

DIASTEREOSELECTIVE SYNTHESIS OF β - AND γ_2 -MUUROLENE: A CARBOCATIONIC
PATHWAY FROM MONO- TO SESQUITERPENES

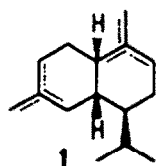
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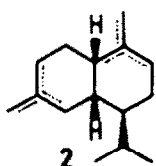
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Abstract. The Lewis acid catalysed addition of the piperityl chlorides **6** to isoprene yields adduct **7**, which undergoes a cis-stereoselective cyclisation to give the diastereoisomeric muurolene monohydrochlorides **8**. Treatment with potassium tert-butoxide affords β - and γ_2 -muurolene **2**.

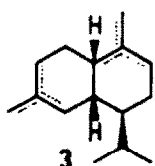
Various representatives of the cadalane series - cadinenes **1**, muurolenes **2**, bulgarenes **3**, and amorphenes **4** - with double bonds in different positions ($\alpha, \beta, \gamma, \delta, \epsilon, \gamma_1, \gamma_2$) have been found in nature¹, and syntheses for many of these compounds have been reported.²⁻⁵ In this article we describe the stereoselective synthesis of rac β - and γ_2 -muurolene, two members of this family, which have not been reported previously.



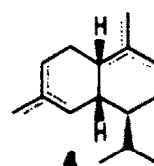
Cadinenes



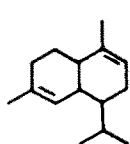
Muurolenes



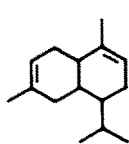
Bulgarenes



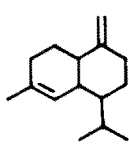
Amorphenes



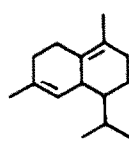
α



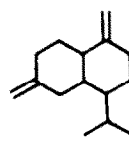
β



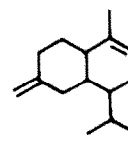
γ



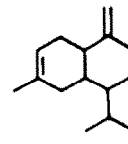
δ



ϵ

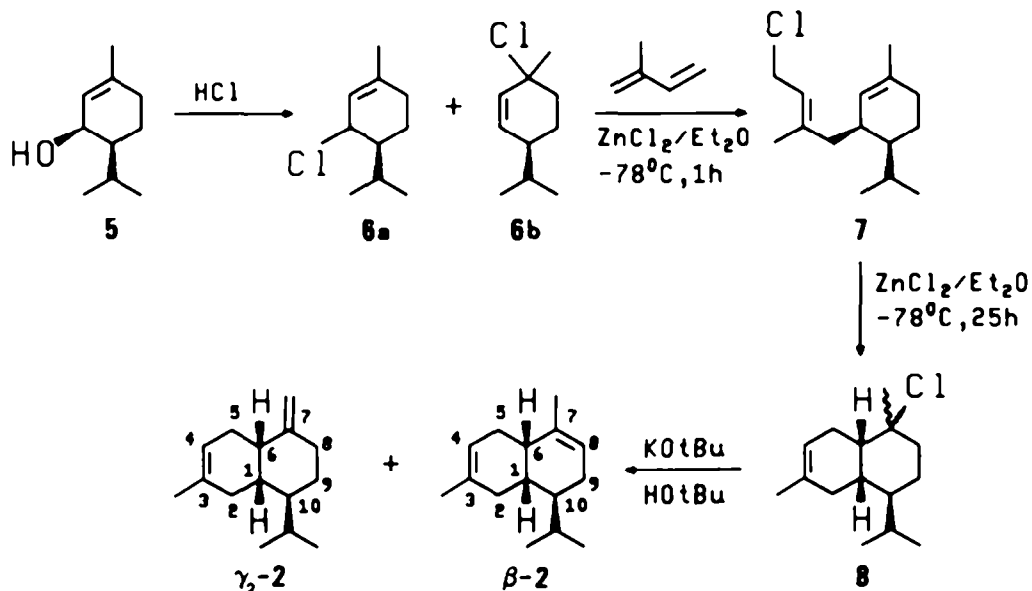


γ_1



γ_2

Results. A 2:1 mixture of the allylic chlorides **6a** and **6b** was obtained, when the commercially available trans-piperitol **5** was reacted with concentrated hydrochloric acid at ambient temperature.⁷ In accord with previous predictions,⁸ the $ZnCl_2/Et_2O$ catalysed reaction of **6a,b** with isoprene can be terminated at the 1:1 product stage, since the terminally trialkylated allyl cation **9** formed from **6a,b** is better stabilised than the terminally dialkylated allyl cation **10** formed from **7**.¹⁰ The $ZnCl_2/Et_2O$ catalysed cyclisation of **7**, which is carried out after removal of the unreacted isoprene, yields an 85:15-mixture of two diastereoisomeric tertiary chlorides **8**, which is treated with potassium tert-butoxide in tert-butanol to give the muurolenes β -2 and γ -2.



Structural Assignments. The observation of only 15 resonances in the ^{13}C NMR spectrum of **7** (Table 1) indicates that the reaction of **6** with isoprene is regio- and stereoselective,¹¹ but the configuration of **7** (cis or trans) could not be assigned at this stage. We were also unable to assign the configurations of the diastereomeric compounds **8** (85:15) on the basis of their NMR spectra. Since treatment of this mixture with base gave only two isomers (β -2 and γ -2) in 1:1 ratio, both isomers of compound **8** and the resulting elimination products have identical relative configurations at C-1, C-6, and C-10, and the two diastereoisomeric chlorides **8** differ in the relative configuration of C-7.

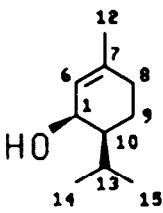
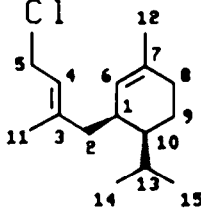
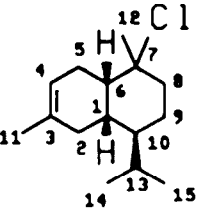
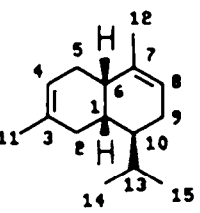
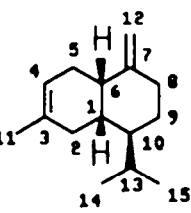
The 200 MHz NMR spectrum of the isomer with the exocyclic double bond (γ -2) showed a resonance at δ 2.50 (6-H) with couplings of approximately 5, 3, and 2 Hz. Since a coupling constant $J_{ax,ax} > 8$ Hz should be observable, if the two six-membered rings were trans annelated, structures **1** and **3** can be excluded, leaving compounds with muurolene (**2**) and amorphene (**4**) structure. In accord with this conclusion, the cadinenes β -1 and γ -1 have been found to show NMR spectra^{1,12} which differ from those reported in this work.

The diastereotopic protons of the isopropyl group in various compounds with amorphene structure have been reported to show 1H NMR signals between δ 0.86 and 0.98 with $\Delta\delta < 0.02$ ppm.⁸ Analogously, the chemical shift differences of the corresponding ^{13}C nuclei have been found to be < 0.9 ppm

for seven different derivatives of 4.⁶ The observed ¹H NMR absorptions of the isopropyl group at δ 0.77 and 0.87 (β -2) and δ 0.77 and 0.91 (γ_2 -2) as well as the corresponding ¹³C NMR shifts at δ 15.24 and 21.04 (β -2) and δ 16.60 and 21.47 (γ_2 -2), therefore, exclude amorphene structures. As the observed resonances fall into the range reported for muurolenes,⁶ the assignment to structures β -2 and γ_2 -2 could be made. Furthermore, in all amorphene derivatives studied, C-10 shows a NMR absorption at δ 46-49,⁶ whereas in the compounds, which we assign to β - and γ_2 -2, all methine carbons absorb at δ < 41.

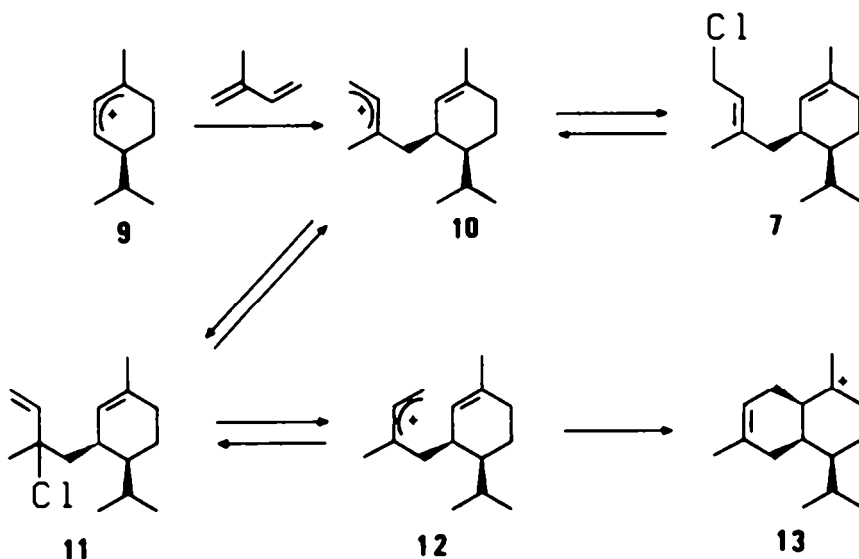
In contrast to cadinenes, bulgarenes, and amorphenes, the muurolenes have been found to adopt various conformations with isopropyl in equatorial or axial position.⁶ The ¹H NMR signal of 1-H, which should give information about the position of the isopropyl group, was overlapped by other resonances in both γ_2 - and β -2. In the case of γ_2 -2, a separation of the 1-H signal was possible by adding AgNO₃ and Eu(fod)₃,¹³ and on irradiation of the 6-H resonance, a quartet with $J = 3$ Hz was observed for 1-H, indicating an axial position of the isopropyl group. Since both 1-H and 6-H do not show couplings > 5 Hz, a boat like structure of the cyclohexene ring is suggested. As this conformation was not found to be a minimum by MM2 calculations,¹⁴ the possibility that the conformational equilibrium is influenced by the shift reagents has to be considered.

Table 1. ¹³C NMR chemical shifts for β - and γ_2 -muurolene and their precursors^a

| |  |  |  |  |  |
|------|---|--|--|--|---|
| | 5 | 7 | 8 | β -2 | γ_2 -2 |
| C-1 | 68.96 | 35.40 | 33.01, 35.24 | 37.76 | 39.55 |
| C-2 | | 44.87 | 31.40, 31.98 | 30.80 | 31.58 |
| C-3 | | 141.58 | 132.00, 130.58 | 131.96 | 131.81 |
| C-4 | | 124.42 | 118.33, 119.90 | 119.29 | 119.19 |
| C-5 | | 40.94 | 25.65, 26.10 | 29.16 | 27.77 |
| C-6 | 125.53 | 122.18 | 45.96, 45.74 | 34.74 | 40.95 |
| C-7 | 137.24 | 133.81 | 76.82, 75.81 | 138.82 | 152.28 |
| C-8 | 30.12 | 28.95 | 36.38, 37.39 | 119.75 | 31.02 |
| C-9 | 20.82 | 21.11 | 20.71, 22.56 | 24.92 | 25.95 |
| C-10 | 47.74 | 43.14 | 36.98, 36.95 | 34.93 | 38.30 |
| C-11 | | 16.07 | 23.69, 23.59 | 23.92 | 23.94 |
| C-12 | 23.16 | 23.70 | 31.11, 30.25 | 21.93 | 106.29 |
| C-13 | 26.38 | 27.06 | 27.03, 26.78 | 27.11 | 27.00 |
| C-14 | 17.26 | 17.85 | 15.03, 14.97 | 15.24 | 16.60 |
| C-15 | 21.26 | 21.79 | 21.36, 21.43 | 21.04 | 21.47 |

a) The assignments are based on DEPT spectra and estimated shift increments, and are not unequivocal within a group (CH, CH₂, CH₃) of resonances.

Reaction Mechanism. In analogy to the reactions of allyl cations with other alkenes,¹⁰ the initially generated allyl cation 9 is regioselectively attacked at the less substituted terminus (steric control), and the steric effect of the isopropyl group must be responsible for the exclusive formation (>90%) of the anti compound 7.¹¹ As in other electrophilic alkylations,¹² isoprene is selectively attacked at C-1 to give the (E)-configured 1,4-adduct. The initial formation of 7 can be explained by the fact that 10 does not possess the proper configuration for cyclisation. Since the rotational barrier for the conversion 10 → 12 is estimated to be approximately 12-15 kcal/mol,¹³ the stereomutation 10 → 12 is assumed to proceed via the intermediate 11. cis-Specific cyclization¹⁷ finally yields 13, which accepts chloride ions from both sides to give the two diastereoisomers of 8.



EXPERIMENTAL

NMR: XL 200 (Varian), ¹³C NMR are given in Table 1. TMS was used as internal standard. Mass spectra: 70-250 (VG); only the most intensive peaks are listed. IR: IR-435 (Shimadzu). Commercially available *trans*-piperitol (FLUKA) was used for the preparation of 6a,b.⁷

***trans*-3-(4-Chloro-2-methyl-2(E)-butenyl)-4-isopropyl-1-methylcyclohex-1-ene (7).** A solution of 6a and 6b (5.18 g, 30 mmol) in 75 mL of CH₂Cl₂ was added dropwise with stirring to a cooled (-78°C) solution of isoprene (2.04 g, 30 mmol) and ZnCl₂ (1.36 g) in 125 mL of ether (1.6 mL)⁸ in 125 mL of CH₂Cl₂. The reaction mixture was kept at -78°C for 1 h, then washed with concentrated aqueous ammonia, dried (Na₂SO₄), concentrated and distilled (83-90°C (bath)/0.2 mbar) to give 7 (4.62 g, 64%) as a colourless oil. - ¹H NMR (CDCl₃): δ 0.82, 0.92 (2 d, J = 6.8 Hz, 6 H, (CH₃)₂CH), 0.78-2.20 (m, 9 H), 1.64 (br. s, 3 H, 2'-CH₃), 1.72 (br. s, 3 H, 1-CH₃), 4.13 (d, J = 8 Hz, 2 H, CH₂Cl), 5.22 (mc, 1 H, 2-H), 5.46 (br. t, 8 Hz, 1 H, 3'-H). - Mass spectrum (70 eV): m/z = 242, 240 (0.26%, 0.85%, M⁺), 204 (34), 161 (52), 137 (50), 119 (66), 105 (43), 93 (70), 81 (100), 69 (25), 41 (36). - IR (neat): 2953, 2923, 2870, 1660, 1460, 1446, 1385, 1367, 1251, 834, 667 cm⁻¹.

7-Chloro-10-isopropyl-3,7-dimethylbicyclo[4.4.0]dec-3-ene (8). A solution of 3.61 g (15 mmol) of 7 in 30 mL of CH₂Cl₂ was added dropwise to a cooled (-78°C) solution of ZnCl₂ (1.84 g) in 2.2 mL of ether and 70 mL of CH₂Cl₂. The reaction mixture was then kept at -78°C for 25 h. The reaction mixture was successively washed with concentrated aqueous ammonia solution and water. The organic layer was separated, dried (Na₂SO₄) and distilled to give 8 (2.52 g, 70%) as a mixture (85:15) of two diastereoisomers. - ¹H NMR (CDCl₃) of the major isomer: δ 0.79, 0.89 (2 d, J = 7.0 Hz, 6.9 Hz, 6 H, (CH₃)₂CH), 0.72-2.18 (m, 12 H), 1.57 (s, 3 H, 7-CH₃), 1.65 (br. s, 3 H, 3-CH₃), 5.26 (mc, 1 H, 4-H). - Mass spectrum (12 eV): m/z = 242, 240 (2.8%, 3.5%, M⁺), 204 (100), 161 (65), 136 (35), 119 (40), 93 (34), 92 (23). - IR (neat): 2953, 2927, 2871, 1459, 1445, 1378, 1368, 788 cm⁻¹.

8- and γ₂-Muurolenes 2. Compound 8 (1.20 g, 5 mmol) was added to a well stirred suspension of potassium tert-butoxide (3.37 g, 30 mmol) in 30 mL of tert-butanol and refluxed for 50 h. The

reaction mixture was cooled, poured onto crushed ice, acidified with 20% aqueous acetic acid, extracted with CH_2Cl_2 , concentrated and distilled (70-75°C (bath)/0.5 mbar) to give a mixture of β -2 and γ -2. These two isomers were separated by MPLC (C18-phase, methanol/ether = 9/1) to give 0.45 g (44%) of β -2 and 0.40 g (39%) of γ -2 (colourless liquids).

rac β -Muurolene (10-isopropyl-3,7-dimethylbicyclo[4.4.0]dec-3,7-diene) β -2. - $^1\text{H NMR}$ (C_6D_6): δ 0.77, 0.87 (2 d, $J = 6.7$ Hz, 6.9 Hz, 6 H, $(\text{CH}_3)_2\text{CH}$), 1.45-2.40 (m, 10 H), 1.68 (br. s, 6 H, 3- CH_2 , 7- CH_2), 5.36 (mc, 2 H, 4-H, 8-H). - IR (neat): 2953, 2917, 2906, 2892, 1463, 1444, 1436, 1385, 1377, 1366, 821, 786 cm^{-1} . - Mass spectrum (70 eV): $m/z = 204$ (17%, M^+), 161 (17), 136 (17), 119 (16), 105 (23), 93 (100), 92 (48), 91 (22), 77 (16). Anal. Calcd. for $\text{C}_{15}\text{H}_{24}$ (204.4): C, 88.16; H, 11.84. Found: C, 88.11; H, 11.77.

rac γ -Muurolene (10-isopropyl-3-methyl-7-methylenebicyclo[4.4.0]dec-3-ene) γ -2. - $^1\text{H NMR}$ (CDCl_3): δ 0.77, 0.91 (2 d, 6.8 Hz, 6.9 Hz, 6 H, $(\text{CH}_3)_2\text{CH}$), 1.50-2.38 (m, 12 H), 1.64 (br. s, 3 H, 3- CH_2), 2.50 (mc, 1 H, 6-H), 4.62 (mc, 2 H, - CH_2), 5.33 (mc, 1 H, 4-H). - IR (neat): 2947, 2915, 1646 (= CH_2), 1462, 1443, 1383, 1366, 884, 786 cm^{-1} . - Mass spectrum (70 eV): $m/z = 204$ (15%, M^+), 161 (62), 136 (21), 119 (17), 105 (16), 94 (19), 93 (100), 92 (17), 91 (24), 80 (14), 79 (14), 77 (15). - Anal. Calcd. for $\text{C}_{15}\text{H}_{24}$ (204.4): C, 88.16; H, 11.84. Found: C, 88.11; H, 11.87.

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- 11) Small additional peaks in the ^{13}C NMR spectrum of 7 (< 10%) may be attributed to 11 or to stereoisomers of 7.
- 12) We thank Dr. F.J. Hammerschmidt, Fa. Dragoco for informing us about the 60 MHz ^1H NMR data of β -cadinene.
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