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THE PREPARATION OF 4-ALKYLATED DERIVATIVES OF APOPINENE

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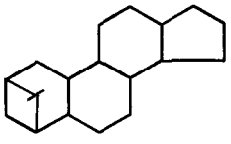
Abstract—Grignard reagents coupling with bromo-apopinene, which was prepared by NBS treatment of apopinene, leads to 4-alkylated derivatives of apopinene in high yields. Of particular interest is the convenient preparation of *trans* δ-pinene. The stereochemistry of these new compounds was established on the basis of NMR considerations.

We wish to report a convenient stereo-specific synthesis of new *trans*-4-substituted derivatives (**4**) of apopinene, which can be key-intermediates for obtaining polycyclic compounds of type **1**;† In addition, these derivatives (**4**) depending on the nature of R, are of potential interest for photochemical studies.[1,†]



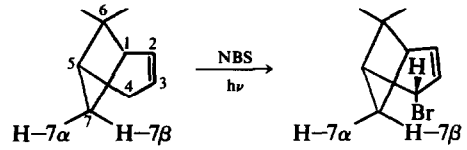
1

4

The starting material, *trans*-bromo-apopinene (**3**) was prepared free from the *cis*-stereoisomer, by NBS treatment of apopinene **2** ($[\alpha]_D - 45°$, cyclohexane) in nearly quantitative yield, based on recovered apopinene (actual yield was 76%).

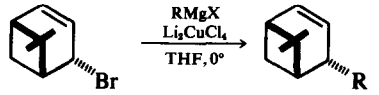
The *trans* configuration of compound **3** is the result of a stereoselective attack by the brominating agent to the opposed side of the *gem*-dimethyl bridge.[2,‡]

Further evidence of the *trans* configuration of the bromine atom is supported by the NMR spectrum of **3**, in which a 0·3 ppm deshielding of H-7β proton (doublet: $^2J = 9$ Hz) is observed[3] relative to the equivalent proton of apopinene, due to through-space interaction with the Br atom.



2 **3**

Coupling of Grignard reagents with allylic bromide **3**,[4] afforded derivatives of **4** in high yields. The Grignard reagents used and products obtained are summarized in chart I.



3 **4**

4a: R = CH_3—
4b: R = C_2H_5—
4c: R = CH_2=$C(CH_3)$—CH_2—
4d: R = C_6H_5—CH_2—
4e: R = *m*—HO—C_6H_4—CH_2—CH_2—

This method has the advantage of providing a particularly convenient synthesis of pure *trans*-δ-pinene. None of the methods hitherto proposed for the synthesis of this compound[6] have resulted in satisfactory yields of *trans*-δ-pinene.

An attempt to couple vinylmagnesium bromide and bromo-apopinene in the presence of $FeCl_3$[4] did not afford the expected iso-nopadiene **5** but mainly (66%) apopinene dimer **6**, which was also the only product of the reaction of magnesium with allylic bromide **3** (together with some starting material).

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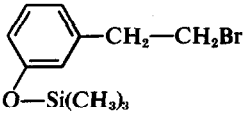
†Research in this area is in progress in our laboratories.

‡The stereochemistry of these systems is defined in relation to the *gem*-dimethyl bridge.

Chart I.

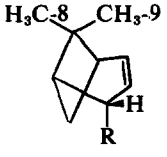
RX	Final compound	yield (%)
CH_3I	**4a**	86[a]
C_2H_5Br	**4b**	81[a]
$CH_2{=}C(CH_3){-}CH_2{-}Cl$	**4c**	88[b]
$C_6H_5{-}CH_2{-}Cl$	**4d**	86[b]
	**4e**	64[a,c]

[a]Actual yield based on purified (distilled) product.
[b]Calculated yield from VPC analysis.
[c]Cleavage of trimethylsilyl-ether was achieved simultaneously.[5]

Condensation of methyl acetoacetate with bromoapopinene **3** (sodium hydride, 65°, 12 hr) gave a quantitative yield of β-keto ester **7**.

Double treatment of methyl acetoacetate with sodium hydride in THF and with n-butyllithium generated the dianion $^{\ominus}CH_2{-}CO{-}\overset{\ominus}{C}H{-}COOCH_3$ which was readily alkylated with allylic bromide **3**, in 65% yield[7] to give β-keto ester **8**.

Chart II. Chemical shifts of *gem*-dimethyls (60 MHz spectrums, Solvent: CCl_4, δ, ppm)



	CH_3-8	CH_3-9
4a	1·28	0·90
4b	1·30	0·90
4c	1·31	0·88
4d	1·30	0·88
4e	1·30	0·90
7	1·30	0·95
8	1·30	0·95

Examination of the NMR spectra of **7** and **8** provides some evidence that the β-keto ester group on carbon **4** of the apopinene skeleton is *trans*- oriented by the analogy which exists between the chemical shifts of *gem*-dimethyls in compounds **4a**, **4b**, **4c**, **4d**, **4e**, **7** and **8**. (Chart II).

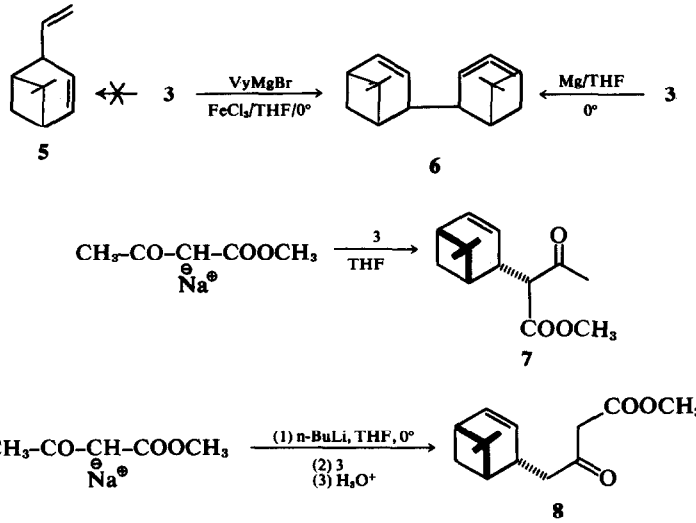
EXPERIMENTAL

All m.ps and b.ps are uncorrected. IR of liquid films were recorded on a Perkin-Elmer 257 spectrophotometer. NMR spectra were obtained on the Varian A 60 instrument using TMS as internal standard. They are reported in δ units (ppm, multiplicity, number of hydrogens). Analytic GLC was performed on an Aerograph 90 P apparatus. The column used was SE 52 silicone 16% on chromosorb AW-DMCS, 4 m long.

trans-4-Bromo-6,6-dimethyl-bicyclo[3.1.1]*hept-2-ene* **3**. Apopinene (48·8 g, 0·40 mole)[8] and benzoyl peroxide (150 mg) were stirred and heated under reflux in dry CCl_4 (500 ml) and N-bromosuccinimide (71·2 g, 0·40 mole) was added in two or three portions as soon as the exothermic reaction had started. The mixture was then heated under reflux for another hr. This mixture was cooled in an iced bath, and after removal of the succinimide by filtration, the CCl_4 was removed at 0° under reduced pressure. The resulting residue was dissolved in cold n-pentane (100 ml) then filtered, and the solvent was evaporated. Distillation of the residue gave 61·4 g (76%) of **3**: b.p. 80–81° (20 mm); IR (neat) 3045, 1615, 745 (c=c); NMR (CCl_4) δ 6·25 (m, 1, H_3), 5·70 (m, 1, H2), 4·92 (t, 1, H4), 1·37 (s, 3, Me-8), 0·94 (s, 3, Me-9).

trans-4-Methyl-6,6-dimethyl-bicyclo[3.1.1]*hept-2-ene* (**4a**) (*trans*-δ-pinene). MeMgI (0·170 mole, 3 equiv.), was prepared under dry N_2 from MeI (25·0 g, 0·176 mole) and Mg turnings (4·28 g) in dry THF. The mixture was cooled at 0° (ice-salt), and **3** (11·5 g, 57 mmoles) was added dropwise in 10 min. Then a soln of dilithium tetrachlorocuprate[4] (1·5 ml) was added, and the slurry was stirred for 3 hr at 0–5°. The mixture was hydrolysed with 0·1 N HCl, and extracted with ether.

The ethereal extract was dried ($MgSO_4$), concentrated, and distilled giving 6·6 g (86%) of *trans*-δ-pinene **4a**: b.p. 56–58° (20 mm) lit. (g) b.p. 54° (15 mm); IR (neat) 3030, 1625, 725, 712 (c=c); NMR (CCl_4) δ 6·10 (m, 1, H3),



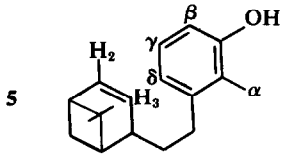
5·40 (m, 1, H2) 1·28 (s, 3, Me-8), 0·98 (d, 3, $J = 7$ Hz, Me-10), 0·89 (s, 3, Me-9).

trans-4-Ethyl-6,6-dimethyl-bicyclo[3.1.1]*hept-2-ene* **4b**. EtMgBr was prepared, at room temp, from EtBr (2·5 g, 23 mmoles, 3 equiv), and Mg turnings (550 mg), in dry THF (60 ml). A soln of bromo-apopinene (1·57 g, 78 mmoles) in 15 ml dry THF, was added at 0° to the stirred mixture, then 0·7 ml of dilithium tetrachlorocuprate soln[4] was added dropwise. The mixture was stirred at 0–5° for 3 hr, then hydrolysed with 0·1 N HCl, and extracted with ether. The ethereal extract was dried ($MgSO_4$), concentrated, and distilled, giving 0·95 g (81%) of **4b**; b.p. 60–62° (12 mm); IR (neat) 3030, 1625, 725, 712 (c=c); NMR (CCl_4) δ 6·12 (m, 1, H3), 5·50 (m, 1, H2), 1·30 (s, 3, Me-8), 0·93 (t, 3, $J = 7$ Hz, Me-11), 0·90 (s, 3, Me-9). (Found: C, 87·8; H, 12·0. $C_{11}H_{18}$ requires: C, 87·92; H, 12·07%).

trans-4-[2-Methylprop-2-ene]-yl-6,6-dimethyl-bicyclo [3.1.1]*hept-2-ene* **4c**. Methallylmagnesium chloride was prepared, at 5°, from methallylchloride 0·50 g, 5·5 mmoles, 1·1 equiv) and Mg turnings (135 mg) in dry THF (40 ml). A soln of bromo-apopinene (1 g, 5 mmoles) in 5 ml dry THF, was added at 0°, followed by 0·5 ml dilithium tetrachlorocuprate soln.[4] The slurry was stirred at 0–5° for 3 hr, then at room temp for 2 hr. After hydrolysis (0·1 N HCl), the mixture was extracted with ether. The ethereal extract was dried ($MgSO_4$), concentrated to give 0·90 g of a crude product, which consisted (VPC and NMR analysis) of 20% methallyl dimer and 80% **4c** (88% yield from **3**), which was separated as a colorless liquid; IR (neat) 3030, 1625, 735, 715 (-CH=CH-); 3075, 1645, 890 (vinyl); NMR (CCl_4) δ 6·17 (m, 1, H3), 5·60 (m, 1, H2), 4·82 (m, 2, CH_2=C), 1·30 (s, 3, Me-8) 0·88 (s, 3, Me-9). (Found: C, 88·6; H, 11·4. $C_{13}H_{20}$ requires: C, 88·56; H, 11·43%).

trans-4-Benzyl-6,6-dimethyl-bicyclo[3.1.1]*hept-2-ene* **4d**. Benzylmagnesium chloride was prepared from 400 mg (0·0165 atom-gram) Mg turnings, and 1·90 g benzyl chloride (15 mmoles) in dry THF. The soln was cooled to 0°, and a soln of bromo-apopinene (1 g, 5 mmoles) in 10 ml of dry THF was added, with 0·5 ml dilithium tetrachlorocuprate soln.[4] The mixture was stirred for 3 hr at 0–5°, then overnight at room temp. After hydrolysis (0·1 N HCl), the mixture was extracted with ether. The ethereal extracts were dried ($MgSO_4$) and concentrated, giving 1·73 g of a crude product, which consisted (VPC analysis) of 52% benzyl dimer, and 48% **4d** (86% yield from **3**), which was isolated as a colorless liquid; IR (neat) 3030, 1600, 1580, 1480, 750, 700 (aromatic), 1625, 725 (c=c); NMR (CCl_4), δ 7·10 (s, 5, aromatic protons), 6·10 (m, 1, H3), 5·50 (m, 1, H2), 2·65 (d, 2, $-CH_2$-Ph), 1·30 (s, 3, Me-8), 0·88 (s, 3, Me-9). (Found: C, 90·5; H, 9·5. $C_{16}H_{20}$ requires: C, 90·50; H, 9·49%).

trans-4-(m-Hydroxyphenethyl)-6,6-dimethyl-bicyclo [3.1.1]*hept-2-ene* **4e**. 2-(*m*-Trimethylsilyloxyphenyl)-1-bromoethane[5] (4·76 g, 17·5 mmoles) was added dropwise, in 3 hr, to a suspension of Mg turnings (460 mg) in 120 ml dry THF. Then, the dark organometallic mixture was stirred magnetically, cooled to 0°, and a soln of bromo-apopinene (3·55 g, 17·6 mmoles) in 25 ml dry THF, was added in 10 min, followed by 1 ml dilithium tetrachlorocuprate soln.[4] The mixture was stirred for 3 hr at 0°, then overnight at room temp. THF was distilled off, and 30 ml 70% aqueous EtOH was added dropwise. The mixture was then refluxed for 15 min. Work up afforded 4·35 g of crude product as a yellow oil. Molecular distillation yielded 2·72 g (64% from **3**) of colorless, partially crystallised product, which could be used without further purification. Purification by TLC on Merck HF 254 silicagel (eluent: benzene-acetone 5:1) gave pure **4e** which was sublimated as white cristals: m.p. 87–89°; IR (neat), 3350 (broad, phenol), 3030, 1620, 725 and 710 (C=C) 3040, 1600, 1580, 1480, 900 and 775 (aromatic); NMR ($CDCl_3$), δ 7·15 (m, 1, Hα), 6·70 (m, 3, Hβγδ), 6·18 (m, 1, H_3), 5·70 (m, 1, phenol proton), 5·55 (m, 1, H_2),



1·30 (s, 3, Me-8), 0·90 (s, 3, Me-9). (Found: C, 84·3; H, 9·1. $C_{17}H_{22}O$ requires: C, 84·27; H, 9·15%). Mass spectrum *m/e*: 242 (M^+) major peaks at M^+-15, M^+-43, M^+-99, base peak at *m/e* 43.

Methyl [6,6-*dimethyl-norpin-2-enyl*]*acetylacetate* **7**. Methyl acetoacetate (0·87 g, 7·5 mmoles) was added dropwise to a slurry of NaH (0·45 g of 50% oil dispersion) in 30 ml anhydrous THF at 0°. The mixture was stirred at this temp for 15 min, then bromo-apopinene (1·34 g, 6·6 mmoles) was added dropwise. The mixture was then stirred at 60° during 12 hr. Work up afforded 1·43 g (92% from **3**) of practically pure **7** (VPC analysis) as a pale yellow oil, IR (neat),† 3030, 1625, 730 and 712 (C=C), 1750 and 1715 (C=O); NMR (CCl_4),† δ 6·20 (m, 1, H_3), 5·40 (m, 1, H_2), 3·67 (s, 3, O-CH_3), 2·17 (s, 3, CH_3-CO), 1·30 (s, 3, Me-8), 0·95 (s, 3, Me-9).

Methyl 4-[6,6-*dimethyl-norpin-2-enyl*]-3-*oxobutanoate* **8**. Methyl acetoacetate (8·20 g, 51 mmoles) was added dropwise to a slurry of NaH (3·82 g of 50% oil dispersion) in dry THF at 0°. Stirring was maintained during 15 min at this temp, then n-BuLi (36 ml of 20% soln in hexane) was added dropwise at 0° in 10 min.[7] Bromo-apopinene (15·32 g, 76 mmoles) was added dropwise to the orange soln at 0°. The mixture was stirred at this temp for 2 hr, then at room temp for 1 hr. After treatment with 14 ml conc HCl, then 35 ml water, then 100 ml ether, the organic layer was washed with water until neutral then dried over $MgSO_4$. Distillation of the residue after removal of the drying agent and solvent gave 11·0 g (63% from **3**) of **8**, b.p. 118° (0·3 mm), as a yellowish liquid; IR (neat)† 3030, 1630, 730 and 710 (C=C), 1750 and 1720 (C=O); NMR (CCl_4),† δ 6·15 (m, 1, H_3), 5·40 (m, 1, H_2), 3·70 (s, 3, O-CH_3) 3·32 (s, 2, CO-CH_2-CO), 1·31 (s, 3, Me-8), 0·96 (s, 3, Me-9).

†Spectrum of the non-enolysed form.

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