

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

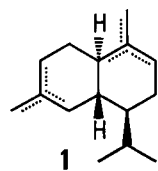
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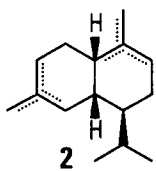
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Abstract. The Lewis acid catalysed addition of the piperityl chlorides **6** to isoprene yields adduct **7**, which undergoes a cis-stereoselective cyclisation to give the diastereoisomeric muurolene monohydrochlorides **8**. Treatment with potassium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

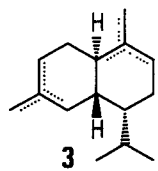
Various representatives of the cadalane series - cadinenes **1**, muurolenes **2**, bulgarenes **3**, and amorphenes **4** - with double bonds in different positions ($\alpha, \beta, \gamma, \delta, \epsilon, \gamma_1, \gamma_2$) have been found in nature¹, and syntheses for many of these compounds have been reported.²⁻⁶ 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.



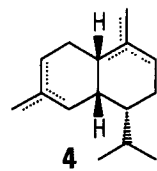
Cadinenes



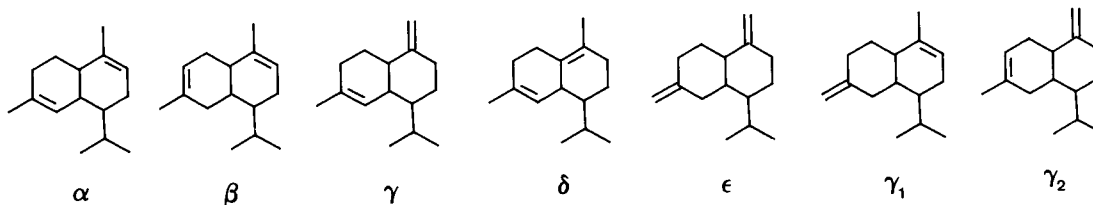
Muurolenes



Bulgarenes



Amorphenes



α

β

γ

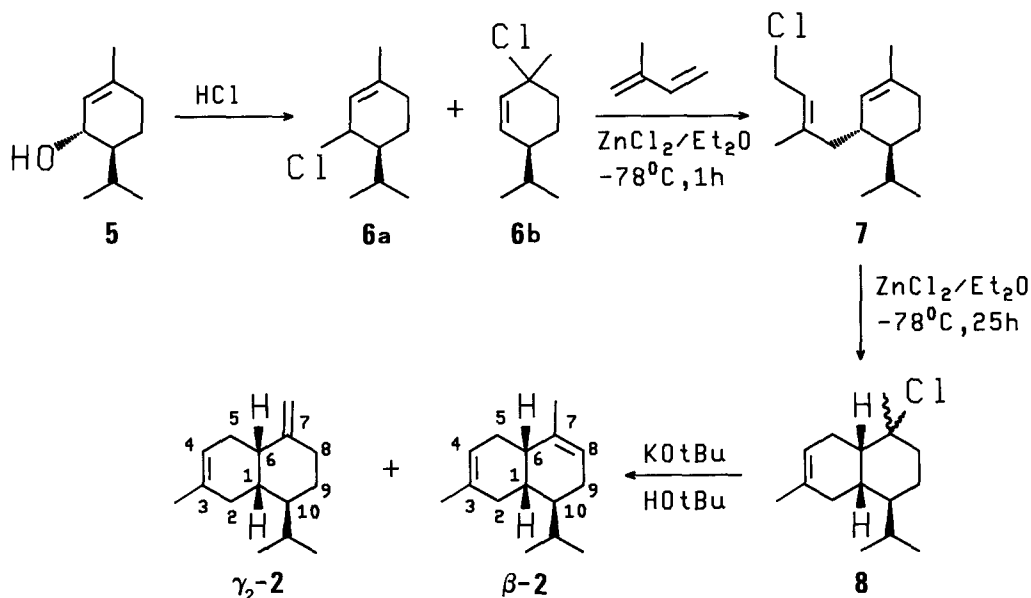
δ

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 $\text{ZnCl}_2/\text{Et}_2\text{O}$ 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 $\text{ZnCl}_2/\text{Et}_2\text{O}$ 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.

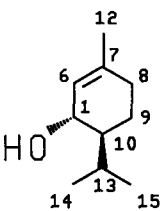
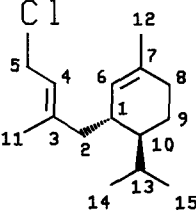
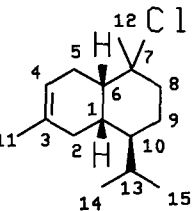
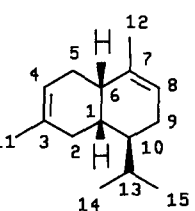
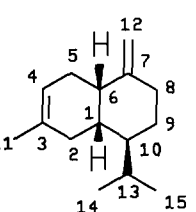
The 200 MHz NMR spectrum of the isomer with the exocyclic double bond (γ -2) showed a resonance at δ 2.50 (6-H) with couplings of approximately 5, 3, and 2 Hz. Since a coupling constant $J_{\text{ax,ax}} > 8$ Hz should be observable, if the two six-membered rings were trans annelated, structures **1** 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^{3,5,12} 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.⁶ 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.

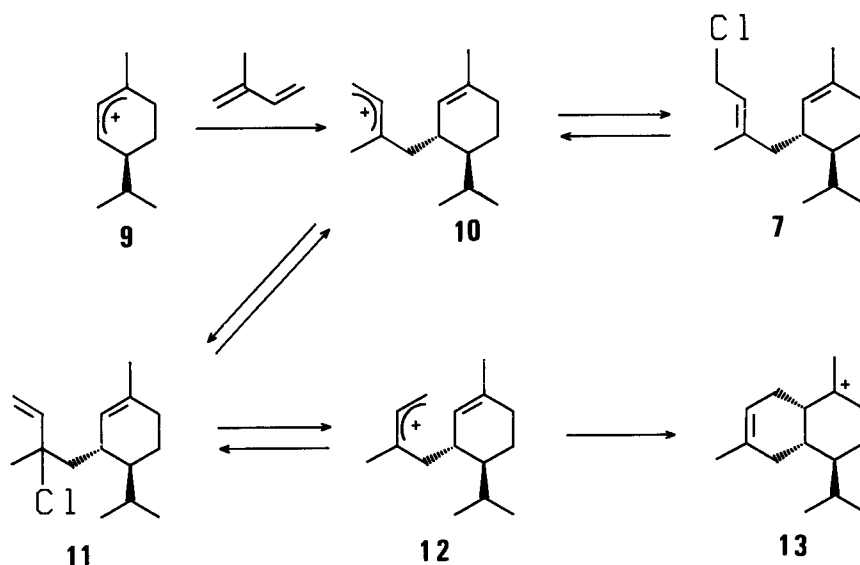
In contrast to cadinenes, bulgarenes, and amorphenes, the muurolenes have been found to adopt various conformations with isopropyl in equatorial or axial position.⁶ The ¹H NMR signal of 1-H, which should give information about the position of the isopropyl group, was overlapped by other resonances in 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,¹⁵ 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,¹⁶ 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)/ether (1.6 mL)⁹ 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.

β- and γ-Murolenes 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 -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 -2 (colourless liquids).

rac β -Muurolene (10-isopropyl-3,7-dimethylbicyclo[4.4.0]dec-3,7-diene) β -2. - ^1H 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_3 , 7- CH_3), 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_2 -Muurolene (10-isopropyl-3-methyl-7-methylenebicyclo[4.4.0]dec-3-ene) γ_2 -2. - ^1H 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_3), 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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