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PRENYLATION OF CAMPHENE - A CARBOCATIONIC ROUTE TO ISOSANTALENE AND ITS DERIVATIVES

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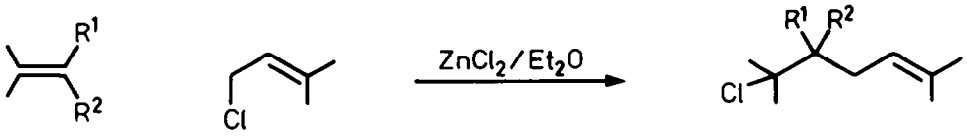
Abstract: Camphene **1** is converted into 8-chloromethylcamphene **3** via Prins reaction. Treatment of **3** with zinc chloride/ether in the presence of isobutene gives the 1:1 adduct **11**, from which isosantalene **7**, its isomer **6**, and the corresponding alcohol **5** are obtained.

The acid catalysed prenylation of readily available monoterpenes with definite stereochemistry appears to be an attractive method for the synthesis of sesquiterpenes. Julia and coworkers have used this approach for the synthesis of bisabolane sesquiterpenoids by generating the prenyl cation from 2-methyl-3-buten-2-ol or its allylic isomer and a Bronsted acid in the presence of limonene and carvone [1]. In a similar way, the synthesis of monoterpenes [2] and of sesqui-ionones has been achieved. In order to obtain monoprenylation products in fair yields, these reactions have to be terminated at a very low degree of conversion [1-3].

In accordance with the rules of Lewis acid catalysed alkyl halide additions towards alkenes [4], we found prenyl chloride to give good yields of monoadducts when treated with zinc chloride in the presence of 1,1-dialkyl- or higher alkylated ethylenes (Scheme 1). These conditions may offer an alternative to Julia's procedure.

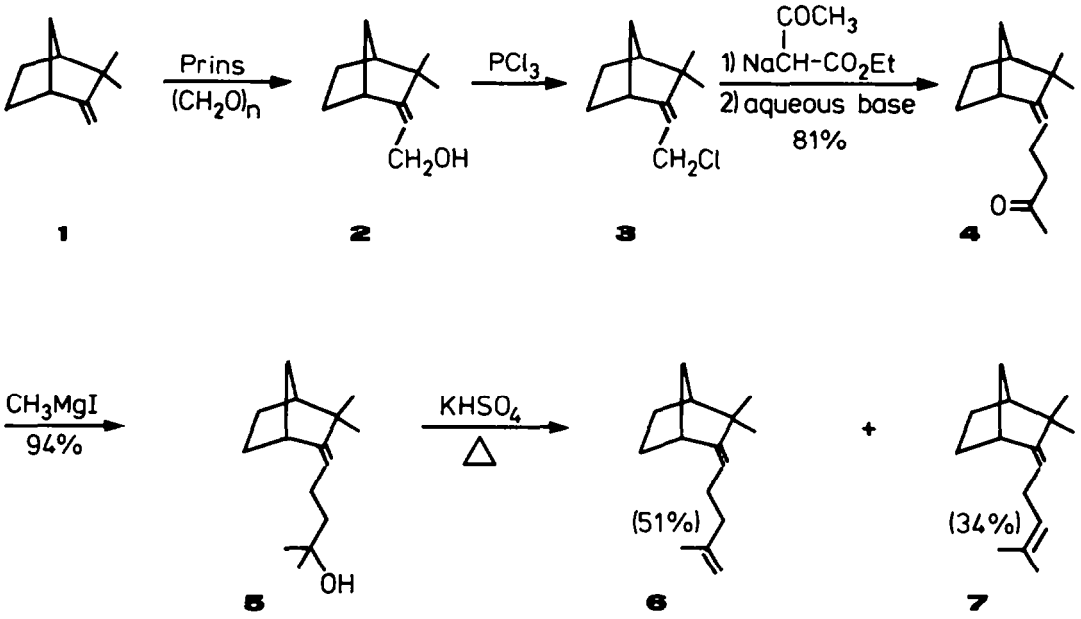
Scheme 1 [5]



R^1,R^2 = H ,H : 65%
CH_3,H : 78%
CH_3,CH_3: 76%

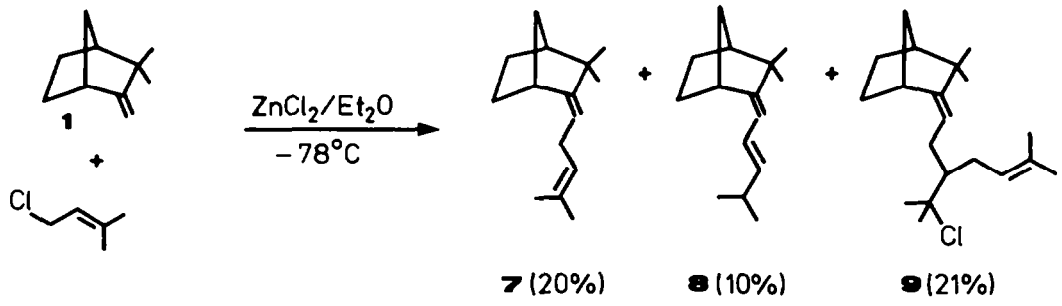
We report now, that treatment of camphene **1** with prenyl chloride in the presence of Lewis acids gives only low yields of isosantalene **7**. An alternative carbocationic prenylation route has been elaborated, however, which converts camphene into isosantalene **7** more directly and selectively than the previously published procedure, which is summarized in Scheme 2 [6].

Scheme 2 [7]



When 2 equivalents of camphene 1 were treated with prenyl chloride in the presence of $ZnCl_2/Et_2O$ under the conditions which have been used for the prenylation of ordinary alkenes [5], isosantalene 7 was obtained in 20% yield along with its isomer 8 and higher prenylated compounds, among which 9 (mixture of diastereomers) was identified. Hydrogen chloride, which is liberated during this process, is trapped by 1 to give bornyl chloride. Therefore, a large excess of 1 would be needed to considerably increase the yield of 7.

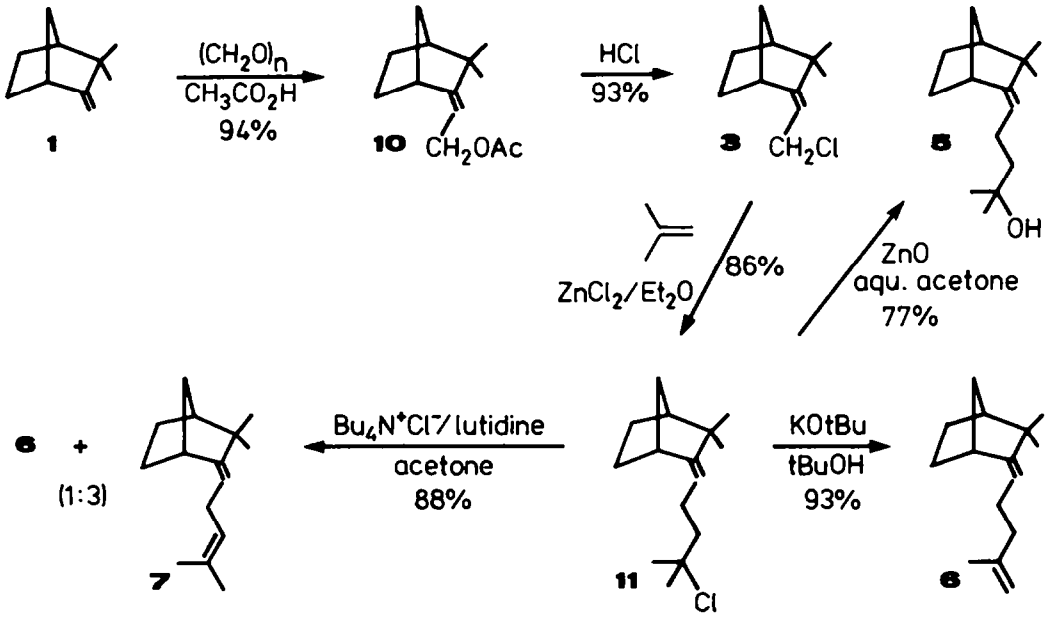
Scheme 3



An alternative approach (Scheme 4) introduces the C_5 fragment in two steps. As in Scheme 2 [7], the allyl chloride 3 was used as an intermediate. In contrast to the published procedure [7], the initial Prins product 10 was not hydrolysed to give 2, but was treated with concentrated hydrochloric acid to give 3 directly. Since tertiary alkyl chlorides ionise less readily than terminally dialkylated allyl chlorides [4b], the $ZnCl_2/Et_2O$ catalysed [9] reaction of 3 with isobutene gives a high yield of the 1:1 product 11, which now serves as the precursor of 5, 6 and 7.

As shown in Scheme 4, 11 is smoothly converted into the tertiary alcohol 5 by treatment with ZnO in 80% aqueous acetone [10]. Whereas the Hoffmann elimination product 6 can be generated selectively by treating 11 with potassium tert.butoxide, the Saytzeff product 7 was formed along with 25% of 6 when 11 was treated with tetrabutylammonium chloride and lutidine in refluxing acetone [11].

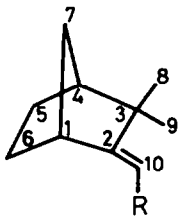
Scheme 4



In accordance with previous reports [7], the Prins reaction of camphene proceeds with high stereoselectivity to give the (E)-isomer **10**. The stereochemical assignment can be based on the ^{13}C NMR chemical shifts of C-1 and C-3. The table shows that C-3 is almost unaffected when R = H is replaced by a carbon chain, while C-1 experiences a 7 ppm upfield shift. Since the methyl carbons in cis-2-butene are shielded by 5.4 ppm with respect to the methyl carbons in trans-2-butene, and similar trans- and cis-alkyl effects have been found in other alkenes [13], the cis-orientation of R and C-1 can be derived from the ^{13}C NMR chemical shifts (Table).

Conclusion: The introduction of a C_4-fragment into 3, which has been achieved by the acetoacetate method, ketone cleavage and Grignard reaction (carbanionic route, Scheme 2) is more efficiently carried out by the $ZnCl_2$ catalysed addition of 3 to isobutene (carbocationic route, Scheme 4). This example again demonstrates that in many cases the carbocationic pathway is superior to the carbanionic alternative.

Table. ^{13}C NMR chemical shifts (δ) for camphene and derivatives.



R	H[12]	$^{11}CH_2$ $^{12}CH_2$ ^{13}C	$^{11}CH_2$ $^{12}CH_2$ ^{13}C	$^{11}CH_2$ ^{12}CH ^{13}C	^{11}CH ^{12}CH ^{13}CH	$^{11}CH_2$ $^{12}CH_2$ ^{13}C
		Cl	OH			Cl
			H_3C^{15} $^{14}CH_3$	H_3C^{15} $^{14}CH_2$	H_3C^{15} $^{14}CH_3$	H_3C^{15} $^{14}CH_3$ H_3C^{15} $^{14}CH_3$
	1	**3**	**5**	**6**	**7**	**8**	**11**
C- 1	48.20	41.10	41.17	41.24	41.27	41.77	40.98
C- 2	165.90	162.51	155.73	155.68	155.33	157.57	155.93
C- 3	41.70	42.02	41.62	41.70	41.77	42.17	41.48
C- 4	47.00	47.55	47.99	48.10	48.12	47.91	47.81
C- 5	23.80	23.48	23.84	23.92	23.87	23.84	23.66
C- 6	28.90	27.84	28.26	28.41	28.33	28.12	28.14
C- 7	37.40	37.05	37.29	37.38	37.31	37.39	37.11
C- 8	29.40	28.69	29.20	29.51	29.48	28.99	29.25
C- 9	25.80	25.44	26.06	26.17	26.16	25.73	25.93
C-10	99.10	111.53	115.08	114.68	113.89	115.82	113.88
C-11	-	42.30	24.17	27.35	28.10	124.86	24.73
C-12	-	-	44.00	38.48	123.97	138.06	46.34
C-13	-	-	71.01	145.73	130.81	31.28	70.67
C-14	-	-	29.39	109.85	25.73	22.65	32.26
C-15	-	-	29.24	22.55	17.68	22.63	32.23

EXPERIMENTAL

NMR: XL 200 (Varian), ^{13}C NMR data are given in the Table. TMS was used as internal standard. Mass spectra: 70-250 (VG); only the most intensive peaks are listed. 8-Hydroxymethylcamphene acetate **10** was synthesized from commercially available camphene (Fluka) according to literature procedure [8].

Direct Prenylation of Camphene. A solution of 1-chloro-3-methyl-2-butene (2.1 g, 20 mmol) in 10 mL of CH_2Cl_2 was added dropwise with stirring to a cooled (-78°C) solution of camphene (5.4 g, 40 mmol) and $ZnCl_2$ (2.1 g)/ether (2.5 mL) in 30 mL of CH_2Cl_2. The reaction mixture was kept at -78°C for 18 h, then washed with concentrated aqueous ammonia, dried (Na_2SO_4) and concentrated. After removing unreacted camphene (1.5 g) and bornyl chloride (1.3 g) in vacuo (40 - 50°C, 0.4 mbar), the residue was separated by MPLC (C_{18}-phase, methanol/ether = 9/1) to give **7** (0.80 g, 20%), **8** (0.40 g, 10%), and **9** (0.65 g, 21%). Analytical data of **7** see below.

4-Methyl-1-(3',3'-dimethylbicyclo[2.2.1]hept-2-ylidene)pent-2-ene 8. ^1H NMR ($CDCl_3$): δ 1.01 (d, J = 6.8 Hz, 6 H, $CH(CH_3)_2$), 1.01, 1.04 (2 s, 6 H, 3'-CH_3), 1.2 - 1.7 (m, 6 H, 5',6',7'-H), 1.87 (mc, 1 H, 4'-H), 2.33 (mc, 1 H, 4-H), 3.09 (mc, 1 H, 1'-H), 5.50 (dd, J = 15.3 Hz, 6.9 Hz, 1 H, 3-H), 5.59 (d, J = 10.8 Hz, 1 H, 1-H), 6.16 (ddd, J = 15.3 Hz, 10.8 Hz, 1.3 Hz, 1 H, 2-H). - Mass spectrum (70 eV): m/z = 204 (100%, M^+), 189 (74), 161 (80), 133 (42), 121 (50), 119 (59), 116 (50), 105 (58), 95 (81), 93 (72), 81 (39), 79 (32), 69 (43).

5-(1-Chloro-1-methyl-ethyl)-2-methyl-7-(3',3'-dimethylbicyclo[2.2.1]hept-2-ylidene)-hept-2-ene 9 (mixture of diastereomers). ^1H NMR ($CDCl_3$): δ 0.97, 1.00 (2 s, 6 H, 3'-CH_3), 1.58 (br s, 6 H, $(CH_3)_2Cl$), 1.62, 1.68 (2 br s, 6 H, =$C(CH_3)_2$), 1.17 - 1.72 (m, 6 H, 5',6',7'-H), 1.88 (mc, 1 H, 4'-H), 1.90 - 2.13 (m, 3 H, 2,3-H), 2.25 - 2.40 (m, 2 H, 4-H), 2.92 (mc, 1 H, 1'-H), 4.92 (t, J = 7.2 Hz, 1 H, 1-H), 5.16 (br t, J = 7.2 Hz, 1 H, 5-H). - ^{13}C NMR ($CDCl_3$): δ 17.89, 17.92 (2 q),

23.89 (t), 25.83, 25.86, 25.98, 26.05 (4 q), 27.82, 27.93, (2 t), 29.31, 29.34 (2 q), 29.59, 29.81, 30.61, 30.69 (4 t), 30.80, 30.92, 31.08, 31.46 (4 q), 37.29 (t), 41.19, 41.33 (2 d), 41.74 (s), 48.02, 52.54, 52.66 (3 d), 76.18 (s), 114.35, 114.65, 124.21, 124.25, (4 d), 131.21, 131.44, 155.26, 155.44 (4 s). - Mass spectrum (20 eV): m/z = 272 (76%, M^+-HCl), 257 (10), 229 (24), 203 (32), 149 (100), 123 (49), 93 (31).

1-Chloro-2-(3',3'-dimethylbicyclo[2.2.1]hept-2'-ylidene)ethane (8-Chloromethylcamphene) 3. 110 mL (1.32 mol) of 37% HCl was added within 1 h to a well stirred and cooled (0°C) solution of **10** (40.0 g, 192 mmol) in 60 mL of ether. The reaction mixture was stirred for 3 h at 0°C. The organic layer was separated, concentrated and distilled (41 - 42°C / 0.25 mbar) to give **3** as a colourless oil (32.9 g, 93%). - ^{1}H NMR ($CDCl_3$): δ 1.04, 1.06 (2 s, 6 H, 3'-CH_3), 1.19 - 1.77 (m, 6 H, 5',6',7'H), 1.95 (mc, 1 H, 4'-H), 3.05 (mc, 1 H, 1'-H), 4.14 (dd, J = 7.9 Hz, 1.7 Hz, 2 H, CH_2Cl), 5.22 (t, J = 7.9 Hz, 1 H, vinyl-H). - Mass spectrum (70 eV): m/z = 186, 184 (12%, 32%, M^+), 171, 169 (22, 68), 149 (87), 135 (37), 107 (65), 93 (100), 81 (46), 67 (45), 55 (40), 41 (64).

2-Chloro-2-methyl-5-(3',3'-dimethylbicyclo[2.2.1]hept-2'-ylidene)pentane 11. A solution of $ZnCl_2$ (3.40 g) in 4 mL of ether and 8 mL of CH_2Cl_2 was added to a precooled (-78°C) solution of isobutene (3.08 g, 54.9 mmol) in 35 mL of CH_2Cl_2. Compound **3** (9.25 g, 50.0 mmol) was added slowly with stirring and the reaction mixture was then kept at -78°C for 1 h. The cold mixture was washed with concentrated aqueous ammonia, dried (Na_2SO_4), concentrated and distilled (62 - 63°C/0.25 mbar) to give **11** (10.4 g, 86%) as pure colourless oil. - ^{1}H NMR ($CDCl_3$): δ 0.97, 1.00 (2 s, 6 H, 3'-CH_3); 1.58 (s, 6 H, $(CH_3)_2Cl$), 1.14 - 1.79 (m, 8 H, 3,5',6',7'-H), 1.88 (mc, 1 H, 4'-H), 2.12 - 2.24 (m, 2 H, 4-H), 2.93 (mc, 1 H, 1'-H), 4.88 (t, J = 7.3 Hz, 1 H, vinyl-H). - Mass spectrum (70 eV): m/z = 242, 240 (8%, 25%, M^+), 204 (30), 189 (28), 169 (18), 149 (90), 135 (52), 107 (64), 93 (100), 81 (58), 69 (57), 55 (49), 41 (86).

2-Methyl-5-(3',3'-dimethylbicyclo[2.2.1]hept-2'-ylidene)pentan-2-ol 5. A solution of **11** (3.60 g, 14.9 mmol in 5 mL of acetone) was added to a warm suspension of ZnO (0.57 g, 7.0 mmol) in 20 mL of 80% aqueous acetone and the reaction mixuture was refluxed for 15 h with stirring. The mixture was washed with water, extracted with CH_2Cl_2, concentrated and distilled at 72 - 75°C (bath)/0.20 mbar to give **5** (2.55 g, 77%) as a colourless viscous oil. - ^{1}H NMR ($CDCl_3$): δ 0.98, 1.00 (2 s, 6 H, 3'-CH_3); 1.13 - 1.70 (m, 8 H, 3,5',6',7'-H), 1.21 (s, 6 H, -$C(CH_3)_2OH$), 1.89 (br s, 2 H, 4'-H, OH), 2.04 - 2.12 (m, 2 H, 4-H), 2.94 (mc, 1 H, 1'-H), 4.91 (t, J = 7.3 Hz, 1 H, vinyl-H). - Mass spectrum (12.5 eV): m/z = 222 (7%, M^+), 204 (100), 189 (14), 161 (6), 149 (34).

2-Methyl-5-(3',3'-dimethylbicyclo[2.2.1]hept-2'-ylidene)pent-1-ene 6. Compound **11** (3.85 g, 16.0 mmol) was added to a well stirred suspension of potassium tert.butoxide (5.40 g, 48 mmol) in 35 mL of tert.butanol and refluxed for 30 h. The reaction mixture was cooled, poured over crushed ice, neutralized with 20% aqueous acetic acid, extracted with CH_2Cl_2, concentrated and distilled at 71 - 77°C (bath)/ 0.20 mbar to give **6** (3.04 g, 93%) as colourless oil. - ^{1}H NMR ($CDCl_3$): δ 0.97, 1.00 (2 s, 6 H, 3'-CH_3), 1.12 - 1.69 (m, 6 H, 5',6',7'-H), 1.72 (br s, 3 H, =C-CH_3), 1.86 (mc, 1 H, 4'-H), 2.01 - 2.18 (m, 4 H, 3,4-H), 2.90 (mc, 1 H, 1'-H), 4.68 (mc, 2 H, =CH_2), 4.88 (t, J = 6.8 Hz, 5-H). - Mass spectrum (70 eV): m/z = 204 (9%, M^+), 149 (100), 123 (18), 107 (31), 93 (87), 81 (56), 69 (29), 55 (38), 41 (43).

2-Methyl-5-(3',3'-dimethylbicyclo[2.2.1]hept-2-ylidene)pent-2-ene (Isosantalene) 7. Compound **11** (3.61 g, 15.0 mmol) was added to a well stirred suspension of tetrabutylammonium chloride (13.3 g, 48 mmol) in lutidine (2.46 g, 23 mmol) and 30 mL of acetone. The mixture was then stirred for 56 h at 75°C, cooled, poured onto crushed ice, acidified with 5% HCl, extracted with CH_2Cl_2 and concentrated. The crude product was distilled (40 - 43°C/0.2 mbar) to yield 2.70 g (88%) of a colourless oil (**7**:**6** = 74:26 by GC). - ^{1}H NMR ($CDCl_3$): δ 0.98, 1.00 (2 s, 6 H, 3'-CH_3), 1.09 - 1.72 (m, 6 H, 5',6',7'-H), 1.62, 1.69 (2 s, 6 H, -$C(CH_3)_2$), 1.87 (mc, 1 H, 4'-H), 2.68 (t, J = 7.2 Hz, 4-H), 2.93 (mc, 1 H, 1'-H), 4.85 (t, J = 7.2 Hz, 1 H, 5-H), 5.08 (br t, J = 7.2 Hz, 1 H, 3-H). - Mass spectrum (70 eV): m/z = 204 (8%, M^+), 149 (20), 121 (31), 117 (40), 107 (19), 93 (37), 67 (23), 55 (29), 43 (100), 41 (61).

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