Synthesis of Bridgehead-Substituted Bicyclo[2.2.1]heptanes by Radical Cyclization

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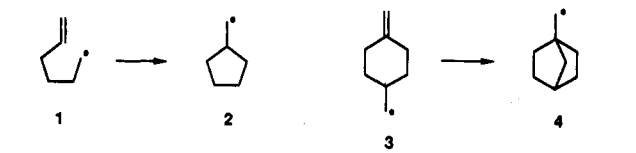
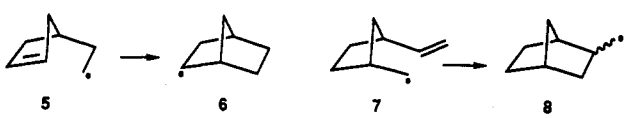
A kinetic investigation shows that the rate of cyclization (k_C) of the (4-methylenecyclohexyl)methyl radical **3** at 25 °C is 4.4×10^2 s^{-1}, which is considerably slower than that (2.3×10^5 s^{-1}) of the parent 5-hexenyl radical. The energy of activation for the process **3** → **4** is 12.8 kcal mol^{-1}, which is in excellent agreement with theoretical values derived from force-field calculations. Ring-closure of appropriately substituted (4-methylenecyclohexyl)methyl radical precursors allows the synthesis of bicyclo[2.2.1]heptyl systems with useful functionality at the bridgehead to be achieved readily and in high yield. An interesting example is given of the application of an iodine-atom-transfer cyclization to the synthesis of a bicyclo[2.2.1]heptane functionalized at C7 and C1.

The past decade has seen an explosive growth in the synthesis of organic molecules via radical intermediates.[2-7] One of the popular and highly successful radical processes employed to construct carbon–carbon bonds is based on the regioselective 5-*exo trig* cyclization of the 5-hexenyl radical **1** to the isomeric cyclopentylmethyl radical **2**.[8]



1 **2** **3** **4**



5 **6** **7** **8**

We have recently been attempting to devise procedures which provide ready access to bridgehead-substituted bicycloalkanes for NMR and solvolytic studies[9] and were attracted to the potential of the transformation **1** → **2** as an entry into the bicyclo[2.2.1]heptyl system. Specifically, capture of the radical **4** derived from an analogous cyclization of the (4-methylenecyclohexyl)methyl radical **3** would generate the required bridgehead-substituted bicycloalkane. In fact, there are two reports in the literature of the synthesis of the bicyclo[2.2.1]heptyl system via intramolecular radical cyclization. The first example[10] concerns ring-closure of the 2-(Δ^3-cyclopentenyl)ethylene radical **5** to give the bicyclic isomer **6** and the second involves the isomerization of the monocyclic radical **7** to **8** described by Beckwith and his associates.[11] However, the starting radicals in these cases are structurally unrelated to the (4-methylenecyclohexyl)methyl radical **3**, and in neither case is a bicyclo[2.2.1]heptane obtained having substitution at the bridgehead position. Thermodynamically, the enthalpy change associated with the conversion **3** → **4** is favorable; formation of a σ-bond in lieu of a π-bond is expected to compensate for the additional strain associated with the bicycloalkane. Further encouragement is provided by inspection of molecular models, which demonstrate that the reaction centers in **3** are in close proximity and in the appropriate alignment[12] for ring-closure when the six-membered ring adopts a flexible conformation. Ultimately, of course, the success or failure of the isomerization **3** → **4** would be determined by its kinetics.

Beckwith and his associates,[6,12,13] in particular, in addition to several other groups[14-16] have made a major contribution to our understanding of the factors which control radical cyclizations of the type **1** → **2**. In studies directed toward providing a rationale for the regiochemistry of ring-closure of the 5-hexenyl radical **1**, and its alkylated derivatives, both Beckwith and Schiesser[6,12] and Spellmeyer and Houk[17] have independently shown that force-field calculations[18] provide a reliable estimate of the activation energy for the process **1** → **2**. The essential difference between the procedures adopted by the two groups in their MM2 treatment of the respective transition-state models is that whereas Beckwith and Schiesser employ a fixed transition-state geometry, Spellmeyer and

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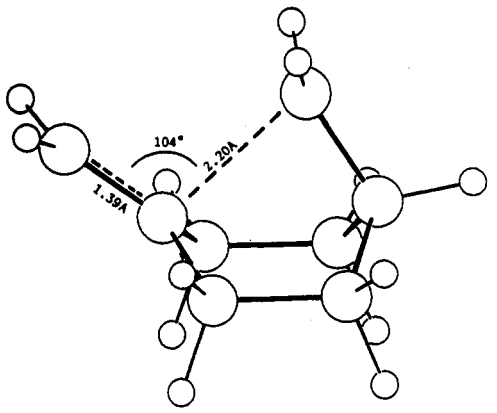


Figure 1. Calculated transition structure for the ring closure of (4-methylenecyclohexyl)methyl radical 3.

Table I. Calculated and Experimental Activation Barriers[a] to Cyclization of the 5-Hexenyl Radicals 1, 3, and 19

	calculated E_{act}[b]		
radical	B/S	S/H	experimental E_{act}
1	7.5[c]	6.8[d]	6.8[e], 6.9[f]
3	13.5	12.5	12.8
19	11.4	11.6	na[g]

[a] In kcal mol^{-1}. [b] B/S ≡ Beckwith–Schiesser method;[6,12] S/H ≡ Spellmeyer–Houk method.[17] [c] Reference 12. [d] Reference 17. [e] Reference 19. [f] Reference 15. [g] na ≡ not available.

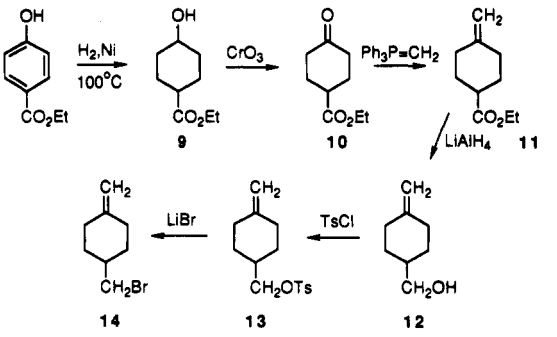
Houk have developed parameters to model the reacting centers in the transition state itself, thus making it flexible. The calculated barriers so derived by the two groups for a series of 5-hexenyl radical cyclizations are generally in good agreement with each other, and also with the experimentally-determined values.

We have undertaken a similar theoretical analysis of ring-closure of the (4-methylenecyclohexyl)methyl radical **3** in order to gain some insight into its feasibility. Molecular mechanics calculations of the activation energy associated with the cyclization **3** → **4** were performed using the two procedures described.[12,17] The Beckwith–Schiesser model predicted an energy barrier of 13.5 kcal mol^{-1}, corresponding to a transition structure depicted in Figure 1, and the Spellmeyer–Houk method a value of 12.5 kcal mol^{-1}. The reasonably close agreement between the two methods is impressive; as expected, both suggest that cyclization of **3** is considerably less favorable kinetically than that of the parent acyclic radical **1** (Table I).

At this stage we embarked on the experimental study. The target precursor to the radical **3** was (4-methylenecyclohexyl)methyl bromide (**14**), the synthesis of which was accomplished starting from ethyl *p*-hydroxybenzoate by the application of standard transformations (depicted in Scheme I).

GC analysis of the product obtained from treatment of a 0.027 M solution of the bromide **14** in *tert*-butylbenzene at 80 °C with 1 equiv of tributyltin hydride in the presence of AIBN showed it to consist of a 21:79 mixture of 1-methylbicyclo[2.2.1]heptane (**15**) and 4-methylmethylenecyclohexane (**16**), both of which were identified by comparison with authentic specimens. This result was encouraging from the point of view of its synthetic potential; it also provides qualitative confirmation of the conclusions reached by the force-field calculations, viz., that the isomerization **3** → **4** does have a significant energy barrier. A quantitative estimate of the activation energy

Scheme I



Scheme II

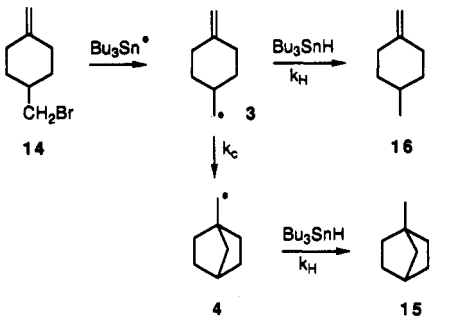


Table II. Kinetic Data for Cyclization of (4-Methylenecyclohexyl)methyl Radical 3 in *tert*-Butylbenzene

		product ratios		
temp, °C	[Bu_3SnH], M	15	16	k_C/k_H, M
80	0.026	7.2	92.8	2.04×10^{-3}
90	0.026	10.2	89.8	2.97×10^{-3}
100	0.026	14.0	86.0	4.26×10^{-3}
110	0.026	17.6	82.4	5.70×10^{-3}
120	0.026	21.5	78.5	7.20×10^{-3}

associated with the cyclization process **3** → **4** was obtained by performing kinetic experiments under pseudo-first-order conditions (10 equiv of Bu_3SnH) (Scheme II). The ratio of the isomeric hydrocarbon products **15** and **16** was determined by GC analysis, and the kinetic data so derived are collected in Table II. The integrated rate equation (eq 1) corresponding to Scheme II can be established readily:

$$\frac{k_C}{k_H} = \frac{[15]}{[16]}[Bu_3SnH] \qquad (1)$$

in which k_C is the rate constant for the cyclization process **3** → **4** and k_H is the rate constant for abstraction of a hydrogen atom from Bu_3SnH by the radical **3**. The Arrhenius parameters for the cyclization of **3** were derived by standard single variable regressional analysis of the data displayed in Table II with errors expressed at the 95% confidence level:

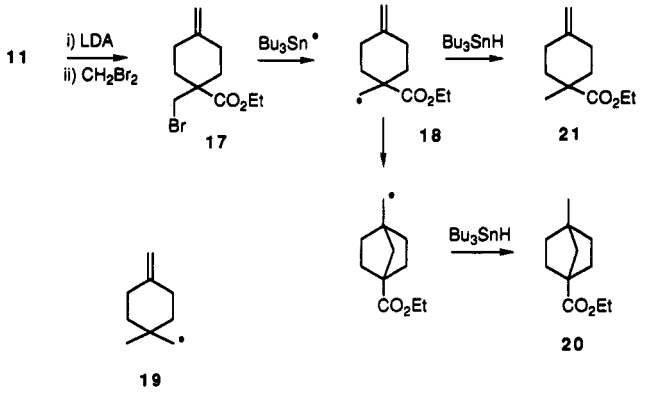
$$\log \frac{k_C}{k_H} = 2.93 \pm 0.33 - \frac{9.10 \pm 0.56}{2.3RT}$$

Using the typical primary radical rate of H-abstraction from Bu_3SnH[15] as the value of k_H

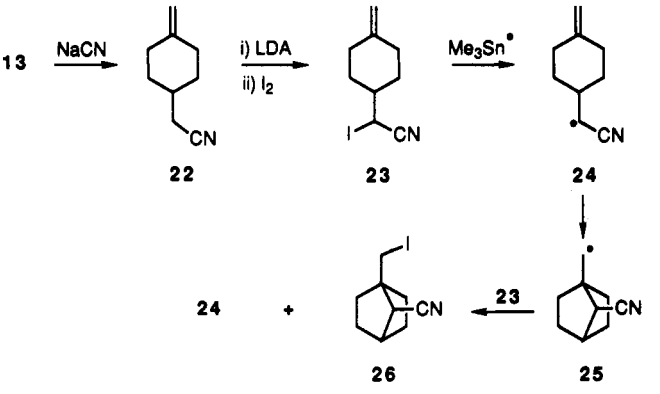
$$\log k_H = 9.07 \pm 0.24 - \frac{3.69 \pm 0.32}{2.3RT}$$

leads to the expression

Scheme III



Scheme IV



$$\log k_C = 12.0 \pm 0.4 - \frac{12.8 \pm 0.6}{2.3RT}$$

from which the value of k_C at 25 °C is calculated to be 4.4 × 10^2 s^{-1}. As anticipated, the rate of ring-closure of the (4-methylenecyclohexyl)methyl radical **3** is considerably slower than that determined[19] for cyclization of the parent 5-hexenyl radical **1** (2.3 × 10^5 s^{-1}). The value of log *A*, the preexponential term, is 12.0 which is in accord with the commonly observed values of log *A* for 5-hexenyl radical cyclizations.[19] The energy barrier is 12.8 kcal mol^{-1} and the close agreement between this experimentally-determined value and the calculated values cited above is impressive (Table I). The larger activation energy for cyclization of **3** over that associated with closure of **1** (6.8 kcal mol^{-1}) is a reflection of the increased amount of strain generated during cyclization of the former system.

These encouraging observations stimulated the move toward our next objective, the design of practical syntheses of bicyclo[2.2.1]heptyl derivatives having functionality at the bridgehead more amenable to manipulation. At the same time, if this were to be a viable synthetic strategy, we were conscious of the need to improve the yield of the bicycloalkane.

One simple expedient thought likely to fulfill both requirements involves the modified bromide **17**. According to the Thorpe–Ingold effect,[20] ring-closure of the derived radical **18** should be facilitated, an expectation we found to be supported by force-field calculations. To simplify the MM2 calculations, the energy barrier to cyclization was determined for the related model species, (1-methyl-4-methylenecyclohexyl)methyl radical **19**, in which a methyl group has replaced the ester function. The Beckwith–Schiesser method yielded a value of 11.4 kcal mol^{-1} for the activation energy of ring-closure of **19**, for which the Spellmeyer–Houk procedure predicted 11.6 kcal mol^{-1} (Table I). In practice, bromo ester **17** was synthesized readily by alkylation of the enolate anion of ester **11** with dibromomethane. Dropwise addition over 3 h of a 0.05 M solution of Bu_3SnH in benzene containing AIBN to a 0.05 M solution of the bromo ester **17** in boiling benzene was found to lead to a significant enhancement in the proportion of cyclized product (Scheme III). GC analysis showed the ratio of ethyl 4-methylbicyclo[2.2.1]heptane-1-carboxylate (**20**) to its open-chain isomer **21** to be 87:13. When benzene was replaced with toluene, the ratio of **20**:**21** produced at 110 °C was increased to 91:9. A simple workup procedure involving treatment of the crude product with bromine followed by distillation gave ethyl 4-methylbicyclo[2.2.1]heptane-1-carboxylate (**20**) in excellent yield (83%) and in a high state of purity.

In summary, the transformation depicted in Scheme III represents an excellent route to the norbornyl ester **20**, a compound which has not previously been reported. Starting with commercially-available keto ester **10**, the sequence consists of three relatively easy steps which afford the ester **20** in an overall yield of 46%.

In an attempt to further exploit the ring-closure **3** → **4**, we directed our attention to the key atom-transfer cyclization technique described by Curran[21] and employed so successfully by him and his associates[22] in organic synthesis. For this investigation, we chose to use the iodo nitrile **23** as substrate, and this was prepared in two steps from the tosylate **13** as illustrated (Scheme IV).

Generation of the radical **24** was to be effected via deiodination of the iodide **23** with a catalytic quantity of trialkyltin radical. Now, unlike the system **3** → **4**, the enthalpy difference between the stabilized radical **24** and its cyclized isomer **25** is no longer as favorable in terms of the latter. Nevertheless, the anticipation was that the yield of bicyclic product **26** arising from ring-closure of **24** would be high because abstraction of an iodine atom from the starting iodide **23** by **25** is essentially irreversible (Scheme IV). Indeed, we find that treatment of the iodide **23** (ca. 0.022 M) with hexamethylditin (1 mol %) in boiling benzene under irradiation with a 300-W tungsten lamp proceeded to give the bicyclic iodide **26** in excellent yield (82%). It is essential that the reaction be performed under the reasonably dilute conditions specified; the appearance of byproducts is thus minimized and a simple distillation affords the product **26** which was found to be homogeneous by GC. Production of the iodide **26** may be especially valuable as a synthetic strategy. On the one hand the system possesses a highly malleable functional group at the bridgehead; furthermore this procedure also serves as an entry into the bicyclo[2.2.1]heptyl system with useful functionality in the C7 position. A particular advantage of the derived compound **26** is that the substituents at C1 and C7 can be manipulated independently.

In conclusion, this study demonstrates that the transformations depicted above represent an additional entry into the bicyclo[2.2.1]heptyl system with useful func-

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tionality at the bridgehead. Importantly, the procedures can be readily scaled up to give workable quantities of the products.

We are continuing our studies in this area in order to determine whether these radical cyclization processes can be extended to the synthesis of other bridgehead-substituted bicycloalkanes, including the production of heterocyclic compounds.

Experimental Section

Molecular mechanics calculations[23] were carried out on a Macintosh II si, using PCMODEL. Spectral, chromatographic, and other general procedures were as described previously.[24] Bicyclo[2.2.1]heptane-1-carboxylic acid was available from previous work. Kinetic experiments were performed as discussed in earlier work.[25]

Ethyl 4-Hydroxycyclohexanecarboxylate (9). Ethyl 4-hydroxybenzoate (35 g, 0.21 mol) dissolved in ethanol (200 mL) containing Raney nickel (2 g) was added to a high-pressure hydrogenation autoclave. Hydrogen gas was added (100 atm) and the bomb heated at 100 °C for 48 h. Separation of the catalyst by filtration and removal of the solvent followed by distillation yielded the hydroxy ester **9** (31.5 g, 88%), bp 96–97 °C (0.5 mm) (lit.[26] bp 88–90 °C (0.3 mm)); IR (neat) 3389, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.12 (q, 2 H), 2.6–1.1 (m, 11 H), 1.25 (t, 3 H).

Ethyl 4-Oxocyclohexanecarboxylate (10). An aqueous solution of sodium dichromate (9.7 g, 37.0 mmol) and sulfuric acid (7.4 g, 37.7 mmol) was slowly added to a mixture of ethyl 4-hydroxycyclohexanecarboxylate (**9**) (7.0 g, 13.5 mmol) in ether (50 mL) over 15 min. The mixture was stirred for a further 3 h and then poured into water and extracted with ether (3 × 50 mL). The combined extracts were washed successively with saturated sodium bicarbonate, water (2 × 100 mL), and saturated NaCl and then dried ($MgSO_4$), and the solvent was evaporated. Distillation of the residue gave the title keto ester **10** as a clear oily liquid (6.35 g, 92%): bp 86–88 °C (0.7 mm) (lit.[27] bp 70 °C (0.5 mm)); IR (neat) 1728 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.19 (q, 2 H), 2.9–1.8 (m, 9 H), 1.26 (t, 3 H).

Ethyl 4-Methylenecyclohexanecarboxylate (11). Sodium hydride (0.99 g, 41.2 mmol) was stirred in dry dimethyl sulfoxide (45 mL) at 80 °C for 1.5 h. Methyltriphenylphosphonium iodide (16.6 g, 41.2 mmol) was added to the cooled mixture and stirring continued for a further 2 h. Ethyl 4-oxocyclohexanecarboxylate (**10**) (5.0 g, 29.4 mmol) in dry DMSO (5 mL) was then added and stirring continued at 50 °C for another 2 h. The reaction mixture was cooled, poured into water (100 mL), and extracted with pentane (3 × 75 mL). The combined extracts were washed successively with water (2 × 100 mL) and saturated NaCl and then dried ($MgSO_4$), and the solvent was removed to give a pale oil. Column chromatography (silica gel, 5% ether/95% hexane) of the residue and distillation (Kugelrohr, 115–120 °C (20 mm)) yielded the title compound **11** as a clear oil (3.8 g, 77%): ^1H NMR ($CDCl_3$) δ 4.63 (s, 2 H), 4.13 (q, 2 H), 2.55–1.43 (m, 9 H), 1.22 (t, 3 H); ^{13}C NMR ($CDCl_3$) δ 175.0 (CO_2R), 147.4 (C_4), 107.6 ($C{=}CH_2$), 60.0 (CH_2CH_3), 42.4 (C_1), 33.5 ($C_{3,5}$), 30.0 ($C_{2,6}$), 14.1 (CH_2CH_3); mass spectrum *m/z* (relative intensity) 168 (M^+, 14), 139 (9), 122 (55), 94 (100); HRMS calcd for $C_{19}H_{16}O_2$ 168.1150, found 168.1156. Anal. Calcd for $C_{19}H_{16}O_2$: C, 71.4; H, 9.6. Found: C, 71.6; H, 9.7.

(4-Methylenecyclohexyl)methanol (12). To a stirred solution of $LiAlH_4$ (4.56 g, 0.12 mol) in dry ether (70 mL) was added a solution of the ester **11** (5 g, 29.8 mmol) in ether (5 mL) in a dropwise manner. The solution was heated under reflux for 2 h. The cooled (0 °C) mixture was quenched with saturated aqueous sodium sulfate and then filtered, and the solids were washed thoroughly with ether. The combined filtrate was dried ($MgSO_4$) and the volatile components were removed in vacuo to yield a colorless oil. Distillation (Kugelrohr, 90 °C (0.5 mm)) (lit.[28] bp 40–41 °C (0.001 mm)) afforded the alcohol **12** (3.75 g, 92%): ^1H NMR ($CDCl_3$) δ 4.65 (s, 2 H), 3.45 (d, J = 6 Hz, 2 H), 2.4–0.9 (m, 9 H); ^{13}C NMR ($CDCl_3$) δ 149.4 (C_4), 107.1 ($CH_2{=}C$), 67.6 (CH_2OH), 39.9 (C_1), 34.2 ($C_{3,5}$), 30.8 ($C_{2,6}$).

1-[(Tosyloxy)methyl]-4-methylenecyclohexane (13). To a solution of the alcohol **12** (5.40 g, 42.9 mmol) in pyridine (20 mL) was added *p*-toluenesulfonyl chloride (8.98 g, 47.1 mmol), and the mixture was allowed to stir at room temperature for 24 h. A few drops of water were added and the mixture was stirred for 30 min before being extracted with CH_2Cl_2 (3 × 50 mL). The combined extracts were washed successively with water (3 × 50 mL), 5% HCl, and saturated NaCl, after which the solvent was evaporated, affording an off-white solid. Recrystallization from hexane gave the tosylate **13** as a white crystalline solid (12 g, 95%), mp 66–68 °C: ^1H NMR ($CDCl_3$) δ 7.8, 7.3 (dd, J = 8.6 Hz, 4 H), 4.60 (s, 2 H), 3.82 (d, J = 6 Hz, 2 H), 2.46 (s, 3 H), 2.3–0.8 (m, 9 H); ^{13}C NMR ($CDCl_3$) δ 148.2 (C_4), 144.7 (C_{ipso}), 133.1 (C_p), 129.8 (C_m), 127.9 (C_o), 107.8 ($CH_2{=}C$), 74.6 (CH_2OTs), 36.8 (C_1), 33.7 ($C_{3,5}$), 30.3 ($C_{2,6}$), 21.7 (CH_3); mass spectrum *m/z* (relative intensity) 126 (14), 108 (96), 93 (100). Anal. Calcd for $C_{15}H_{20}O_3S$: C, 64.3; H, 7.2. Found: C, 64.5; H, 7.0.

(4-Methylenecyclohexyl)methyl Bromide (14). To a stirred solution of the tosylate **13** (0.65 g, 2.3 mmol) in THF (15 mL) was added 4 equiv of lithium bromide (0.81 g, 9.3 mmol), and the mixture was allowed to reflux for 36 h. After being cooled, the mixture was poured into water (100 mL) and extracted with pentane (3 × 30 mL). The combined extracts were washed successively with water (2 × 40 mL) and saturated NaCl and then dried ($MgSO_4$). Removal of the solvent gave a yellow liquid which upon distillation (Kugelrohr, 110 °C (20 mm)) afforded the bromide **14** as a clear liquid (0.32 g, 72%): IR (neat) 1649, 891 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.63 (s, 2 H), 3.28 (d, J = 6 Hz, 2 H), 2.5–0.9 (m, 9 H); ^{13}C NMR ($CDCl_3$) δ 148.4 (C_4), 107.6 ($C{=}CH_2$), 39.7 (C_1), 39.6 (CH_2Br), 34.0 ($C_{3,5}$), 32.8 ($C_{2,6}$); mass spectrum *m/z* (relative intensity) 189, 187 (M^+, 16, 14), 109, 107 (31, 26), 57, 55 (100); HRMS calcd for $C_8H_{13}Br$ 189.0103, found 189.0115. Anal. Calcd for $C_8H_{13}Br$: C, 50.8; H, 6.9. Found: C, 50.9; H, 7.2.

4-Methylene-1-methylcyclohexane (16). The bromide **14** (0.4 g, 2.12 mmol) was added to deoxygenated tributylstannane (3 g) under nitrogen and subjected to irradiation with a 300-W tungsten lamp for 60 min. The volatile component was removed from the reaction mixture under reduced pressure (1 mm) and it collected as a clear liquid in a liquid nitrogen/acetone trap (~−100 °C): ^1H NMR ($CDCl_3$) δ 4.58 (s, 2 H), 2.6–0.85 (m, 9 H), 0.90 (d, 3 H); ^{13}C NMR ($CDCl_3$) δ 149.8 (C_4), 106.6 ($CH_2{=}C$), 36.5 ($C_{2,6}$), 34.75 ($C_{3,5}$), 32.3 (C_1), 22.0 (CH_3). The spectral data were in accord with those reported[29] for 4-methylene-1-methylcyclohexane (**16**).

1-Methylbicyclo[2.2.1]heptane (15). Reduction of bicyclo[2.2.1]heptane-1-carboxylic acid by $LiAlH_4$ under standard conditions gave (hydroxymethyl)bicyclo[2.2.1]heptane (0.59 g, 4.36 mmol) which was dissolved in CH_2Cl_2 (10 mL) containing pyridine (0.69 g, 8.7 mmol) and treated with *p*-toluenesulfonyl chloride (0.915 g, 4.8 mmol). The mixture was left to stir under nitrogen for 4 days after which it was poured into water and extracted with CH_2Cl_2 (3 × 20 mL). The combined extracts were washed successively with water (3 × 40 mL) and saturated NaCl and then dried ($MgSO_4$). The solvent was evaporated in vacuo to give a white crystalline solid. Recrystallization from hexane yielded 1-[(tosyloxy)methyl]bicyclo[2.2.1]heptane (0.97 g, 80%), mp 78–80 °C (lit.[30] mp 78.9–80 °C): ^1H NMR ($CDCl_3$) δ 7.8, 7.3 (dd, J = 8.6 Hz, 4 H), 4.14 (s, 2 H), 2.42 (s, 3 H), 2.3–1.1 (m, 11 H). A stirred solution of the tosylate (0.45 g, 1.6 mmol) in THF (25 mL) containing 4 equiv of lithium bromide (0.55 g, 6.4 mmol) was allowed to reflux under nitrogen for 48 h. The mixture was poured into water (40 mL) and extracted with pentane (3 × 30 mL). The combined extracts were washed with water (2 × 40 mL) and saturated NaCl solution and then dried ($MgSO_4$).

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Removal of the volatile components gave a pale liquid which upon distillation (Kugelrohr, 90–95 °C (20 mm)) (lit.[31] bp 89 °C (20 mm)) gave 1-(bromomethyl)bicyclo[2.2.1]heptane as a clear liquid (0.25 g, 83%): ^{1}H NMR ($CDCl_3$) δ 3.58 (s, 2 H), 2.4–1.2 (m, 11 H) which was consistent with that reported.[32] The bromide (0.2 g, 1.06 mmol) was added to deoxygenated tributylstannane (2 g) under nitrogen and subjected to irradiation with a 300-W tungsten lamp for 60 min. The volatile product was removed from the reaction mixture under reduced pressure (1 mm) and was collected in a liquid nitrogen/acetone trap (~−100 °C). The spectral properties (^{1}H and ^{13}C NMR) of this compound were identical with those previously reported from these laboratories[33] for 1-methylbicyclo[2.2.1]heptane (**15**).

Ethyl 1-(Bromomethyl)-4-methylenecyclohexanecarboxylate (17). A solution of LDA was prepared by the addition of a 1.6 M solution of *n*-BuLi in hexane (6.17 mL, 9.9 mmol) followed by HMPA (6.1 mL) to a solution of diisopropylamine (1.5 g, 9.86 mmol) in dry THF (20 mL) at −40 °C under a nitrogen atmosphere. The mixture was cooled to −80 °C and ethyl 4-methylenecyclohexanecarboxylate (**11**) (1.5 g, 8.93 mmol) in THF (5 mL) was added with the temperature maintained below −70 °C throughout the addition. After 25 min, dibromomethane (7.78 g) was added and the mixture was allowed to warm to room temperature. The mixture was poured into water and extracted with pentane (3 × 40 mL). The combined extracts were washed successively with saturated NH_4Cl (2 × 50 mL) and water (5 × 50 mL), before being dried ($MgSO_4$) and evaporated. The light yellow liquid was distilled (Kugelrohr, 110 °C (0.7 mm)) to give the title compound **17** as a clear liquid (1.50 g, 65%): IR (neat) 1734, 1650 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.69 (s, 2 H), 4.24 (q, 2 H), 3.52 (s, 2 H), 2.5–1.4 (m, 8 H), 1.32 (t, 3 H); ^{13}C NMR ($CDCl_3$) δ 173.4 (CO_2CH_2), 147.2 (C_4), 108.0 (CH_2=C), 61.0 (CH_2CO_2), 47.9 (C_1), 40.1 (CH_2Br), 34.1 ($C_{3,5}$), 31.2 ($C_{2,6}$), 14.3 (CH_2CH_3); mass spectrum *m/z* (relative intensity) 262,260 (M^+, 1), 135 (36), 107 (100); HRMS calcd for $C_{11}H_{17}O_2Br$ 262.0393, found 262.0399. Anal. Calcd for $C_{11}H_{17}O_2Br$: C, 50.6; H, 6.5. Found: C, 50.5; H, 6.4.

Ethyl 4-Methylbicyclo[2.2.1]heptane-1-carboxylate (20). Tributylstannane (0.37 g, 1.26 mmol) in dry toluene (5 mL) containing a few crystals of AIBN was slowly added over a period of 3 h to a solution of ethyl 1-(bromomethyl)-4-methylenecyclohexanecarboxylate (**17**) (0.3 g, 1.149 mmol) in refluxing toluene (25 mL). After the reaction had gone to completion (GC analysis), the mixture was cooled and a few drops of bromine were added. The solvent was removed in vacuo leading a yellow liquid. Careful distillation (Kugelrohr, 110 °C (20 mm)) afforded ethyl 4-methylbicyclo[2.2.1]heptane-1-carboxylate (**20**) (0.174 g, 83%) as a clear liquid: ^{1}H NMR ($CDCl_3$) δ 4.12 (q, 2 H), 2.3–1.0 (m, 10 H), 1.25 (t, 3 H), 1.1 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 176.3 (CO_2CH_2), 60.0 (CH_2CO_2), 52.9 (C_1), 48.4 (C_7), 44.9 (C_4), 36.8 ($C_{3,5}$), 34.4 ($C_{2,6}$), 20.7 (CH_3), 14.3 (CH_2CH_3); mass spectrum *m/z* (relative intensity) 182 (M^+, 9), 154 (29), 125 (22), 109 (100); HRMS calcd for $C_{11}H_{18}O_2$ 182.1306, found 182.1302. Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.5; H, 9.9. Found: C, 72.9; H, 9.6.

Ethyl 1-Methyl-4-methylenecyclohexanecarboxylate (21). Sodium borohydride (0.4 g, 5.5 mmol) was added to a stirred solution of ethyl 1-(bromomethyl)-4-methylenecyclohexanecarboxylate (**17**) (0.36 g, 1.38 mmol) in HMPA (4 mL) under a nitrogen atmosphere. After 2 h the mixture was poured into water (40 mL) and extracted with pentane (3 × 30 mL). The combined extracts were washed successively with water (5 × 50 mL) and saturated NaCl before being dried ($MgSO_4$) and evaporated. Distillation of the residue (Kugelrohr, 90–95 °C (20 mm)) afforded the title ester **21** as a colorless liquid (0.185 g, 88%): ^{1}H NMR ($CDCl_3$) δ 4.58 (s, 2 H), 4.23 (q, 2 H), 2.5–1.4 (m, 8 H), 1.25 (t, 3 H), 1.15 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 177.3 (CO_2CH_2), 148.4, (C_4), 107.2 (CH_2=C), 60.3 (CH_2CO_2), 43.0 (C_1), 36.7 ($C_{3,5}$), 31.9 ($C_{2,6}$), 26.1 (CH_3), 14.3 (CH_3CH_2); mass spectrum *m/z* (relative intensity) 182 (M^+, 3), 143 (18), 123 (35), 107 (87), 68 (100); HRMS calcd for $C_{11}H_{18}O_2$, 182.1306, found 182.1294.

(4-Methylenecyclohexyl)acetonitrile (22). 1-[(Tosyloxy)methyl]-4-methylenecyclohexane (**13**) (2.0 g, 7.14 mmol) was added to a stirred solution of sodium cyanide (1.4 g, 28.5 mmol) dissolved in dry DMSO (30 mL), and the mixture was heated at 50 °C for 2 h. The cooled solution was poured into water (50 mL) and extracted with hexane (3 × 40 mL). The combined extracts were washed successively with water (2 × 50 mL) and saturated NaCl and then dried ($MgSO_4$), and the solvent was evaporated in vacuo. Distillation (Kugelrohr, 135 °C (20 mm)) of the residue yielded the title cyanide **22** (0.89 g, 93%): IR (neat) 2249, 1650, 911 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.63 (s, 2 H), 2.6–0.8 (m, 9 H), 2.25 (s, 2 H); ^{13}C NMR ($CDCl_3$) δ 147.3 (C_4), 118.7 (CN), 108.2 (CH_2=C), 34.4 (C_1), 33.9 ($C_{2,6}$), 33.4 ($C_{3,5}$), 24.1 (CH_2CN); mass spectrum *m/z* (relative intensity) 135 (M^+, 26), 124 (36), 81 (15), 57 (100); HRMS calcd for $C_9H_{13}N$ 135.1048, found 135.1045. Anal. Calcd for $C_9H_{13}N$: C, 80.0; H, 9.7. Found: C, 80.0; H, 9.7.

Iodo(4-methylenecyclohexyl)acetonitrile (23). A solution of LDA was prepared by the addition of a 1.6 M solution of *n*-BuLi in hexane (2.04 mL, 3.3 mmol) followed by HMPA (2.0 mL) to diisopropylamine (0.5 mL, 3.26 mmol) in dry THF (8 mL) at −50 °C under a nitrogen atmosphere. The mixture was cooled to −80 °C and (4-methylenecyclohexyl)acetonitrile (**22**) (0.4 g, 2.96 mmol) in THF (2 mL) was introduced with the temperature maintained below −70 °C throughout the addition. After 5 min a solution of iodine (3.0 g, 11.8 mmol) in THF (2 mL) was added and the mixture allowed to warm to room temperature. After removal of the solvent, the residue was poured into water (40 mL) and extracted into pentane (3 × 50 mL). The combined extracts were washed successively with saturated sodium metabisulfite (5 × 40 mL) and saturated NaCl before being dried ($MgSO_4$) and evaporated. Distillation (Kugelrohr, 110 °C (0.1 mm)) of the residue afforded the title compound **23** as a pale yellow oil (0.46 g, 60%): ^{1}H NMR ($CDCl_3$) δ 4.70 (s, 2 H), 4.18 (d, J = 4.6 Hz, 1 H), 2.6–1.0 (m, 9 H); ^{13}C NMR ($CDCl_3$) δ 146.5 (C_4), 118.2 (CN), 108.8 (C=CH_2), 42.4 (C_1), 33.5 (C_3), 33.6 (C_5), 33.0 (C_2), 32.1 (C_6), 5.0 (CHI); mass spectrum *m/z* (relative intensity) 261 (M^+, 26), 134 (77), 118 (40), 107 (73), 93 (100); HRMS calcd for $C_9H_{12}NI$ 261.0016, found 261.0016. Anal. Calcd for $C_9H_{12}NI$: C, 41.4; H, 4.6. Found: C, 42.1; H, 4.3.[34]

1-(Iodomethyl)-7-cyanobicyclo[2.2.1]heptane (26). Iodo(4-methylenecyclohexyl)acetonitrile (**23**) (0.152 g, 0.58 mmol) in *tert*-butylbenzene (25 mL) was deoxygenated by a stream of nitrogen bubbled through the mixture for 5 min. The flask was immersed in a preheated oil bath (90 °C) and placed under irradiation with a 300-W tungsten lamp. Once thermal equilibrium had been reached a catalytic amount of hexamethylditin (1 mol %) was injected into the mixture. After cyclization was complete (GC analysis) the reaction mixture was cooled, poured into water (50 mL), and extracted with pentane (5 × 20 mL). The combined extracts were washed successively with saturated sodium metabisulfite (5 × 40 mL), water (50 mL), and saturated NaCl before being dried ($MgSO_4$). Evaporation of the solvent and distillation (Kugelrohr, 110 °C (0.1 mm)) of the residue afforded the title compound **26** as a light yellow oil (0.124 g, 82%): ^{1}H NMR ($CDCl_3$) δ 3.49, 3.43 (dd, J_{AB} = 10.3 Hz, 2 H), 2.7–1.4 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 118.9 (CN), 52.7 (C_7), 43.1 (C_1), 42.4 (C_4), 34.1 (C_6), 32.6 (C_2), 29.7 (C_5), 29.1 (C_3), 10.1 (CH_2I); HRMS calcd for $C_9H_{12}NI$ 261.0016, found 261.0007. Anal. Calcd for $C_9H_{12}NI$: C, 41.4; H, 4.6. Found: C, 41.9; H, 4.3.[34]

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