong, G.B. *Syn. Commun.*, **1972**, *2*, 389.
9. PMHS = polymethylhydrosiloxane
10. Cf Trost, B.M.; Jebaratnam, D.J. *Tetrahedron Lett.*, **1987**, *28*, 1611.
11. The facility of this homogeneous catalytic 1,4-reduction of a diene to a monoene may be a useful general synthetic method and is under active investigation.
12. The mechanism of the reaction is believed to involve 1) oxidative addition of acetic acid to the Pd(0), 2) regioselective addition of the formed hydridopalladium acetate to the terminal acetylene, 3) intramolecular addition of the formed vinylpalladium species to the olefin, 4) replacement of the acetate by hydride, and 5) reductive elimination to the product with regeneration of a Pd(0) complex. The precise timing of the intervention of the silicon hydride during the sequence of events is only speculative and may very likely occur earlier in the sequence. The competition between non-reductive and reductive cyclization observed herein leads us to favor the above at the moment.

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