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Synthesis of (±)-Nanaimoal and (±)-Nanaimool from N,N-Diethylgeranylamine

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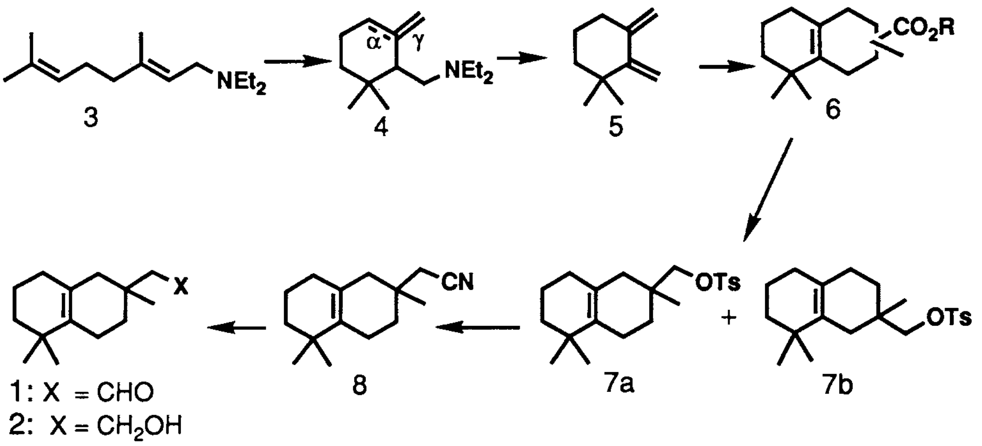
(±)-Nanaimoal and (±)-nanaimool were synthesized via Diels-Alder Reaction of 1,1-dimethyl-2,3-dimethylenecyclohexane, a novel building block for cyclic terpenoids, easily prepared from N,N-diethylgeranylamine.

Cyclic sesquiterpene aldehydes such as polygodial[1]and olepuane[2] are fish antifeedants which are thought to act as chemical defense substances. In 1984 Andersen[3] et al. have isolated Nanaimoal (**1**), a fragrant sesquiterpene aldehyde having a new carbon skeleton, from *Acanthodoris nanaimoensis,* and synthesized its derivative in a very low yield for the confirmation of the structure of **1**. In our continuous studies[4] on the synthesis of terpenoids using N,N-dialkyl geranylamine (**3**),[5,6] we wish to report a simple synthetic method of **1** from 1,1-dimethyl-2,3-dimethylenecyclohexane (**5**), a novel building block for cyclic terpenoids, easily prepared from **3**.

Cyclization[7] of **3** with $BF_3 \cdot Et_2O$ afforded a 81:19 mixture of N,N-diethyl γ- and α-cyclogeranylamines (**4**) (87% yield). Oxidation of **4** with 30% H_2O_2, and subsequent thermal elimination gave selectively[8]1,1-dimethyl-3,4-dimethylenecyclohexane (**5**) in 70% yield. Diels-Alder reaction of **5** with methyl methacrylate (MMA) at 170 °C for 20 h afforded adducts **6** in 91% isolated yield. NMR analysis of **6** (R=Me) showed slightly splitted two singlet peaks at δ 3.61 and 3.63 ($-CO_2C\underline{H}_3$), suggesting that **6** is a mixture of the regioisomers. However, the regioisomers could not be separated by chromatographic methods. Reduction of the mixture (**6**) with $LiAlH_4$, followed by tosylation gave the tosylates (**7**) in 98% yield. Hplc analysis of **7** showed clearly separated two peaks, and the mixture was fractionated to **7a** and **7b** [**7a** : **7b** = 56 : 44].[9,10]



The desired **7a** was treated with NaCN in dimethylsulfoxide (DMSO) at 110-115 °C for 3 h to give the nitrile **8**[11] in 85% yield, and the subsequent reduction of diisobutyl aluminum hydride (DIBALH) afforded (±)-nanaimoal (**1**) (80% yield), which was converted into (±)-nanaimool (**2**) by $NaBH_4$ in a quantitative yield.[12,13]

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References

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8) The reaction products were **5** and α-**4**, and **5** could be separated readily by ether extraction under acidic conditions (dil. HCl). The purity of **5** was more than 99% by GLC analysis (OV-101, 0.2 mm 25 m, He).

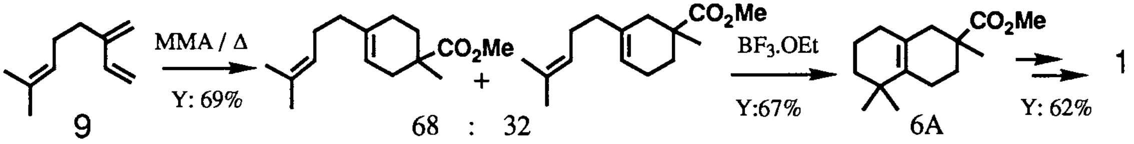
9) Hplc conditions: Shim-pack PREP-ODS, $CH_3CN:H_2O$ = 88:12, 9.0 ml/min.

10) In order to increase the yield of the desired isomer (**7a**), Diels-Alder reactions of **5** with methacrylates were examined. The use of $AlCl_3$ as a catalyst in this reaction (25 °C, 6 h) decreased the ratio of the desired isomer [Yield of **6** (R=Me): 70%, **7a**:**7b**=34:66], but the thermal reaction (170 °C, 17 h) of **5** with t-butyl methacrylate slightly increased the ratio of the desired isomer[Yield of **6** (R=t-Bu): 72%, **7a**:**7b**=59:41].

11) IR: 2230 cm^{-1}; ^{1}H-NMR($CDCl_3$): δ 0.97(6H, s), 1.06(3H, s), 1.2-2.2(12H, m), 2.23(2H, s); HRMS Found: m/z 217.1820. Calcd for $C_{15}H_{23}N$: M, 217.1829.

12) The spectral data of **1** and **2** agreed with those of natural nanaimoal and nanaimool. **1**: IR: 1722 cm^{-1}; ^{1}H-NMR($CDCl_3$): δ 0.97(6H, s), 1.04(3H, s), 1.3-2.2(12H, m), 2.25(2H, d, J=3.1Hz), 9.86(1H, t, J=3.1Hz); HRMS Found: m/z 220.1807. Calcd for $C_{15}H_{24}O$: M, 220.1825. **2**: IR: 3320, 1020 cm^{-1}; ^{1}H-NMR($CDCl_3$): δ 0.88(3H, s), 0.99(6H, s), 1.1-2.1(15H, m), 3.73(2H, d, J=7.6Hz); HRMS Found: m/z 222.1985. Calcd for $C_{15}H_{26}O$: M, 222.1983.

13) Nanaimoal (**1**) could be also synthesized from myrcene (**9**) via the scheme described below.



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