(s), 1450 (w), 1380 (w), 1180 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.27 (d, J = 6.7 Hz, 3 H), 1.41 (d, J = 6.1 Hz, 3 H), 1.53–1.80 (m, 1 H), 2.35–3.05 (m, 2 H), 4.50 (qdd, J = 6.7, 5.3, 3.0 Hz; 1 H); ^{13}C NMR ($CDCl_3$) δ 15.02 (Me-C_2), 20.83 (Me-C-4), 36.27 (C-2), 39.63 (C-3), 74.76 (C-4), 179.34 (C-1); mass spectrum m/z (rel intensity) 114 (M, 1), 99 (34), 71 (33), 70 (100). Anal. Calcd for $C_6H_{10}O_2$: 114.0680. Found: 114.0670.

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Supplementary Material Available: X-ray analysis, ORTEP view, packing diagram, crystal data, positional parameters, anisotropic thermal parameters, bond distances, bond angles, torsional angles, and structure factor amplitudes for **10c** (19 pages). Ordering information is given on any current masthead page.

Synthesis and ^{13}C NMR Analysis of a Series of Bridgehead-Substituted Polycycloalkanes: ^{13}C-Labeled Methyl as the Substituent[1]

Ernest W. Della* and Paul E. Pigou

Contribution from the School of Physical Sciences, Flinders University, Bedford Park, South Australia 5042, Australia.

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Abstract: The synthesis of eight polycycloalkanes substituted at the bridgehead with a ^{13}C-labeled methyl group is described. Their ^{13}C nuclear magnetic resonance spectra have been measured and the various NMR parameters are reported. It is found that there is no linear correlation between coupling involving directly bonded carbon atoms and the product of the s characters of the bonding orbitals. The experimentally determined values of ^3J(CC) are in close agreement with values calculated by using the self-consistent perturbation theory at the INDO level of approximation. In several strained systems, nonbonded interactions provide significant contributions to the vicinal carbon–carbon coupling constants; MO results demonstrate that these interactions oppose through-bond effects. Very good agreement is also noted between the observed ^3J(CC) values and those determined from a Karplus relationship; this includes the substrates in which through-space effects are especially important.

Nuclear spin–spin coupling is normally described in terms of the transmission of indirect nuclear spin interactions via the bonding network. The coupling constant, $J(AB)$, is a parameter which provides a measure of the extent of coupling between the nuclei A and B and is considered to be comprised of the following terms:[2]

$$J(AB)_{total} = J(AB)_O + J(AB)_D + J(AB)_C$$

The first, $J(AB)_O$, refers to the interaction between the field produced by the orbiting electrons and the nuclear magnetic moment; the second, $J(AB)_D$, arises from dipole–dipole interaction between the nuclear and electronic magnetic moments; the final (and frequently major) contribution to the coupling, $J(AB)_C$, occurs as a result of interactions between nuclear and electronic spins. $J(AB)_C$ is referred to as the (Fermi) contact term because it depends on the properties of electrons at the nucleus; accordingly, it is concerned with s electron densities.

Of special interest to the organic chemist is the question of coupling involving the carbon-13 nucleus. Evaluation of carbon–carbon coupling constants, ^nJ(CC), has captured the attention of both experimental and theoretical chemists over recent years, and, despite the fact that C–C couplings are more difficult to obtain, there currently exists an extensive tabulation of such data.[3-8]

In considering one-bond coupling it is generally believed that the extent of coupling between carbon and hydrogen, for example, bears a direct correlation with the degree of s character of the carbon bonding orbital, i.e., the coupling is governed almost exclusively by Fermi contact. Indeed, the tendency has arisen to regard the value of ^1J(CH) as a direct measure of the s content of the carbon orbital, although the need for exercising restraint in too literal an interpretation of this relationship has been emphasised.[9] This correlation has been extended to include carbon–carbon coupling and it is suggested that ^1J(CC) values similarly reflect the product of the s electron densities at the nuclei.[6,10] There are, however, some notable exceptions, for instance, when the carbon atoms form part of a strained ring system[11] or if they are multiply bonded.[10b,12]

Undoubtedly, the most intriguing aspect of long-range nuclear spin interactions is the question of vicinal coupling. Generally speaking, three-bond proton–proton coupling in saturated systems obeys a Karplus relationship. Much attention has been paid to establishing a similar correlation between ^3J(CC) and the torsional

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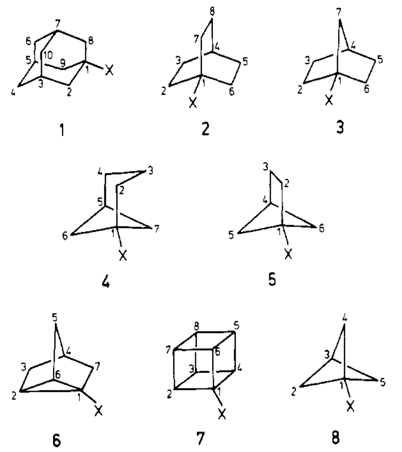


Figure 1. **a**, X = H; **b**, X = F; **c**, X = $^{13}CH_3$; **d**, X = $^{13}COOH$.

angle associated with the nuclei, with limited success.[3,13] Berger[13a] has generated a Karplus curve from a detailed examination of vicinal coupling in a series of alicyclic compounds in which bond and angle strain are minimal. Barfield and his associates[14] have made a thorough investigation of the effect of nonbonded interactions (NBI) on $^3J(CC)$ and they conclude that such effects are superimposed on the trigonometric function. Indeed, in some cases the NBIs, which can be positive or negative, may be the dominant factor determining $^3J(CC)$.[14]

Several years ago we embarked on an investigation of the ^{13}C NMR properties of a number of saturated polycycloalkanes (Figure 1) substituted at the bridgehead with appropriate magnetically active atoms.[15] At this stage we have reported on the parent hydrocarbons **1a–8a**,[16] the bridgehead fluorides **1b–5b** and **8b**,[17] and on several of the systems with $SnMe_3$ at the bridgehead.[18] More recently we directed our attention to the ^{13}C-labeled hydrocarbons **1c–8c**, the results of which form the basis of this report. We chose the systems illustrated in Figure 1, firstly because they represent a series of compounds of increasing constraint at the bridgehead. The effect of this is that along the series there is a gradual increase in the size of the exocyclic angles subtended at the bridgehead carbon atoms whose exocyclic bonding orbitals, therefore, possess enhanced s character. Accordingly, we felt that **1c–8c** would provide an excellent test of whether $^1J(CC)$ correlates with the s content of the carbon bonding orbital.

Secondly, the substrates **1c–8c** are almost all rigid molecules of well-defined geometry and would therefore allow an unambiguous probe of the validity of the suggested dependence of $^3J(CC)$ on the CCCC dihedral angle at least insofar as the nonbridgehead carbon atoms are concerned.

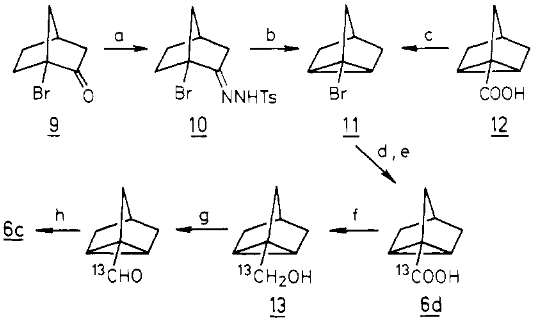
Finally, we wished to determine whether coupling between $^{13}C_{Me}$ and the substituted bridgehead carbon in the bicycloalkanes **2c–5c** and **8c** is affected by through-space interactions between the bridgehead carbons, bearing in mind that the analogous spin–spin couplings $^3J(^{19}F-^{13}C_{bridgehead})$ in the fluorides **3b–5b** and **8b** were found to be profoundly influenced in this way.[17] Electron diffraction data show that the internuclear distance between the carbon atoms at the bridgehead positions decreases within this subgroup of compounds. In bicyclo[1.1.1]pentane (**8a**), for example, the C1–C3 distance is 1.85 Å,[19] and the surprisingly large value (18 Hz) observed[20] for $^4J(H1-H3)$ has been ascribed[21] to the interaction produced by overlap of the rear lobes of the bridgehead carbon–hydrogen orbitals.[22] An even more striking example attributed to this kind of interaction is the enormous four-bond H–F coupling (70.6 Hz) observed in 1-fluorobicyclo[1.1.1]pentane (**8b**).[23] During the course of this investigation, Barfield and his colleagues[24] reported that the presence of such nonbonded interactions has an important bearing on the magnitude of $^3J(^{13}C_{COOH}-C4)$ in the ^{13}C-labeled carboxylic acids **3d** and **5d**. Furthermore, calculations by Barfield's group demonstrate the particular importance of the effect of nonbonded interactions in the bicyclo[1.1.1]pentane system.[24]

Scheme I

$$R\text{-Hal} \xrightarrow{a} R\text{-Li} \xrightarrow{b,c} R\text{-}^{13}COOH \xrightarrow{d} R\text{-}^{13}CH_2OH \xrightarrow{e} R\text{-}^{13}CH_2OTs \xrightarrow{f} R\text{-}^{13}CH_3$$

(a) Li; (b) $^{13}CO_2$; (c) H_3^+O; (d) $LiAlH_4$; (e) TsCl, pyridine; (f) $LiB(Et)_3H$

Scheme II[a]



[a] a, $TsNHNH_2$; b, n-BuLi; c, HgO, Br_2; d, Li; e, $^{13}CO_2$; f, $LiAlH_4$; g, PDC; h, NH_2NH_2, KOH, $HOCH_2CH_2OH$.

Results and Discussion

Syntheses. For economy of operation in the projected synthesis of **1c–8c** an important requirement was to employ as inexpensive a ^{13}C-labeled reagent as possible, and, additionally, to insert the label as late as possible in the sequence, beyond which it was essential that high yields be maintanined. We found that the traditional route outlined in Scheme I satisfied most of these criteria, and that it could be successfully applied to the synthesis of **1c–3c** and **5c** from the known corresponding bridgehead halides.

This route, however, is inappropriate for the synthesis of the caged compounds **6c** and **7c** due to the lability of the corresponding intermediate p-toluenesulfonate esters. For example, rearrangment of cubanyl derivatives such as ((tosyloxy)methyl)cubane is well-documented,[25] the driving force for rearrangement being provided by the relief of strain which accompanies ring expansion. Scheme II depicts the method of preparation of labeled nortricyclene-1-carboxylic acid (**6d**) and the modification adopted for its conversion into the required 1-methylnortricyclene (**6c**).

Methylcubane-9-^{13}C (**7c**) was obtained via an alternative route involving direct alkylation at the bridgehead (eq 1).[26] Although

$$RLi + {}^{13}CH_3OSO_2C_6H_4CH_3 \rightarrow R^{13}CH_3 + LiOSO_2C_6H_4CH_3 \quad (1)$$

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Table I. Carbon-13 Chemical Shifts[a,b] in the ^{13}C-Labeled Methyl-Substituted Hydrocarbons 1c–8c

compd	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10	C_{Me}
1c	29.82 (28.7)	44.69 (38.2)	28.93 (28.7)	36.97 (38.2)	28.93 (28.7)	36.97 (38.2)	28.93 (28.7)	44.69 (38.2)	44.69 (38.2)	36.97 (38.2)	31.45
2c	27.14 (24.0)	33.20 (26.0)	26.61 (26.0)	24.44 (24.0)	26.61 (26.0)	33.20 (26.0)	33.20 (26.0)	26.61 (26.0)			28.78
3c	43.72 (36.6)	36.74 (30.0)	31.22 (30.0)	37.76 (36.6)	31.22 (30.0)	36.74 (30.0)	45.23 (38.6)				21.00
4c	39.70 (34.13)	36.40 (29.36)	16.86 (15.97)	28.47 (29.36)	30.08 (34.13)	38.75 (33.20)	38.75 (33.20)				28.00
5c	48.47 (39.5)	32.98 (26.3)	29.16 (26.3)	36.74 (39.5)	43.77 (39.0)	43.77 (39.0)					19.78
6c	17.89 (10.3)	17.33 (10.3)	34.10 (33.4)	31.98 (29.9)	34.10 (33.4)	17.33 (10.3)	39.00 (33.4)				15.47
7c	55.68 (48.11)	50.10 (48.11)	43.98 (48.11)	48.96 (48.11)	43.98 (48.11)	50.10 (48.11)	43.98 (48.11)	50.10 (48.11)			19.94
8c	42.17 (33.59)	52.18 (50.75)	27.39 (33.59)	52.18 (50.75)	52.18 (50.75)						19.07

[a] ±0.04 ppm. [b] Shifts in parentheses are for the parent hydrocarbon.

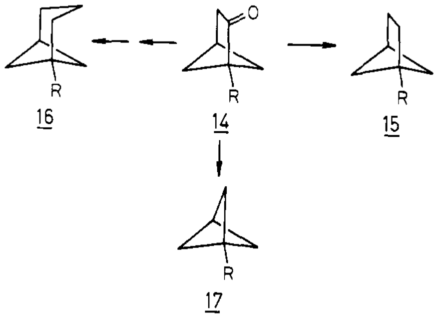


Figure 2.

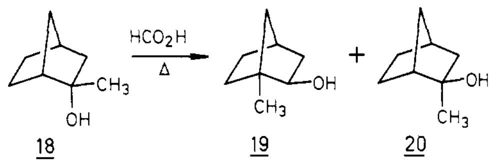


Figure 3.

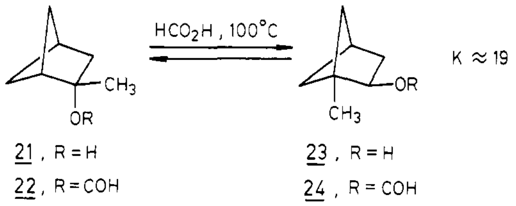
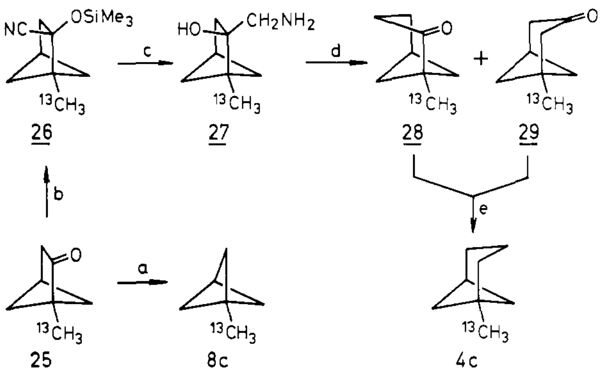


Figure 4.

Scheme III[a]



[a] a, hν; b, Me_3SiCN; c, $LiAlH_4$; d, CH_3COOH, $NaNO_2$; e, KOH, NH_2NH_2, $HOCH_2CH_2OH$.

iodomethane-^{13}C is required as precursor to labeled methyl tosylate, the overall exchange process represented by eq 1 is economically viable because conversion of bromocubane to methylcubane-*9*-^{13}C (**7c**) is effected in one step.

Synthesis of the remaining substrates, **4c** and **8c**, presented a rather more formidable problem. On the one hand monosubstituted derivatives of the bicyclo(3.1.1)heptane skeleton with functional groups such as carboxyl or halogen at the bridgehead are unknown, and although the corresponding derivatives of bicyclo[1.1.1]pentane have been described,[27] the route to these is a protracted one which is also low-yielding. We hoped to obviate both of those problems simultaneously in the following way. An intermediate we had previously shown[16b,17] to be invaluable in the preparation of related compounds is the substituted bicyclo[2.1.1]hexan-2-one (**14**) (R = H, F), which can be converted readily into the illustrated set of homologous bicycloalkanes **15**–**17** (Figure 2).

The success or otherwise in the application of this strategy to the syntheses of **4c** and **8c** rested ultimately on the availability of the precursor **14** (R = $^{13}CH_3$), and the following transformation, it seemed to us, showed great potential as a route to the required labeled ketone. Acid-catalysed isomerism of the adduct **18** obtained from addition of methylmagnesium iodide to norbornanone has been found[28] to yield, after hydrolysis, a mixture of the isomeric alcohols **19** and **20**, of which the former predominates. The key observation here is the production of a substrate bearing a methyl group at the bridgehead position (Figure 3). With the expectation that a similar kind of rearrangement would occur in the case of the lower homologue, we converted bicyclo[2.1.1]hexan-2-one (**14**) (R = H) into the tertiary alcohol **21**, which was then heated in boiling formic acid. To our delight, not only did rearrangement occur, but the isomer **24** proved overwhelmingly to be the thermodynamically favored product (Figure 4). Hydrolysis of the ester **24** and oxidation of the derived alcohol **23** afforded the required ketone **14** (R = CH_3). Scheme III depicts the conversion of the labeled ketone **25** into the hydrocarbons **4c** and **8c**. Decarbonylation of **25** to give 1-methylbicyclo[1.1.1]pentane-*6*-^{13}C (**8c**) was accomplished by gas-phase photolysis through silica. Although this process yields **8c** contaminated with isomeric alkenes, the latter can be removed efficiently by treatment of the product with either bromine or potassium permanganate solution. Ring expansion of **25** was performed as described for the unlabeled isomer[29] by treatment firstly with trimethylsilyl cyanide to give the adduct **26**, which was reduced with lithium aluminum hydride to the aminoalcohol **27**. Exposure of the latter to aqueous sodium nitrite and hydrochloric acid afforded a 9:1 mixture of the ketones **28** and **29**, which were deoxygenated under

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Table II. $^{13}C-^{13}C$ Coupling Constants, $^{n}J(CC)$, in the Hydrocarbons **1c–8c**[a]

compd	$^{1}J^{b}$	$^{2}J^{c}$	$^{3}J^{c}$	$^{4}J^{c}$
1c	36.75	≤0.4 (C2, C8, C9)	3.22 (C3, C5, C7)	≤0.5 (C4, C6, C10)
2c	38.09	0.34 (C2, C6, C7)	3.39 (C3, C5, C8)	0.31 (C4)
3c	39.45	1.56 (C2, C6)	3.36 (C3, C5)	
		1.07 (C7)	3.96 (C4)	
4c	37.90	1.10 (C2)	2.91 (C3)	0.27 (C4)
		0.66 (C6, C7)	5.82 (C5)	
5c	39.65	2.44 (C2)	2.77 (C3)	
		ncd (C5, C6)	7.50 (C4)	
6c	48.48	ncd (C2, C6)	0.50 (C3, C5)	
		1.96 (C7)	2.26 (C4)	
7c	37.02	2.03 (C2, C4, C6)	2.58 (C3, C5, C7)	0.51 (C8)
8c	37.62	ncd (C2, C4, C5)	9.71 (C3)	

[a] ncd ≡ no coupling was detected. [b] ±0.1 Hz. [c] ±0.02 Hz.

modified Wolff–Kischner conditions to give **4c**.

^{13}C NMR Data. The NMR parameters were generally obtained on substrates with 90% enrichment, although in several cases 66% labeled compounds were used.

Chemical Shifts. Carbon-13 chemical shifts were assigned on the basis of signal intensities, off-resonance decoupling experiments, comparison with those in the unsubstituted hydrocarbon, and, in some cases, according to literature data. Table I contains the shifts of the substrates **1c–8c** together with those of the parent hydrocarbons **1a–8a**. It can be seen that the magnitude of the α-effect arising from introduction of the methyl substituent spans quite a large range, from +1.1 ppm in 1-methyladamantane to about +9 ppm in 1-methylbicyclo[2.1.1]hexane. Although the methyl SCS appears to bear some correlation with the degree of strain at the bridgehead, this trend holds only for the first few members of the series, i.e., **1c–3c**.

β-Effects of allkyl groups are paramagnetic and normally quite large; this is generally true also in this series of compounds in which the methyl group consiststently causes a downfield shift of 6.8 ± 0.4 ppm in the β-carbons. Two exceptions which display much smaller β-effects are methylcubane (**7c**) (2.0 ppm) and 1-methylbicyclo[1.1.1]pentane (**8c**) (1.4 ppm).

The γ-substituent effects vary widely with no apparent systematic trend. Thus γ_{Me} ranges from −6.2 ppm in **8c** to +2.9 ppm (at C3) in **5c**. The presence of multiple γ paths to some carbon centers along with possible δ contributions to others complicates the situation regarding the magnitude and sign of γ_{Me}. For example the large diamagnetic shift observed for C3 in **8c** is associated with three γ pathways.

The ^{13}C chemical shifts of the methyl carbon in **1c–8c** present an interesting array. Some time ago Lippmaa and his co-workers[30] reported the existence of a linear correlation between δ_{Me} of several methyl-substituted polycycloalkanes with the one-bond bridgehead carbon–hydrogen coupling constant in the parent hydrocarbon. While the results of Table I show that in general terms an increase in strain is associated with enhanced shielding of the methyl carbon, the linear dependence suggested by Lippmaa[30] does not apply to the series of compounds under study here. These workers also observed a linear relationship between δ_{Me} and the α-effect of the methyl group, a feature which is substantiated by the chemical shift data of Table I.

Carbon–Carbon Coupling Constants. These parameters were recorded by direct measurement of the labeled substrates. Table II lists the measured coupling constants between C_{Me} and the various ring carbons in **1c–8c**. Of the one-bond couplings, $^{1}J(CC)$ in 1-methylnortricyclene (**6c**) is substantially larger than the others. This is not surprising inasmuch as **6c** is the only substrate in which the methyl group is attached to a three-membered ring, and, according to Stöcker and Klessinger,[31] the value of $^{1}J(C_{Me}-C1)$ in methylcyclopropane is characteristically large (43.4 Hz). In the remaining compounds however, the values of $^{1}J(CC)$ fall within a very narrow range, 38.2 ± 1.5 Hz, despite the wide variation in the s characters of the bridgehead carbon bonding orbitals. Initially, a trend was apparent in the series **1c–3c** and **5c**, which represent popular choices of model compounds of increasing constraint, and in which a regular increase in the magnitude of the directly bonded couplings can be seen. Beyond these, however, the values of $^{1}J(CC)$ essentially occur randomly, a pattern which contrasts with observations of the corresponding parameter $^{1}J(^{19}F-^{13}C)$ in the analogous fluorides **1b–5b** and **8b**. The latter couplings were found[17] to increase linearly with values of $^{1}J(^{1}H-^{13}C)$ in the parent hydrocarbons and the interpretation given was that the sum of the effects of the orbital and dipolar contributions is essentially constant throughout the series. Like the one-bond tin–carbon couplings in the related trimethylstannanes,[18] the magnitude of $^{1}J(CC)$ in the methylated analogues **1c–8c** bears little relationship to the s electron density of the relevant carbon bonding orbitals.

Although many experimentally determined $^{2}J(CC)$ values have been reported, very little is known of the factors which influence such coupling. Recently, Klessinger and Stöcker[32] reported that in substituted propanes $^{2}J(CC)$ is dependent on the C–C–C bond angle and the degree of substitution at the carbons. They also suggested that $^{2}J(CC)$ depends linearly on the product of the bond-orbital s character of the three carbon atoms according to the expression

$$^{2}J(CC) = -370(s_1 \cdot s_2 \cdot s_3 \cdot s_4)(-3.4) \qquad (2)$$

In the case of the substrates under study here the two-bond couplings to the labeled methyl carbon are invariably small and do not appear to follow the above relationship. For example, in strain-free 1-methyladamantane (**1c**) $^{2}J(CC)$ is 0.4 Hz, and in the highly constrained bicyclo[1.1.1]pentyl derivative **8c** coupling was not even detected; yet the relevant orbital hybridization is very different in the two systems. 1-Methylbicyclo[2.1.1]hexane (**5c**) is another interesting illustration because it possesses two two-bond coupling arrangements, one in which $^{2}J(^{13}C_{Me}-^{13}C2)$ is relatively large (2.44 Hz) but the other (to C5, 6) could not be detected.

In view of their interesting behavior, the experimental vicinal coupling constants for **1c–8c** are reproduced in Table III along with other relevant data. In a study involving the labeled carboxylic acids **2d**, **3d**, and **5d**, Barfield and his colleagues[24] noted that the magnitude of vicinal coupling involving the bridgehead carbon increases, as expected, with the number of essentially equivalent three-bond pathways available for transmission of such coupling. At the same time they observed that the rate of enhancement is less than that based on simple additives. Barfield[24] attributed this behavior to the presence of increased nonbonded interactions along the series, interactions which were shown by MO calculations to give coupling constant contributions of opposite sign to those arising from through-bond effects. Not surprisingly, we find that the same phenomenon occurs in the case of the compounds **1c–8c**. For example, in 1-methylbicyclo[2.2.1]heptane (**3c**), in which there is one vicinal pathway, $^{3}J(^{13}C_{Me}-^{13}C4)$ is 3.96 Hz, yet in **4c**, **5c**, and **7c** in which coupling is relayed by two

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(31) Stöcker, M.; Klessinger, M. *Liebigs Ann. Chem.* **1979**, 1960.

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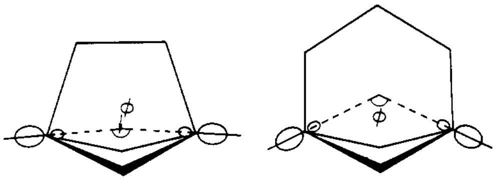
Table III. Experimental and Calculated Values of ${}^3J({}^{13}C_{Me}-{}^{13}C_x)$ in the Hydrocarbons **1c**–**8c**

compd	coupled atom, C_x	exptl J, Hz	bridgehead C–C distance, Å	calcd J, Hz[a]	ϕ, deg[b]	calcd J, Hz[c]	θ, deg[d]
1c	C3	3.22		3.32		3.73	180
2c	C3	3.39		3.72		3.73	180
3c	C3	3.36		3.11		2.89	153.7
	C4	3.96	2.32	3.84	123	3.73	180
4c	C3	2.91		2.95		3.20	159.5
	C5	5.82	2.14	5.36	102	4.14	141.7
5c	C3	2.77		2.85		3.73	180
	C4	7.50	2.17	5.71	169	7.37	173.6
6c	C3	0.50				1.92	140
	C4	2.26				3.73	180
7c	C3	2.58	2.19	2.71	109.5	3.10	135
8c	C3	9.71	1.85	8.95	180	11.20	180

[a] INDO SCF MO Calculation. [b] Bridgehead interorbital angle. [c] Calculated value employing the expression derived by Berger (ref 13a). [d] CH_3-C-C-C dihedral angle.

three-bond pathways, the values of ${}^3J$(CC) are 5.82 (to C5), 7.50 (to C4), and 2.58 (to C3) Hz, respectively. Furthermore in the substrate **8c** where coupling is transmitted by three three-bond pathways, the vicinal coupling constant is 9.71 Hz, which is significantly lower than that anticipated. By and large these experimental values agree very well with data obtained from MO results based on the finite perturbation theory[33] in the INDO approximation of SCF MO theory.[34] These calculated ${}^3J$(CC) values[35] which give an estimate of Fermi contact contributions are also displayed on Table III. Significantly, the MO results show that as the internuclear distance between the bridgehead carbon atoms decreases, e.g., as in **3c** → **4c** = **5c** → **8c**, the contribution to the coupling associated with "through-space" bridgehead orbital interactions increases. As noted above,[24] the net result is a reduction in the magnitude of ${}^3J$(CC) because through-space effects provide negative contributions to the observed coupling. For example, in the bicyclo[1.1.1]pentyl system **8c** the through-bond contribution to vicinal coupling is estimated to be 22.05 Hz and that associated with through-space interaction −13.10 Hz, giving a net calculated value of 8.95 Hz. Interestingly, in the case of the fluorides **1b**–**5b** and **8b** greatly enhanced ${}^3J$(CF) values were observed[17] because these effects reinforce each other.



(a) ϕ=169° (b) ϕ=102°

Figure 5. Bridgehead interorbital angle, ϕ, in (a) bicyclo[2.1.1]hexane and in (b) bicyclo[3.1.1]heptane.

The excellent agreement between the calculated and measured vicinal carbon-carbon couplings is gratifying, especially when the degree of uncertainty associated with some of the electron diffraction data is taken into account. Furthermore, the electron diffraction measurements[36] refer to the geometry of the unsubstituted hydrocarbon, and it is not known what structural distortion to the ring systems is caused by introduction of a methyl group at the bridgehead. Nevertheless, one instance where the correspondence between theory and experiment is disappointing relates to ${}^3J({}^{13}C_{Me}-{}^{13}C_{bridgehead})$ in each of the hydrocarbons **4c** and **5c**. In assessing the relevance of through-space interactions, the most important factor which must be considered is the extent of overlap of the rear-lobe orbitals of the bridgehead carbons. Distance, clearly, is one parameter which determines the efficiency of overlap; another is the size of the interorbital angle, ϕ (Figure 5).[37] The electron diffraction data[36] show that the internuclear distance between the bridgehead carbons is essentially the same in **4c** and **5c**. The magnitude of the interorbital angle is, however, substantially different in the two cases, being larger in the case of **5c** (ϕ 169°) than in **4c** (ϕ 102°). Hence orbital overlap in the bicyclo[2.1.1]hexyl system **5c** (Figure 5a) is expected to be much more effective than it is in 1-methylbicyclo[3.1.1]heptane (**4c**) (Figure 5b). As a result through-space interactions should be greater in **5c** than in **4c**. While the MO results suggest that the ${}^3J$(CC) values should be approximately the same, experimentally it is found that ${}^3J({}^{13}C_{Me}-{}^{13}C5)$ in **4c** is 5.82 Hz and ${}^3J({}^{13}C_{Me}-{}^{13}C4)$ in **5c** is 7.50 Hz.

In this connection it is worth noting that another distinguishing feature of compounds **4c** and **5c** is the relative size of the CH_3–C–C–$C_{bridgehead}$ dihedral angles (**4c**, 142°; **5c**, 173°). It occurred to us that the measured ${}^3J$(CC) values may simply reflect a response to this angular difference, and it seemed appropriate, therefore, to test the existence or otherwise of a correlation between ${}^3J$(CC) and the CH_3–C–C–$C_{bridgehead}$ dihedral angle. In the event we found that application of the empirical relationship devised by Berger[13a] for alicyclic systems (eq 3) gave calculated values

$$ {}^3J(\mathrm{CC}) = 1.67 + 0.176 \cos \theta + 2.24 \cos 2\theta \qquad (3) $$

for ${}^3J({}^{13}C_{Me}-{}^{13}C_{bridgehead})$ in **4c** and **5c** in the correct direction and in reasonable agreement with those observed (Table III). Indeed, as the entries in Table III illustrate, the Karplus expression can be employed quite generally for the systems under study here when due allowance is made for the number of vicinal pathways involved. Thus, although Berger suggests[13a] that eq 3 be limited to relatively strain-free substrates, we find that its rather wider application copes satisfactorily with coupling in highly strained molecules such as **7c** and **8c**. Finally, although it can be seen that several values of ${}^3J$(CC) so determined do not agree quite as closely with the experimental values as is desirable, better agreement may be possible if allowance is made for the small contributions from four- and five-bond pathways.

In summary then we are led to conclude that there is strong evidence for the view[24] that through-space interactions play an important role in determining the magnitude of the vicinal coupling constants in the majority of the substrates **1c**–**8c**. That this applies particularly to those constrained systems in which the distance between the bridgehead carbons is substantially decreased is supported by MO calculations. At the same time, however, we

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(33) Pople, J. A.; McIver, Jr., J. W.; Ostlund, N. S. *J. Chem. Phys.* **1968**, *49*, 2960, 2965.

(34) Pople, J. A.; Beveridge, D. L.; Dobosh, P. A. *J. Chem. Phys.* **1967**, *47*, 2026.

(35) The program employed was QCPE Program FINITE No. 224 and incorporating several modifications introduced by Professor N. V. Riggs. The magnitude of the through-space interactions was determined as described previously.[23,24]

(36) For electron diffraction data on: **1a**, Hargittai, I.; Hedberg, K. *J. Chem. Soc., Chem. Commun.* **1971**, 1499; **2a**, Yokozeki, A.; Kuchitsu, K.; Morino, Y. *Bull. Chem. Soc. Jpn.* **1970**, *43*, 2017; **3a**, Chiang, J. F.; Wilcox, Jr., C. F.; Bauer, S. H. *J. Am. Chem. Soc.* **1968**, *90*, 3149; **4a**, Dallinga, G.; Toneman, L. H. *Recl. Trav. Chim. Pays-Bas.* **1969**, *88*, 185; **5a**, Chiang, J. F. *J. Am. Chem. Soc.* **1971**, *93*, 5044; **8a**, ref 19. For X-ray data on **7a** see: Fleischer, E. B. *J. Am. Chem. Soc.* **1964**, *86*, 3889.

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draw attention to the correlation between the observed couplings and the relevant dihedral angles, although empirical relationships such as eq 3 should be employed with caution and with due regard for the complex nature of $^3J(CC)$.

Experimental Section

Infrared spectra were recorded on a Perkin-Elmer 237 grating spectrometer. Routine ^1H NMR spectra were obtained on a Varian A60-D instrument and precise ^1H spectra as well as all ^{13}C NMR spectra were measured on a JEOL FX90Q instrument operating at 89.56 and 22.53 MHz, respectively. Unless otherwise specified, samples were dissolved in $CDCl_3$ which also served as internal lock; chemical shifts are referenced to Me_4Si. For chemical shift measurements, ^{13}C spectra were normally run at 4000-Hz spectral width using 8K data points, corresponding to 0.04 ppm digital resoltuion. Accurate measurement of coupling constants was performed by running spectra at 200–400 Hz with 16K/32K data points, giving 0.02 Hz digital resolution. Mass spectra were determined on an AEI MS30 spectrometer. Analytical GC was performed on a Varian 1740 chromatograph using 10 ft × 0.125 in. stainless steel columns packed with 5% SE-30 on Chromasorb W or 5% Carbowax 20M on Chromasorb G. Preparative GC was carried out on a Varian Aerograph 920 instrument using 10 ft × 0.25 in. stainless steel columns filled with the above packings and employing helium as carrier gas. Microanalyses were performed by the Australian Microanalytical Service, Melbourne. Methyl-^{13}C *p*-toluenesulfonate was prepared from iodomethane-^{13}C as described for the unlabeled isomer.[38]

Adamantane-1-carboxylic-*11*-^{13}C- Acid (1d). A dry 100-mL three-necked flask fitted with a flexible Nichrome wire stirrer, a reflux condenser, and a serum cap was charged with dry hexane (50 mL) and 2% sodium–lithium alloy shot (large excess). Crushed glass was added to cleanse the alloy surface throughout the reaction.[39] The contents were stirred vigorously and heated to reflux under an argon atmosphere while a solution of 1-chloroadamantane[40] (0.75 g, 4.4 mmol) in dry hexane (5 mL) was added dropwise via a syringe through the serum cap.

After 5 h the reaction was complete and the mixture was allowed to cool to room temperature before the lithio derivative, as a suspension in the hexane, was transferred into a 100-mL pressure bottle via a stainless steel transfer line. The bottle was maintained under a nitrogen atmosphere while it was cooled to −80 °C. Carbon dioxide (66% ^{13}C) was generated by slow addition of concentrated sulfuric acid onto ^{13}C-enriched barium carbonate (0.9 g, 4.5 mmol) and condensed in the bottle by way of a fine needle placed well below the surface of the hexane. The last traces of carbon dioxide were swept into the bottle by a gentle stream of nitrogen. The bottle was then sealed and shaken at ambient temperature for two days. Normal workup of the mixture afforded upon sublimation (100 °C (0.01 mm)) pure adamantane-1-carboxylic-*11*-^{13}C acid (0.5 g, 63%) whose physical properties coincided with those reported for the unlabeled acid.

1-Methyladamantane-*11*-^{13}C (1c). Adamantane-1-carboxylic-*11*-^{13}C acid (**1d**) (0.5 g, 2.78 mmol) dissolved in dry ether (20 mL) was added in a dropwise manner to an ice-cold solution of lithium aluminum hydride (0.2 g, 5.2 mmol). The mixture was stirred at room temperature, under a nitrogen blanket, for 2 days. The flask was again cooled in an ice bath while excess hydride was destroyed by careful addition of water until the fine suspension suddenly coagulated. The ether was decanted and the solids were thoroughly extracted with fresh portions of ether (2 × 20 mL). Evaporation of the solvent followed by sublimation (80 °C 0.1 mm)) of the residue furnished 1-(hydroxymethyl)adamantane-*11*-^{13}C (0.40 g, 87%).

A solution of the latter in pyridine (3 mL) was stirred at 0 °C as *p*-toluenesulfonyl chloride (0.5 g, 2.6 mmol) was added. Stirring was continued for 24 h at ambient temperature, after which ice chips were added and 15 min later the contents were poured onto cold 15% hydrochloric acid (20 mL). The precipitated solid was collected by vacuum filtration, dried in vacuo, and recrystallised from pentane to yield 1-((tosyloxy)methyl)adamantane-*11*-^{13}C (0.75 g, 97%).

A 1.0 M solution of lithium triethylborohydride in tetrahydrofuran (0.5 mL, 0.5 mmol) was introduced slowly into a solution of the above tosylate (80 mg, 0.25 mmol) in tetrahydrofuran (0.5 mL) stirred at 0 °C. The mixture was heated at reflux for 16 h. On cooling it was treated successively with water (0.5 mL) and 3 M aqueous sodium hydroxide (2 mL) and 2 h later with 30% w/w aqueous hydrogen peroxide (2 mL). After 1 h the reaction mixture was extracted with pentane, the pentane extracts were thoroughly washed with water and then dried ($MgSO_4$), the solvent was evaporated, and the residue was sublimed (40 °C (20 mm)) to give **1c** as a colorless crystalline solid (24 mg, 66%) whose physical properties were in accord with those reported in the literature for the unlabeled material: ^1H NMR δ ($CDCl_3$) 0.75 (t, 3 H, J = 125 Hz).

Bicyclo[2.2.2]octane-1-carboxylic-*9*-^{13}C Acid (2d). A procedure identical with that used to prepare **1d** was employed to synthesize **2d** (0.75 g, 69%) from 1-chlorobicyclo[2.2.2]octane.[41] The acid **2d** had the correct physical properties.

1-Methylbicyclo[2.2.2]octane-*9*-^{13}C (2c). The labeled acid **2d** (0.7 g, 4.5 mmol) was reduced to 1-(hydroxymethyl)bicyclo[2.2.2]octane-*9*-^{13}C (0.55 g, 86%) as described above for reduction of **1d**. The derived alcohol was converted into the tosylate ester (1.0 g, 99%) by the usual method. Reduction of the latter was effected by lithium triethylborohydride, and the solution thus obtained was carefully concentrated by distillation of the pentane. Preparative GC of the concentrate afforded crystalline **2c** (0.15 g, 38%) whose physical properties corresponded with those of the unlabeled isomer: ^1H NMR δ ($CDCl_3$) 0.73 (t, 3 H, J = 124.5 Hz).

Bicyclo[2.2.1]heptane-1-carboxylic-*8*-^{13}C Acid (3d). The lithiation procedure used in the synthesis of **1d** was employed to generate 1-bicyclo[2.2.1]heptyllithium from 1-bromobicyclo[2.2.1]heptane[18] (0.6 g, 3.4 mmol), although crushed glass is not needed in this case. Meanwhile ^{13}C-labeled carbon dioxide was generated and condensed into dry ether (100 mL) cooled to −70 °C. The alkyllithium dissolved in hexane was added slowly to the cold ether solution, and after 30 min the stirred solution was allowed to warm slowly to room temperature. Normal workup afforded **3d** (0.2 g, 42%), which had the expected physical properties.

1-Methylbicyclo[2.2.1]heptane-*8*-^{13}C (3c). The carboxylic acid **3d** (180 mg, 1.3 mmol) was reduced in the same manner as that employed above for reduction of **1d**, to give 1-(hydroxymethyl)bicyclo[2.2.1]heptane-*8*-^{13}C (140 mg, 88%). The derived tosylate was reduced by lithium aluminum hydride in ether giving 1-methylbicyclo[2.2.1]heptane-*8*-^{13}C (**3c**), which displayed the expected physical properties: ^1H NMR δ ($CDCl_3$) 1.13 (t, 3 H, J = 124 Hz).

Bicyclo[2.1.1]hexane-1-carboxylic-*7*-^{13}C Acid (5d). 1-Bromobicyclo[2.1.1]hexane[42] (1.0 g, 6.2 mmol) was similarly treated with lithium and the alkyllithium thus obtained was converted into the labeled acid **5d** (0.3 g, 38%) as described above, employing 90% enriched carbon dioxide.

1-Methylbicyclo[2.1.1]hexane-*7*-^{13}C (5c). Following the procedure above, the acid **5d** (0.25 g, 2 mmol) was reduced to the hydroxymethyl derivative (0.2 g, 90%), which was esterified with tosyl chloride and the derived tosylate treated with 1.0 M lithium triethylborohydride. The volatile product **5c** was isolated by extraction with fluorotrichloromethane: ^1H NMR δ ($CDCl_3$) 1.13 (t, 3 H, J = 124.5 Hz).

1-Bromobicyclo[2.2.1]heptane-2-one Tosylhydrazone (10). A mixture of 1-bromobicyclo[2.2.1]heptan-2-one (**9**)[42] (1.5 g, 7.9 mmol), (*p*-tolylsulfonyl)hydrazine (1.5 g, 8.0 mmol), and acetic acid (0.1 mL) in ethanol (12 mL) was heated at reflux for 15 h. The product crystallized on cooling (−10 °C) and was recrystallized (twice) from ethanol to afford the pure tosylhydrazone **10** (2.55 g, 86%): mp 180–181 °C; IR (Nujol) 3275, 1595 cm^{-1}; ^1H NMR δ ($CDCl_3$) 8.08–7.20 (m, 5 H), 2.63–2.32 (m, 4 H), 2.45 (s, 3 H), 2.32–1.19 (m, 8 H); mass spectrum, *m/e* 359, 357, M + 1 (0.7, 0.7%), 358, 356 M (0.8, 0.9%), 203 (32%), 202 (14%), 201 (29%), 200 (13%), 167 (7%), 166 (60%), 159 (8%), 157 (6%), 140 (12%), 139 (12%), 124 (38%), 94 (14%), 93 (100%), 92 (21%), 91 (82%). Anal. ($C_{14}H_{17}BrN_2O_2S$) Calcd: C, 47.07; H, 4.80. Found: C, 47.32; H, 4.83.

1-Bromotricyclo[2.2.1.0^{2,6}]heptane (11). Method A.[43] The tosylhydrazone **10** (1.8 g, 5.04 mmol) was treated with sodium methoxide (3.1 g, 57 mmol) in dry diethylene glycol dimethyl ether (13 mL) and the mixture heated at reflux for 3 h. On cooling, ice water (100 mL) was added, the aqueous solution was extracted with chlorotrifluoromethane, and the combined extracts were washed with cold water and dried ($MgSO_4$). Evaporation of the solvent left a light brown oil (1.2 g) which on distillation furnished **11** as a colorless liquid (0.85 g, 97%): ^1H NMR δ ($CFCl_3$) 1.95 (m, 1 H), 1.65 (d, 2 H, J = 1.7 Hz), 1.58–1.27 (m, 4 H), 1.16 (m, 2 H); ^{13}C NMR δ ($CFCl_3$) 42.52 (t, C1), 34.06 (t, C3, C5), 32.81 (d, C4), 30.34 (s, C1), 20.98 (d, C2, C6); mass spectrum, *m/e* 174, 172 M (51, 51%), 159, 157 (12, 12%), 146, 144 (16, 16%), 94 (9%), 93 (100%), 92 (10%), 91 (56%), 78 (21%), 77 (98%), 66 (12%), 65 (32%).

Method B. The carboxylic acid **12** (0.5 g, 3.6 mmol), a byproduct in the preparation of **9**,[42] was converted into the corresponding bromide **11** (0.3 g, 48%) under conditions previously reported[44] for use with other bridgehead carboxylic acids.

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Tricyclo[2.2.1.0^{2,6}]heptane-1-carboxylic-*8*-^{13}*C* Acid (6d). This synthesis was achieved by the same method used for the preparation of **1d**. The bromide **11** (0.3 g, 1.73 mmol) gave **6d** (84 mg, 32%) as a white crystalline solid after sublimation (70 °C (0.5 mm)). Physical data were consistent with those of the unlabeled substance **12**.

1-Methyltricyclo[2.2.1.0^{2,6}]heptane-*8*-^{13}*C* (6c). Reduction of **6d** (84 mg, 0.60 mmol) by lithium aluminum hydride as described in the preparation of **1c** gave a quantitative yield of 1-(hydroxymethyl)tricyclo[2.2.1.0^{2,6}]heptane-*8*-^{13}*C* (**13**) (76 mg): ^{1}H NMR δ ($CDCl_3$) 3.77 (t, 2 H, J = 140.6 Hz), 2.12 (br s, 1H), 2.01 (br s, 1 H), 1.52–0.83 (m, 8 H). A mixture of **13** (75 mg, 0.60 mmol), acetic acid (0.02 mL), and pyridinium chromate on silica gel[45] (1.0 g) in dry dichloromethane (2.0 mL) was stirred at room temperature, under nitrogen, in a stoppered flask for 3 h (reaction followed by GC). The reaction mixture was diluted with ether (5 mL) and filtered through a Celite pad, and the solids were rinsed with fresh portions of ether (2 × 5 mL). The combined filtrates were washed successively with 5% aqueous hydrochloric acid, water, saturated aqueous sodium hydrogen carbonate, and brine and then dried ($MgSO_4$). The solvents were removed in vacuo without external heating, and the crude aldehyde then added to a solution of potassium hydroxide (0.4 g, 85% w/w) and hydrazine (0.3 g, 9.4 mmol) in diethylene glycol (1.0 mL). Reduction was effected in the same manner as outlined below in the preparation of **16** (R = CH_3) and gave **6c** (60 mg, 92%): ^{1}H NMR δ ($CDCl_3$) 1.91 (m, 1 H), 1.65–1.00 (m, 9 H), 1.22 (t, 3 H, J = 125.5 Hz) 0.8 (br s, 2 H).

Methylcubane-*9*-^{13}*C* (7c). Lithiation of bromocubane[46] under the standard conditions employed above for the other halides occurred very slowly. The reaction was facilitated by sonication, however. A mixture of bromocubane (0.3 g) and a large excess of lithium shot in cyclohexane was heated under reflux while being irradiated with ultrasound (200 W, 45 KHz) for 2 days. Cavitation produced vigorous agitation at the surface of the metal, converting the shot into a powder. Methyl-^{13}*C* tosylate (0.3 g) was added at room temperature and the contents stirred for 1 h, after which water was added and the mixture then acidified. The organic layer was washed with water and brine, then dried ($MgSO_4$), and filtered through a short column packed with Florisil. The bulk of the solvent was distilled through a short fractionating column, and the residue cooled in ice while the remainder of solvent was removed under vacuum (ca. 20 mm). The product was purified by sublimation (0.1 mm) into a cold trap. Analysis (GC and ^{1}H and ^{13}C NMR) showed it to consist of a mixture of cubane and methylcubane-*9*-^{13}*C* (**7c**): ^{1}H NMR δ ($CDCl_3$) 4.0 (m, 7 H), 1.27 (t, 3 H, J = 126.0 Hz); mass spectrum, *m/e* 119 M (21%), 118 M – 1 (100%), 117 (27%), 116 (54%), 104 (25%), 103 (62%), 93 (25%), 92 (87%), 91 (28%), 79 (14%), 78 (70%), 77 (45%).

2-Methylbicyclo[2.1.1]hexan-2-ol (21). A solution of methylmagnesium iodide was prepared by addition of a cool solution of iodomethane (3.7 g, 26 mmol) in anhydrous ether (40 mL) to magnesium turnings (3.0 g, 120 mmol) and iodine (ca. 1 mg) in anhydrous ether (40 mL) cooled to –5 °C. Bicyclo[2.1.1]hexan-2-one[47] (**14**) (R = H) (2.5 g, 26.0 mmol) was then introduced by syringe in a dropwise manner, after which the mixture was treated with dilute hydrochloric acid, shaken with ether, and then filtered, and the aqueous filtrate and solids were thoroughly washed with fresh ether. The combined organic fractions were washed successively with saturated aqueous sodium hydrogen carbonate, water, and brine and then dried ($MgSO_4$). The solvent was evaporated to give **21** (2.8 g, 97%) of sufficient purity for direct use in subsequent reactions. Distillation yielded the pure alcohol (2.7 g, 94%) as a colorless solid: mp 27.5–28.5 °C (lit.[48] mp 8–9 °C); bp (Kugelrohr) 60 °C (20 mm); ^{1}H NMR δ (CCl_4) 2.60–2.08 (m, 2 H), 1.96 (s, 1 H), 1.88–1.52 (m, 6 H), 1.40 (s, 3 H); ^{13}C NMR δ ($CDCl_3$) 77.36 (s, C2), 51.70 (d, C1), 44.03 (t, C3), 40.31 (t, C5 or C6), 38.49 (d, C4), 38.10 (t, C6 or C5), 26.39 (q, CH_3); IR (neat) 3305 cm^{-1}; mass spectrum, *m/e* M 112 (3%), 111 (2%), 97 (35%), 79 (79%), 77 (17%), 71 (100%), 58 (63%).

1-Methylbicyclo[2.1.1]hexan-2-ol (23). A mixture of (**21**) (2.7 g, 24.1 mmol) and 98% formic acid (22 mL) was heated at 100 °C for 4 h. After being allowed to attain room temperature the mixture was basified with 50% aqueous potassium hydroxide and stirred for 2 h. Dilute hydrochloric acid was then added to bring the mixture to pH 8. The product was extracted with ether and the ether extracts were washed with water, brine and then dried ($MgSO_4$) and the solvent was evaporated. Distillation of the dark oily residue afforded pure **23** (2.1 g, 78%) as a colorless solid: mp 33–34 °C; bp 67.5–68 °C (23 mm); ^{1}H NMR δ ($CDCl_3$) 3.90 (s, 1 H) 3.56 (s, 1 H) 2.40–2.17 (m, 1 H) 1.72–0.95 (m, 6 H) 1.16 (s, 3 H); ^{13}C NMR δ ($CDCl_3$) 75.24 (d, C2), 52.35 (s, C1), 43.86 (t, C5 or C6), 40.26 (t, C3), 39.09 (t, C5 or C6), 34.98 (d, C4), 16.25 (q, CH_3); IR (neat) 3335 cm^{-1}; mass spectrum, *m/e* 112 M (7%), 111 (7%), 97 (26%), 79 (35%), 71 (100%), 57 (33%), 56 (33%).

1-Methylbicyclo[2.1.1]hexan-2-one (14, R = CH_3). Method A. A mixture of pyridinium dichromate[49] (5.87 g, 15.6 mmol), pyridinium trifluoroacetate (3.6 mL of a 1.0 M solution in dichloromethane), and **23** (1.0 g, 8.9 mmol) in dichloromethane (20 mL) was stirred at room temperature under a nitrogen atmosphere for 24 h (90% completion by GC). The mixture was diluted with ether (100 mL) and filtered, and the filtrate was washed with water and dried, and the solvent was evaporated. The residue was chromatographed on silica gel. The product **14** (R = CH_3) (0.75 g, 77%) was eluted by 1% ether in pentane and had physical properties identical with those reported:[50] ^{13}C NMR δ ($CDCl_3$) 214.09 (C=O), 60.91 (C1), 44.95 (C5, C6), 41.47 (C4), 30.93 (C3), 12.56 (CH_3).

Method B. 1-Methylbicyclo[2.1.1]hexan-2-ol (**23**) (0.9 g, 8.0 mmol) was dissolved in ether (40 mL), and chromic acid on silica gel[45] (10.2 g, 4.3 mmol $Cr_2O_7^{2-}$) was added in one portion at room temperature. The mixture became warm and the reaction was complete within 10 min. The solution was then filtered through a cone of silica gel, which was rinsed with further portions of ether, and the ether was distilled to afford **14** (R = CH_3) (0.85 g, 96%) (pure by GC).

1-Methylbicyclo[2.1.1]hexan-2-one-*7*-^{13}*C* (25). This ketone was prepared from bicyclo[2.1.1]hexan-2-one using 90% enriched methyl-^{13}*C* iodide and following the procedure used above for the synthesis of the unlabeled substrate.

1-Methylbicyclo[1.1.1]pentane (17, R = CH_3). A flame-dried cylindrical quartz vessel (1600 mL) previously rinsed with base was flushed with nitrogen and charged with **14** (R = CH_3) (0.15 g, 1.36 mmol) and a small drop of mercury. A stopcock was fitted to the vessel which was cooled in liquid nitrogen before being evacuated (0.01 mm) and sealed. The vessel was placed in an oven at 120 °C for 10 min and then quickly secured on a sand bath preheated to 130 °C inside a Rayonet photochemical reactor fitted with 254-nm lamps. After 1 h of irradiation the vessel was removed and allowed to cool to room temperature. The reaction products (45 mg) were collected at 6 mm in a cold trap (ca. –100 °C) and alkene contaminants were removed by treatment with bromine, after which the residue was extracted with deuteriochloroform, and the extracts were washed with aqueous sodium metabisulfite. The organic phase was dried ($MgSO_4$) and the volatiles were collected at 12 mm in a cold trap (ca. –100 °C). This afforded a clean solution of 1-methylbicyclo[1.1.1]pentane (**17**) (R = CH_3) in $CDCl_3$ suitable for NMR analysis: ^{1}H NMR δ ($CDCl_3$) 2.48 (s, 1 H), 1.66 (s, 6 H), 1.10 (s, 3 H); mass spectrum, *m/e* 82 M (21%), 81 (15%), 67 (100%).

1-Methylbicyclo[1.1.1]pentane-*6*-^{13}*C* (8c). Irradiation of 1-methylbicyclo[2.1.1]hexan-2-one-*7*-^{13}*C* (**25**) under the above conditions produced **8c**: ^{1}H NMR δ ($CDCl_3$) 1.10 (t, 3 H, J = 125 Hz).

1-Methylbicyclo[3.1.1]heptane (16, R = CH_3). 1-Methylbicyclo[2.1.1]hexan-2-one (**14**) (R = CH_3) was converted into the 9:1 mixture of 1-methylbicyclo[3.1.1]heptan-2-one and 1-methylbicyclo[3.1.1]heptan-3-one as previously reported.[29] The mixture of derived ketones (0.6 g, 4.8 mmol), potassium hydroxide (3.7 g), and anhydrous hydrazine (2.6 g) in diethylene glycol (10 mL) was heated at 110 °C for 30 min, after which the temperature was raised to 180 °C for 1 h. A gentle flow of nitrogen over the reaction mixture carried the hydrocarbon produced into a cold trap (–70 °C). The colorless liquid which collected was pure 1-methylbicyclo[3.1.1]heptane (**16**) (R = CH_3) (0.44 g, 83%): ^{1}H NMR δ ($CDCl_3$) 2.40–2.07 (m, 1 H), 1.88–1.12 (m, 10 H), 0.95 (s, 3 H); mass spectrum, *m/e* 110 M (5%), 95 (65%), 82 (100%), 81 (35%), 68 (55%), 67 (73%). Anal. (C_8H_{14}) Calcd: C, 87.19; H, 12.81. Found: C, 87.36; H, 13.01.

1-Methylbicyclo[3.1.1]heptane-*8*-^{13}*C* (4c). A mixture of **25** (0.6 g, 5.45 mmol) and several mg of anhydrous zinc iodide was stirred at 0 °C under a nitrogen atmosphere and treated with cyanotrimethylsilane (0.6 g, 6.06 mmol) as described.[29] The adduct **26**, which was obtained cleanly within 10 min and had the expected spectral data (^{1}H and ^{13}C NMR and MS), was diluted with ether (15 mL) and then reduced with lithium aluminum hydride (0.3 g, 8.7 mmol) in boiling ether overnight. Workup[29] gave the amino alcohol **27** (0.6 g, 78%) as a crystalline solid. When **27** was dissolved in acetic acid (20 mL) and treated with sodium nitrite as reported for the unlabeled isomer,[29] it afforded a 9:1 mixture (0.38 g, 80%) of the isomeric ketones **28** and **29** whose properties were consistent with those of the unlabeled compounds. The mixture was reduced under the modified Wolff–Kischner conditions outlined above giving the

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hydrocarbon **4c** (0.31 g, 83%), which had the expected spectral properties: ^{1}H NMR δ ($CDCl_3$) 0.95 (t, 3 H, J = 124.5 Hz).

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Registry No. 1 (X = Cl), 935-56-8; **1** (X = $^{13}CH_2OH$), 65305-16-0; **1** (X = $^{13}CH_2OTs$), 87984-84-7; **1c**, 85553-56-6; **1d**, 50530-21-7; **2** (X = Cl), 2064-03-1; **2** (X = $^{13}CH_2OH$), 73948-81-9; **2** (X = $^{13}CH_2OTs$), 87969-53-7; **2c**, 80326-44-9; **2d**, 73948-77-3; **3** (X = Br), 13474-70-9; **3** (X = $^{13}CH_2OH$), 73948-82-0; **3c**, 76450-98-1; **3d**, 73948-78-4; **4c**, 80326-45-0; **5** (X = $^{13}CH_2OH$), 73948-83-1; **5** (X = Br), 77379-00-1; **5c**, 80326-46-1; **5d**, 73948-79-5; **6c**, 87969-51-5; **6d**, 87969-55-9; **7** (X = Br), 59346-69-9; **7c**, 87969-52-6; **8c**, 80326-47-2; **9**, 77378-99-5; **10**, 87969-54-8; **11**, 31991-53-4; **13**, 87969-56-0; **14** (R = H), 5164-64-7; **14** (R = CH_3), 20609-40-9; **16** (R = CH_3), 87969-60-6; **17** (R = CH_3), 10555-48-3; **21**, 87969-57-1; **23**, 87969-58-2; **25**, 87969-59-3; **27**, 87969-61-7; **28**, 87969-62-8; **29**, 87969-63-9; *p*-toluenesulfonylhydrazine, 1576-35-8; methyl iodide, 74-88-4.

Total Syntheses with Tricyclooctanone Building Blocks. Loganin Aglucon 6-Acetate[1]

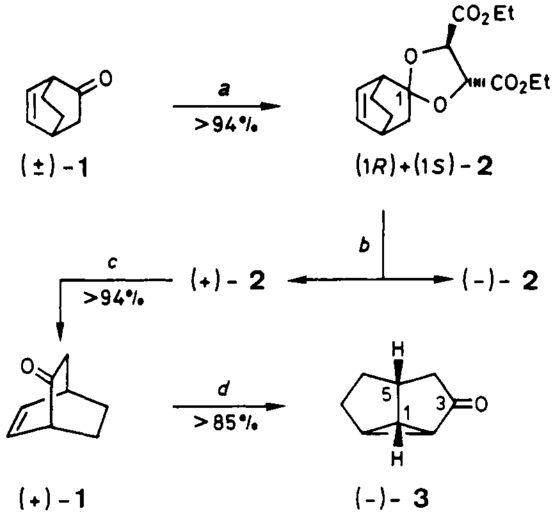
Martin Demuth,* Sosale Chandrasekhar, and Kurt Schaffner

Contribution from the Max-Planck-Institut für Strahlenchemie, D-4330 Mülheim a. d. Ruhr, West Germany. *Received June 2, 1983*

Abstract: A total synthesis of the monoterpene loganin aglucon 6-acetate in 17 steps from 1,3-cyclohexadiene is described. It involves the photochemical generation of enantiomerically pure tricyclo[3.3.0.0^{2,8}]octan-3-one as the key step and it employes an improved procedure for the resolution of bicyclo[2.2.2]octenone, the starting material for the triplet-sensitized rearrangement to the key building block. The synthesis is distinguished by a higher overall yield (ca. 7% in 17 steps from 1,3-cyclohexadiene) than previous efforts and is devoid of any separation problems, so that it can be carried through in multigram batches.

We have recently outlined the concept of a very versatile approach to the synthesis of polycyclopentanoid natural products with readily accessible optically active building blocks.[2] The concept involves the photochemical generation of *enantiomerically pure* tricyclo[3.3.0.0^{2,8}]octan-3-ones as the key step. The parent and most versatile of these structural units, **3**, is formed in >85% yield[3] in the acetone-sensitized oxadi-π-methane rearrangement of **1** (Scheme I).[4,5] Compound **3** is readily accessible in multigram batches from 1,3-cyclohexadiene, as a racemate, in four steps and ca. 54% overall yield and in optically active form in six steps and 19% overall yield for each enantiomer. Subsequent to our initial report[2a] the use of *racemic*, more highly substituted tricyclo[3.3.0.0^{2,8}]octan-3-ones of less versatile synthetic potential has been described.[6]

Scheme I[3]



^{a} Diethyl (*R*,*R*)-tartrate, *p*-TsOH, toluene, reflux. ^{b} Chromatography, see Experimental Section. ^{c} 1 N HCl, THF, 40 °C. ^{d} 1% acetone solution, $h\nu$ (λ = 300 nm); see ref 4.

We now report the synthesis of enantiomerically pure (enantiomeric excess >98%) loganin aglucon 6-acetate (**11**)[7] from (1*S*,5*R*)-(−)-**3** (Scheme II), which also includes an improved procedure for the resolution of (±)-**1** into its enantiomers. The iridoid loganin[7] is a key biosynthetic intermediate for indole and monoterpene alkaloids and other natural products.[8] In earlier

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(3) All yields refer to isolated pure products.

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