of **18**, which was therefore unequivocally shown to proceed highly regio- as well as diastereoselectively to form the complete steroid nucleus.

**Acknowledgment.** We are indebted to the National Institutes of Health, the National Science Foundation, and to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research. We also wish to thank Drs. N. Cohen and G. Saucy of Hoffmann-La Roche Inc. for arranging for us to receive a generous specimen of the 17$\alpha$ form of substance **36**.

**Registry No.** (*E,E,E*)-**5**, 87305-79-1; **6**, 6139-84-0; (±)-**7**, 87305-80-4; (*E*)-**8**, 87318-47-6; (*E*)-**9**, 87305-81-5; (*E*)-**10**, 87305-82-6; (*x,E*)-**11**, 87305-83-7; (*E*)-**12**, 87318-48-7; (*E*)-**13**, 87318-49-8; (*E*)-**14**, 87305-84-8; (*E*)-**15**, 41143-17-3; (*E,E,Z,E*)-**18**, 87305-85-9; **19**, 74377-87-0; (*Z*)-**20**, 87305-86-0; (±)-(*Z*)-**21**, 87305-87-1; (*Z,E*)-**22**, 87305-88-2; (*Z,E*)-**23**, 87305-89-3; (±)-**24**(17$\alpha$), 87305-90-6; (±)-**24**(17$\beta$), 87334-72-3; (±)-**25**(17$\alpha$), 87305-91-7; (±)-**25**(17$\beta$), 87334-73-4; (±)-**26**(17$\alpha$), 87305-92-8; (±)-**26**(17$\beta$), 87334-74-5; (±)-**27**(17$\alpha$), 87305-93-9; (±)-**27**(17$\beta$), 87334-75-6; (±)-**28**(17$\alpha$), 87305-94-0; (±)-**28**(17$\beta$), 87334-76-7; (±)-**29**(17$\alpha$), 87305-95-1; (±)-**29**(17$\beta$), 87334-77-8; (±)-**30**(17$\alpha$), 87305-96-2; (±)-**30**(17$\beta$), 87334-78-9; (±)-**31**(17$\alpha$), 87305-97-3; (±)-**31**(17$\beta$), 87334-79-0; (±)-**32**(17$\alpha$), 87305-98-4; (±)-**32**(17$\beta$), 87334-80-3; (±)-**33**(17$\alpha$), 87305-99-5; (±)-**33**(17$\beta$), 87334-81-4; (±)-**34**(17$\alpha$), 87306-00-1; (±)-**34**(17$\beta$), 87334-82-5; (±)-**35**(17$\alpha$), 87306-01-2; (±)-**35**(17$\beta$), 87334-83-6; (±)-**36**(17$\alpha$), 87334-84-7; (±)-**36**(17$\beta$), 87334-85-8; $CH_2$=$C(CH_3)Br$, 557-93-7; $CH_3OCH_2(C_6H_5)_3PCl$, 4009-98-7; 1,3-propanedithiol di-*p*-toluenesulfonate, 3866-79-3; progesterone, 57-83-0; 17$\alpha$-progesterone, 2000-66-0; (±)-17$\alpha$-progesterone, 73889-98-2; (±)-progesterone, 14546-13-5.

**Supplementary Material Available:** IR, NMR, mass spectral, and analytical data (6 pages). Ordering information is given on any current masthead page.

# Discrimination between Exo- and Endo-3,2-Methyl Shifts in Substituted 2-Norbornyl Cations on the (+)-Camphenilone Route to (−)-Albene

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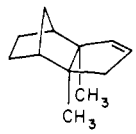
*Received May 2, 1983*

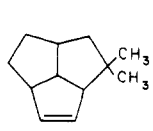
**Abstract:** One key step in the synthetic route leading from (+)-camphenilone to (−)-albene, a chloro olefin annelation reaction, occurs with concomitant diminution of optical purity. An investigation of this reaction with a $^{13}C,^{2}H_2$-labeled version of the chloro olefin accords with a recent reassignment of the absolute stereochemistry of (−)-albene as (1*S*,2*S*,6*S*,7*R*)-2-*endo*,6-*endo*-dimethyltricyclo[5.2.1.$0^{2,6}$]dec-3-ene and demonstrates that neither enantiomer of the rearrangement product depends on an endo-3,2-methyl shift in a substituted 2-norbornyl cationic intermediate.

(−)-Albene, a tricyclic olefin first isolated in 1962 from *Petasites albus*,[1] is now known to be the 1*S*,2*S*,6*S*,7*R* enantiomer of 2-*endo*,6-*endo*-dimethyltricyclo[5.2.1.$0^{2,6}$]dec-3-ene (**1**).[2]

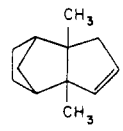



**1**

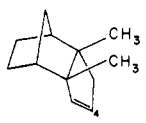
Accurate structural, stereochemical, and absolute configurational assignments for this natural product have not been secured without difficulty. The first tentative structural proposal advanced in 1964,[3] the dimethyltetrahydrotriquinacene formulation **2**, was



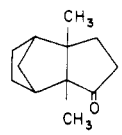

**2**




**3**




**4**




**5**

abandoned in 1972 as additional evidence, including a chemical correlation between (−)-albene and (+)-camphene, was interpreted in terms of the correct structure (**3**) but the wrong stereochemistry (**4**).[4] Structure **4** was supported in 1973 through independent work providing a synthesis of a degradation product, albanone (**5**; 2,6-dimethyltricyclo[5.2.1.$0^{2,6}$]decan-3-one), from camphenilone.[5] The correct stereochemistry but the wrong absolute configuration were assigned in 1978 in work that included an X-ray crystallographic structure determination[6] for the 4-phenylthio derivative of (±)-isoalbene ((±)-**4**), careful $^{13}C$ NMR comparisons between albene and isoalbene,[7] and a total synthesis of (−)-albene from (+)-camphenilone.[8,9]

The correct structural and absolute stereochemical representation of (−)-albene has thus been notably elusive in spite of extensive efforts employing a variety of degradative and synthetic studies relating this comparatively small molecule to natural products of known stereochemistry and absolute configuration. Part of that chemistry, then, must be imperfectly understood and formulated according to invalid mechanistic assumptions.

(1) Hochmannová, J.; Novotný, L.; Herout, V. *Collect. Czech. Chem. Commun.* **1962**, *27*, 2711-2714. See also: Novotný, L.; Herout, V. *Ibid.* **1965**, *30*, 3579-3581.
(2) Baldwin, J. E.; Barden, T. C. *J. Org. Chem.* **1983**, *48*, 625-626.
(3) Herout, V.; Hochmannová, J.; and Šorm, F. Lecture at the Third International IUPAC Symposium on the Chemistry of Natural Products, Kyoto, Japan, April 12-18, 1964; *Angew. Chem.* **1964**, *76*, 789.
(4) Vokáč, K.; Samek, Z.; Herout, V.; Šorm, F. *Tetrahedron Lett.* **1972**, 1665-1668.
(5) Lansbury, P. T.; Boden, R. M. *Tetrahedron Lett.* **1973**, 5017-5020.
(6) Kreiser, W.; Janitschke, L.; Sheldrick, W. S. *J. Chem. Soc., Chem. Commun.* **1977**, 269-270. Kreiser, W.; Janitschke, L.; Voss, W.; Ernst, L.; Sheldrick, W. S. *Chem. Ber.* **1979**, *112*, 397-407.
(7) Kreiser, W.; Janitschke, L.; Ernst, L. *Tetrahedron* **1978**, *34*, 131-134.
(8) Kreiser, W.; Janitschke, L. *Tetrahedron Lett.* **1978**, 601-604.
(9) Kreiser, W.; Janitschke, L. *Chem. Ber.* **1979**, *112*, 408-422.

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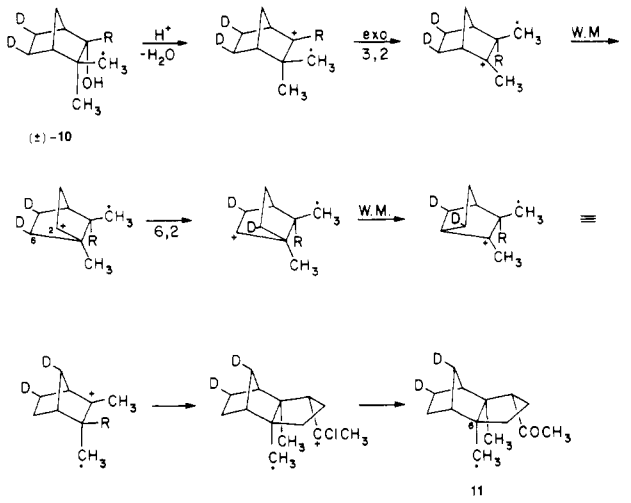
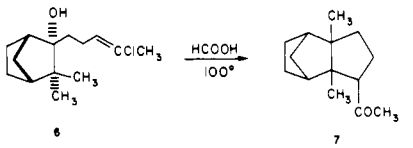
Scheme I. Major Stereochemical Path[a]



[a] R = $CH_2CH_2CH{=}CClCH_3$, *C = $^{13}C$.

Consideration of this problem led us to speculate that the rearrangement of the chloro alcohol **6** in formic acid at reflux to the tricyclic ketone **7**, a reaction used to secure (±)-albanone from

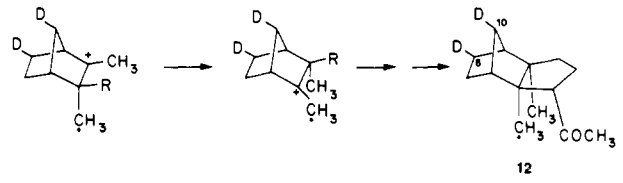


(±)-camphenilone[5] and (−)-albene from (+)-camphenilone,[8,9] may have been misconstrued twice and that (−)-albene might be the 1*S*,2*S*,6*S*,7*R* enantiomer **1**. Conformation of the second supposition through a chemical correlation of methyl ketone **8** with β-santalene of known absolute stereochemistry[2] prompted this detailed investigation of the rearrangement **6** → **7**.[10]

Lansbury and Boden utilized this chloro olefin annelation reaction in their synthesis of albanone (**5**). They found that only one isomer of product **7** was formed, and recognizing the well-known preference of exo-3,2-methyl shifts over the corresponding endo shifts in norbornyl cations,[11] they concluded that **7** had exo-2,6-methyl groups.[5] When Kreiser and Janitschke employed this reaction in their total synthesis of (−)-albene,[8,9] they knew that the 2,6-methyl groups in the product **7** had the endo configuration: hence they formulated the reaction as one involving an endo-3,2-methyl shift.[8,9] This interpretation, one presupposing the first example of an endo shift of an alkyl group in the Nametkin rearrangement,[12] led to an erroneous assignment of absolute stereochemistry for (−)-albene. Thus, neither simple rationale for the conversion **6** → **7**, that is neither the exo-3,2-methyl shift postulate (leading to exo-2,6-methyl groups) nor the endo-3,2-methyl shift alternative (leading to the mirror image of the observed product), is in agreement with experimental fact.

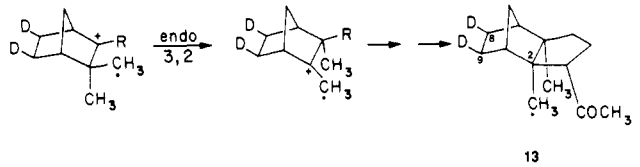
During our work that established the absolute stereochemistry of (−)-albene we determined the stereochemical course of the reaction **6** → **7** and discovered that it occurs with considerable racemization. The chiral precursor (−)-**8** was found to give (+)-**9** and (−)-**9** in a 65:35 ratio.[2] One must explain, then, both the formation of (+)-**9** as the dominant product and (−)-**9** as a substantial coproduct.

Scheme II. Minor Stereochemical Path without Endo Shift[a]

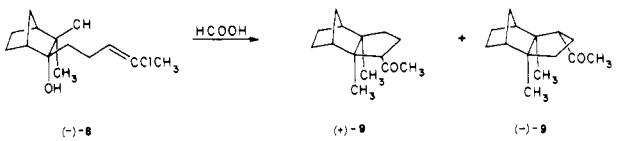


[a] R = $CH_2CH_2CH{=}CClCH_3$, *C = $^{13}C$.

Scheme III. Minor Stereochemical Path with Endo Shift[a]



[a] R = $CH_2CH_2CH{=}CClCH_3$, *C = $^{13}C$.



The additional complications that must be considered are well-known but easily neglected: Wagner–Meerwein rearrangements and 6,2-hydride shifts.[12] A plausible explanation for the predominant stereochemical course of the annelation reaction, (−)-**8** → (+)-**9**, can be formulated in terms of an exo-3,2-methyl shift, Wagner–Meerwein rearrangements, and 6,2-hydride shifts. The minor pathway, (−)-**8** → (−)-**9**, could be rationalized through postulating an endo-3,2-methyl shift, but an alternative possibility was also considered reasonable. These various mechanistic descriptions of the conversion **8** → **9** were tested with the aid of $^{13}C$- and $^{13}C,^2H_2$-labeled substrates.

## Experimental Design

With the aid of isotopically labeled but achiral substrates, the mechanistic concerns outlined above were tested as projected in Schemes I–III.

These three schemes predict that a $^{13}C$ label present in starting alcohol in the exo C(3) methyl group will appear in both methyl groups of the product: the relative distribution of the $^{13}C$-label between C(6) and C(2) $CH_3$ should parallel the absolute stereochemical course of the reaction. Thus, the $^{13}C$ label serves as surrogate for chirality: it provides an internal standard for the chiral course of the annelation reaction even though racemic substrate, not a chiral substrate, is employed. It was anticipated that the exact extent of racemization during the conversion **8** → **9** might be quite sensitive to reaction conditions–Kreiser and Janitschke, one may now calculate,[13] got a 58:42 instead of a 65:35 ratio of the enantiotopic ketones[9]–and thus some internal measure of that potential variable was required. The $^{13}C$ label does *not* discriminate between Schemes II and III, the two alternatives leading to the byproduct which are to be tested.

The deuterium labels in Scheme II appear at C(8) and C(10) of the product **12**, while Scheme III has them at C(8) and C(9)

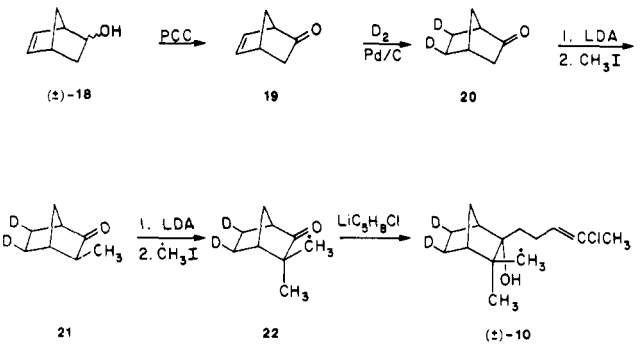
(10) A preliminary account of this work has been presented: Barden, T. C.; Baldwin, J. E. *Abstr. Pap.–Am. Chem. Soc.* **1983**, *185th*, ORGN 177. T. Money has expressed reticence toward the earlier[8,9] interpretation of the chloroannelation reaction **6** → **7** and anticipated the present findings: Money, T. *Terpenoids Steroids* **1979**, *9*, 94. Roberts, J. S. *Ibid.* **1981**, *10*, 20.

(11) See footnote 21 of ref 2 for representative literature dealing with this selectivity.

(12) For a particularly cogent treatment of these rearrangements, see: Huang, E.; Ranganayakulu, K.; Sorensen, T. S. *J. Am. Chem. Soc.* **1972**, *94*, 1780–1782. Haseltine, R.; Huang, E.; Ranganayakulu, K.; Sorensen, T. S. *Can. J. Chem.* **1975**, *53*, 1056–1066. Haseltine, R. P.; Sorensen, T. S. *Ibid.* **1975**, *53*, 1067–1083. Haseltine, R.; Huang, E.; Ranganayakulu, K.; Sorensen, T. S.; Wong, N. *Ibid.* **1975**, *53*, 1876–1890. Haseltine, R.; Wong, N.; Sorensen, T. S.; Jones, A. J. *Ibid.* **1975**, *53*, 1891–1900. Haseltine, R.; Ranganayakulu, K.; Wong, N.; Sorensen, T. S. *Ibid.* **1975**, *53*, 1901–1914. For an alternative formal description of rearrangement routes, see: Collins, C. J.; Johnson, C. K.; Raaen, V. F. *J. Am. Chem. Soc.* **1974**, *96*, 2524–2531.

(13) From the reported[9] rotations for **6** and **7** and the established[2] relationships between rotations and optical purities for these compounds. The (−)-albene synthesized by Kreiser and Janitschke, $[\alpha]^{20}_D$ −6.5°, was about 16% optically pure; the highest reported rotation for (−)-albene is $[\alpha]^{20}_D$ −33.9° ($CHCl_3$).[3] (±)-Albene has been synthesized unambiguously three times. Baldwin, J. E.; Barden, T. C. *J. Org. Chem.* **1981**, *46*, 2442–2445. Trost, B. M.; Renaut, P. *J. Am. Chem. Soc.* **1982**, *104*, 6668–6672. Manzardo, G. G. G.; Karpf, M.; Dreiding, A. S. *Helv. Chim. Acta* **1983**, *66*, 627–632.

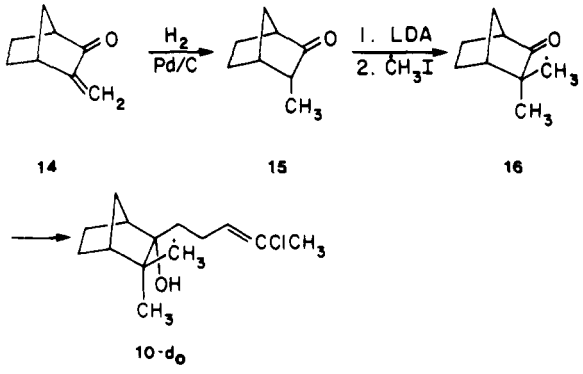
Scheme IV




of **13**. That distinction, then, provides the basis for selecting between the two rationales for the reaction (−)-**8** → (−)-**9**. The possibility that *both* schemes II and III contribute to the formation of the minor product is also accommodated by the experimental design.

## Results

**Syntheses.** Preliminary work with substrate labeled only with carbon-13 at the exo-3-methyl carbon tested the proposition that the majority of this label should appear at C(6) $CH_3$ = C(12) of the product and that the proportion of label C(12):C(11) should be about 65:35, the ratio of enantiomers formed from chiral unlabeled substrate (−)-**8**. The $^{13}C$-labeled alcohol was prepared from 3-methylene-2-norbornanone through catalytic reduction, alkylation[14] with iodomethane-$^{13}C$ by way of the enolate anion prepared with lithium diisopropylamide in tetrahydrofuran and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (abbreviated DMPU: *N,N'*-dimethyl-*N,N'*-propylene urea)[15] as a cosolvent, and treatment of the $^{13}C$-labeled camphenilone intermediate with 1-lithio-4-chloropent-3-ene[16] (**14** → **15** → **16** → **10-$d_0$**).




The literature reports numerous instances in which enolate anions of substituted 2-norbornanones undergo highly stereoselective alkylations from the exo face.[17] High-field $^1H$ NMR of the camphenilone **16** confirmed that this selectively prevailed in the conversion **15** → **16**. No $^{13}CH_3$ doublet was observed for the endo methyl group.

To secure the deuterium- and $^{13}C$-labeled chloro olefin **10**, the route of Scheme IV was employed. Commercial bicyclo[2.2.1]hept-5-en-2-ol (**18**), a mixture of endo and exo isomers, was oxidized with pyridinium chlorochromate (PCC) to give bicyclo[2.2.1]hept-5-en-2-one (**19**).[18] Reduction of the double bond with deuterium gas over 5% palladium on charcoal gave the 5-*exo*,6-*exo*-dideuterio ketone **20**.[19] Alkylation with iodomethane gave 5-*exo*,6-*exo*-dideuterio-3-*exo*-methylbicyclo[2.2.1]heptan-2-one (**21**). Repetition of the alkylation procedure with iodomethane-$^{13}C$ gave the desired camphenilone (**22**) having both deuterium and carbon-13 labels as depicted. From the same reaction mixture there was recovered some 5-*exo*,6-*exo*-dideuterio-3-*endo*-methylnorbornanone; mass spectroscopic analysis showed it to be 92% $d_2$ and 8% $d_1$. The $^{13}C$ incorporation of camphenilone **22** at the exo C(3) $CH_3$ carbon was estimated to be 96% by 360-MHz $^1H$ NMR spectroscopy. Again, no endo C(3) $^*CH_3$ was detected. The labeled camphenilone **22** was treated with 1-lithio-4-chloropent-3-ene[16] to give the alcohol (±)-**10**, the desired starting material (Scheme IV).

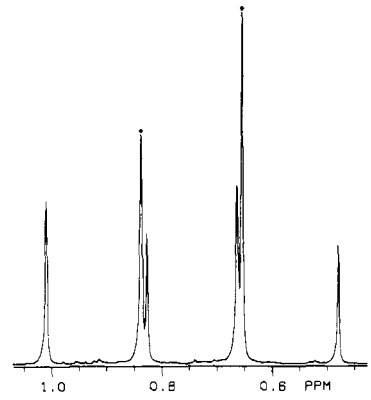
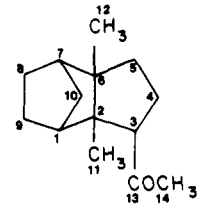



**Figure 1.** 360-MHz $^1H$ NMR spectrum of C(11)$H_3$ and C(12)$H_3$ in the product mixture **11** and **12** + **13** from chloro olefin **10**. The upfield methyl is C(11); the dominant labeled methyl is $^{13}C$(12).

**Annelation Reactions.** The rearrangement **6** → **7** was conducted with the labeled substrates **10-$d_0$** and **10**, making every effort to reproduce the experimental conditions recorded in the literature.[5,9] Treating **10-$d_0$** or **10** for 2 h in 97–100% formic acid at reflux gave the tricyclic $^{13}C$ and $^{13}C,^2H_2$ methyl ketone products in 74–75% yield after Kugelrohr distillation. Final purifications before NMR spectroscopic analyses were done through preparative gas chromatography on a Carbowax 20M column.

**$^1H$ and $^{13}C$ NMR Assignments.** Although all of the $^1H$ and $^{13}C$ NMR absorptions for ketone **7** had been assigned by earlier workers,[9] we felt obligated to reconsider these assignments afresh, for a proper interpretation of the spectra would obviously be highly sensitive to those assignments. We were substantially aided in this matter by having two labeled versions of **7** available.




**7**

The 100-MHz $^1H$ NMR assignments of 0.84 ppm to the C(12) methyl and 0.65 ppm to the C(11) methyl group[9] were first verified by examining the effect of increasing portions of the shift reagent Eu(hfbc)$_3$[20] to an oxygen-free, $C_6D_6$ solution of methyl ketone (+)-**9** remaining from previous work.[2] The proton resonance originally at 0.65 ppm moved downfield roughly 3.5 times faster than the 0.84 resonance in the presence of added shift reagent. Since the closer of the two angular methyl groups to the carbonyl moiety is expected to undergo the most rapid downfield shift with added europium shift reagent,[21] the prior assignments are confirmed.

(14) Compare Kirmse, W.; Hartmann, M.; Siegfried, R.; Wroblowsky, H.-J.; Zang, B.; Zellmer, V. *Chem. Ber.* **1981**, *114*, 1793–1808.
(15) Mukhopadhyay, T.; Seebach, D. *Helv. Chim. Acta* **1982**, *65*, 385–391. Barker, B. J.; Rosenfarb, J.; Caruso, J. A. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 503–507.
(16) Cf.: Newman, M. S.; Kaugars, G. *J. Org. Chem.* **1966**, *31*, 1379–1381. Lansbury, P. T.; Haddon, V. R.; Stewart, R. C. *J. Am. Chem. Soc.* **1974**, *96*, 896–898.
(17) For earlier examples, see: Corey, E. J.; Hartmann, R.; Vatakencherry, P. A. *J. Am. Chem. Soc.* **1962**, *84*, 2611–2614. Wolinski, J.; Dimmel, D. R.; Gibson, T. W. *J. Org. Chem.* **1967**, *32*, 2087–2097.
(18) Lightner, D. A.; Gawrônski, J. K.; Bowman, T. D. *J. Am. Chem. Soc.* **1980**, *102*, 5749–5754. Compare Barco, A.; Benetti, S.; Pollini, G. P. *J. Org. Chem.* **1980**, *45*, 4776–4778.
(19) Compare Creary, X.; Geiger, C. C. *J. Am. Chem. Soc.* **1982**, *104*, 4151–4162.
(20) Aldrich Chemical Co. Eu(hfbc)$_3$ is also abbreviated Eu(hfc)$_3$.
(21) Kime, K. A.; Sievers, R. E. *Aldrichimica Acta* **1977**, *10*, 54–62.

Table I. $^{13}C$ NMR Assignments for Ketones 7, [$^{13}C$]-7, and [$^{13}C,^{2}H_2$]-7

| carbon, type: number | prior assignment[a] | chemical shift, ppm (appearance) | | |
|---|---|---|---|---|
| | | 7 from 6[a] | 7 from 10-$d_0$[b] | 7 from 10[c] |
| $CH_3$:11 | 12 | 15.18 | 15.36 (s) | 15.38 (q of d, $J$ = 125, 4.9 Hz; cf. Figure 2) |
| $CH_3$:12 | 11 | 20.26 | 20.41 (s) | 20.43 (q of t, $J$ = 125, 5.9 Hz; cf. Figure 2) |
| $CH_3$:14 | 14 | 30.68 | 30.92 (s) | 30.94 (q, $J$ = 127 Hz) |
| $CH_2$:4 | 10 | 24.67 | 24.77 (s) | 24.76 (t, $J$ = 129 Hz) |
| $CH_2$:5 | 4 | 40.01 | 40.13 (s) | 40.11 (t, $J$ = 127 Hz) |
| $CH_2$:10 | 5 | 33.86 | 34.04 (weak s), 33.68 (t of d, $J$ = 20, 2 Hz; cf. Figure 3) | 34.03 (t of dd, $J$ = 133, 7.6, 6.7 Hz) |
| CH:1 | 7 | 47.10 | 47.24 (weak s), 47.12, 47.07 (s) (cf. Figure 4) | 47.20 (d, $J$ = 141 Hz) |
| CH:3 | 3 | 63.94 | 64.10 (s) | 64.09 (d, $J$ = 124 Hz) |
| CH:7 | 1 | 47.58 | 47.68 (weak s), 47.57, 47.51 (s) (cf. Figure 4) | 47.67 (d, $J$ = 138 Hz) |
| C:2 | 2 | 51.19 | 51.33 (s + d, $J$ = 37.8 Hz) | 51.36 (s + d, $J$ = 37.9 Hz) |
| C:6 | 6 | 50.45 | 50.59 (s + d, $J$ = 38.2 Hz) | 50.62 (s + d, $J$ = 38.1 Hz) |
| CO:13 | 13 | 209.89 | 210.40 (s) | 210.42 (s) |

[a] Reference 9. [b] $^1H$ decoupled. [c] $^1H$ coupled.

In the $^{13}C,^{2}H_2$-labeled product from alcohol **10**, $^{13}C$–H spin–spin coupling gives absorptions on either side of the two $^{12}CH_3$ singlets (marked with * in Figure 1) with relative intensities indicative of the distribution of $^{13}C$ label at the two angular methyl positions.

The excess $^{13}C$ originally incorporated in the exo methyl group of the precursor appears in the product ketone at both C(12) and C(11) in a 62:38 ratio, according to the $^1H$ NMR integrations. The ratio of $^{13}C$ at C(12) and C(11) in the ketone derived from monolabeled alcohol **10-$d_0$** (66:34) was similar to but not identical with that found for the ketone produced from **10**.

Careful comparisons of the proton-coupled and -decoupled $^{13}C$ NMR spectra of product ketones from **10** and **10-$d_0$** allowed unambiguous assignments to be made for all but two carbon atoms, C(8) and C(9), without recourse to any mechanistic assumptions regarding labels at certain carbons (Table I). Discrimination between C(8) vs. C(9) was made later, through interpretation of the proton-decoupled $^{13}C$ NMR spectrum of $^{13}C,^{2}H_2$ product after mechanistic issues had been resolved.

The majority of these assignments could be made quite straightforwardly by considering chemical shift, direct $^{13}C$–H coupling, and in some cases the long-range $^{13}C$–C–C–H coupling constants shown by ketone **11** and **12 + 13** (column 3, Table I). Several features of the spectrum of this mixture of ketones, however, do deserve explicit comment. In particular, the patterns observed for C(11) and C(12), C(1) and C(7), and C(10) in the $^1H$-decoupled $^{13}C$ NMR spectrum of the $^{13}C,^{2}H_2$ ketone mixture require added explanation.

Long-range $^{13}C$–C–C–H coupling, seen in C(10), C(11), and C(12), permitted individual assignments of these carbons as well as of C(5). Inspection of a molecular model indicates that a favorable dihedral angle exists for spin–spin coupling between C(10) and the endo hydrogens on C(8) and C(9), C(12) and both hydrogens on C(5), and C(11) and the single hydrogen on C(3).[22] The carbon moxt extensively labeled, assigned as C(12) from $^1H$ NMR spectral analysis (Figure 2), does show the expected $^{13}C$–C–C–$H_2$ couplings ($J$ = 5.9 Hz) to two hydrogens, while C(11) is split by a single $^{13}C$–C–C–H interaction ($J$ = 4.9 Hz). Further confirmation for the C(12) and C(11) assignments comes from the quantitative agreement between C(12):C(11) peak height ratios in the proton-decoupled $^{13}C$ spectra of ketones **11**:**12 + 13** (62:38) and of the corresponding mixture of ketones from **10-$d_0$** (64:36) with the ratio determined by $^1H$ NMR.

To the extent that in ketones **11** and **12 + 13** C(11) and C(12) are artificially enriched in $^{13}C$, direct $^{13}C$–$^{13}C$ coupling causes C(2) and C(6), respectively, to appear as doublets, centered around the singlets due to the uncoupled C(2)–$^{12}$C(11) and C(6)–$^{12}$C(12) moieties. The unequal intensities of the doublets and singlets must correspond with the established $^{13}C$ distribution between C(11) and C(12); thus, the distinction between C(2) and C(6) can be made with confidence.

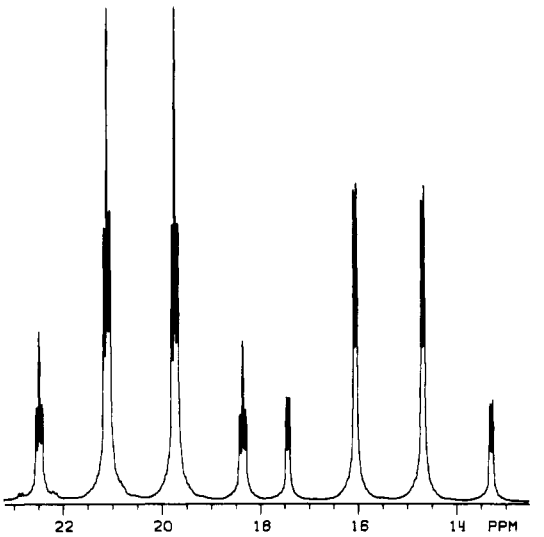



**Figure 2.** Long-range $^{13}C$–C–C–H spin–spin coupling at C(12) (downfield methyl) and C(11) in the product mixture **11** and **12 + 13** from chloro olefin **10**.


**Figure 3.** $^1H$-decoupled $^{13}C$ NMR spectrum of C(7) (downfield) and C(1) in the product mixture from chloro olefin **10**. Each carbon has singlet peaks for environments with 0, 1, or 2 deuterium atoms on adjacent carbons.

Deuterium substitution at a carbon imparts an upfield shift of about 0.1 ppm to immediately adjacent carbons.[23,24] The effect is additive: a carbon adjacent to two deuterium-bearing carbons is shifted upfield by about 0.2 ppm. The C(7) and C(1) signals are readily rationalized and assigned on this basis: Scheme I predicts that the most intense component of the C(1) resonance

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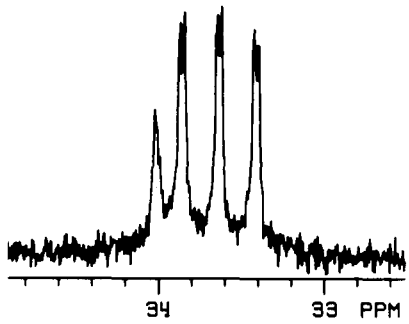



**Figure 4.** The C(10) region of the proton-decoupled $^{13}C$ NMR spectrum of the product from chloro olefin **10**; $J_{^{13}C-D}$ = 20 Hz, $J_{^{13}CD-C-C-^{13}C(11,12)}$ = 2 Hz.

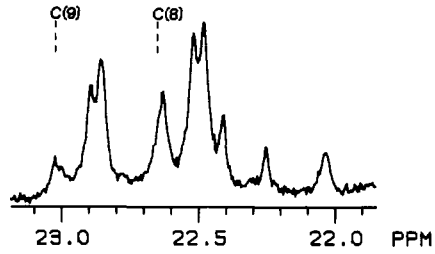



**Figure 5.** Observed natural abundance C(8) and C(9) proton-decoupled $^{13}C$ NMR spectrum for ketones **11** + **12** from the chloro annelation of **10**.

should be shifted upfield through interaction with two adjacent deuterium-bearing carbon atoms, C(9) and C(10), while C(7) is anticipated to have its larger signal component shifted upfield only by deuterium at C(10). This anticipation is independent of the balance between Schemes II and III. From these projections based on Scheme I and either Scheme II or III, the observed spectrum requires one to assign the more downfield of the two patterns shown in Figure 3 as due to C(7).

The proton-decoupled $^{13}C$ lines for C(10)HD at 33.68 ppm show the triplet from $J_{^{13}C-D}$ and long-range coupling to $^{13}C$ label at C(11) and C(12), as expected for structures **11** and **12**. The downfield line at 34.04 ppm from a minor $C(10)H_2$ component is consistent with expectations whether or not Scheme III contributes to the reaction, for **10** was not completely dideuterated and the intensity of the $C(10)H_2$ carbon resonance would be magnified by a larger NOE enhancement (Figure 4).

Of the three remaining $CH_2$ carbons, only C(4) should, according to Schemes I–III, never carry a deuterium label in the product mixture derived from **10**; hence, C(4) is the carbon at 24.77 ppm, while C(8) and C(9), carbons that show the complications of partial deuterium substitution and partial deuteration on an adjacent carbon, have chemical shifts of 22.65 and 23.03 ppm (lit.[9] values 22.49 and 22.88 ppm, respectively).

The $^{13}C\{^1H\}$ spectrum for C(8) and C(9) in the mixture of ketones derived from **10** makes it clear that C(8) falls at higher field (Figure 5). The apparent doublets at about 22.5 and 22.9 ppm are due to long-range spin–spin coupling of $C(8)H_2$–C–C–$^{13}C(12)$ in product **11** and $C(9)H_2$–C–C–$^{13}C(11)$ in ketone **12** + **13**, while the two sets of triplets that overlap in part with the doublets are associated with C(8)HD centered at $\delta$ 22.26 and C(9)HD at $\delta$ 22.63. Schemes I and II give C(8) and C(9) coupled either with an attached deuterium or a $^{13}C$ three bonds removed, but not with both. The relatively minor C(9) component near 23.0 ppm from $C(9)H_2C(8)H_2$, comparable to the downfield absorption in the C(10) $^{13}C$ NMR spectrum (Figure 4), stems from incompletely deuterated substrate; the corresponding C(8) absorption is obscured by one line of the C(9)HD triplet centered at 22.63 ppm.

**Spectral Interpretation.** Assignments of chemical shifts to all carbons in ketone **7** have been made rigorously without presumption as to the relative importance of Schemes II and III, and the perturbations in the spectra of ketones derived from **10** and **10-$d_0$** are in full agreement with the mechanistic schemes presupposed. One must now attempt to discriminate between Schemes II and III.

The degree of upfield shift and relative intensities of the minor components of the $^{13}C\{^1H\}$ signals ascribed to C(7) and C(1) (Figure 3), the nearly complete monodeuteration of C(10) (Figure 4), and the pattern of absorptions observed for C(8) and C(9) (Figure 5) are all consistent with the presence of a significant amount of **12** in the product mixture. They provide no direct evidence for ketone **13**.

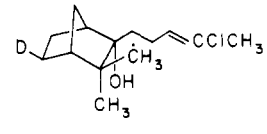
The C(9) $^{13}C\{^1H\}$ absorptions for ketone **13** would include a triplet of doublets (approximate $J$ = 20, 3 Hz) centered at about 22.52 ppm, and C(8) of ketone **13** would show a triplet ($J \approx 20$ Hz) at 22.13 ppm. While some of the C(9) peaks might be obscured by absorptions of **11** and **12**, the entire C(8) triplet of **13** would be clearly observable. No such peaks can be seen (Figure 5).

What error limits may be ascribed to the conclusion that **13** is not a component of the reaction mixture? How large a contribution of the Scheme III mechanism might be present and yet remain undetected? Clearly the signal/noise ratio obtained in the $^{13}C$ NMR experiment itself must be considered limiting if one attempts to use Figure 5 to establish these limits. Even so, as little as 3% should be observable since the relative noise level is low.

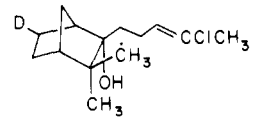
Two additional estimates can be obtained by consideration of the relative peak intensities of the $^{13}C\{^1H\}$ resonances associated with C(7) and C(1). The first assumes the same nuclear Overhauser enhancement (NOE) for both C(7) and C(1) and considers only dideuterio-labeled material. No complications then arise from incomplete deuteration of the starting material or from potential loss of deuterium during the rearrangement. The second method takes monodeuterated product into consideration and assumes that the rearrangement proceeds without loss of deuterium.[12]

In the first approach, the relative intensities of the most upfield $^{13}C\{^1H\}$ resonances for C(1) and C(7), that is those affected by *two* adjacent CD units, are compared. If only Schemes I and II apply, in the 62:38 ratio as determined by the disposition of the $^{13}C$ label, the C(1):C(7) intensity ratio should be 62:38 = 1.6. Should Scheme III contribute as little as 3% overall, this ratio is predicted to increase to 1.8. The observed ratio is 1.5 ± 0.1, just less than or equal to the value predicted by theory. Any contribution from Scheme III only makes the ratio larger. The NOE of the two signals would have to differ by a factor of 1.2 in the requisite sense before a 3% contribution would be masked.

Alternatively, in the second approach, one could compare the relative intensities of the two $^{13}C\{^1H\}$ C(7) resonances shifted upfield by one and two adjacent CD moieties. While the C-(1)$(CD)_1$:C(1)$(CD)_2$ ratio remains constant regardless of the contribution of Scheme III, the correspondng ratio for C(7) is predicted to be extremely sensitive to even small amounts of Scheme III; here, no assumption of relative NOE values is needed since both peaks are, in fact, from the same carbon. One may stipulate that the 8% of $d_1$ material known to be present in alcohol **10** is represented by a 4% contribution each of alcohols **10a** and **10b**. If there is no contribution from Scheme III, the C(7)(C-




10a




10b

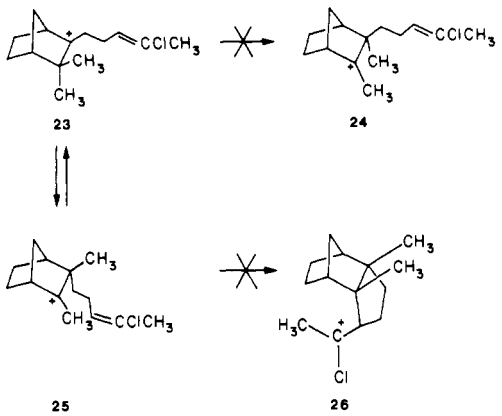
$D)_1$:C(7)$(CD)_2$ ratio should be 1.78. The corresponding ratio if 3% and 5% of Scheme III were to contribute is predicted to be 2.02 and 2.20, respectively. The observed ratio of 1.8 ± 0.1 is in quantitative agreement with theory if Scheme III is completely nonparticipatory in the overall rearrangement process.

## Discussion

The chloro olefin annelation reaction **6** → **7**, as followed in detail for the labeled analogues **10** → **11** + **12**, occurs without any contribution from the endo-3,2-methyl shift formalized in Scheme III. The labeling results are consistent with Schemes I and II,

involving Wagner–Meerwein rearrangements, exo-3,2-methyl and -alkyl shifts, and endo-6,2-hydride shifts.

The central findings of this study accord well with results obtained for the rearrangement of longifolene to isolongifolene[25] and that proposed for the acid-catalyzed interconversion of copacamphene and sativene.[26] The fundamental structural reasons that favor multistep processes in Schemes I and II, pathways that totally eschew endo-3,2-methyl shifts, probably do not involve substantial σ-participation in the 2-norbornyl cations generated. Although the experimental and theoretical evidence favoring the bridged or nonclassical structural formulation for the parent 2-norbornyl cation appears overwhelmingly convincing,[27] tertiary 2-norbornyl cations, such as 2-methyl-2-norbornyl and camphenehydro cations, are classical, unbridged intermediates.[12] Nevertheless, the detailed structure of putative intermediate **23** does not allow a kinetically competitive endo-3,2-methyl shift to afford products derived from **24**, and intermediate **25** does not permit reaction from the endo approach to give **26**.




A likely rationale for these striking stereochemical propensities of classical tertiary 2-norbornyl cations may be found in the suggestions of Schleyer:[28] torsional effects in such cations may well be of sufficient magnitude to control stereochemical options so decisively.

## Conclusions

The labeling strategy adopted for this mechanistic investigation permitted an efficient resolution of the issue posed by earlier reports: the rearrangement of chloro olefin **6** to both isomers of ketone **7** occurs through well-precedented carbonium ion paths, without intrusion of an endo-3,2-methyl migration in a substituted norbornyl cation. The recent revision of assignment for the absolute stereochemistry of (−)-albene[2] was confirmed, and the intimate relationships between mechanistic understandings of intermediates and reactions and practical applications were once again exemplified. Only reactions of securely known structural and absolute stereochemical propensities provide sure grounds for deducing structures and absolute stereochemical assignments through chemical correlations between known and unknown compounds.

## Experimental Section

Unless noted otherwise, reactions were conducted under a nitrogen atmosphere with magnetic stirring in flame-dried or oven-dried (130 °C, overnight) glassware; organic solutions of crude products were dried over magnesium sulfate, filtered, and concentrated by rotary evaporation. Commercial *n*-butyllithium in hexanes and *tert*-butyllithium in pentane (Aldrich) were standardized with diphenylacetic acid.[29] Dichloromethane and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU)[15] were dried over activated 4-Å molecular sieves. Diisopropylamine was distilled from KOH pellets and stored over activated 3-Å molecular sieves. Tetrahydrofuran (THF) was dried over sodium and benzophenone, and diethyl ether was dried over lithium aluminum hydride; each was distilled under a positive nitrogen pressure directly into reaction vessels as required. Vapor-phase chromatography (VPC) was performed on a Varian Aerograph A90-P3. Gas chromatography column A was a 6.4 mm × 1.22 m aluminum column packed with 20% Carbowax 20M on 60/80 mesh Chromasorb W-AWDMCS; column B was a 2.5-m long version of column A. Analytical samples of **16**, **22**, **10**, **10-$d_0$**, and **11** + **12** were obtained on these columns before any spectra were recorded. $^1$H NMR, $^2$H NMR, and $^{13}$C NMR spectra were recorded in $CDCl_3$ solutions; chemical shift values reported are relative to one of the following internal standards: $Me_4Si$ at 0.0 ppm ($^1$H), $CHCl_3$ at 7.27 ppm ($^1$H), $CDCl_3$ at 7.27 ppm ($^2$H), $CDCl_3$ at 77.00 ppm ($^{13}$C). Unless noted $^1$H NMR spectra were obtained at 100 MHz on a Varian XL-100 instrument; all other NMR spectra were obtained on a Nicolet NT-360 instrument operating in the Fourier transform mode. Infrared spectra were obtained on a Sargent-Welch 3-200 infrared spectrophotometer with $CDCl_3$ solutions except where noted. Mass spectra were determined on either a CEC21-110B or a Hewlett-Packard HP5930M mass spectrometer. Melting points were obtained in sealed capillary tubes and are uncorrected. The obvious physical properties of all compounds described below agreed with those reported in the literature for the unlabeled analogues.

**Bicyclo[2.2.1]hept-5-en-2-one (19).** Pyridinium chlorochromate (29.51 g, 0.137 mol) was suspended in 150 mL of $CH_2Cl_2$, the suspension was stirred at room temperature for 15 min, and then the flask was cooled in ice; 5-norbornen-2-ol (7:3 mixture of endo and exo alcohols, 9.53 g, 0.086 mol) in $CH_2Cl_2$ (10 mL) was added quickly. The ice bath was removed and the reaction mixture was stirred for 5 h with occasional water-bath cooling to keep the reaction mixture from boiling. Ether (300 mL) was added, the reaction mixture was stirred another 1 h, and the ethereal mixture was filtered through Florisil. The black gum still in the reaction vessel was washed with more ether (2 × 100 mL); these extracts were filtered through the same Florisil. Concentration of the filtrate by careful rotary evaporation followed by distillation at 16 torr gave 4.73 g (50%) of **19** as a colorless liquid: bp 54–56 °C (16 torr) [lit.[18] bp 69–70 °C (25 torr)]: NMR δ 6.56 (dd, $J$ = 3, 6 Hz, 1 H), 6.11 (dd, $J$ = 4, 6 Hz, 1 H), 3.18 (m, 1 H), 3.00 (m, 1 H), 1.82–2.3 (c, 4 H).

**5-*exo*,6-*exo*-Dideuteriobicyclo[2.2.1]heptan-2-one (20).**[30] Keto olefin **19** (3.32 g, 30.7 mmol) was dissolved in ether (100 mL) in a 250-mL Morton flask, the system was flushed with nitrogen, and 5% palladium on charcoal (0.30 g) was added. A 50-mL burette was filled with water and inverted into a large beaker partially filled with water such that the lower end was below the surface of the water. The burette was repeatedly charged with deuterium gas from a lecture bottle (Matheson; reported 99.5%), and the liquid was allowed to flow from the top of the burette into the bottom of the vigorously stirred reaction mixture through a long needle until the theoretical amount of deuterium had been used. The catalyst was removed by gravity filtration and the ether was distilled through a Vigreux column. Ketone **20** (2.92 g, 85%) was obtained as a white solid by adding pentane to the distillation residue and slowly cooling the resultant solution to −78 °C: mp 94–96 °C (lit.[30] mp 90–93 °C); NMR δ 2.52–2.80 (br m, 2 H), 1.20–2.20 (c, 6 H); IR ($CHCl_3$) 3005, 2950, 2880, 2200, 2170, 1735, 1405, 960 cm$^{-1}$.

**5-*exo*,6-*exo*-Dideuterio-*exo*-3-methylbicyclo[2.2.1]heptan-2-one (21).** A solution of diisopropylamine (5.0 mL, 35.3 mmol) in THF (70 mL) and DMPU[15] (35 mL) was cooled to −35 to −40 °C in a dry ice/acetonitrile bath. A solution of *n*-butyllithium (1.4 M, 21.4 mL, 30.0 mmol) was added dropwise in 5 min; the reaction mixture was stirred for 30 min, the cooling bath was replaced with a dry ice/acetone bath at −78 °C, and then ketone **20** (2.82 g, 25.1 mmol) in THF (3 mL) was added in 20 min to the solution of lithium diisopropylamide (LDA). The reaction mixture

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(31) Both C(3) epimers of 3-methylnorbornanone were recovered from the reaction mixture. The VPC-purified endo isomer (*endo*-**21**) was analyzed by mass spectrometry at a low-ionizing voltage; unlabeled ketone **15** served as a reference standard. The deuterium incorporation in *endo*-**21** was 92% $d_2$ and 8% $d_1$ (at "10 eV").

was stirred at −78 °C for another 1.5 h, and then methyl iodide (2.1 mL, 33.7 mmol) was added dropwise; the solution was allowed to warm to room temperature over 11 h. Ether (200 mL) was added to the orange product mixture; the ethereal solution was washed with water (7 × 150 mL) and brine (100 mL), dried, and carefully concentrated by rotary evaporation at 10 °C. Purification through medium-pressure liquid chromatography on silica gel with ethyl acetate/hexanes (3:17) as eluent followed by careful removal of solvents by distillation gave 1.42 g (45%) of pure ketone **21** as a colorless liquid: NMR δ 2.52 (br s, 1 H), 2.30 (br s, 1 H), 1.20–1.96 (c, 5 H), 1.05 (d, $J$ = 8 Hz, 3 H); IR ($CHCl_3$) 3005, 2960, 2880, 2205, 2190, 2170, 1735, 1470, 1450, 965, 955, 905 $cm^{-1}$.

**5-*exo*,6-*exo*-Dideuterio-3-*endo*-methyl-3-*exo*-(methyl-$^{13}C$)bicyclo[2.2.1]heptan-2-one (22).** A solution of LDA in THF (10 mL) and DMPU (5 mL) at −45 to −50 °C was prepared as before from diisopropylamine (0.85 mL, 6.0 mmol) and *n*-butyllithium (1.6 M in hexanes, 3.5 mL, 5.6 mmol). At −78 °C, the neat ketone **21** (0.65 g, 5.1 mmol) was added, and the reaction mixture was stirred at this temperature for 2.3 h. The enolate thus generated was quenched by addition of iodomethane-$^{13}C$ (99 atm % reported, Merck; 0.19 mL, 3.0 mmol) at −78 °C, followed by another 7 h of stirring. Wet ether (50 mL) was added; the reaction mixture was allowed to warm to room temperature and was washed successively with water (6 × 20 mL) and brine (30 mL). After being dried and filtered, the ethereal solution was carefully concentrated by rotary evaporation and purified by medium-pressure liquid chromatography on silica gel with ethyl acetate/hexanes (1:9) giving 0.23 g (55%) of the $^{13}$C-labeled camphenilone **22** as a white solid:[31] $^1$H NMR (360 MHz) δ 2.57 (br s, 1 H), 2.23 (br s, 1 H), 1.98 (br d, 1 H), 1.72 (br d, 1 H), 1.40–1.50 (m, 2 H), 1.06 (s, exo $^{12}CH_3$, 0.12 H), 1.06 (d, $J$ = 128 Hz, exo $^{13}CH_3$, 2.88 H), 1.02 (s, endo $CH_3$, 0.12 H), 1.02 (d, $J$ = 6 Hz, endo $CH_3$, 2.88 H); $^2$H NMR (55 MHz) δ 1.82 (br d, 1.0 D), 1.60 (br d, 1.0 D); IR ($CHCl_3$) 3005, 2960, 2880, 2205, 2180, 1735, 1380, 1360, 905 $cm^{-1}$.

**2-[2-Chloroprop-2-en-5-yl]-5-*exo*,6-*exo*-dideuterio-3-*endo*-methyl-3-*exo*-(methyl-$^{13}C$)bicyclo[2.2.1]heptan-2-ol ((±)-10).** 1-Iodo-4-chloropent-3-ene[16] (0.75 g, 3.2 mmol) in ether (5 mL) and under an argon atmosphere was cooled to −78 °C. A 1.8 M solution of *tert*-butyllithium (2.6 mL, 4.7 mmol) was added dropwise and the resultant solution at −78 °C was stirred 20 min. Ketone **22** (0.17 g, 1.2 mmol) in ether (0.5 mL) was added dropwise; the reaction mixture was stirred for 30 min at −78 °C and then for 16 h at room temperature. Brine (5 mL) was added, and the two phases were well mixed and separated. The aqueous phase was extracted with ether (10 mL), acidified with 10% HCl, and extracted with more ether (2 × 10 mL). The combined ethereal phases were dried, filtered, and concentrated; Kugelrohr distillation of the residue gave 0.23 g (76%) of alcohol **(±)-10** as a viscous, colorless oil, collected from 75 to 85 °C (oven temperature) at 0.03 torr: NMR δ 5.38–5.70 (m, 1 H), 2.00–2.20 (c, 2 H), 2.09 (m, 3 H), 0.80–1.90 (c, 8 H), 0.97 (d, $J$ = 128 Hz, ~3 H), 0.92 (d, $J$ = 5 Hz, ~3 H); IR ($CHCl_3$) 3600, 3450, 3010, 2990, 2950, 2880, 2430, 2390, 2180, 1660, 1470, 1445, 1430, 1380, 1360 $cm^{-1}$.

**3-*endo*-Acetyl-2-*endo*,6-*endo*-dimethyltricyclo[5.2.1.0$^{2,6}$]decane-$^2H_2$,$^{13}CH_3$ 11 + 12.** Chloro alcohol **10** (0.23 g, 0.92 mmol) was dissolved in 97–100% formic acid (1.3 mL), and the mixture was heated at reflux for 2 h. The dark reaction solution was then cooled in ice, 25% aqueous NaOH (5.5 mL) was added, and the resultant solution was extracted with $CH_2Cl_2$ (4 × 15 mL). Kugelrohr distillation of the residue from the combined, dried, filtered, and concentrated organic phases gave 0.14 g (75%) of ketone **11 + 12** as a colorless liquid, collected from 65 to 75 °C (oven temperature) at 0.3–0.4 torr. The last traces of impurities were removed by VPC on column A: NMR (360 MHz) δ 2.57 (dd, $J$ = 12,6 Hz, 1 H), 2.22 (br s, 1 H), 2.12 (s, 3 H), 1.25–1.85 (c, 9 H), 0.84 (s, $^{12}CH_3$ at C(12), 1.36 H), 0.84 (d, $J$ = 126 Hz, $^{13}$C at C(12), 1.72 H), 0.67 (s, $^{12}$C at C(11), 1.84 H), 0.67 (d, $J$ = 126 Hz, $^{13}CH_3$ at C(11), 1.08 H); $^2$H NMR (55 MHz) δ 1.31 (br s, skewed upfield from deuterium at C(8) and C(9), 1.00 D), 1.00 (br s, symmetric, deuterium at C(10), 1.00 D); $^{13}$C NMR (90 MHz) see column 1, Table I; IR ($CHCl_3$) 2990, 2950, 2870, 2430, 2400, 2200, 2170, 1695, 1385, 1370, 1355 $cm^{-1}$.

***endo*-3-Methylbicyclo[2.2.1]heptan-2-one (15).** 3-Methylenebicyclo-[2.2.1]heptan-2-one (7.02 g, 55.7 mmol) was dissolved in absolute ethanol (100 mL) in a 250-mL Parr pressure bottle. A slurry of 5% palladium on charcoal (0.65 g) in ethanol (10 mL) was added, and the bottle was placed in the shaking apparatus. The bottle was then thrice evacuated (aspirator) and filled with hydrogen. After the final evacuation the hydrogen pressure was adjusted to 4 atm and the bottle was shaken for 1.5 h, until the theoretical amount of hydrogen was consumed. The catalyst was removed by gravity filtration, and the ethanol was distilled at atmospheric pressure. Pure methyl ketone **15** (4.92 g, 71%) was obtained as a colorless liquid by distillation at 16 torr: bp 68 °C; NMR δ 2.42–2.66 (c, 2 H), 1.20–2.20 (c, 7 H), 1.01 (d, $J$ = 7 Hz, 3 H); IR 2970, 2870, 1730, 1450, 1295, 1170, 1095, 1030 $cm^{-1}$.

**3-*endo*-Methyl-3-*exo*-(methyl-$^{13}C$)bicyclo[2.2.1]heptan-2-one (16).** A solution of LDA was prepared at −50 °C as previously described from diisopropylamine (0.65 mL, 4.5 mmol) and a 1.3 M solution of *n*-butyllithium (3.5 mL, 4.5 mmol) in a mixture of THF (10 mL) and DMPU (5 mL). The cooling bath was then replaced with dry ice/acetone at −78 °C, and neat ketone **15** (0.57 g, 4.6 mmol) was added dropwise to the reaction mixture. After the reaction mixture was stirred for another 3 h, iodomethane-$^{13}C$ (0.27 mL, 4.3 mmol) was added to quench the enolate; stirring was continued for 2.5 h at −78 °C and for 11.5 h at room temperature. The orange solution was diluted with ether (50 mL), washed with water (6 × 20 mL) and brine (50 mL), dried, filtered, and carefully concentrated to 2 mL by rotary evaporation. Final purification by medium-pressure liquid chromatography on silica gel was effected with ethyl acetate/hexanes (1:9) giving 0.29 g (48%) of pure $^{13}$C-labeled ketone **16**: NMR δ 2.50–2.62 (m, 1 H), 2.23 (br s, 1 H), 1.22–2.10 (c, 6 H), 1.06 (d, $J$ = 128 Hz, exo $^{13}CH_3$, 3 H), 1.03 (d, $J$ = 5 Hz, endo $^{12}CH_3$, 3 H); IR 2960, 2920, 2870, 1735, 1485, 1465, 1380, 1355, 1290, 1155, 1100, 1055 $cm^{-1}$.

**2-[2-Chloroprop-2-en-5-yl]-3-*endo*-methyl-3-*exo*-(methyl-$^{13}C$)bicyclo[2.2.1]heptan-2-ol (10-$d_0$).** 1-Lithio-4-chloropent-2-ene was generated under argon at −78 °C as before by combination of 1-iodo-4-chloropent-2-ene (0.49 g, 2.1 mmol) and a 1.8 M solution of *tert*-butyllithium (1.9 mL, 3.4 mmol) in ether (5 mL). Camphenilone **16** (0.20 g, 1.4 mmol) was added, and the solution was stirred at −78 °C for 30 min and then at room temperature for 17 h. Brine (5 mL) was added, the two layers were separated, and after acidification the aqueous layer was extracted with additional ether (3 × 10 mL). The combined ethereal phases were dried and concentrated by rotary evaporation. Kugelrohr distillation of the residue at 0.15 torr gave 0.30 g (86%) of pure alcohol **10-$d_0$**, collected as a viscous liquid from 70 to 90 °C (oven temperature): NMR δ 5.38–5.70 (m, 1 H), 2.00–2.20 (c, 2 H), 2.09 (m, 3 H), 0.80–1.90 (c, 10 H), 0.97 (d, $J$ = 26 Hz, exo $^{13}CH_3$, 3 H), 0.93 (d, $J$ = 5 Hz, endo $^{12}CH_3$, 3 H); IR 3600, 3465, 2950, 2870, 1660, 1465, 1450, 1430, 1380, 1360, 1355 $cm^{-1}$.

**3-*endo*-Acetyl-2-*endo*,6-*endo*-dimethyltricyclo[5.2.1.0$^{2,6}$]decane-$^{13}CH_3$.** A mixture of chloro alcohol **10-$d_0$** (0.26 g, 1.1 mmol) and 97–100% formic acid (1.5 mL) was heated at reflux for 2 h and then cooled in ice; the acid was neutralized by addition of 25% aqueous NaOH (6.4 mL). Extraction was performed with $CH_2Cl_2$ (4 × 10 mL), and the combined organic phases were dried and concentrated by rotary evaporation. Pure ketone **11 + 12-$d_0$**, a viscous oil, was obtained from the dark residue by Kugelrohr distillation; 0.16 g (74%) was collected between 60 and 80 °C (oven temperature) and at 0.4 torr: NMR δ 2.68 (dd, $J$ = 10, 6 Hz, 1 H), 2.12 (br s, 1 H), 2.14 (s, 3 H), 1.02–1.94 (c, 11 H), 0.86 (s, $^{12}CH_3$ at C(12), 1.29 H), 0.86 (d, $J$ = 126 Hz, $^{13}CH_3$ at C(12), 1.97 H), 0.67 (s, $^{12}CH_3$ at C(11), 1.67 H), 0.67 (d, $J$ = 126 Hz, $^{13}CH_3$ at C(11), 1.06 H); $^{13}$C NMR (90 MHz) see column 2, Table I; IR 2940, 2870, 1645, 1470, 1385, 1365, 1355, 1235, 1170 $cm^{-1}$.

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