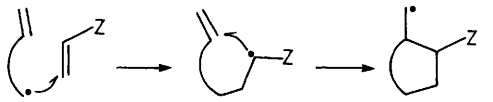
Bridged Systems *via* Radical Cyclisations: Synthesis of Chiral Bicyclo-[3.3.1]nonanes by Sequential Inter- and Intra-molecular Radical Michael Addition

Adusumilli Srikrishna * and Parthasarathy Hemamalini
Department of Organic Chemistry, Indian Institute of Science, Bangalore 560 012, India

A stereoselective synthesis of functionalised chiral bicyclo[3.3.1]nonanes, by a sequential inter- and intra-molecular radical Michael addition of the radical (**4**), generated in two steps from (*S*)-carvone (**1**), in the presence of an excess radicophile (**5**), is described.

Radical cyclisations continue to excite interest,[1] and both inter- and intra-molecular[2] radical additions, using the commonly employed tin method to multiple bonds, have been exploited to construct fused carbo- and hetero-cycles. However, relatively little attention has been paid to bridged systems.[3] A combination of inter- and intra-molecular radical additions in a single sequence, radical annulation [equation (1)], to achieve

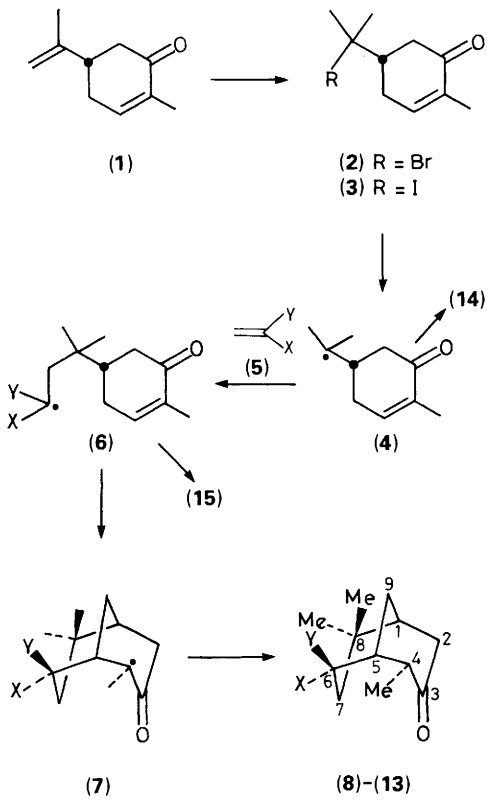


(1)

highly functionalised compounds is appealing from a synthetic standpoint.[4] Combining these two aspects, we now describe a stereoselective route to functionalised chiral bicyclo[3.3.1]-nonanes starting from (*S*)-carvone (**1**) by a sequential inter- and intra-molecular radical Michael addition (see Scheme).

Generation of the radical (**4**), in the presence of an excess of the radicophile (**5**), adds in an intermolecular Michael fashion to generate the new radical (**5**), which on 5-*exo trigonal* radical cyclisation [→(**7**)] followed by hydrogen abstraction from tin furnishes the bicyclo[3.3.1]nonane. The requisite radical precursors, the bromide (**2**) and iodide (**3**), were obtained from (*S*)-carvone (**1**) by the addition of gaseous HBr[5] and *in situ* generated HI (TMSCl–NaI–H_2O).[6]† Refluxing a 0.02M benzene solution of the bromide (**2**) with tributyltin hydride (TBTH) (1 equiv.), acrylonitrile (**5a**) (5 equiv.) and a catalytic amount of azoisobutyronitrile (AIBN) for 30 min furnished a 2:1 mixture of the bicyclic ketonitriles (**8a**) and (**8b**) in 68% yield after chromatographic (silica gel column) purification. On the other hand, reaction with various other radicophiles (see Table) yielded only one isomer, (**9**)—(**13**), with excellent stereoselectivity. The structures and the stereochemistry of the

† Prior to use, hexane solutions of (**2**) and (**3**) were washed with 1M aqueous NaOH to remove the 5-isopropyl-2-methylphenol, the decomposition product of the halides (**2**) and (**3**).



	X	Y		X	Y
(**8a**)	CN	H	(**5a**)	CN	H
(**8b**)	H	CN	(**5b**)	CO_2Me	H
(**9**)	CO_2Me	H	(**5c**)	Ac	H
(**10**)	Ac	H	(**5d**)	Ph	H
(**11**)	Ph	H	(**5e**)	Me	CN
(**12**)	Me	CN	(**5f**)	Cl	CN
(**13**)	Cl	CN			

Scheme.

Table. Chiral bicyclo[3.3.1]nonanes from (*S*)-carvone hydrohalides

Entry	Halide	Method[a]	% Yield[b]	Radicophile	Product	M.p. (°C)	$[\alpha]_D$/°
1	(2)	A	68	(5a)	(8a)	102	+30
2	(2)	D	32				
3	(3)	A	56[d]		(8b)	70	−20
4	(2)	A	42[e]	(5b)	(9)	98	+16
5	(2)	D	34				
6	(3)	A	48[f]				
7	(2)	A	38 (85)	(5c)	(10)	110	+4
8	(2)	C	30 (40)				
9	(2)	D	25 (45)				
10	(3)	A	46				
11	(2)	B	36[g]	(5d)	(11)	125	+64
12	(3)	B	46[d]				
13	(2)	B	53[d]	(5e)	(12)	110	−8
14	(3)	B	40				
15	(2)	A	41 (63)	(5f)	(13)	Liq.	+62
16	(2)	C	42 (73)				
17	(3)	A	51				

[a] Method A: Halide (1 equiv.) in C_6H_6 (0.02M), TBTH (1 equiv.), AIBN (cat.), (5) (5 equiv.), 30 min reflux. Method B: slow additon of TBTH and AIBN to a refluxing benzene solution of halide and (5) (5 equiv.) over 20 min. Method C: Simultaneous addition of solutions of TBTH (+AIBN) and (5) (5 equiv.) to a refluxing solution of halide in benzene over 20 min. Method D:[10] Halide in Bu^tOH (0.2M), Bu_3SnCl (0.1 equiv.), AIBN (cat.), (5) (5 equiv.), reflux for 30 min. [b] Isolated yields. Yields in parentheses are based on starting material consumed. [c] 2:1 Mixture of (8a) and (8b). [d] 15% of (14) was also isolated. [e] 37% of (15) was also isolated. [f] 33% of (14) was also isolated. [g] 52% of (14) was also isolated.

products (8)—(13) were readily established through their interrelated spectral data.* In particular, the ^{13}C n.m.r. triplet resonance at δ *ca.* 33 (C-9)[7] and the various H, H coupling constants in the ^1H n.m.r. (270 MHz) spectrum[8] indicated the twin chair conformation shown in the Scheme. The equatorial orientation of the 6-X group was indicated by coupling of the axial 6-H [in (8a), (9)—(11)] to the vicinal protons (*J* 13, 4.5, and 4 Hz). Similarly, the equatorial orientation of the 4-methyl group was indicated by the quintet (*J* 6 Hz) resonance for 4ax-H ($J_{4eq,5}$ is known to be <3 Hz).[8] Further, in compound (11), the 4-methyl doublet resonated at δ 0.62, as a result of the phenyl ring shielding effect; this clearly established the *syn* orientation of these two groups, which can be explained only in terms of their diequatorial orientation at C-4 and C-6. Four improvements to the reaction were tried and the results are summarised in the Table. The salient features are as follows. The cyclisation of the radical (6) to (7), the addition of an electrophilic radical (?) to an enone; the latter is supported by Giese's concept of the borderline nature of carbon radicals with one electron-withdrawing group.[9] In addition to the products (8)—(13), varying amounts (0—52%) of dihydrocarvone (14) and/or mono-Michael adduct (15) were formed by competing side reactions. The bromide (2) was found to be better than the iodide (3). Excellent control of the stereochemistry, with generation of the thermodynamic products, can be explained by a product-like transition state in the cyclisation of the radical (6). Control of the stereochemistry of three new centres (C-4, -5, -6), starting with one chiral centre.

In conclusion, we have described here a route to chiral 4,8,8-trimethylbicyclo[3.3.1]non-3-one with an additional functional group at C-6 by a sequential inter- and intra-molecular radical Michael addition reaction of (*S*)-carvone hydrohalide. Currently we are extending this strategy to other bridged systems of general interest and those found in natural products.

* Spectral data for (8a): $\nu_{max.}(CCl_4)$ 2 260, 1 700, and 1 460 cm^{-1}; δ_H (270 MHz, $CDCl_3$) 2.95 (1 H, ddd, *J* 13, 4.5, 4 Hz, 6-H), 2.72 (1H, dt, *J* 15.5, 2.5 Hz, 2eq-H), 2.65 (2 H, m, 4-, 5-H), 2.38 (1 H, dd, *J* 15.5, 5.5 Hz, 2ax-H), 2.14 (1 H, dq, *J* 14, 2.8 Hz, 9a-H), 1.97 (1 H, dt, *J* 14, 2.8 Hz, 9b-H), 1.9 (1 H, br s, 1-H), 1.55 (1 H, dd, *J* 13, 4.5 Hz, 7eq-H), 1.45 (1 H, t, *J* 13 Hz, 7ax-H), 1.39 (3 H, d, *J* 6.8 Hz, 4-Me), 1.05 (3 H, s), and 0.99 (3 H, s); δ_C(22.5 MHz, $CDCl_3$) 211.6 (s), 121.8 (s), 48.3 (d), 43.8 (t), 40.8 (d), 38.6 (d), 34.7 (t), 33.5 (s), 31.7 (t), 28.1 (q), 27.1 (q), 26.7 (d), and 12.8 (q). For (8b): $\nu_{max.}(CCl_4)$ 2 240, 1 710, and 1 470 cm^{-1}; δ_H(270 MHz, $CDCl_3$) 2.92 (1 H, br d, *J* 6 Hz, 6-H), 2.67 (1 H, d, *J* 15.5 Hz, 2eq-H), 2.45—2.6 (3 H, m, 1-, 4-, 5-H), 2.38 (1 H, dd, *J* 15.5, 5 Hz, 2ax-H), 1.96 (2 H, br s, 9-H), 1.52 (1 H, d, *J* 15.5 Hz, 7eq-H), 1.29 (3 H, s, 8ax-Me), 1.22 (1 H, dd, *J* 15.5, 6 Hz, 7ax-H), 1.07 (3 H, d, *J* 6.5 Hz, 4-Me) and 0.92 (3 H, s, 8eq-Me); δ_C(22.5 MHz, $CDCl_3$) 211.8 (s), 123.0 (s), 47.6 (d), 44.1 (t), 41.5 (d), 40.0 (d), 33.7 (s), 32.4 (t), 29.6 (q), 28.2 (2 C, t and q), 25.0 (d), and 11.9 (q). Similarly all the other products exhibited satisfactory spectral data, and the stereochemistry of other products (9)—(13) were assigned by comparing their ^1H n.m.r. (270 MHz) spectra with those of (8a) or (8b).

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