Pergamon

Tetrahedron Vol. 50, No. 29, pp. 8781-8792, 1994

0040-4020/94 $7.00+0.00

0040-4020(94)00474-9

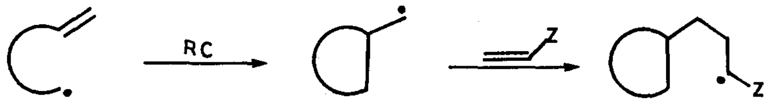
A Regiospecific Radical Annulation Strategy to Functionalised Chiral Bicyclo[3.3.1]nonanes[1]

Adusumilli Srikrishna,*
Parthasarathy Hemamalini and Somepalli Venkateswarlu

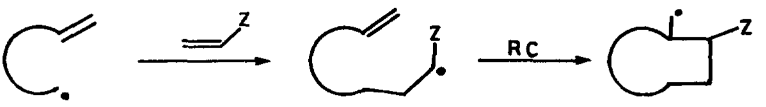
Department of Organic Chemistry, Indian Institute of Science
Bangalore - 560 012, India.

ABSTRACT: A radical annulation, i.e. an intermolecular radical Michael addition followed by an intramolecular Michael addition of the resultant radical (radical cyclisation) has been employed for the construction of chiral functionalised bicyclo[3.3.1]-nonanes. Thus reaction of carvone hydrohalides 7 with ^{n}Bu$_3$SnH and AIBN in the presence of excess of radicophiles 4 furnished, regiospecifically bicyclo[3.3.1]nonanes 8-14, introducing three new chiral centres in a stereoselective manner. Analogously the bromide 18 generated the bridgehead substituted bicyclo[3.3.1]-nonanes 19-21.

In the last decade, there has been an upsurge of interest in the application of radical mediated addition reactions in organic synthesis. Both inter- and intramolecular radical additions to olefinic and acetylenic systems have been employed for the synthesis of various functional moieties and also to a variety of natural products.[2] A combination of inter- and intramolecular radical additions in a single sequence, to achieve highly functionalised molecules, is appealing from a synthetic standpoint. The most straight forward approach involves sequencing of a rapid intramolecular addition, i.e. radical cyclisation (R.C), followed by an intermolecular trapping of the cyclised radical (Eq. 1). On the other



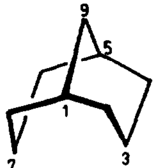
(Eq. 1)



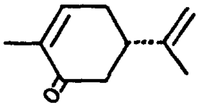
(Eq. 2)

hand, the reverse sequence, *i.e.* an intermolecular addition of a radical onto a radicophile followed by the intramolecular addition of the resultant radical (radical cyclisation) can provide functionalised ring systems from acyclic precursors (Eq. 2), and the overall sequence results in an annulation.[3] However, in the design of such processes, reactivity and selectivity requirements for each intermediate radical must be carefully assessed.

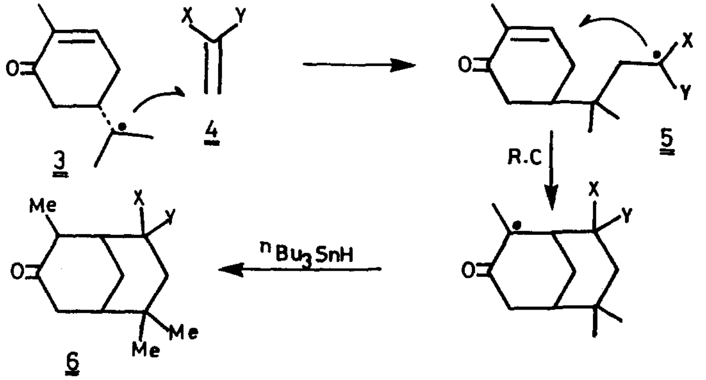
The bicyclo[3.3.1]nonane ring system (**1**) is present in several natural products, in particular terpenoids and alkaloids. This ring system has received considerable attention from both synthetic[4] as well as theoretical[5] point of view. In addition, these bridged compounds have also been utilised as synthons for the construction of other interesting ring systems, enroute to various natural products.[6] In continuation of our interest in the synthesis of chiral bridged systems employing radical mediated reactions,[3,7] herein we describe a radical annulation methodology (Eq. 2) for the construction[7a] of functionalised bicyclo[3.3.1]nonane derivatives starting from carvone (**2**).



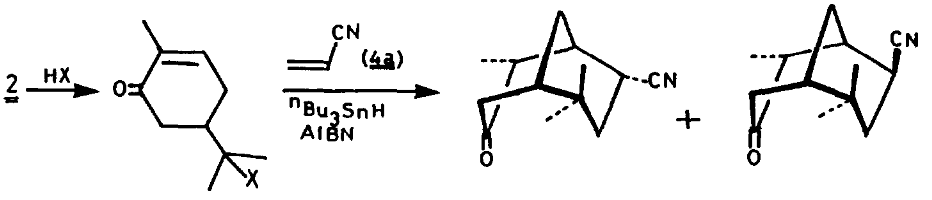
1



2



It was anticipated that the nucleophilic tertiary radical **3**, derived from carvone (**2**), can add to an electrophilic radicophile **4** in an intermolecular Michael fashion resulting in a new radical **5**, which can undergo a 6-*exo* trig cyclisation followed by abstraction of hydrogen from ^{n}Bu$_3$SnH leading to the regiospecific formation of bicyclo[3.3.1]nonane system **6**. The tertiary halides **7a** and **7b** were opted as the radical precursors. The regiospecific addition of freshly generated gaseous HBr to the electron rich double bond of (S)-carvone (**2**) furnished the carvone hydrobromide **7a**.[8] Whereas, reaction of (S)-carvone (**2**) with an *in situ* generated HI (TMSCl-NaI-H$_2$O)[9] in acetonitrile afforded the iodide **7b** in 32% yield. As anticipated, refluxing a 0.02 molar benzene solution of the bromide **7a** with 1.1 equivalents of tri-n-butyltin hydride and 5 equivalents of acrylonitrile

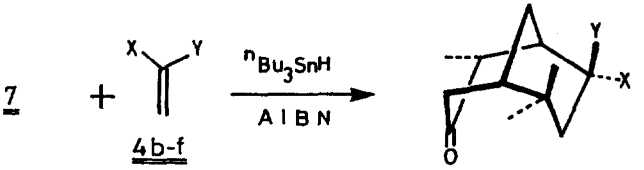


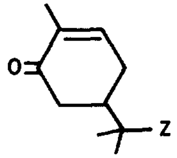
7a. X = Br
7b. X = I

8 **9**

(**4a**) in the presence of a catalytic amount of AIBN for 30 minutes furnished the bicyclic keto-nitriles **8** and **9** in 68% yield, in 2:1 ratio. The conformation and structure of the products were deduced from their spectral data. The mass spectrum of both keto-nitriles **8** and **9** showed the molecular ions at 205 ($C_{13}H_{19}NO$) representing 1:1 adducts. The IR spectrum of **8** showed bands due to nitrile (2250) and cyclohexanone (1700 cm^{-1}) moieties. The absence of olefinic proton and olefinic carbon resonances in the ^1H and ^{13}C NMR spectra confirmed the cyclic structure of the product. The ^1H NMR spectrum revealed a signal at δ 2.96 due to the N≡C–CH, a doublet at 1.39 for the secondary methyl group, two singlets at 1.05 and 0.99 ppm for the two methyl groups at C–8 in addition to other expected resonances. The ^{13}C NMR spectrum exhibited resonances at δ 211.6 (s, C=O), 121.8 (s, C≡N), 48.3 (d, CH–C=O), 40.8 (d, CH–C≡N), 34.7 (t, C–9), 28.1 (q) and 27.1 (q) (2 x *tert*–Me), 12.8 (q, *sec*–Me) ppm establishing the structure of the keto-nitrile **8**. The twin chair conformation was assigned based on the triplet resonance at δ 34.7 ppm for the C–9 carbon in the ^{13}C NMR spectrum, as it was well established[10] that the resonances due to C–9 appear at *ca*. δ 34.4, 28.6 and 23.7 ppm for the twin chair, boat chair and twin boat conformations of the bicyclo[3.3.1]nonanes respectively. The isomeric keto-nitrile **9** exhibited bands at 2240 (C≡N) and 1715 cm^{-1} (C=O) in the IR spectrum and in the ^1H NMR spectrum appearance of a doublet at δ 2.92 ($J_{6eq,7ax}$ 6 Hz) for N≡C–CH, a methyl doublet at 1.07 ppm (J 6.5 Hz) in addition to other resonances indicated that the structure is complimentary to that of **8** and hence axial orientation was assigned to the cyano group at C–6. The presence of resonances at δ 211.8 (s, C=O), 123.0 (s, C≡N), 47.6 (d, CH–C=O), 44.1 (t, CH_2–C=O), 41.5 (d, CH–C≡N), 40.0 (d, C–1) 33.7 (s, C–Me_2), 32.4 (t, C–9), 29.6 (q) and 28.2 (q) (2 x *tert*–Me) and 11.9 ppm (q, *sec*–Me) in the ^{13}C NMR spectrum confirmed the structure of the keto-nitrile **9**.

To test the generality of the methodology, radical annulation reactions were carried out with several other radicophiles (**4b–f**). Thus reaction of the bromide **7a** with ^{n}Bu$_3$SnH and AIBN in the presence of methyl acrylate (**4b**), methyl vinyl ketone (**4c**), styrene (**4d**), α-methylacrylonitrile (**4e**) and α-chloroacrylonitrile (**4f**) furnished the annulated products, bicyclo[3.3.1]nonanes **10**-**14**, respectively in a highly stereoselective manner, in contrast to that of the reaction with acrylonitrile. The structures of the annulated products **10**-**14** were derived from the comparison of their spectral data with that of the keto-nitriles **8** and **9**. The stereochemistry at C-2 and 6 were assigned based on the various H-H coupling constants[11] in the interrelated (270 MHz) ^{1}H NMR spectra of the products **8**, **10**-**14**. Thus, the presence of a trans diaxial coupling (13 Hz) for the C-6 proton in **8** at δ 2.96 ppm (ddd, *J* 13, 4.6 and 2.8 Hz) fixed the equatorial orientation of the cyano group. Similarly, the equatorial orientation of the methyl group at C-4 was assigned based on the quintet resonance for the C-4 axial proton in **10** at δ 2.49 ppm (*J* 6 Hz), as the $J_{4eq,5}$ will be less than 2 Hz,[11d] based on dihedral angles. The diequatorial orientation of the groups (X and Me) at C-6 and 4 was further confirmed by the upfield shift of the methyl doublet (δ 0.40 ppm) in the annulated product **12** as a result of the shielding effect due to the C-6 phenyl ring.





10. X = COOMe Y = H
11. X = COMe Y = H
12. X = Ph Y = H
13. X = Me Y = CN
14. X = Cl Y = CN

15. Z = H
16. Z = CH_2CHXY

To improve the efficiency of the reaction several other variations were attempted, *e.g.* the iodide **7b** was employed in the place of the bromide **7a**; the use of the *in situ* generated catalytic ^{n}Bu$_3$SnH (^{n}Bu$_3$SnCl, NaBH$_3$CN, ^{t}BuOH)[12] in the presence of an excess of radicophile; simultaneous addition of the solutions of ^{n}Bu$_3$SnH and the radicophile in benzene to a refluxing solution of the bromide **7a**; slow addition of a solution of ^{n}Bu$_3$SnH and AIBN in benzene to a refluxing solution of the bromide **7a** and the radicophile; and the results are summarised in Table I. In general, the bromide **7a** was found to be a better radical precursor than the iodide **7b**, perhaps due to rapid decomposition of **7b**. In addition to the annulated products varying amounts of dihydrocarvone (**15**) and the uncyclised adducts **16** were also formed from competing side reactions, namely the reduction of the intermediate radicals **3** and **5**. The formation of mainly thermodynamic

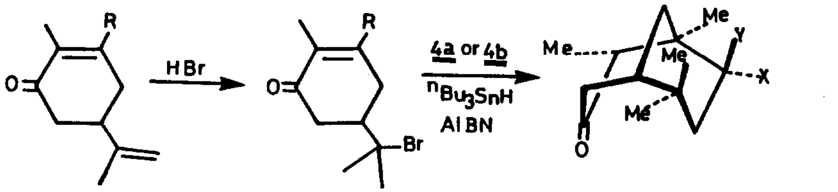
Table I: Chiral Bicyclo[3.3.1]nonan-3-ones *via* Radical Annulation

Halide	Radicophile	Product	Method^{a}	Yield (%)^{b}	m.p. (°C)
7a			A	68^{c}	
7a	**4a**	**8**	B	32	102
7b		**9**	A	56^{d}	70
7a			A	42^{c}	
7a	**4b**	**10**	B	34	98
7b			A	48^{f}	
7a			A	38(85)	
7a	**4c**	**11**	B	25(45)	110
7a			C	30(40)	
7b			A	46	
7a	**4d**	**12**	D	36^{g}	125
7b			D	46^{d}	
7a	**4e**	**13**	D	53^{d}	110
7b			D	40	
7a			A	41(63)	
7a	**4f**	**14**	C	42(73)	liq.
7b			A	51	
18	**4a**	**19**	D	61^{h}	172
		20			liq.
18	**4b**	**21**	D	52	liq.

a. see experimental section. **b.** Yields in parenthesis are based on the recovered starting material. **c.** 2:1 mixture of **8** & **9**; **d.** 15% of **15** was also isolated; **e.** 37% of **16b** was also isolated; **f.** 33% of **15** was also isolated; **g.** 52% of **15** was also isolated; **h.** 6:1 mixture of the keto-nitriles **19** and **20**.

products can be explained by a product like transition state in the cyclisation of the radical **5**. Since the 6-*exo* trig cyclisation of the adduct radical **4** resulted in the formation of a stable electrophilic radical which abstracted hydrogen from $^{n}Bu_3SnH$ without adding to one more molecule of the radicophile. Intramolecular addition of the electrophilic radical **5** on to the enone is in line with the Giese's suggestion[13] of borderline nature of carbon radicals containing one electron withdrawing group.

In order to test the feasibility of this radical annulation methodology for the creation of one more quaternary carbon atom and in particular to construct the bridgehead methyl substituted bicyclo[3.3.1]nonanes, the readily available[14] β-methylcarvone **17** was opted as the starting material. Thus, addition of freshly generated gaseous HBr to β-methylcarvone **17**



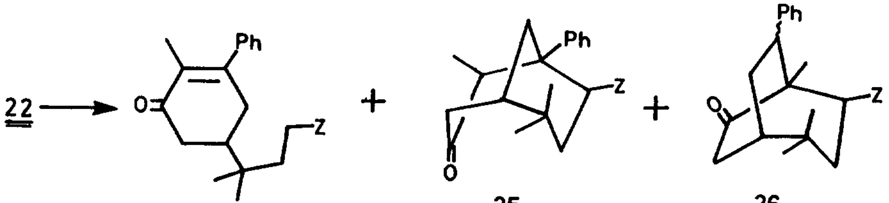
17. R = Me
23. R = Ph

18. R = Me
22. R = Ph

19. X = CN, Y = H
20. X = H, Y = CN
21. X = COOMe, Y = H

furnished the requisite radical precursor, bromide **18** in 62% yield. The radical annulation reaction of the bromide **18** with ^{n}Bu$_3$SnH (1.1 equiv.) and AIBN (catalytic) in the presence of an excess of acrylonitrile (**4a**) furnished, as expected the isomeric keto-nitriles **19** and **20** in 61% yield in 6:1 ratio. In a similar manner the keto-ester **21** was obtained in 52% yield by employing methyl acrylate (**4b**) as the radicophile. The structures of the annulated products were established by comparison of their spectral data with those of **8** and **9**.

In order to investigate the possibility of construction of bicyclo-[3.2.2]nonane system via the 7-*exo* cyclisation of the radical **5** the sequence has been carried out with the corresponding phenyl derivative.[15] However, in contrast to our expectations, reaction of the bromide **22**, derived from β-phenylcarvone **23**, with ^{n}Bu$_3$SnH and AIBN in the presence of an excess of either acrylonitrile or methyl acrylate resulted in a mixture of products (by NMR) containing mainly the uncyclised addition product **24** with only trace amounts of annulated products **25** and **26**.



24 **25** **26**

Z = CN or COOMe

In conclusion, a radical annulation methodology has been developed for the regiospecific formation of bicyclo[3.3.1]nonane ring system with simultaneous formation of three new stereocentres (C–4, 5 and 6) starting from only one chiral centre in a stereoselective manner. This methodology has the flexibility for the formation of chiral 4,8,8-trimethylbicyclo-[3.3.1]nonan-3-ones with a variety of functional groups at C–6, and also can be extended to bridgehead methyl substituted systems.

EXPERIMENTAL SECTION

IR spectra were recorded on Perkin-Elmer 781 and Hitachi 270-50 spectrophotometers. ^{1}H (90, 270 MHz) and ^{13}C NMR (22.5 MHz) spectra were recorded on JEOL FX-90Q and Brucker WH-270 spectrometers. The chemical shifts (δ ppm) and the coupling constants (Hz) are reported in standard fashion with reference to either internal tetramethylsilane (for ^{1}H) or the central line (77.1 ppm) of $CDCl_3$ (for ^{13}C). In the ^{13}C NMR spectra off-resonance multiplicities, when recorded, are given in parentheses. Low and High-resolution mass measurements were carried out with a JEOL JMS-DX 303 GC-MS instrument using a direct inlet mode. Optical rotations for *ca* 0.5-1.0% solutions were measured using a Jasco DIP-303 polarimeter. Acme's silica gel (100-200 mesh) was used for column chromatography. Dry benzene was obtained by washing with H_2SO_4 followed by distillation over sodium, and stored over sodium wire. Dry *tert*-butanol was obtained by distillation over sodium. Acrylonitrile, methyl acrylate, methyl vinyl ketone, styrene, α-methacrylonitrile and α-chloroacrylonitrile were distilled prior to use. AIBN was recrystallised from methanol. Prior to the radical annulation reactions, hexane solutions of the halides **7a-b** were washed with 10% aq. NaOH solution to remove the 5-isopropyl-2-methylphenol, the decomposition product of the halides **7**.

(S)-5-(2-Iodoprop-2-yl)-2-methylcyclohex-2-en-1-one *(**7b**)*: To a magnetically stirred solution of sodium iodide (1.8 gm, 12 mmol) in MeCN (15 ml) were added sequentially trimethylchlorosilane (1.5 ml, 12 mmol), water (0.1 ml, 6 mmol) and (S)-carvone (**30**, 1.5 gm, 10 mmol), and the solution was stirred at room temperature for 1 hr. The reaction was quenched with water (20 ml) and extracted with ether (20 ml x 3). The ether layer was washed with aqueous $Na_2S_2O_3$ solution (10 ml x 3) followed by brine and dried (Na_2SO_4). Solvent was evaporated and the residue was taken in hexane (30 ml), washed with 10% aqueous NaOH solution (10 ml x 2) followed by brine and dried (Na_2SO_4). The solvent was removed under reduced pressure to furnish the iodide **36** (875 mg, 32%) as a pale yellow oil. The iodide was used immediately for reactions. IR (neat): ν_{max} 1675, 1370, 1100 cm^{-1}. ^{1}H NMR (90 MHz, $CDCl_3$): δ 6.76 (1 H, m, C=CH), 2.1-2.9 (5 H, m), 1.98 (3 H, s) and 2.0 (3 H, s) [$(CH_3)_2$ C–I], 1.8 (3 H, s, C_7–Me).

General methods of radical annulation reactions:

Method A: To a 0.02 M solution of the halide **7** in dry benzene, $^nBu_3SnH$ (1.1 *equiv*), freshly distilled radicophile **4** (5 *equiv*) and AIBN (catalytic) were added, and the reaction mixture was refluxed for 30-45 min. The reaction mixture was cooled, washed with 1% aqueous NH_4OH solution (20 ml x 3) followed by brine and dried (Na_2SO_4). Solvent was removed under reduced pressure and the products were purified by column chromatography.

Method B: To a 0.2 M solution of the halide **7** in *tert*-butanol, $^nBu_3SnCl$ (0.1 *equiv*), $NaBH_3CN$ (1.2 *equiv*), freshly distilled radicophile (5 *equiv*) and AIBN (catalytic) were added. The reaction mixture was refluxed for 1 hr and worked-up as described in method A.

Method C: To a refluxing 0.1 M solution of the halide **7** in dry benzene (10 ml) was added simultaneously a 0.05 M solution of $^nBu_3SnH$ (1.1 *equiv*) and AIBN (catalytic) in dry benzene, and a 0.25 M solution of the radicophile (5 *equiv*) in dry benzene over a period of 30 min. The reaction mixture was

refluxed further for 60 min and worked-up as described in method A.
Method D: To a refluxing 0.05 M solution of the halide **7** and freshly distilled radicophile (5 *equiv*) in dry benzene was added a 0.03 M solution of ^{n}Bu$_3$SnH (1 *equiv*) and AIBN (catalytic) in dry benzene over a period of 30 min. The reaction mixture was refluxed further for 15 min and worked-up as described in method A.

*(+)-(1S,4R,5S,6R) & (−)-(1S,4R,5S,6S)-6-Cyano-4,8,8-trimethylbicyclo[3.3.1]nonan-3-ones (**8** & **9**):* Radical annulation reaction of the bromide **7a** (231 mg, 1 mmol) with ^{n}Bu$_3$SnH (0.27 ml, 1 mmol), acrylonitrile (**4a**, 0.33 ml, 5 mmol) and AIBN (catalytic) for 30 min using the method A followed by purification of the products over a silica gel (15 g) column using ethyl acetate-hexane (1:3) as eluent furnished the annulated products **8** & **9** (2:1, 139 mg, 68%) as colourless solids and were recrystallised from hexane.

Compound 8: m.p. 102°C; $[\alpha]_D^{26}$: +30° (CHCl$_3$); IR (CCl$_4$) ν_{max}: 2250, 1700, 1370, 1180, 1090, 1020, 740 cm^{-1}. ^{1}H NMR (270 MHz, CDCl$_3$): δ 2.96 (1 H, ddd, *J* 13, 4.6 and 2.8, C$\underline{H}$–CN), 2.72 (1 H, t of ½ AB q, *J* 15.7 and 2.5, 2–H eq), 2.65 (2 H, m, 4,5–H), 2.38 (1 H, d of ½ AB q, *J* 15.6 and 5.6, 2–H ax), 2.14 (1 H, q of ½ AB q, *J* 14 and 3, 9–H a), 1.97 (1 H, t of ½ AB q, *J* 14 and 2.8, 9–H b), 1.9 (1 H, br s, 1–H), 1.55 (1 H, dd, *J* 13 and 4.5, 7–H eq), 1.45 (1 H, t, *J* 13, 7–H ax), 1.39 (3 H, d, *J* 6.8, *sec*–Me), 1.05 (3 H, s) and 0.99 (3 H, s) (2 x *tert*–Me). ^{13}C NMR (22.5 MHz, CDCl$_3$): δ 211.6 (s, C=O), 121.8 (s, C≡N), 48.3 (d), 43.8 (t, CO$\underline{C}$H$_2$), 40.8 (d), 38.6 (d), 34.7 (t, C–9), 33.5 (s, C–8), 31.7 (t), 28.1 (q) and 27.1 (q) (2 x *tert*–Me), 26.7 (d), 12.8 (q, *sec*–Me). Mass: m/z 205 (M$^+$), 190 (M$^+$–15, 10%), 178 (22), 110 (45), 109 (100), 95 (25) and 81 (60). HRMS: Found: M$^+$, 190.1214. C$_{12}$H$_{16}$NO (M$^+$-Me) requires 190.1232.

Compound 9: m.p. 70°C; $[\alpha]_D^{26}$: −20° (CHCl$_3$); IR (CCl$_4$): ν_{max} 2240, 1715, 1370, 1385 cm^{-1}. ^{1}H NMR (270 MHz, CDCl$_3$): δ 2.92 (1 H, br d, *J* 6, C$\underline{H}$–CN), 2.67 (1 H, d, *J* 15.5, 2–H eq), 2.45-2.6 (3 H, m), 2.38 (1 H, d of ½ AB q, *J* 15.5 and 6, 2–H ax), 1.96 (2 H, br s, 9–H$_2$), 1.52 (1 H, ½ AB q, *J* 15.5, 7–H eq), 1.29 (3 H, s) and 0.92 (3 H,s) (2 x *tert*–Me), 1.22 (1 H, d of ½ AB q, *J* 15.5 and 6, 7–H ax), 1.07 (3 H, d, *J* 6.5, *sec*–Me). ^{13}C NMR (22.5 MHz, CDCl$_3$): δ 211.8 (s, C=O), 123.0 (s, C≡N), 47.6 (d), 44.1 (t, CO$\underline{C}$H$_2$), 41.5 (d), 40.0 (d), 33.7 (s, C–8), 32.4 (t, C–9), 29.6 (q), 28.2 (2 C, t and q), 25.0 (d), 11.9 (q, *sec*–Me). Mass: m/z 205 (M$^+$, 100%), 190 (M$^+$–Me, 15), 178 (27) and 109 (95). Anal: Found: C,76.06; H,9.33; N,6.82%. C$_{13}$H$_{19}$NO requires C,76.07; H,9.63; N,6.85%.

*(+)-Methyl (1S,4R,5R,6R)-4,8,8-trimethylbicyclo[3.3.1]nonan-3-one-6-carboxylate (**10**):* Radical annulation reaction of the bromide **7a** (231 mg, 1 mmol) with ^{n}Bu$_3$SnH (0.27 ml, 1 mmol), freshly distilled methyl acrylate (**4b**, 0.45 ml, 5 mmol) and AIBN (catalytic) in dry benzene (50 ml) using the method A followed by purification of the product mixture over a silica gel (15 g) column with ethyl acetate-hexane (1:9) as eluent furnished the uncyclised adduct **16b** (88 mg, 37%) as a pale yellow oil. ^{1}H NMR (90 MHz, CDCl$_3$): δ 6.76 (1 H, m, olefinic), 3.68 (3 H, s, COOCH$_3$), 1.79 (3 H, s, C$_2$–Me), 1.0–2.75 (9 H, m,), 0.96 (3 H, s) and 0.9 (3 H, s) (2 x *tert* Me). Further elution of the column with the same solvent furnished the annulated keto-ester **10** (100 mg, 42%) which was recrystallised from hexane. m.p. 98°C; $[\alpha]_D^{26}$: +16° (CHCl$_3$); IR (CCl$_4$): ν_{max} 1730, 1700, 1360, 1290, 1090,

1040, 1010 cm^{-1}. ^{1}H NMR (270 MHz, CDCl$_3$): δ 3.66 (3 H, s, COOCH$_3$), 2.93 (1 H, br s, 5–H), 2.71 (1 H, m, 2–H eq), 2.67 (1 H, m, C$\underline{\mathrm{H}}$–COOMe), 2.49 (1 H, quintet, *J* 6.3, 4–H), 2.33 (1 H, d of ½ AB q, *J* 15.9 and 5.7, 2–H ax), 2.22 (1 H, q of ½ AB q, *J* 14 and 3.1, 9–H a), 1.98 (1 H, t of ½ AB q, *J* 14 and 3, 9–H b), 1.87 (1 H, br s, 1–H), 1.49 (1 H, d of ½ AB q, *J* 15 and 4, 7–H eq), 1.32 (1 H, *J* 14.9, 7–H ax), 1.02 (3 H, s) and 0.99 (3 H, s) (2 x *tert*–Me), 0.96 (3 H, d, *J* 6.9, *sec*–Me). ^{13}C NMR (22.5 MHz, CDCl$_3$): δ 212.4 (s, C=O), 175.0 (s, O–C=O), 51.1 (q, OMe), 48.4 (d), 44.1 (t, CO$\underline{\mathrm{C}}$H$_2$), 41.5 (2 C, d), 39.8 (d), 33.6 (s, C–8), 33.1 (t) and 32.9 (t) (C–7 and 9), 28.9 (q) and 27.2 (q) (2 x *tert*–Me), 11.6 (q, *sec*–Me). Mass: m/z 238 (M$^+$, 18%), 210 (39), 129 (30), 109 (100), 108 (30), 107 (25) and 95 (20). HRMS: Found: M$^+$, 238.1578. $C_{14}H_{22}O_3$ requires 238.1569.

*(+)-(1S,4R,5S,6R)-6-Acetyl-4,8,8-trimethylbicyclo[3.3.1]nonan-3-one(**11**)*: Radical annulation reaction of the bromide **7a** (231 mg, 1 mmol) with ^{n}Bu$_3$SnH (0.27 ml, 1 mmol), methyl vinyl ketone (**4c**, 0.4 ml, 5 mmol) and AIBN (catalytic) in dry benzene (50 ml) using method A followed by purification of the product mixture over a silica gel (15 g) column with ethyl acetate-hexane (1:3) as eluent furnished first the unreacted starting material **7a** (128 mg) followed by the annulated product **11** (84 mg, 85%, based on the recovered starting material) which was recrystallised from hexane. m.p. 110°C; $[\alpha]_D^{26}$: +4° (CHCl$_3$); IR (CCL$_4$) ν_{max} 1710, 1470, 1360, 1200, 870 cm^{-1}. ^{1}H NMR (270 MHz, CDCl$_3$): δ 3.03 (1 H, br s, 5–H), 2.70 (1 H, t of ½ AB q, *J* 15.6 and 2.5, 2–H eq), 2.53 (2 H, m, 4–H and C$\underline{\mathrm{H}}$–COCH$_3$), 2.33 (1 H, d of ½ AB q, *J* 15.5 and 5.8, 2–H ax), 2.26 (1 H, m, 9–H a), 2.21 (3 H, s, COCH$_3$), 2.02 (1 H, t of ½ AB q, *J* 14 and 3, 9–H b), 1.89 (1 H, br s, 1–H), 1.45 (1 H, d of ½ AB q, *J* 15 and 3.7, 7–H eq), 1.31 (1 H, t, *J* 15, 7–H ax), 1.01 (3 H, s) and 1.00 (3 H, s) (*tert*–Me), 0.92 (3 H, d, *J* 7, *sec*–Me). ^{13}C NMR (22.5 MHz, CDCl$_3$): δ 212.1 (s, C=O), 210.6 (s, $\underline{\mathrm{C}}$OCH$_3$), 51.0 (d), 48.8 (d), 44.3 (t, CO$\underline{\mathrm{C}}$H$_2$), 41.8 (d), 40.1 (d), 33.7 (2 C, t and s), 32.7 (t), 29.0 (q) and 27.5 (q) (2 x *tert*–Me), 28.0 (q, CO$\underline{\mathrm{C}}$H$_3$), 12.6 (q, *sec*–Me). Mass: m/z 222 (M$^+$, 15%), 194 (20), 179 (22), 166 (18), 150 (15), 123 (15), 121 (20), 109 (75), 108 (78), 107 (40) and 95 (40). HRMS: Found: M$^+$, 222.1608. $C_{14}H_{22}O_2$ requires 222.1620.

*(+)-(1S,4R,5S,6R)-6-Phenyl-4,8,8-trimethylbicyclo[3.3.1]nonan-3-one(**12**)*: Radical annulation reaction of the bromide **7a** (231 mg, 1 mmol) with ^{n}Bu$_3$SnH (0.27 ml, 1 mmol), AIBN (catalytic) and styrene (**4d**, 0.57 ml, 5 mmol) for 30 min using method D followed by purification of the product mixture over a silica gel (15 g) column with ethyl acetate-hexane (1:9) as eluent furnished first dihydrocarvone (**15**, 80 mg, 52%) followed by the annulated product **12** (92 mg, 36%) which was recrystallised from hexane. m.p. 125°C; $[\alpha]_D^{26}$: +64° (CHCl$_3$); IR (CCl$_4$): ν_{max} 1710, 1450, 700 cm^{-1}. ^{1}H NMR (270 MHz, CDCl$_3$): δ 7.24 (5 H, m, aromatic), 3.21 (1 H, td, *J* 13 and 3.6, C$\underline{\mathrm{H}}$–Ph), 2.80 (1 H, br s, 5–H), 2.75 (1 H, td, *J* 15.6 and 2.5, 2–H eq), 2.49 (1 H, quintet, *J* 6.8, 4–H), 2.38 (2 H, m, 2–H ax and 9–H a), 2.03 (1 H, td, *J* 13.3 and 3, 9–H b), 1.96 (1 H, br s, 1–H), 1.68 (1 H, ½ AB q, *J* 14, 7–H eq), 1.58 (1 H, m, 7–H ax), 1.10 (3 H, s) and 1.08 (3 H, s) (2 x *tert*–Me), 0.40 (3 H, d, *J* 7, *sec*–Me). ^{13}C NMR (22.5 MHz, CDCl$_3$): δ 214.1 (C=O), 145.2, 128.0 (2 C), 127.4 (2 C) and 126.0 (aromatic), 50.0, 44.9 (2 C), 42.5, 41.3, 35.7, 34.7 (2 C), 29.6, 27.9, 13.8. Mass: m/z 256 (M$^+$, 60%), 145 (80), 109 (100) and 91 (72). HRMS: Found: M$^+$, 256.1828. $C_{18}H_{24}O$ requires 256.1827.

(−)-(1S,4R,5S,6S)-6-cyano-4,6,8,8-tetramethylbicyclo[3.3.1]nonan-3-one (**13**): Radical annulation reaction of the bromide **7a** (231 mg, 1 mmol) with $^{n}Bu_3SnH$ (0.27 ml, 1 mmol), α-methacrylonitrile (**4e**, 0.42 ml, 5 mmol) and AIBN (catalytic) using the method D followed by purification of product mixture over a silica gel (15 g) column with ethyl acetate-hexane (1:3) as eluent furnished first the dihydrocarvone (**15**, 23 mg, 15%) followed by the annulated product **13** (116 mg, 53%) which was recrystallised from hexane. m.p. 110°C; $[\alpha]_D^{26}$: −8° ($CHCl_3$); IR (CCl_4): ν_{max} 2240, 1710, 1370, 1190, 1030, 930 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$): δ 2.85 (1 H, m, 4-H), 2.70 (2 H, d, *J* 15, 2-H eq and 9-H a), 2.57 (1 H, br s, 5-H), 2.39 (1 H, dd, *J* 15.4 and 6, 2-H ax), 1.98-2.1 (2 H, m, 1-H and 9-H b), 1.62 and 1.4 (2 H, AB q, *J* 15, 7-H_2), 1.44 (3 H, s), 1.32 (3 H, s) and 0.96 (3 H,s) (3 x *tert*-Me), 1.21 (3 H, d, *J* 7, *sec*-Me). ^{13}C NMR (22.5 MHz, $CDCl_3$): δ 211.5 (s, C=O), 125.7 (s, C≡N), 49.2 (d, C-4), 45.9 (d), 43.8 (s, C-6), 42.5 (t, C-2), 41.6 (d), 37.1 (s, C-8), 34.2 (t) and 31.6 (t) (C-7 and 9), 29.5 (q), 27.3 (2 C, q) (3 x *tert*-Me), 14.3 (q, *sec*-Me). Mass: m/z 219 (M^+, 18%), 109 (100) and 81 (16). HRMS: Found: 219.1613. $C_{14}H_{21}NO$ requires 219.1623.

(+)-(1S,4R,5S,6R)-6-Chloro-6-cyano-4,8,8-trimethylbicyclo[3.3.1]nonan-3-one (**14**): Radical annulation reaction of the bromide **7a** (231 mg, 1 mmol) with $^{n}Bu_3SnH$ (0.27 ml, 1 mmol), α-chloroacrylonitrile (**4f**, 0.4 ml, 5 mmol) and AIBN (catalytic) using method A followed by purification of product mixture over a silica gel (15 g) column with ethyl acetate-hexane (1:3) as eluent furnished first the unreacted starting material **7a** (81 mg) followed by the annulated product **14** (98 mg, 63%, based on recovered starting material) as a pale yellow oil. $[\alpha]_D^{26}$: +62° ($CHCl_3$); IR (neat): ν_{max} 2240, 1710, 1385, 1370, 1160, 1090, 730 cm^{-1}. ^1H NMR(270 MHz, $CDCl_3$): δ 2.98 (1 H, br s, 5-H), 2.90 (1 H, m, 4-H), 2.69-2.77 (2 H, m, 2-H eq and 9-H b), 2.44 (1 H, dd, *J* 15.3 and 5.6, 2-H ax), 2.22 (1 H, td, *J* 15 and 1.5, 9-H a), 2.12 and 1.79 (2 H, AB q, *J* 15, 7-H_2), 2.02 (1 H, br s, 1-H), 1.38 (3 H, d, *J* 7, *sec*-Me), 1.32 (3 H, s) and 1.01 (3 H, s) (2 x *tert*-Me). ^{13}C NMR (22.5 MHz, $CDCl_3$): δ 210.1 (s, C=O), 120.5 (s, C≡N), 59.8 (s, C-6), 49.2 (d), 47.8 (d), 45.7 (t, C-2), 43.7 (t), 40.4 (d), 36.6 (s, C-8), 31.9 (t, C-9), 28.9 (q) and 27.5 (q) (2 x *tert*-Me), 14.4 (q, *sec*-Me). Mass: m/z 239 (M^+, 36%), 241 (M^++2, 15), 204 (28), 160 (20), 132 (20), 118 (20), 110 (40) and 109 (100). HRMS: Found: M^+, 239.1080. $C_{13}H_{18}ClNO$ requires 239.1077.

(+)-(S)-2,3-Dimethyl-5-(2-bromoprop-2-yl)-cyclohex-2-en-1-one (**18**): A solution of (S)-6-methylcarvone (**17**, 1.3 g, 8 mmol) in dry ether (10 ml) was added to ice-cold glacial acetic acid (30 ml) saturated with HBr gas (generated by dropwise addition of 4.6 g of bromine to a magnetically stirred 4 ml of tetralin), the reaction mixture was stirred at 0°C for 30 min and poured into ice-cold water. The ether layer was separated and the aqueous layer was extracted with ether (8 ml x 3). The combined ether extract was washed with water, saturated aqueous $NaHCO_3$ and brine, and dried (Na_2SO_4). Evaporation of the solvent under reduced pressure furnished the bromide **18** (1.2 g, 62%). $[\alpha]_D^{26}$: +38.9° ($CHCl_3$); IR (neat): ν_{max} 1668, 1455, 1383, 1326, 1104, 1047, 708 cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$): δ 2.2-2.76 (5 H, m), 1.95 (3 H, s, C_3-Me), 1.82 (3 H, s), 1.72 (3 H, s, C_2-Me). Mass: m/z 244 (M^+, 27%), 246 (M^++2, 27), 165 (100), 164 (35), 123 (90), 109 (78), 96 (46) and 95 (42). HRMS: Found: M^+ and M^++2, 244.0435 and 246.0432. $C_{11}H_{17}BrO$ requires 244.0463 and 246.0443.

(+)-(1S,4R,5S,6R) & (1S,4R,5S,6S)-4,5,8,8-Tetramethyl-6-cyanobicyclo-[3.3.1]nonan-3-ones (***19*** *&* ***20***)*:* Radical annulation reaction of the bromide **18** (222 mg, 0.9 mmol) with $^nBu_3SnH$ (**4b**, 0.27 ml, 0.99 mmol), acrylonitrile (**4a**, 0.33 ml, 5 mmol) and AIBN (catalytic) using method D followed by purification of the product over a silica gel (15 g) column with ethyl acetate-hexane (1:3) as eluent furnished the keto-nitriles **19** and **20** (6:1, 120 mg, 61%).

Compound 19: m.p. 172-173°C (hexanes); $[\alpha]_D^{26}$: +20° ($CHCl_3$); IR (CCl$_4$): ν_{max} 2250, 1710 cm^{-1}. ^{1}H NMR (270 MHz, $CDCl_3$): δ 2.71 (1 H, dt, *J* 15.6 and 2.4, 2-H eq), 2.63 (1 H, dd, *J* 13.2 and 4.3, C<u>H</u>-CN), 2.37 (1 H, dd, *J* 15.6 and 4.4, 2-H ax), 2.25 (1 H, q, *J* 6.2, 4-H), 1.87 (3 H, m, 9-H$_2$ and 1-H), 1.57 (1 H, dd, *J* 14.5 and 4.3, 7-H eq), 1.45 (1 H, d, *J* 13, 7-H ax), 1.36 (3 H, s), 1.04 (3 H, s) and 0.99 (3 H,s) (3 x *tert*-Me), 1.34 (3 H, d, *J* 7.1, *sec*-Me). ^{13}C NMR (22.5 MHz, $CDCl_3$): δ 211.2 (s, C=O), 120.9 (s, $C\equiv N$), 53.9 (d), 43.6 (t, C-2), 40.6 (2 C, d and s), 40.1 (t), 36.1 (t, C-9), 33.9 (d), 33.3 (s), 28.8 (q), 27.7 (q) and 26.9 (q) (3 x *tert*-Me), 9.1 (q, *sec*-Me). Mass: m/z 219 (M^+, 13%), 123 (100) and 95 (14). HRMS: Found: M^+, 219.1633. $C_{14}H_{21}NO$ rquires 219.1623.

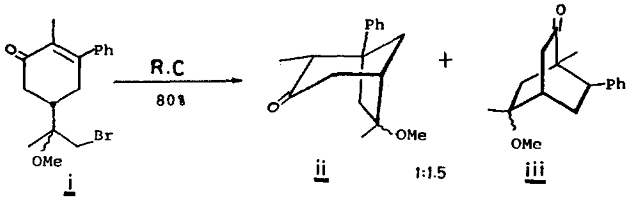
Compound 20: $[\alpha]_D^{26}$: +7.9° ($CHCl_3$); IR (CCl_4): ν_{max} 2250, 1710 cm^{-1}. ^{1}H NMR (270 MHz, $CDCl_3$): δ 2.69 (1 H, br d, *J* 6, C<u>H</u>-CN), 2.61 (1 H, dt, *J* 15.5 and 2.6, 2-H eq), 2.26-2.35 (2 H, m, 1-H and 2-H ax), 2.13-2.2 (1 H, m, 4-H), 1.49-1.98 (4 H, m), 1.23 (3 H, s), 1.18 (3 H, s) and 0.87 (3 H,s) (3 x tert-Me), 0.97 (3 H, d, *J* 6.8, *sec*-Me). Mass: m/z 219 (M^+, 67%), 204 (22), 148 (26), 124 (100), 109 (29) and 95 (54). HRMS: Found: M^+, 219.1617. $C_{14}H_{21}NO$ requires 219.1623.

(+)-Methyl (1S,4R,5R,6R)-4,5,8,8-trimethylbicyclo[3.3.1]nonan-3-one-6-carboxylate (***21***)*:* Radical annulation reaction of the bromide **18** (222 mg, 0.9 mmol) with $^nBu_3SnH$ (0.27 ml, 1 mmol), methyl acrylate (0.45 ml, 5 mmol) and AIBN (catalytic) using the method D followed by purification of the product mixture over a silica gel (15 g) column with ethyl acetate-hexane (1:9) as eluent furnished the annulated keto-ester **21** (120 mg, 52%) as a light yellow oil. $[\alpha]_D^{25}$: +4.0° ($CHCl_3$); IR (neat): ν_{max} 1725, 1690, 1662, 1173, 1014 cm^{-1}. ^{1}H NMR (270 MHz, $CDCl_3$): δ 3.63 (3 H, s, O-Me), 2.69 (1 H, br d, *J* 15.6, 2-H eq), 2.41 (1 H, dd, *J* 12.3 and 5.3, C<u>H</u>COOMe), 2.33 (1 H, dd, *J* 15.6 and 5.7, 2-H ax), 2.12 (1 H, q, *J* 7, 4-H), 2.05 (1 H, t of ½ AB q, *J* 13.8 and 2.9, 9-H a), 1.8 (1 H, br s, 1-H), 1.75 (1 H, d of ½ AB q, *J* ca 13.8 and 2.8, 9-H b), 1.2-1.4 (2 H, m, 7-H$_2$), 1.34 (3 H, s), 1.00 (3 H, s) and 0.98 (3 H, s) (3 x *tert*-Me), 0.96 (3 H, d, *J* ca 7.5, *sec*-Me). ^{13}C NMR (22.5 MHz, $CDCl_3$): δ 211.6 (s, C=O), 174.1 (s, O-C=O), 54.1 (d), 51.1 (q, OMe), 47.1 (d), 43.7 (t), 42.5 (t), 41.9 (s), 41.1 (d), 35.0 (t, C-9), 33.4 (s), 28.7 (2 C, q) and 27.3 (q) (3 x *tert*-Me), 8.2 (q, *sec*-Me). Mass: m/z 252 (M^+, 15%), 224 (20), 181 (20), 129 (20), 123 (100), 121 (60) and 95 (30).

ACKNOWLEDGEMENT: We thank Professor G.S. Krishna Rao for the generous gift of S-carvone used in this work. PH and SV thank the C.S.I.R., New Delhi for the award of research fellowships.

REFERENCES AND NOTES

1. Chiral synthons from carvone Part 11. Part 10, see Srikrishna, A.; Sharma, G.V.R.; *Indian J. Chem.* (in press).
2. Giese, B.; *Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds*; Pergamon Press: Oxford, **1986**; Strok, G.; Radical mediated cyclisation process. In *Selectivity-A goal for synthetic efficiency*; Eds. W. Bartmann, B.M. Trost; work shop conference, Hoechst; Verlag Chemie: Basel, **1984**; Vol 14; Giese, B.; *Angew. Chem., Int. Ed. Engl.*, **1983**, *22*, 753 and **1985**, *24*, 553; Hart, D.J.; *Science*, **1984**, *223*, 883; Ramaiah, M.; *Tetrahedron*, **1987**, *43*, 3541; Srikrishna, A.; *Current Science*, **1987**, *56*, 392; Curran, D.P.; *Synthesis*, **1988**, 417 and 489; Pattenden, G.; *Chem. Soc. Rev.*, **1988**, *17*, 361; Jasperse, C.P.; Curran, D.P.; Fevig, T.L.; *Chem. Rev.*, **1991**, *91*, 1237; Curran, D.P.; *Synlett*, **1991**, 63.
3. Srikrishna, A.; Hemamalini, P.; Sharma, G.V.R.; *J. Org. Chem.*, **1993**, *58*, 2509 and references cited therein.
4. Peters, J.A.; *Synthesis*, **1979**, 321.
5. Peters, J.A.; Baas, J.M.A.; van de Graaf, B.; van der Toorn, J.M.; van Bekkum, H.; *Tetrahedron*, **1978**, *34*, 3313.
6. Boeckman, R.K. Jr.; Bershas, J.P.,; Clardy, J.; Solheim, B.; *J. Org. Chem.*, **1977**, *42*, 3630; Gambacorta, A.; Botta, M.; Turchetta, S.; *Tetrahedron*, **1988**, *44*, 4837; Schultz, A.G.; Dittami, J.P.; *J. Org. Chem.*, **1984**, *49*, 2615.
7. (a) Srikrishna, A.; Hemamalini, P.; *J. Chem. Soc., Perkin Trans. 1*, **1989**, 2511 (preliminary communication); (b) Srikrishna, A.; Hemamalini, P.; *J. Org. Chem.*, **1990**, *55*, 4883; (c) Srikrishna, A.; Sharma, G.V.R.; Hemamalini, P.; *J. Chem. Soc., Chem. Commun.*, **1990**, 1681; (d) Srikrishna, A.; Hemamalini, P.; Sharma, G.V.R.; *Tetrahedron Lett.*, **1991**, *32*, 6609; (e) Srikrishna, A.; Hemamalini, P.; *Tetrahedron*, **1992**, *48*, 3429.
8. Wolinsky, J.; Hamsher, J.J.; Hutchins, R.O.; *J. Org. Chem.*, **1970**, *35*, 207.
9. Irifune, S.; Kibayashi, T.; Ishii, Y.; Ogawa, M.; *Synthesis*, **1988**, 366.
10. Senda, Y.; Ishiyama, J.-I.; Imaizumi, S.; *J. Chem. Soc., Perkin Trans. 2*, **1981**, 90; Peters, J.A.; van der Toorn, J.M.; van Bekkum, H. *Tetrahedron*, **1977**, *33*, 349.
11. Baker, A.J.; Frazer, D.V.; *J. Chem. Soc., Chem. Commun.*, **1985**, 290; Jaime, C.; Osawa, E.; Takeuchi, Y.; Camps, P.; *J. Org. Chem.*, **1983**, *48*, 4514; Mcdonald, I.A.; Drieding, A.S.; Hutmacher, H.-M.; Musso, H.; *Helv. Chim. Acta*, **1973**, *56*, 1385; Mcdonald, I.A.; Drieding, A.S.; *ibid.* **1973**, **56**, 2523; Peters, J.A.; van der Toorn, J.M.; van Bekkum, H.; *Tetrahedron*, **1974**, *30*, 633; **1975**, *31*, 2273.
12. Stork, G.; Sher, P.M.; *J. Am. Chem. Soc.*, **1986**, *108*, 303.
13. Giese, B.; He, J.; Mehl, W.; *Chem. Ber.*, **1988**, *121*, 2063.
14. Srikrishna, A.; Hemamalini, P.; *Indian J. Chem.*, **1990**, *29B*, 152.
15. Since the radical cyclisation reaction of the bromide **i** is shown[7e] to furnish both the bicyclo [3.2.1] and [2.2.2] octanes **ii** and **iii**, *via* competitive 5-*exo-trig* and 6-*exo-trig* modes of cyclisation.



(*Received in UK* 26 *April* 1994; *revised* 23 *May* 1994; *accepted* 27 *May* 1994)