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High diastereoselectivity in Claisen rearrangement in a sterically congested cyclopentane system. Total synthesis of (±)-β-necrodol

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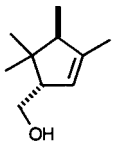
Abstract—Total synthesis of the monoterpene β-necrodol has been accomplished. The key step involves an *ortho*-ester Claisen rearrangement in a highly sterically congested cyclopentane derivative resulting in a high level of 1,3-*trans* diastereoselection. A novel photo-induced decarboxylation of the obtained γ,δ-unsaturated acid afforded β-necrodol. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

The defensive spray of the red-lined carrion beetle, *Necrodes surinamensis*, has been found to contain two novel monoterpenses,[1] α-necrodol **1** and β-necrodol **2**. Structurally, both the necrodols have 1,2,2,3,4-pentamethylcyclopentane (necrodane) as the core structural unit with 1,3-*trans* disposed Me and CH_2OH groups. The necrodols exhibit strong antiinsectant activity. Owing to their fascinating structures and biological activities, these compounds continue[2]to be the targets of synthetic investigations. Earlier synthetic attempts reveal that necrodols pose a considerable synthetic challenge. First, the construction of the sterically congested, highly substituted cyclopentane nucleus is not trivial, but the most difficult task lies in the generation of thermodynamically unfavorable *trans* relationship between the 1- and 3-substituents. The best ratio of 1,3-*trans* to *cis*-isomers reported[2c] so far is 5:1. The synthesis of β-necrodol is associated with an additional problem in generating an *exo*-methylene unit through olefination of enolizable cyclopentanone derivatives.[2a] Intrigued by the synthetic challenges associated with necrodols, we undertook a program for the synthesis of β-necrodol as part of our interest[3] in cyclopentanoid natural products. A detail account[4] of this investigation is presented here.



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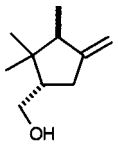

2

Keywords: terpenes and terpenoids; Claisen rearrangement; decarboxylation; photochemistry.

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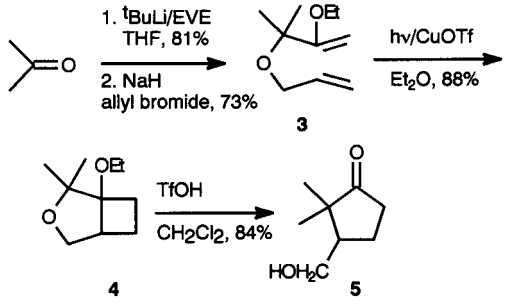
2. Results and discussion

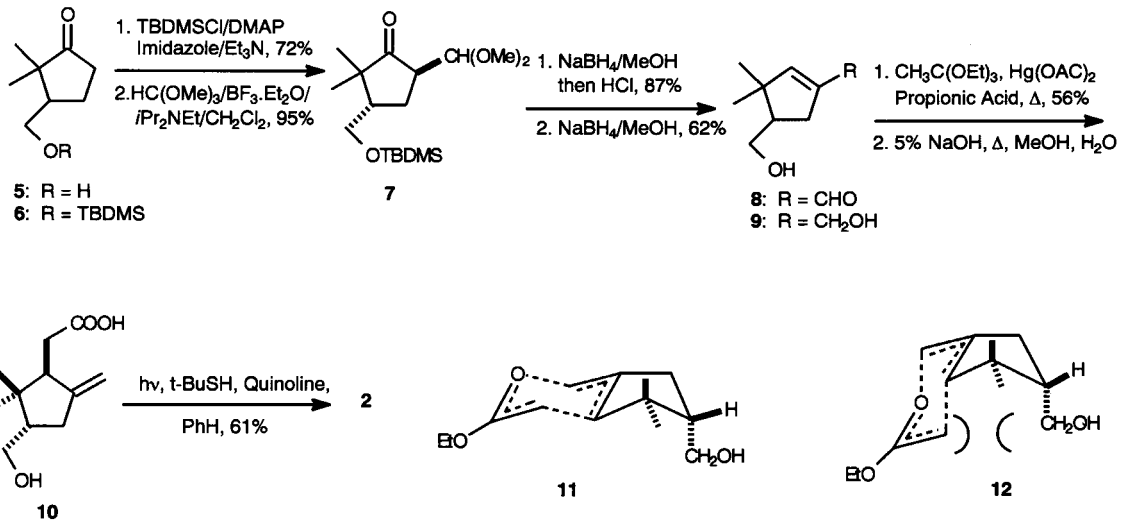
The key step in our synthesis is an *ortho*-ester Claisen rearrangement in an appropriately constructed cyclopentane derivative **9**. It established the required *trans* relationship between the 1,3-substitutents of β-necrodol with simultaneous generation of the exo methylene unit. The unsaturated alcohol **9** was easily obtained from the cyclopentanone derivative **5**. The ketone **5** was prepared through our previously published procedure,[5] based on a methodology developed for the synthesis of vicinally substituted cyclopentanones[3a–e] and spirocyclopentanones.[3f,g] Thus, the diene **3** (Scheme 1) obtained from acetone, on reaction with ethoxyvinyl lithium followed by allylation, afforded the cyclobutane derivative **4** on irradiation in the presence of CuOTf as catalyst. An acid induced rearrangement of the cyclobutane derivative **4** afforded the desired cyclopentanone **5** in 84% yield.

The ketone **5** was then transformed to the unsaturated aldehyde **8** (Scheme 2), following the protocol described by Ghatak et al.[6] Toward this end, the hydroxyl group of the hydroxyketone **5** was protected to give the silyl ether **6** in 72% yield. The ketone **6** was then converted to the β-ketoacetal **7** as a single diastereoisomer in 79% yield using



Scheme 1.

PII: S0040-4020(01)00019-9



Scheme 2.

Mock's procedure.[7] The *trans*-disposition of the CH_2OH and $CH(OMe)_2$ groups could be established from comparison of the chemical shifts[8] of the geminal Me protons at δ 0.95 and 1.02 with those reported in the literature for similar structures. The formation of the *trans* diastereoisomer is also expected from addition of the dialkoxy carbonium ion to the enolate from the face opposite to the $CH_2OTBDMS$ group. Treatment of the keto-acetal **7** with $NaBH_4$ in MeOH followed by aqueous 6N HCl led to the reduction of carbonyl group with concomitant deketalization, dehydration and desilylation to afford the unsaturated aldehyde **8** in 87% yield. Brief exposure of the aldehyde **8** into $NaBH_4$–MeOH at room temperature gave the diol **9** in 62% yield.

The *ortho*-ester Claisen rearrangement of the unsaturated diol **9** was carried out with an excess of triethyl orthoacetate, in the presence of mercuric acetate and propionic acid, in a sealed tube at 200°C for 6 h. The crude rearrangement product was directly hydrolyzed to afford the acid **10** along with its *cis* epimer in ca. 10:1 ratio (from integration of the geminal methyl protons in the ^1H NMR spectrum). Column chromatography of the crude product followed by crystallization, afforded the acid **10** as a white crystalline solid, mp 68°C in 40% yield. While the gross structure of the acid was clearly evident from the ^1H and ^{13}C NMR spectra, the stereochemical assignment to the major acid **10** was based on comparison of the chemical shifts[8] of the geminal methyls (δ 0.89 and 0.95) with those reported for β-necrodol (δ 0.80 and 0.92). On the other hand, the chemical shifts of the geminal methyl protons of the minor isomer (δ 0.57 and 1.09) were comparable to those reported for epi-β-necrodol (δ 0.51 and 1.04). The formation of the *trans* diastereomer as the major component during *ortho*-ester Claisen rearrangement of the diol **9** may be attributed as follows. During rearrangement, the hydroxymethyl group dictated the C–C bond formation to take place from its opposite face[9] through the transition state **11**. The alternative transition state **12**, leading to C–C bond formation from the side of the hydroxymethyl group, will be destabilized by an unfavorable 1,3-diaxial interaction. Finally, irradiation of a benzene solution of the hydroxy acid **10** in the presence of quinoline and *t*-butylmercaptan led to smooth decarboxylation,[10] affording β-necrodol **2** (containing a trace amount of epi-β-necrodol) in 61% yield. ^1H and ^{13}C NMR spectral data of this sample were identical with those reported in the literature.[2a]

3. Conclusions

We have demonstrated that a high level of 1,3-*trans* diastereoselection can be achieved in a sterically congested cyclopentane derivative through [3.3]-sigmatropic rearrangement. Finally, the synthesis of β-necrodol could be achieved through a photo-induced decarboxylation of the corresponding γ,δ-unsaturated acid.

4. Experimental

4.1. General

Melting points were measured in open capillary tubes, in a sulfuric acid bath, and are uncorrected. The organic extracts were dried over anhydrous Na_2SO_4. Column chromatography was performed on silica gel (60–120 mesh). Petroleum refers to fraction of petroleum ether boiling in the range 60–80°C. IR spectra were recorded as thin films. Unless otherwise stated, ^1H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively, in $CDCl_3$ solutions using TMS as internal standard.

4.1.1. 3,3-Dimethyl-4-hydroxymethylcyclopent-1-ene-carboxaldehyde (8). A solution of the hydroxy ketone **5**[5] (1.09 g, 7.04 mmol), TBDMSCl (1.6 g, 10.6 mmol), triethylamine (2.1 g, 20.8 mmol), DMAP (10 mg) and imidazole (10 mg) in dichloromethane (20 mL) was stirred under nitrogen for 12 h at rt. The mixture was then washed with brine, dried and concentrated. The residue was chromatographed (5% Et_2O/petroleum) to afford the silyl ether **6** (1.3 g, 72%) as a colorless liquid [Found: C, 65.78; H, 10.89. $C_{14}H_{28}O_2Si$ requires C, 65.57; H, 11.00%]; ν_{max} 1741, 1467 cm^{-1}; δ_H 3.57–3.67 (2H, m, OCH_2), 1.93–2.36

(4H, m, CH_2), 1.51–1.58 (1H, m, C*H*), 1.04 (3H, s, *Me*), 0.88 (3H, s, *Me*), 0.83 (9H, s, CMe_3), 0.01 (6H, s, SiMe_2); δ_C 223.4 (CO), 64.0 (CH_2), 48.9 (CH), 47.2 (C), 35.9 (CH_2), 25.8 (Me), 24.5 (Me), 22.5 (CH_2), 18.2 (C), 18.0 (Me), −5.6 (Me).

A solution of freshly distilled $BF_3{\cdot}Et_2O$ (1.7 g, 12 mmol) in dichloromethane (10 mL) was added dropwise to freshly distilled trimethylorthoformate (1.0 g, 9.55 mmol) with stirring at −30°C under argon. The mixture was warmed to 0°C and allowed to stand at that temperature for 15 min. It was then cooled to −78°C and a solution of the silyl ether **6** (1.24 g, 4.84 mmol) in dichloromethane (5 mL) was added dropwise, followed by addition of *N*,*N*-diisopropylethylamine (1.85 g, 14.35 mmol). The mixture was stirred at −10 to −20°C for 2 h. It was then poured into saturated aqueous $NaHCO_3$ solution (10 mL). The organic layer was washed with brine (3×5 mL), dried and concentrated. Chromatography of the residue (5% Et_2O/petroleum) afforded the ketoacetal **7** (1.26 g, 79%) as a colorless liquid [Found: C, 61,94; H, 10.20. $C_{17}H_{34}O_4Si$ requires C, 61.77; H, 10.36%]; ν_{max} 1740, 1463 cm^{-1}; δ_H 4.51 (1H, d, *J*=3.4 Hz, C*H*(OMe)$_2$), 3.59 (2H, ABX, *J*=9.0, 6.0, 3.0 Hz, OCH_2), 3.34 (3H, s, OMe), 3.33 (3H, s, OMe), 2.69–2.76 (1H, m, COC*H*), 2.20 (1H, dt, *J*=13.2, 6.9 Hz), 1.99–2.03 (1H, m), 1.67–1.72 (1H, m), 1.02 (3H, s, *Me*), 0.96 (3H, s, *Me*), 0.83 (9H, s, CMe_3), 0.02 (6H, s, SiMe_2); δ_C 221.5 (CO), 105.7 (CH), 64.4 (CH_2), 56.8 (Me), 55.0 (Me), 50.1 (CH), 47.9 (C), 46.9.(CH), 25.8.(Me), 24.2 (Me), 23.5 (CH_2), 18.8 (Me), 18.1 (C), −5.6 (Me).

To a well-stirred solution of the acetal **7** (400 mg, 1.2 mmol) in MeOH (3 mL), $NaBH_4$ (180 mg, 4.2 mmol) was added and the mixture was stirred for 12 h at rt. Then, the reaction mixture was quenced with ice cold 6N HCl (4 mL) and stirred for an additional 1.5 h. MeOH was then evaporated in vacuum and the mixture was extracted with ether (3×25 mL). The ether layer was dried and concentrated. Column chromatography (5% Et_2O/petroleum) of the residual mass afforded the *title compound* **8** as a colorless liquid (160 mg, 87%) [Found: C, 69.92; H, 9.22. $C_9H_{14}O_2$ requires C, 70.10; H, 9.15%]; ν_{max} 3407, 1677 cm^{-1} δ_H 9.69 (1H, s, C*H*O), 6.62 (1H, s, C═C*H*),3.62–3.79 (2H, m, OCH_2), 2.85 (1H, brs, O*H*), 2.73 (1H, q, *J*=9 Hz), 2.26 (1H, d, *J*=9 Hz), 2.20 (1H, d, *J*=9 Hz), 1.26 (3H, s, *Me*), 1.04 (3H, s, *Me*); δ_C 191.0 (CHO), 163.0 (CH), 143.3 (C), 63.3 (CH_2), 50.5 (CH), 47.4 (C), 31.6 (CH_2), 28.3 (Me), 21.2 (Me).

4.1.2. 3,3-Dimethyl-1,4-dihydroxymethyl cyclopentene (9). $NaBH_4$ (180 mg, 4.73 mmol) was added in small portions to a solution of the aldehyde **8** (370 mg, 2.36 mmol) in MeOH (2 mL) with stirring at rt. Stirring was continued for an additional 1 h. After diluting with water (1 mL), MeOH was removed and the residue was extracted with ether (3×5 mL). The ether layer was dried and concentrated. The residue was chromatographed (30% EtOAc/petroleum) to afford the *title compound* **9** (230 mg, 62%) as a colorless liquid [Found: C, 69.12; H, 10.20. $C_9H_{16}O_2$ requires C, 69.18; H, 10.33%]; ν_{max} 3327 cm^{-1}; δ_H 5.36 (1H, s, C═C*H*), 4.10 (2H, s, CH_2OH), 3.72–3.78 (1H, m, CH_2OH), 3.55–3.61 (1H, m, CH_2OH), 2.78 (2H, br, O*H*), 2.46 (1H, m), 2.07–2.18 (2H, m, CH_2), 1.12 (3H, s, *Me*), 0.90 (3H, s, *Me*); δ_C 140.0 (C), 136.3 (CH), 63.5 (CH_2), 61.7 (CH_2), 50.8 (CH), 45.4 (C), 35.6 (CH_2), 28.9 (Me), 21.9 (Me).

4.2. *ortho*-Ester Claisen rearrangement of the allyl alcohol 9

4.2.1. 2,2-Dimethyl-3α-hydroxymethyl-5-methylene-cyclopent-1β-yl acetic acid (10). A mixture of the allyl alcohol **9** (154 mg, 1 mmol), triethylorthoacetate (1 mL, 5.5 mmol), propionic acid (20 mg, 0.27 mmol) and mercuric acetate (20 mg, 0.06 mmol) was heated in a sealed tube at 200°C for 6 h. The crude rearrangement product was hydrolyzed by refluxing its solution in MeOH (4 mL) with aqueous NaOH (1.5 mL, 5%). The reaction mixture was then cooled to rt, diluted with water (5 mL) and acidified with HCl (6N) (2 mL). It was then extracted with ethyl acetate (3×10 mL), and the ethyl acetate layer was washed with saturated $NaHCO_3$ solution (3×1 mL). The $NaHCO_3$ washing was acidified with cold HCl (12N) and extracted with ethyl acetate (3×5 mL). The ethyl acetate layer was dried, concentrated in vacuum and the residue was chromatographed (30% EtOAc/petroleum). The solid mass obtained was repeatedly crystallized (EtOAc/pentane) to afford the hydroxy acid **10** along with a trace amount of its *cis*-epimer (80 mg, 40%); mp 68°C [Found: C, 66.25; H, 9.10. $C_{11}H_{18}O_3$ requires C, 66.62; H, 9.16%]; ν_{max} 3433, 1713, 1658 cm^{-1}; δ_H 5.75 (2H, brs, O*H*), 4.90 (1H, d, *J*=2.1 Hz, C═CH_2), 4.86 (1H, d, *J*=2.1 Hz, C═CH_2), 3.76 (1H, dd, *J*=1.7, 4.3 Hz, CH_2OH) 3.53 (1H, dd, *J*=8.3, 10.3 Hz, CH_2OH), 2.23–2.63 (5H, m) 1.88 (1H, m), 0.97 (3H, s, *Me*), 0.90 (3H, s, *Me*); δ_C 178.7 (CO), 152.6 (C), 107.0 (CH_2), 63.8 (CH_2), 50.5 (CH), 48.4 (CH), 42.2 (C), 34.6 (CH_2), 33.6 (CH_2), 23.8 (Me), 22.8 (Me).

4.2.2. Decarboxylation of the acid 25. Synthesis of β-necrodol (2). A solution of the hydroxy acid **25** (50 mg, 0.25 mmol) in benzene (6 mL) was irradiated in the presence of quinoline (40 mg) and *t*-BuSH (0.3 mL) with a medium pressure 450 W Hanovia Hg vapor lamp, with a pyrex filtered light, for 3 h under Ar. The reaction mixture was then washed successively with HCl (4 mL, 6N), saturated $NaHCO_3$ solution (3×2 mL) and brine (3 mL). Evaporation of the solvent followed by column chromatography (25% Et_2O/petroleum) afforded β-necrodol **2** (containing a trace of its *cis*-epimer) (23 mg, 61%) as a clear liquid; ν_{max} 3360, 3070, 2960, 1657, 1454, 1386, 1167, 1028, 874 cm^{-1}; δ_H 4.85 (1H, app. quintet, *J*=2.2 Hz, C═CH_2), 4.79 (1H, app. quintet, *J*=2.2 Hz, C═CH_2), 3.77 (1H, dd, *J*=5.3, 10.3 Hz, CH_2OH), 3.46 (1H, dd, *J*=8.6, 10.3 Hz, CH_2OH), 2.59 (1H, m), 2.27 (1H, m), 2.15 (1H, m), 1.85 (1H, m), 0.93 (3H, s, *Me*), 0.93 (3H, d, *J*=7 Hz, CH*Me*), 0.82 (3H, s, *Me*); δ_C 156.0 (C), 105.1 (CH_2), 64.4 (CH_2), 48.9 (CH), 48.4 (CH_2), 42.2 (C), 33.8 (CH_2), 23.7 (Me), 23.1 (Me), 13.5 (Me). These spectral data were identical to those reported in the literature.[2a]

Acknowledgements

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References

1. Roach, B.; Eisner, T.; Meinwald, J. *J. Org. Chem.* **1990**, *55*, 4047–4051.
2. (a) Jacobs, R. T.; Feutrill, G. I.; Meinwald, J. *J. Org. Chem.* **1990**, *55*, 4051–4062. (b) Oppolzer, W.; Schneider, P. *Helv. Chim. Acta* **1986**, *69*, 1817–1820. (c) Trost, B. M.; Braslau, R. *Tetrahedron Lett.* **1988**, *29*, 1231–1234. (d) Schulte-Elte, K. H.; Pamingle, H. *Helv. Chim. Acta* **1989**, *72*, 1158–1163. (e) Taber, D. F.; Yu, H. *J. Org. Chem.* **1997**, *62*, 1687–1690.
3. (a) Ghosh, S.; Patra, D. *Tetrahedron Lett.* **1993**, *34*, 4565–4566. (b) Patra, D.; Ghosh, S. *J. Org. Chem.* **1995**, *60*, 2526–2531. (c) Ghosh, S.; Patra, D.; Samajdar, S. *Tetrahedron Lett.* **1996**, *37*, 2073–2076. (d) Haque, A.; Ghatak, A.; Ghosh, S.; Ghoshal, N. *J. Org. Chem.* **1997**, *62*, 5211–5214. (e) Samajdar, S.; Patra, D.; Ghosh, S. *Tetrahedron* **1998**, *54*, 1789–1800. (f) Ghosh, S.; Patra, D.; Saha, G. *J. Chem. Soc., Chem. Commun.* **1993**, 783–784. (g) Patra, D.; Ghosh, S. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2635–2641.
4. A portion of this work appeared as a preliminary communication: Samajdar, S.; Ghatak, A.; Ghosh, S. *Tetrahedron Lett.* **1999**, *40*, 4401–4402.
5. Patra, D.; Ghosh, S. *Synth. Commun.* **1994**, *24*, 1663–1668.
6. Dasgupta, R.; Ghatak, U. R. *Tetrahedron Lett.* **1985**, *26*, 1581–1584.
7. Mock, W. L.; Tsou, H. R. *J. Org. Chem.* **1981**, *46*, 2557–2561.
8. Meinwald et al. noted that in a series of 1,3-disubstituted necrodane structures, the geminal methyl protons in NMR always appeared around δ 0.92 and 0.95 for the *trans*-isomer and δ 0.76 and 1.16 for the *cis*-isomer. The difference in chemical shifts of the geminal methyl protons was always less for the *trans* isomers (δ 0.03) than for the *cis*-isomers (δ 0.40). Cf. Ref. 2a.
9. Mehta, G.; Krishnamurthy, N.; Rao Karra, S. *J. Am. Chem. Soc.* **1991**, *113*, 5765–5775.
10. Okada, K.; Okubo, K.; Oda, M. *Tetrahedron Lett.* **1989**, *30*, 6733–6736.