SILICA AND ALUMINA CATALYSED REACTIONS OF SOME MONOTERPENE DERIVATIVES

C. R. Hughes, D. F. MacSweeney and R. Ramage

The Robert Robinson Laboratories, University of Liverpool

Abstract—Chromatography of some aryl alcohols, (11, 18, 25) derived from Grignard reactions on D(+)-camphor (10), carvone–camphor (20), and nopinone (24), has been shown to give products formed by migration of bond (b) or cleavage of bond (a). The reactions are stereospecific and selective, avoiding the complex mixtures, formed by normal acid-catalysed rearrangement of such systems. Alumina treatment has been found to give mixtures, in which the normal product of dehydration predominates.

REARRANGEMENT of the bornane and pinane ring systems often gives rise to many products and has provided excellent means of studying steric and electronic effects in rearrangements of bridged ring systems.[1] Paradoxically, these interesting mechanistic complexities pose a synthetic challenge to find conditions for selective rearrangements of these monoterpene ring systems.

Dehydration of 2-phenylisoborneol (1), with potassium hydrogen sulphate was found[2] to give 1-phenylcamphene (2), but further investigation[3] by Deno showed this to produce three components. This is not surprising since the intermediate carbonium ion, produced by protonation of 1, can deprotonate in two ways to give 2-phenylbornene (3) or, with rearrangement followed by proton-loss affording 1-phenylcamphene (2). The situation is further complicated by the possibility of acid-catalysed equilibration of the norbornene with the phenyltricyclene (4).[4] Later work by Kleinfelter[5] clarified the acid-catalysed equilibration of bicyclo[2:2:1]heptyl systems and confirmed the presence of camphene, bornene and tricyclene types. It was found that the proportions of each varied with the substituents at positions 2 and 3 of the isoborneol. Especially pertinent at this point, are the results obtained on acid-catalysed dehydration of 2-phenylisoborneol (1), which gave 60% 2-phenylbornene (3), 40% 1-phenylcamphene (2) together with 1% of the tricyclene derivative (4).

In the pinane series, it is known[6] that both *cis-* and *trans-*methylnopinols, (5 and 6) respectively, rearrange on treatment with acetic anhydride to give a mixture of fenchyl acetate (7), bornyl acetate (8) and terpenyl acetate (9). Similar products are obtained on hydrogen chloride treatment of 5 and 6 showing the propensity of the pinanols to rearrangement and ring-cleavage.

We sought to find a method of introducing some selectivity into the reactions of borneols and nopinols and chose the aryl-substituted derivatives as substrates because of their possible future synthetic utility and greater reactivity. D(+)-Camphor (10) was treated with 2-methoxy-5-methylphenylmagnesium bromide to give a mixture of products (11 and 12), from *endo* and *exo* attack of the Grignard reagent, in which the former largely predominated[8] due to the presence of the 7-*syn* Me

substituent of camphor (10). Crystallisation afforded the 2-arylisoborneol (11), in which the 7-*syn* Me group experiences deshielding in the NMR spectrum[9] due to the proximity of the *exo* OH function and is observed at 8·75 τ compared with the other Me substituents at C-7 and C-1, which were found at 9·13 τ. The minor product, the 2-arylborneol (12), showed three Me resonances between 9·00 and 9·10 τ. As expected from previous work, acid treatment of 11 gave a mixture of hydrocarbons, which could not be satisfactorily separated.
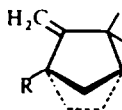
Adsorption catalysis on various types of surface e.g. clays,[10] or alumina-silica mixture[11] have been used to rearrange α-pinene (13) and norbornene derivatives. Passage of the 2-arylisoborneol (11) through Woelm grade I neutral alumina produced the 2-arylbornene (14) and the 1-arylcamphene (15) in the ratio 3:2. The 2-arylbornene (14) was also prepared by phosphorus oxychloride dehydration of 11 and showed the expected low field proton doublet at 4·22 τ. Chromatography of the 2-arylisoborneol (11) over silica gave the alternative product of rearrangement, 1-arylcamphene (15) almost exclusively (90% yield). The NMR spectrum showed the *exo*-methylene protons at 5·55 and 5·85 τ and this structural feature was corroborated by IR absorption at 890 cm⁻¹.

Chromatography over silica of the mixture of 11 and 12, isolated from the Grignard reaction, gave the 1-arylcamphene (15) followed by the pure 2-arylborneol (12), which was subsequently shown to be recovered substantially unchanged on further silica treatment, although a little (5%) of the 2-arylbornene (14) was produced from 12. Thus chromatography over silica proved to be a selective method of producing the camphene system. Further, the silica-catalysed reaction showed remarkable stereospecificity in that only the *exo* alcohol rearranged; a situation analogous to the greater reactivity of isoborneol (16) compared with borneol (17) found in solution reactions.[12]
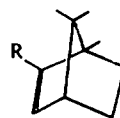
In order to investigate the effects of ring strain on these adsorption reactions, the aryl alcohols (18 and 19) were prepared from carvone-camphor (20). The ratio of *endo* to *exo* attack by the Grignard reagent was 3:2, as indicated by NMR. The cyclobutane ring in carbone-camphor (20) obviously eases the steric hindrance by the *syn* Me substituent towards *exo* attack at the CO function. Crystallisation gave the *exo*-3-aryl-2,6-dimethyltricyclo[3.2.1.0²·⁶]octan-3-ol (18) showing Me resonances
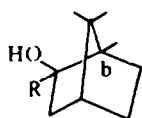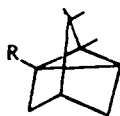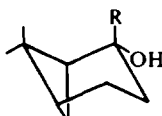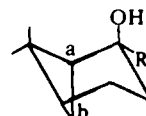

1. R = Ph
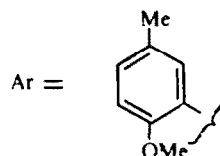11. R = Ar
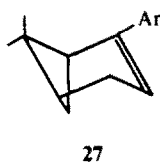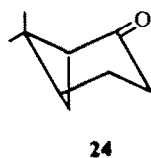16. R = H

2. R = Ph
15. R = Ar

3. R = Ph
14. R = Ar

4. R = Ph

5. R = Me

6. R = Me
25. R = Ar

7

8

9. $R_1 = Me$, $R_2 = Ac$
26. $R_1 = Ar$ $R_2 = H$

10

12. $R = Ar$
17. $R = H$

13

18. $R = Ar$

19. $R = Ar$

20

21 $R_1 = Me$, $R_2 = OH$
or
$R_1 = OH$, $R_2 = Me$

22

23

24

27

$Ar =$
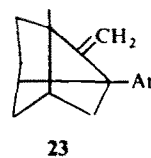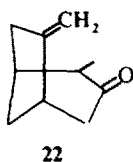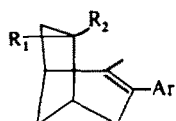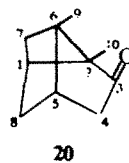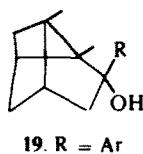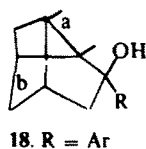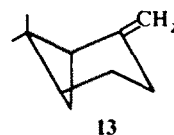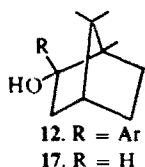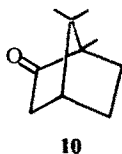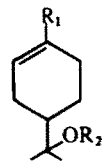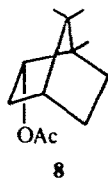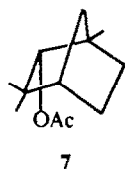
at 8·70 and 8·85 τ compared with the *endo* isomer (**19**), which had the corresponding NMR values at 8·97 and 9·17 τ.

Chromatography of the *exo*-alcohol (**18**) over silica afforded a small amount of olefinic material and as the major product, a crystalline tertiary alcohol, which showed no olefinic protons in the NMR spectrum. Apart from the Me substituents associated with the aryl moiety, two other Me groups were observed at 8·58 and 8·55 τ. The former is in agreement with a Me substituent on a carbon bearing oxygen and the latter is assigned to a vinyl Me group. Structure **21** is postulated for the rearrange-

ment product, although the stereochemistry of the OH function is unknown at present. The relatively high field of the vinyl Me in the NMR spectrum can be explained by shielding from the aryl moiety if the styrene chromophore were non planar. Support for this is given by the relatively low extinction of the styrene absorption in the UV at 282 nm (2,800). Thus rearrangement involves cleavage of bond (a) in contrast to the previous example of silica catalysed rearrangement of the 2-arylisoborneol (11). A close analogy for the formation of 21 is the conversion of carvone–camphor (20) to isocarvone–camphor (22) by the action of highly active alumina.[13] No products of migration of bond (b) could be identified from the silica treatment of 18, possibly due to the increased strain in the product (23) of such a rearrangement.

Since there were great differences in the reactivity of the 2-arylisoborneol (11) and the 2-arylborneol (12) towards rearrangement on silica, the *endo* alcohol (19) was also chromatographed over silica and found to be unreactive. The differing reactivities of the 2-arylisoborneol (11) and the 2-arylborneol (12) can be explained in terms of the favoured *trans* coplanar disposition of the migrating bond and the departing oxygen function. However, in the tricyclo[3.2.1.0^{2,6}]octyl series the observation was that the departing oxygen function is *cis* to the bond undergoing fission.

Only one epimer could be isolated from the reaction of the aryl Grignard reagent with nopinone (24) and this was assigned structure 25, since nopinone is normally attacked by nucleophilic rearrangements from the less hindered α-face.[7,14] Silica chromatography of 25 afforded analogous results to those obtained in the tricyclo [3,2,1,0^{2,6}]octyl series; a small amount of olefine and a tertiary alcohol as the major product. The structure 26 assigned to the latter is consistent with the NMR spectrum, which indicated two equivalent Me groups at 8·85 τ and an olefinic proton at 4·41 τ. The UV absorption at 281 nm (2,600) supported the presence of a styrene chromophore. Thus the major product (26), which was found to be resistant to dehydration on further silica treatment, results from cleavage of bond (a), which is *cis* to the departing oxygen function, followed by nucleophilic attack at the electron deficient centre formed. No products arising from migration of bond (b) were observed, nor those derived by cleavage of bond (b) an unlikely process, since this would formally require a primary carbonium ion intermediate.

Chromatography of 25 on Woelm (I) neutral alumina resulted in the formation of two olefins of which the normal dehydration product (27) predominated, in close agreement with the behaviour of the 2-arylisoborneol (11). The aryl nopinene (27) was isolated from phosphorus oxychloride dehydration of 26 under mild conditions and it is of interest to note that, under these conditions, (18) failed to dehydrate and was recovered unchanged.

The variation in the reaction on silica of 18 compared with 11 can be explained by the fact that formation of the cyclobutane ring distorts the molecule (18) so that bond (b) and the OH function are not perfectly *trans* coplanar, prerequisite for facile bond migration. Also, migration of bond (b) in 18 would lead to a highly strained ring system, again a consequence of the cyclobutane ring of carvone–camphor (20). In the case of 25, bond (b) is not coplanar to the OH substituent and this again precludes rearrangement. When concerted rearrangement is not possible, bond cleavage occurs if a tertiary carbonium ion intermediate is possible and, in the cases so far investigated, if the bond broken is *cis* to the departing oxygen function.

EXPERIMENTAL

All m.ps and b.ps are uncorrected. UV spectra were measured in EtOH soln on a Unicam SP 800 spectrometer. IR spectra were determined using a Unicam SP 200 spectrometer. NMR spectra were taken on a Varian A56–60A spectrometer, using TMS as an internal standard. Analytical GLC was carried out with a Perkin–Elmer F.11 gas chromatograph. Optical rotation measurements are for $CHCl_3$ solns using a Bendix–Ericsson ETL–NPL automatic polarimeter type 143.A.

Starting materials. Nopinone was kindly supplied by Dr. D. Whittaker, carbone–camphor was prepared by photolysis of carvone according to published procedures.[15] Light petroleum refers to the fraction bp 40°–60°. Silica was supplied by Silica Gel Ltd. (Grace).

2-(2-*Methoxy-5-methylphenyl*) *isoborneol* (11). A soln of 3-bromo-4-methoxytoluene[16] (80 g, 0·4 m) in anhydrous ether (100 ml) was added slowly with stirring to Mg filings (9·8 g, 0·4 g atom) covered with anhyd ether (100 ml). After the addition, and subsequent reflux for 1·5 hr to complete the formation of the Grignard reagent, the soln was cooled to 0°. D(+)-Camphor (61 g, 0·4 m) in ether (100 ml) was added slowly to the ice-cooled Grignard reagent, and the mixture refluxed for 1·5 hr. The complex was decomposed at 0° by a saturated aqueous solution of NH_4Cl. The ethereal layer was separated, dried over $NaSO_4$ and the solvent removed *in vacuo* to give an oil (107 g) as crude product.

Steam distillation of this material gave a viscous oil (42·5 g) as the non-steam volatile fraction which crystallised on standing. Low temperature crystallisation from light petroleum afforded 11 (30 g, 28%) m.p. 56°; $[\alpha]_D^{20}$ −32° ($CHCl_3$, c 4·5%); IR (melt) ν 3520 cm^{-1}; NMR (CCl_4) τ 5·15 (S, H, disappears on D_2O shake), 6·20 (S, 3H), 7·7 (S, 3H), 8·75 (S, 3H), 9·15 (S, 6H), 3–3·5 (M, 3H aryl). (Found: C, 78·77; H, 9·48. Calc. for $C_{18}H_{26}O_2$, C, 78·79; H, 9·55%).

Alumina treatment of 11. 2-Arylisoborneol 11 (4·0 g) was adsorbed on alumina (120 g Woelm Grade I neutral). Elution with benzene–light petroleum (111) afforded a hydrocarbon fraction (3·1 g, 83%), which was shown by NMR to be a 3:2 mixture of 14 and 15.

2-*Arylbornene* (14). 2-Arylisoborneol 11 (2·0 g) in pyridine (3 ml) was treated with $POCl_3$ (0·75 g) at 0° for 72 hr. Pentane (20 ml) was added followed by water (15 ml). After extraction the organic layer was washed with dil HCl then water and $NaHCO_3$ aq. Further washing with water and drying with Na_2SO_4 gave, on removal of the solvent, a colourless oil (1·6 g, 86%) b.p. 193°/15 mm; UV λ_{max} 286 nm (ε 3300); NMR (CCl_4) τ 4·22 (d, J = 3 c/s, H), 6·28 (S, 3H), 7·74 (S, 3H), 9·07 (S, 3H), 9·13 (S, 3H), 9·19 (S, 3H). (Found: C, 84·47; H, 9·72. Calc. for $C_{18}H_{24}O$, C, 84·32; H, 9·44%).

2-(2-*Methoxy-5-methylphenyl*) *borneol* (12). The mother liquors from crystallisation of 11 were chromatographed on silica (360 g, Grace silica, 200–300 mesh). After elution of less polar materials with benzene–light petroleum mixtures, the *endo* alcohol 12 was eluted with EtOAc as a viscous oil (5 g, 4·5%), which crystallised from light petroleum in prisms m.p. 94–95°; $[\alpha]_D^{20}$ −12° ($CHCl_3$, c 5%); IR (nujol) ν 3490, 3510 cm^{-1}; NMR (CCl_4) τ 5·35 (S, H, disappears on D_2O shake), 6·30 (S, 3H), 7·73 (S, 3H), 9·00 to 9·10 (3S, 9H). (Found: 79·10; H, 9·73. Calc. for $C_{18}H_{26}O_2$, C, 78·79; H, 9·55%).

Chromatography of 12 over silica (Grace, 200–300 mesh) gave no rearrangement and led to the recovery of starting material.

1-(2-*Methoxy-5-methylphenyl*) *camphene* (15). The 2-arylisoborneol (88 mg) was adsorbed on silica (11 g, Grace, 200–300 mesh). Elution 40% benzene in light petroleum afforded 15 (84 mg; 96%) as a crystalline solid m.p. 66–67° which crystallised from MeOH; $[\alpha]_D^{20}$ +46° ($CHCl_3$, c 5%); IR (melt) ν 890 cm^{-1} (*exo*-methylene); NMR ($CDCl_3$) τ 5·55 (S, H), 5·85 (S, H), 6·30 (S, 3H), 7·70 (S, 3H), 8·90 (S, 6H), 3–3·5 (M, 3H aryl). (Found: C, 84·05; H, 9·53. Calc. for $C_{18}H_{24}O$, C, 84·32; H, 9·44%).

exo-3-(2-*Methoxy-5-methylphenyl*) 2,6-*dimethyl-tricyclo*[3.2.1.0^{2,6}]*octan-3-ol* (18). The Grignard soln was prepared, as before, from 3-bromo-4-methoxytoluene (6·30 g) and Mg (0·80 g) in ether (15 ml). Carvone-camphor (4·0 g) in ether (15 ml) was added slowly to the ice-cold Grignard soln. After the initial reaction, the mixture was refluxed for 2 hr and the crude product isolated as in the preparation of 11. The crude material (5·5 g), after steam distillation, was a mixture of *endo* and *exo* alcohols (18 and 19) in the ratio 3:2, determined by NMR. Crystallisation from light petroleum–ether afforded *exo* 3-(2-methoxy-5-methyl-phenyl)2,6-dimethyl-tricyclo[3.2.1.0^{2,6}]octan-3-ol (2·5 g, 35%) m.p. 135°; $[\alpha]_D^{24}$ −24·3° ($CHCl_3$, 5%); IR ($CHCl_3$) ν 3500 cm^{-1}; NMR ($CDCl_3$) τ 6·18 (S, 3H), 7·76 (S, 3H), 8·70 (S, 3H), 8·88 (S, 3H), 3–3·5 (M, 3H aryl). (Found: C, 79·11; H, 8·87. Calc. for $C_{18}H_{24}O_2$, C, 79·37; H, 8·88%).

endo-3-(2-*Methoxy-5-methylphenyl*)-2,6-*dimethyltricyclo*[3.2.1.0^{2,6}]*octan-3-ol* (19). The crude *endo*-alcohol 19 was isolated from the mother liquors of the crystallisation of 18 and chromatographed on silica (100 g, Grace, 200–300 mesh). Elution with 40% benzene in light petroleum gave pure *endo*-alcohol 19 as a viscous oil (1·0 g, 14%). $[\alpha]_D^{27}$ −40° ($CHCl_3$, c 5%); IR (film) ν 3,550 cm^{-1}; NMR (CCl_4) τ 6·28

(S. 3H), 7·78 (S, 3H), 9·02 (S, 3H), 9·22 (S, 3H), 3-3·50 (M, 3H aryl). (Found C. 79·54 H, 9·08. Calc. for $C_{18}H_{24}O_2$. C, 79 37; H, 8·88%).

Chromatography of **19** over silica (Grace, 200–300 mesh) gave no rearrangement and led to the quantitative recovery of starting material.

3-(2-*Methoxy-4-methylphenyl*)-*2,6-dimethylbicyclo*[3.2.1]*octan-6-ol* (**21**). The *exo*-alcohol **18** (1·0 g) was chromatographed on silica (30 g, Grace, 200–300 mesh). Elution with light petroleum afforded a hydrocarbon (80 mg), which was shown by GLC (50 ft 15% carbowax capillary at 195°) to be essentially one product R_t 2·20 min) with a second minor constituent (R_t 1·87 min); IR (film) 890 cm^{-1} (exomethylene); NMR (CCl$_4$) τ 6·38 (S, 3H), 7·80 (S. 3H), 8·58 (m, 3H) 5·06, 5·19 (H,H, *exo*-methylene), 3-3·5 (m, 3H aryl). Mass spectrum showed a parent ion at 254 16762 ($C_{18}H_{22}O$ requires 254 16706).

Elution with 10% EtOAc in benzene gave crystalline **21** (350 mg, 31%) m.p. 102–105°, which crystallised from light petroleum; $[\alpha]_D^{27}$ −24°; IR (CHCl$_3$) 3550 cm^{-1}; NMR (τ) 6·30 (S, 3H) 7·75 (S, 3H), 8·5 (M, 6H), 3-3·5 (M, 3H aryl); UV λ_{max} 280 nm (ε 2850). (Found: C, 79·39; H, 8·88. Calc. for $C_{18}H_{24}O_2$. C, 79·37; H, 8·88%).

The rearranged alcohol **21** failed to give the above hydrocarbon fraction on repeated silica chromatography.

trans-2-(2-*Methoxy-5-methylphenyl*)-*nopin-2-ol* (**25**). Nopinone (4·0 g) in ether (5 ml) was added to the Grignard reagent from 3-bromo-4-methoxytoluene (7·03 g) and Mg (0·845 g) in ether (30 ml). After 3·5 hr reflux and work up as before. the alcohol **25** (4·7 g, 62%) m.p. 82–84° (pentane); $[\alpha]_D^{27}$ +15° (CHCl$_3$ c 5%). IR (CHCl$_3$) 3500 cm^{-1}. NMR (CCl$_4$) τ 6·33 (S. 3H), 7·78 (S, 3H), 8·72 (S. 3H). 8·80 (S, 3H, 3-3·5 (m, 3H aryl). (Found: C, 78 38; H, 9 32. Calc. for $C_{17}H_{24}O_2$. C, 78·42; H, 9·29%).

Silica rearrangement of **25**. Chromatography of **25** (1·5 g) on silica (30 g. Grace 200–300mesh) afforded an early olefine fraction (300 mg) then, on elution with EtOAc. the major product **26** (870 mg, 61%) b.p. 146°·0·08 mm; $[\alpha]_D^{27}$ −16° (CHCl$_3$ c 5%); IR (film) 3450 cm^{-1}. UV λ_{max} 282 nm (ε 2820); NMR τ 4·40 (m, H), 6·35 (S, 3H), 7·80 (S, 3H), 8·85 (S, 6H), 3·0-3·5 (M, 3H aryl). (Found: C, 78·12 H, 9·45. Calc. for $C_{17}H_{24}O_2$. C. 78·42; H. 9·29%).

The tertiary alcohol **26** was stable to further silica treatment.

Phosphorus oxychloride dehydration of **25**. The arylnopinol **25** (500 mg) in pyridine (2 ml) was treated with POCl$_3$ (2 0 g). After work up as for the preparation of **14**, the olefine **27** (450 mg, 94%) was obtained; $[\alpha]_D^{25}$ 26° (CHCl$_3$ c 0 5%); UV λ 287 nm (ε 3450); NMR 4·48 (M, H), 6·30 (S, 3H), 7·75 (S, 3H), 8·68 (S, 3H), 9·03 (S, 3H), 3·0-3·50 (M, 3H aryl). (Found: C, 84·12; H, 8·95. Calc. for $C_{17}H_{22}O$. C, 84·25; H, 9·15%).

Alumina treatment of **25**. The arylnopinol (1·0 g) chromatographed on alumina (30 g, Woelm Grade 1 neutral). Elution with light petroleum–benzene (1:1) afforded a hydrocarbon fraction (750 mg, 7 %), containing two components as shown by GLC on carbowax capillary (50 ft, temp 200°, N$_2$ carrier gas 30 lbs/in^2). The main (84%) product was the normal dehydration product **27** and the minor product shown by GLC to be identical with the product of phosphorus oxychloride dehydration of **26**.

REFERENCES

[1] For reviews. " C. K. Ingold. *Structure and Mechanism in Organic Chemistry*. p. 482. Cornell University Press. Ithaca, N.Y. (1953);
   [b] J. A. Berson. *Molecular Rearrangements I* (Edited by de Mayo), p. 111. Interscience, N.Y. (1963);
   [c] D. V. Banthorpe and D. Whittaker, *Quarterly Reviews* XX, 373 (1966)
[2] S. S. Nametkin. H. S. Kichkina, and D. N. Kursanov. *J. Russ. Phys.-Chem. Soc.* **61**, 1065 (1929)
[3] N. C. Deno. P. T. Groves. J. J. Jarnzelski. and M. N. Lagasch, *J. Am. Chem. Soc.* **82**, 4719 (1960)
[4] P. von R. Schleyer, *Ibid.* **80**, 1700 (1958)
[5] D. C. Kleinfelter, R. W. Aaron. T. J. Gerteisen, J. M. Miller, Jr., and T. B. Bennett, Jr., *J. Org. Chem.* **32**, 3521 (1967)
[6] W. D. Burrows and R. H. Eastman. *J. Am. Chem. Soc.* **81**, 245 (1959)
[7] W. Huckel and H. Gelchsheimer. *Liebigs. Ann.* **625**, 12 (1959)
[8] K. Alder. G. Stein, and H. F. Rickert, *Ibid.* **525**, 221 (1936)
[9] K. Tori. Y. Hamshima, and A. Takamizawa, *Chem. Pharm. Bull.* **12**, 924 (1964)
[10] V. P. Wystrach. L. H. Barnum, and H. Garber, *J. Am. Chem. Soc.* **79**, 5786 (1957)

[11] G. A. Rudakov, and M. M. Shestaeva, *Zh. Obshchei Khim.* **29**. 2062 (1959)

[12] J. Simonsen, and L. N. Owen, *The Terpenes* Vol. II, p. 349. Cambridge University Press (1949)

[13] G. Buchi, and I. M. Goldman, *J. Am. Chem. Soc.* **79**. 4741 (1957)

[14] T. W. Gibson, and W. F. Erman, *Ibid.* **91**. 4771 (1969)

[15] J. Meinwald, and R. A. Schneider, *Ibid.* **87**. 5218 (1965)

[16] M. S. Carpenter and W. M. Easter, *J. Org. Chem.* **20**. 401 (1955)