Table IV. Time-Dependent NOEs—Broken Chain of Seven Protons[a]

r_{34} =	3 Å		3 Å		4 Å		4 Å	
saturate	4		3		4		3	
spin	τ, s	η^∞	τ, s	η^∞	τ, s	η^∞	τ, s	η^∞
1	0.59	−0.977	0.05	−0.998	2.72	−0.891	0.05	−0.998
2	0.58	−0.977	0.03	−0.998	2.70	−0.891	0.03	−0.998
3	0.56	−0.978	saturate	−1.000	2.69	−0.891	saturate	−1.000
4	saturate	−1.000	0.66	−0.968	saturate	−1.000	3.34	−0.847
5	0.03	−0.997	0.73	−0.966	0.03	−0.997	3.40	−0.845
6	0.08	−0.996	0.78	−0.965	0.08	−0.996	3.46	−0.844
7	0.11	−0.996	0.80	−0.964	0.105	−0.996	3.48	−0.844

[a] For all v_2 = 50 Hz, $\tau_c = 5 \times 10^{-8}$ s, $\omega_0\tau_c = 113$, and r_{ij} = 2 Å except r_{34}, which is indicated.

in the chain. These calculations are for a seven-proton chain with a large distance between spins 3 and 4; either spin 3 or 4 is saturated. The increase in the half-lives as r_{34} is increased goes roughly as $r_{34}{}^6$. For example, comparing the 4-Å calculation to the 3-Å calculation of the half-life of spin 3 when 4 is saturated gives $(3.34/0.66)^{1/6} = 1.31$ and for spin 4 when spin 3 is saturated $(2.69/0.56)^{1/6} = 1.30$.

Of the approximations made in this paper, the most serious is certainly our neglect of the indirect effect of the rf field on the other, off-resonance, spins. This effect is twofold: (1) the steady-state partial saturation of an off-resonance spin and (2) transient effects, commonly called Torrey[13] oscillations. We are currently working on this problem. Extension of the theory to groups of equivalent spins will face complications inherent in degenerate spin systems detailed by ref 10. Reference 14 shows the difficulties which will be encountered if the theory is extended to include *J* coupling.

Listings of the computer programs are available from the authors on request.

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Optical Rotatory Dispersion Studies. 127.[1] Chirality Due to ^{13}C Substitution. Synthesis and Chiroptical Properties of (1*S*)-2-Adamantanone-*4*-^{13}C and (1*S*)-2,4-Adamantanedione-*4*-^{13}C

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Abstract: The synthesis and circular dichroism spectra of (1*S*)-2-adamantanone-*4*-^{13}C (**11**) and (1*S*)-2,4-adamantanedione-*4*-^{13}C (**12**) are reported, two compounds which owe their chirality solely to ^{13}C substitution. The monoketone **11** exhibits a negative Cotton effect, indicating that ^{13}C makes a smaller octant contribution than ^{12}C, while the diketone **12** shows three circular dichroism bands of remarkably large amplitude. Since no intensity changes were observed at 77 K it was concluded that the multiple band pattern does not reflect a dissymmetric solvation equilibrium but that each band corresponds to a different n → π^* transition.

Introduction

The recently recorded[3] syntheses and detection of significant Cotton effects of deuterium-substituted cycloalkanones, whose chirality is solely due to the deuterium atom, have stimulated interest in theoretical work[4] and proved to be of utility in solving some subtle conformational problems.[5] This encouraged us to undertake similar studies on cyclohexanones which owe their chirality only to replacement of one carbon by ^{13}C. That such minor isotopic perturbations produce easily measurable Cotton effects[6] was recently demonstrated[1] by the

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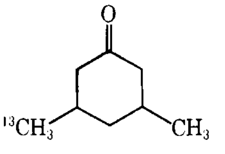

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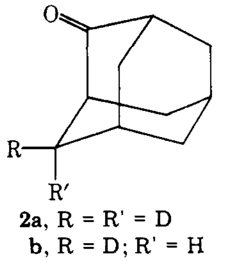
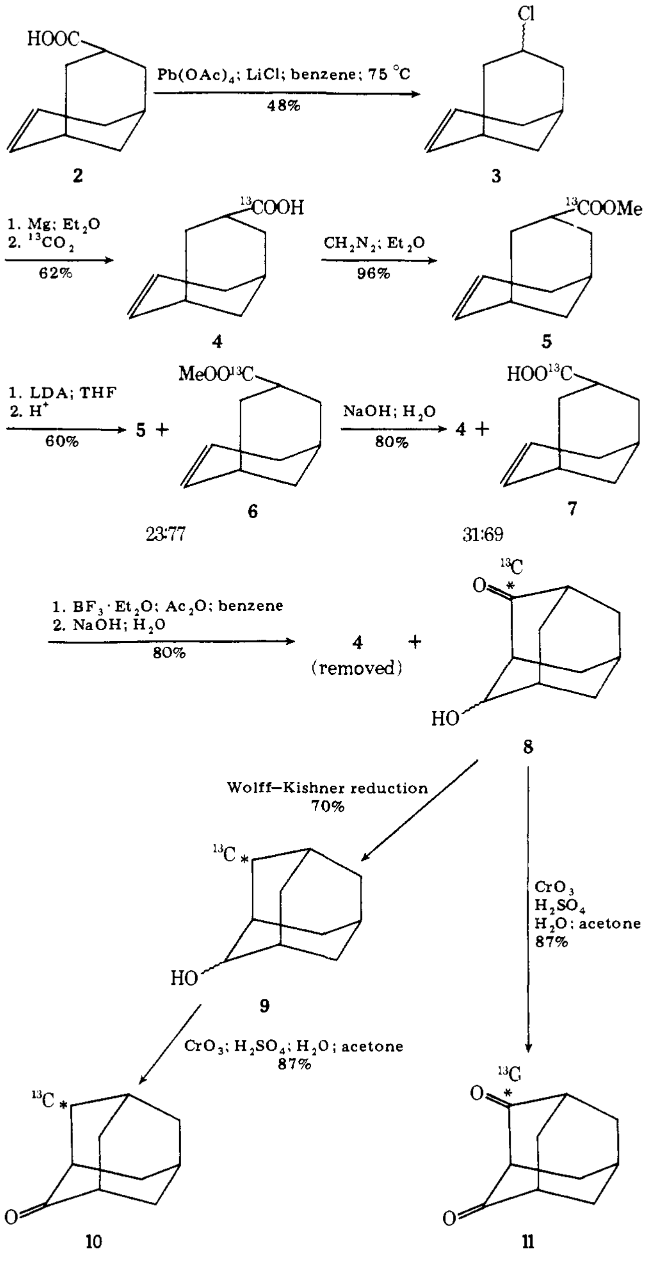


2a, R = R' = D
b, R = D; R' = H
c, R = H; R' = D

synthesis of (3*S*,5*R*)-3-methyl-5-^{13}C-methylcyclohexanone (**1**). Since the rotatory strength of deuterium-substituted cyclohexanones has been found[3] to vary considerably in magnitude with the location of the isotope in the various ring positions (e.g., α,β axial or equatorial), we were interested in investigating a similar location dependency for the ^{13}C isotope, in particular the effect of ^{13}C when incorporated into the six-membered ring. The synthesis by Numan and Wynberg[3e] of three chiral β-deuterioadamantanones (**2a–c**) via the optically active acid **3** has now opened a convenient way to an adamantanone (**11**) in which chirality is solely associated with the replacement of one of the β-ring carbon atoms by ^{13}C.

The resolution of the acid **3**[7] was repeated on a large scale in Groningen[3e] with the subsequent steps (**3** → **11, 12**) being performed at Stanford to generate the chiral (1*S*)-2-adamantanone-*4*-^{13}C (**11**) and the related chiral diketone **12** as outlined below.



(3*R*)-*endo*-Bicyclo[3.3.1]non-6-ene-3-carboxylic acid (**3**) was oxidatively decarboxylated[8] with lead tetraacetate and lithium chloride to the chiral chloride **4** which was obtained as a 26:74 mixture of the endo and exo epimers. Carbonation of its Grignard reagent with $^{13}CO_2$ yielded (3*S*)-*exo*-bicyclo[3.3.1]non-6-ene-3-carboxylic acid-^{13}C (**5**), which was esterified with diazomethane to the exo methyl ester (**6**), followed by epimerization with lithium diisopropylamide, which led to a mixture of methyl esters (**6** + **7**) and thence by saponification to a 31:69 mixture of the (3*S*)-exo (**5**) and (3*R*)-endo (**9**) carboxylic acids. The (1*R*)-4-hydroxy-2-adamantanone-*2*-^{13}C (**9**) was prepared by adapting the reported ring cyclization procedure[3e] to the mixture of **5** and **9**, the unreacted exo acid (**5**) being easily removed by aqueous alkaline extraction. Wolff-Kishner reduction[9] of **9** and Jones oxidation[10] gave (1*S*)-2-adamantanone-*4*-^{13}C (**11**). The chiral diketone, (1*S*)-2,4-adamantanedione-*4*-^{13}C (**12**), was simply prepared by Jones oxidation[10] of (1*R*)-4-hydroxy-2-adamantanone-*2*-^{13}C (**9**).

Results and Discussion

The circular dichroism spectrum (Figure 1a) of the optically active adamantanone **11** is characterized by a negative Cotton effect at 295 nm with a rotational strength of $[R]^{298} = -0.016$ at room temperature. At 77 K the spectrum exhibits some resolved vibrational fine structure but the rotational strength remains essentially unchanged ($[R]^{77} = -0.017$) as would be expected from a conformationally rigid molecule. Since the ^{13}C ring carbon atom is located in a positive octant (see octant diagram in Figure 1a) it follows that ^{13}C makes a smaller octant contribution than ^{12}C. This result is in agreement with that for the earlier reported[1] *cis*-3,5-dimethylcyclohexanone **1** ($[R]^{298} = -0.013$). Comparison of the magnitudes of **1** and **11** shows that the induced rotational strength is only slightly larger when the ^{13}C isotope is part of the ring as compared to the location in the β-equatorial position (**1**). The $[R]^T$ values for **1** and **11** are smaller by approximately a factor of 20 when compared to adamantanone with a deuterium in the β-equatorial position.[3b,e] In both cases, however, the heavier isotope behaves as the weaker perturber; e.g., the sign of the n → π^* Cotton effect is determined by the location of the lighter isotope with respect to the octant diagram. The circular dichroism spectrum (Figure 1b) of the diketone **12** exhibits three bands centered at 321, 290, and 260 nm with positive, negative, and positive signs, respectively, each showing vibrational fine structure which becomes well resolved at 77 K. A quite similar band pattern has been observed by Lightner et al.[11] for the chiral β-diketone (+)-(5*R*)-spiro[4.4]nonane-1,6-dione with the exception that only two oppositely signed CD bands were noted. Although they considered the possibility of both bands corresponding to two different electronic transitions resulting from the splitting of the n → π^* transition through nonbond interactions, the authors[11] preferred to interpret their results as resulting from dissymmetric solvation. However, the circular dichroism spectrum of our diketone **12** was found not to be temperature dependent[12] and the low-temperature spectrum in EPA (ether-isopentane-ethanol, 5:5:2 v/v) (Figure 1b) exhibits only a band sharpening but negligible changes in overall intensity. Therefore we conclude that solvent-solvent interactions are not responsible for the appearance of the multiple bands in the 330–230-nm region for **12**. Spafford et al.[13] have recently identified four distinct n → π^* transitions for the β-diketone tetramethyl-1,3-cyclobutanedione with origins at 370, 332, 312, and 285 nm, respectively. Based on their study it appears therefore more reasonable to assign the observed three circular dichroism bands of **12** (Figure 1b) as belonging to different electronic transitions.

Further studies with other conformationally rigid ketones whose chirality is only due to isotopic substitution (^{34}S, ^{18}O, ^{3}H) are contemplated.

Experimental Section

The circular dichroism spectra were measured with a JASCO J-40 circular dichrometer using an earlier described[14] cell for the low-temperature measurements. Nuclear magnetic resonance spectra were determined on Varian T-60 and Varian XL100 spectrometers. Infrared spectra were measured on a Perkin-Elmer 700A infrared spectrophotometer. Mass spectra were recorded by Mr. R. Ross on an AEI-MS 9 mass spectrometer and GC-MS spectra by Ms. A. Wegmann with a Hewlett-Packard 7610A high-efficiency gas chromatograph interfaced through an all-glass dual-stage Watson-Bieman molecular separator to a Varian-MAT 711 high-resolution mass spectrometer. Polarimetric measurements were performed with a Perkin-Elmer 241 polarimeter.

(3*R*)-*endo*- and (3*S*)-*exo*-Bicyclo[3.3.1]non-6-ene 3-Chloride (4). To a solution of 2 g (12.03 mmol) of (3*R*)-*endo*-bicyclo[3.3.1]non-6-ene-3-carboxylic acid (**3**) ($[\alpha]_{578}$ +114.1°, *c* 1.0, 96% ethanol; enantiomeric excess 75.6%) in 60 mL of dried benzene (distilled over sodium) was added 4.97 g (11.2 mmol) of lead tetraacetate. The solution was stirred for 15 min until nearly homogeneous. Lithium chloride (785.5 mg, 18.53 mmol) was added and the solution was placed under a nitrogen atmosphere in a bath preheated to 75 °C. The solution was stirred at 75 °C for 3 h and for an additional 30 min while cooling to room temperature. The reaction mixture was diluted with 200 mL of benzene and washed twice with 20 mL of water. Removal of solvent under reduced pressure gave a mixture of light yellow liquid and insoluble white solid. The resulting mixture was purified by column chromatography (silica gel, hexane) to give 0.9 g of **4** as a colorless liquid (48% yield): bp 185-187 °C; IR (neat, cm^{-1}) 3030 (m), 2930 (s), 700 (s); NMR (CDCl$_3$, δ ppm) 1.8-3.0 (m, 10 H), 4.1-4.7 (m, 1 H), 5.8 (m, 2 H).

Gas chromatographic analysis (3% OV-25 on 100/120 mesh Gas-Chrom Q, column temperature 100 °C) of this liquid showed that it was a mixture of two components in a ratio of 26:74. GC-MS analysis showed both components to have similar spectra. MS for the first component: *m/e* (rel intensity) 80 (100), 156 (24, M$^+$), 157 (3, M$^+$ + 1), 158 (8, M$^+$ + 2). MS for the second component: *m/e* (rel intensity) 79 (100), 156 (10, M$^+$), 157 (1, M$^+$ + 1), 158 (3, M$^+$ + 2).

This mixture was suitable for subsequent reactions without further purification.

(3*S*)-*exo*-Bicyclo[3.3.1]non-6-ene-3-carboxylic Acid-^{13}*C* (5). In a 50-mL pear-shaped flask, equipped with a reflux condenser and a magnetic stirring bar, were placed 558.4 mg (3.56 mmol) of the mixture of (3*R*)-*endo*- and (3*S*)-*exo*-bicyclo[3.3.1]non-6-ene 3-chloride (**4**), 30 mL of anhydrous ether, 95.3 mg (3.92 mmol) of magnesium turnings, and a crystal of iodine. The reaction mixture was brought to reflux and within a 2.5-h period a gray precipitate started to form. The Grignard reagent was then treated with ^{13}CO$_2$ (isotopic purity 90%) generated[15] from Ba^{13}CO$_3$ (775 mg, 3.92 mmol) and concentrated sulfuric acid. The resulting reaction mixture was quenched with 20% aqueous sulfuric acid and then extracted three times with ether. The ether extract was washed with 25% aqueous sodium hydroxide. After the sodium hydroxide solution was washed with ether, it was neutralized with 20% aqueous sulfuric acid and then extracted three times with ether. The ether extract was dried over anhydrous magnesium sulfate and the solvent was removed under reduced pressure to give 362 mg of **5** as a white solid (62% yield), mp 118-120 °C. Recrystallization from aqueous ethanol gave **5** as white crystals: mp 121-122 °C (lit.[16] mp for the ^{12}C analogue 116.5-119.5 °C); IR (Nujol, cm^{-1}) 1680; NMR (CDCl$_3$, δ ppm) 1.1-3.2 (m, 11 H), 5.7 (m, 2 H), 11.0 (s, 1 H); $[\alpha]_{578}$ 99.1°, *c* 0.57, 96% ethanol (further recrystallization did not change the optical rotation); mass spectrum *m/e* (rel intensity) 81 (100), 166 (5, M$^+$ − 1), 167 (44, M$^+$), 168 (5, M$^+$ + 1), 169 (2, M$^+$ + 2).

Data for the ^{12}C analogue of **5**, *exo*-bicyclo[3.3.1]non-6-ene-3-carboxylic acid: mp 119-120 °C (lit.[16] mp 116.5-119.5 °C); IR (Nujol, cm^{-1}) 1690 (s); NMR (CDCl$_3$, δ ppm) 1.1-3.2 (m, 11 H), 5.7 (m, 2 H), 11.0 (s, 1 H); mass spectrum *m/e* (rel intensity) 81 (100), 166 (54, M$^+$), 167 (6, M$^+$ + 1), 168 (1, M$^+$ + 2).

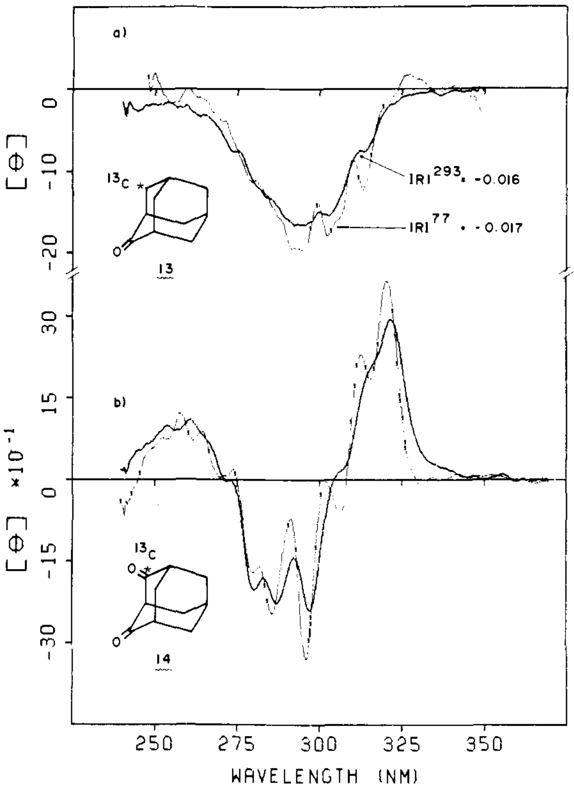


Figure 1. Circular dichroism spectra of (a) (1*S*)-2-adamantanone-*4*-^{13}*C* (**11**) (concentration 7.64 g/L) and (b) (1*S*)-2,4-adamantanedione-*4*-^{13}*C* (**12**) (concentration 0.61 g/L) in EPA (ether–isopentane–ethanol, 5:5:2 v/v) at room temperature (heavy line) and 77 K (light line). The spectra have been corrected to 100% isotopic and optical purity. Note change of scale for (b).

Methyl (3*S*)-*exo*-Bicyclo[3.3.1]non-6-ene-3-carboxylate-^{13}*C* (6). A yellow diazomethane-ether distillate[17] was dropped into a solution of 200 mg of (3*S*)-*exo*-bicyclo[3.3.1]non-6-ene-3-carboxylic acid-^{13}*C* (**5**) in 20 mL of ether until the solution became yellow. The excess diazomethane was removed by a slow stream of nitrogen and the solvent was then evaporated under reduced pressure to give 313 mg of **6** as a colorless oil (96% yield): IR (neat, cm^{-1}) 1740 (w), 1690 (s); NMR (CDCl$_3$, δ ppm) 1.6-3.0 (m, 11 H), 3.8 (s, 3 H), 5.8 (m, 2 H); $[\alpha]_{578}$ 96.7°, *c* 1.29, CHCl$_3$; mass spectrum *m/e* (rel intensity) 79 (100), 81 (94), 180 (8, M$^+$ − 1), 181 (74, M$^+$), 182 (9, M$^+$ + 1), 183 (3, M$^+$ + 2).

Data for the ^{12}C analogue of **6**, methyl *exo*-bicyclo[3.3.1]non-6-ene-3-carboxylate: colorless oil; IR (Nujol, cm^{-1}) 1735 (s); NMR (CDCl$_3$, δ ppm) 1.6-3.0 (m, 11 H), 3.8 (s, 3 H), 5.8 (m, 2 H); mass spectrum *m/e* (rel intensity) 79 (87), 81 (91), 179 (1, M$^+$ − 1), 180 (100, M$^+$), 181 (13.5, M$^+$ + 1), 182 (1, M$^+$ + 2).

Methyl (3*R*)-*endo*-Bicyclo[3.3.1]non-6-ene-3-carboxylate-^{13}*C* (7). In a flame-dried 10-mL round-bottomed flask, fitted with a magnetic stirring bar, were placed 6 mL of tetrahydrofuran (distilled over sodium-benzophenone) and 2.1 mL (20.8 mmol) of freshly distilled diisopropylamine. To this solution, while being kept under an atmosphere of nitrogen and cooled at −20 °C, was added 4.8 mL of *n*-BuLi (2.53 M, 12.1 mmol). The resulting mixture was stirred at −20 °C for an additional 10 min. In a second 25-mL round-bottomed one-necked flask, fitted with a magnetic stirring bar, were placed 723.8 mg (3.99 mmol) of methyl (3*S*)-*exo*-bicyclo[3.3.1]non-3-ene-3-carboxylate-^{13}*C* (**6**) and 30 mL of tetrahydrofuran (distilled over sodium-benzophenone). The solution was cooled in an ice bath and to this was added the lithium diisopropylamide solution within 5 min. After the addition was complete, the ice bath was removed and the reaction mixture was stirred at room temperature for another 5 min. The resulting mixture was poured into water, acidified with diluted hydrochloric acid, and then extracted with ether. After drying over anhydrous magnesium sulfate, the solvent was evaporated under reduced pressure to give 800 mg of a light yellow liquid, which was identified as a 23:77 mixture of the (3*S*)-exo (**6**) and (3*R*)-endo (**7**) (60% yield) by gas chromatographic analysis (OV-25, column temperature 95 °C). The esters **6** and **7** were identical with authentic samples of the corresponding ^{12}C analogue[18] by gas chromatography and thin layer chromatographic comparison.

(3*R*)-*endo*-Bicyclo[3.3.1]non-6-ene-3-carboxylic Acid-^{13}*C* (8). A suspension of the mixture of the (3*S*)-exo and (3*R*)-endo esters (800 mg) in 6 mL of 10% aqueous sodium hydroxide was heated under reflux for 1 h. The aqueous layer was washed with ether to remove the unreacted organic material and then neutralized with 20% aqueous hydrochloric acid to give a white precipitate, which was extracted three times with ether. After drying over anhydrous magnesium sulfate, the solvent was removed under reduced pressure to yield 503.5 mg of **8** as a white solid, which was identified as a mixture of the (3*S*)-exo (**5**) and (3*R*)-endo (**8**) carboxylic acids in the ratio of 31:69 by gas chromatographic analysis of their methyl esters.

(1*R*)-4-Hydroxy-2-adamantanone-*2*-^{13}*C* (9). The mixture of the (3*S*)-exo (**5**) and (3*R*)-endo (**8**) carboxylic acid-^{13}*C* (503 mg), acetic anhydride (3 mL), and boron trifluoride etherate (0.77 mL) in dry benzene (11 mL) was stirred at room temperature for 1 h.[3e] After cooling, cold water was added. The benzene was evaporated and the solution was made alkaline with 10% aqueous sodium hydroxide. The mixture was heated to reflux for 1 h in order to hydrolyze the initially formed acetate. After cooling, the mixture was extracted with chloroform and the extract was washed with water and dried. Evaporation of the solvent under reduced pressure gave a white solid, which was purified by column chromatography (silica gel, hexane–ethyl acetate, 1/1) to give 402 mg of **9** as a white solid: IR (CHCl$_3$, cm^{-1}) 1655 (s), 1675 (s), 3400 (m); NMR spectrum comparable with the published value of the ^{12}C analogue;[7a] mass spectrum *m/e* (rel intensity) 78 (70), 79 (100), 166 (3, M$^+$ − 1), 167 (28, M$^+$), 168 (3, M$^+$ + 1); $[\alpha]_{578}$ −11.27, *c* 1.1, CHCl$_3$.

(1*S*)-2-Adamantanol-*4*-^{13}*C* (10). The carbonyl group of **9** was reduced by Wolff-Kishner reduction.[9] A mixture of 155.6 mg (0.94 mmol) of (1*R*)-4-hydroxy-2-adamantanone-*2*-^{13}*C* (**9**), 3 mL of diethylene glycol, 187 mg of potassium hydroxide, and 0.16 mL of hydrazine hydrate (85%) was heated under reflux (nitrogen atmosphere) for 4 h. After the water and hydrazine were distilled off, the mixture was again heated under reflux for 4 h. The resulting mixture was cooled to room temperature, and after dilution with water it was acidified with 20% aqueous hydrochloric acid. The solution was extracted with chloroform, and the organic layer was washed with water. After drying over anhydrous magnesium sulfate, the solvent was removed under reduced pressure and the white solid was purified by column chromatography (silica gel, ethyl acetate–hexane, 1/5) to give 101 mg of **10** as a white solid (70% yield): mp 285–290 °C (lit.[19] mp for the ^{12}C analogue 296.2–297.7 °C); IR (CHCl$_3$, cm^{-1}) 3330, 1460, 1380; NMR (CDCl$_3$, δ ppm) 1.0–3.3 (br m, 14 H), 3.8 (br m, 1 H); mass spectrum *m/e* (rel intensity) 92 (53), 93 (64), 134 (12), 135 (100), 136 (10), 151 (6), 152 (5), 153 (2, M$^+$). NMR spectral data for the ^{12}C analogue have been published.[20]

(1*S*)-2-Adamantanone-*4*-^{13}*C* (11). (1*S*)-2-Adamantanol-*4*-^{13}*C* (**10**, 30 mg, 0.196 mmol) in acetone (5 mL) was treated under stirring with Jones reagent[10] until the first permanent red color appeared. 2-Propanol was added to remove the excess Jones reagent. After evaporation of acetone, water was added. Successive extraction with ether, drying, and evaporation gave a solid, which was purified by sublimation (45 °C, 0.1 μm) to give 26 mg of **11** as a white solid (87% yield): mp 280–282 °C (lit.[21] mp for the ^{12}C analogue 283 °C); IR (CHCl$_3$, cm^{-1}) 1705; NMR (CDCl$_3$, δ ppm) 2.03 (br d, J = 125 Hz, 1.8 H), 2.03 (br s, 10.2 H), 2.55 (br s, 2 H); mass spectrum *m/e* (rel intensity) 150 (11, M$^+$ − 1), 151 (100, M$^+$), 152 (11, M$^+$ + 1); isotopic purity 90%. The optical purity is assumed to be identical with that of the starting chiral acid **3**, i.e., 75.6%.

(1*S*)-2,4-Adamantanedione-*4*-^{13}*C* (12). (1*R*)-4-Hydroxy-2-adamantanone-*2*-^{13}*C* (**9**, 15 mg, 0.090 mmol) in acetone (5 mL) was treated with Jones reagent[10] and stirred until the first permanent red color appeared. 2-Propanol was added to remove the excess of Jones reagent. After evaporation of acetone, water was added, followed by successive extraction with ether, drying, and evaporation to give a white solid, which was purified by sublimation (45 °C, 0.1 μm) to afford 13 mg of **12** as a white solid (87% yield): mp 288–290 °C (lit.[19] mp for the ^{12}C analogue 280–282 °C); IR (CHCl$_3$, cm^{-1}) 1675, 1725. The chemical shifts of the NMR spectrum were identical with those of the ^{12}C analogue;[7a] however, the peak at δ 3.38 was broader, possibly owing to the β coupling of the 3 proton with the ^{13}C isotope. Mass spectrum: *m/e* (rel intensity) 79 (100), 164 (10.8, M$^+$ − 1), 165 (94, M$^+$), 166 (10.8, M$^+$ + 1). Isotopic purity was 90%. The optical purity is assumed to be identical with that of the starting chiral acid **3**, i.e., 75.6%.

^{13}C NMR (CDCl$_3$, δ ppm) for **11:** 207.819 (very intense), 67.547, 45.734, 45.007, 44.232, 43.976, 29.961, 26.913.

^{13}C NMR (CDCl$_3$, δ ppm) for the ^{12}C analogue: 207.116, 67.786, 44.541, 43.353, 37.509, 29.443, 26.413.

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