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

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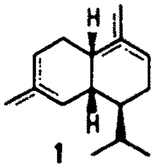
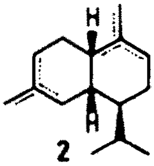
Abstract. The Lewis acid catalysed addition of the piperityl chlorides 6 to isoprene yields adduct 7, which undergoes a cis-stereoselective cyclisation to give the diastereoisomeric muurolene monohydrochlorides 8. Treatment with potassium tert-butoxide affords β- and γ_2- muurolene 2.

Various representatives of the cadalane series - cadinenes 1, muurolenes 2, bulgarenes 3, and amorphenes 4 - with double bonds in different positions (α, β, γ, δ, ε, γ_1, γ_2) have been found in nature[1], and syntheses for many of these compounds have been reported.[2-8] 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.



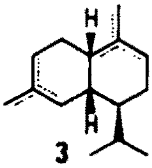
1

Cadinenes



2

Muurolenes



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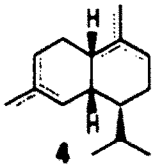
Bulgarenes



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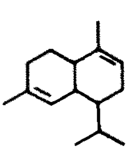
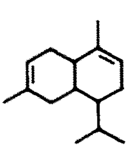
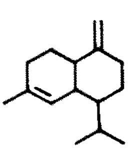
Amorphenes



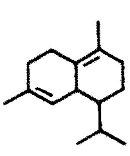
α



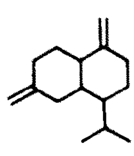
β



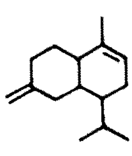
γ



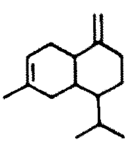
δ



ε

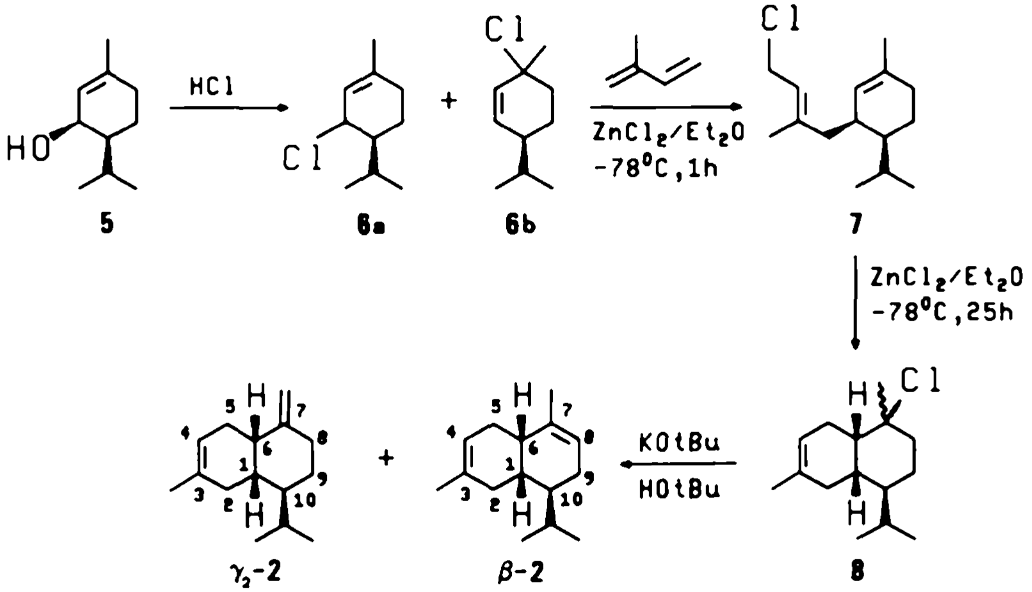


γ_1



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 $ZnCl_2/Et_2O$[9] 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-**2**.



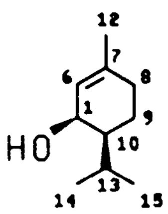
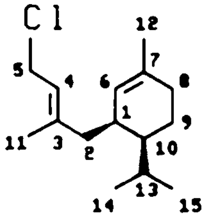
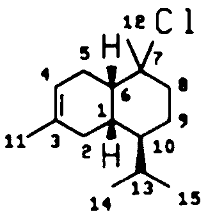
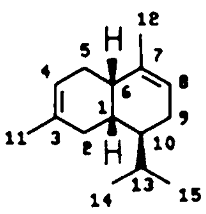
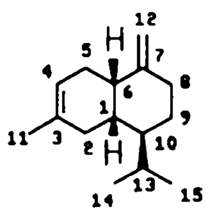
Structural Assignments. The observation of only 15 resonances in the ^{13}C NMR spectrum of **7** (Table 1) indicates that the reaction of **6** with isoprene is regio- and stereoselective,[11] but the configuration of **7** (cis or trans) could not be assigned at this stage. We were also unable to assign 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-**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-**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_2-**1** have been found to show NMR spectra[8,9,12] 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 $\Delta\delta \leq 0.02$ 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.[8] The observed ^{1}H 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 ^{13}C 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,[8] 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,[8] 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.[8] The ^{1}H 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 $AgNO_3$ and $Eu(fod)_3$,[10] 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,[10] the possibility that the conformational equilibrium is influenced by the shift reagents has to be considered.

Table 1. ^{13}C 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

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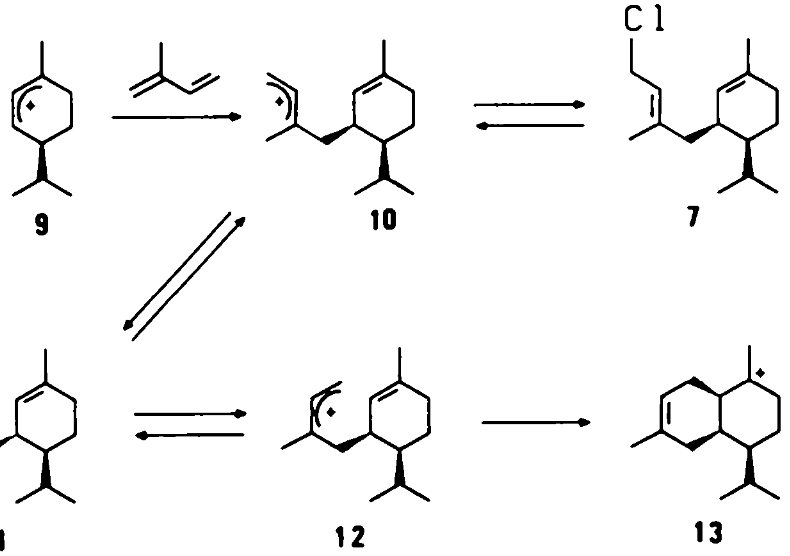
[a] The assignments are based on DEPT spectra and estimated shift increments, and are not unequivocal within a group (CH, CH_2, CH_3) of resonances.

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,[10] isoprene is selectively attacked at C-1 to give the (E)-configurated 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 cyclization[17] finally yields 13, which accepts chloride ions from both sides to give the two diastereoisomers of 8.



EXPERIMENTAL

NMR: XL 200 (Varian), ^{13}C 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 CH_2Cl_2 was added dropwise with stirring to a cooled (-78°C) solution of isoprene (2.04 g, 30 mmol) and $ZnCl_2$ (1.36 g)/ether (1.6 mL)[8] in 125 mL of CH_2Cl_2. The reaction mixture was kept at -78°C for 1 h, then washed with concentrated aqueous ammonia, dried (Na_2SO_4), concentrated and distilled (83-90°C (bath)/0.2 mbar) to give 7 (4.62 g, 64%) as a colourless oil. - ^{1}H NMR ($CDCl_3$): δ 0.82, 0.92 (2 d, J = 6.8 Hz, 6 H, $(CH_3)_2CH$), 0.78-2.20 (m, 9 H), 1.64 (br. s, 3 H, 2'-CH_3), 1.72 (br. s, 3 H, 1-CH_3), 4.13 (d, J = 8 Hz, 2 H, CH_2Cl), 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 CH_2Cl_2 was added dropwise to a cooled (-78°C) solution of $ZnCl_2$ (1.84 g) in 2.2 mL of ether and 70 mL of CH_2Cl_2. 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 (Na_2SO_4) and distilled to give 8 (2.52 g, 70%) as a mixture (85:15) of two diastereoisomers. - ^{1}H NMR ($CDCl_3$) of the major isomer: δ 0.79, 0.89 (2 d, J = 7.0 Hz, 6.9 Hz, 6 H, $(CH_3)_2CH$), 0.72-2.18 (m, 12 H), 1.57 (s, 3 H, 7-CH_3), 1.65 (br. s, 3 H, 3-CH_3), 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_2- 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-**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]deca-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, $(CH_3)_2CH$), 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 $C_{15}H_{24}$ (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, $(CH_3)_2CH$), 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 $C_{15}H_{24}$ (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**.
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