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Quantitative Analyses of Stereoisomeric 3,4-d_2-Cyclohexenes in the Presence of 3,6-d_2-Cyclohexenes

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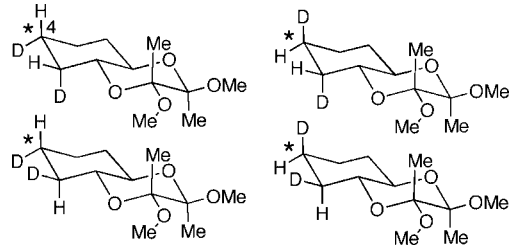

The challenging analytical problem posed by mixtures of the four isomeric 3,4-d_2-cyclohexenes and the three isomeric 3,6-d_2-cyclohexenes has been solved through a novel one-dimensional NMR spectroscopic method dependent on recording ^{13}C resonances while broadband decoupling both proton and deuteron nuclei. Upfield deuterium perturbations of ^{13}C chemical shifts in chair conformationally locked cyclohexane derivatives readily secured from a mixture of the seven deuterium-labeled cyclohexenes allow quantitative analytical assessments of the four possible 3,4-d_2-cyclohexenes in the mixture. This analytical capability is an essential prerequisite for uncovering the relative participations of the four possible stereochemical paths followed by the thermal structural isomerizations of vinylcyclobutane to cyclohexene. The unconventional NMR method validated in this work will likely prove invaluable in related stereochemical investigations.

Introduction

The thermal chemistry of vinylcyclopropane has proved to be more subtle and complex than might have been anticipated when its reactions first received experimental attention nearly 50 years ago. The structural isomerization of vinylcyclopropane to cyclopentene was discovered in 1960,[1] and reactions converting vinylcyclopropane to three isomeric pentadienes were first documented in 1961.[2] A third type of thermal reactions, degenerate stereomutations altering stereochemical relationships at the three carbons of the ring, were demonstrated in 1967 with the aid of deuterium labeling.[3] All three types of reactions were first interpreted mechanistically as involving transient diradical intermediates: homolytic cleavage of a C1−C2 bond would, according to this interpretation, generate a short-lived diradical, which could lead to cyclopentene through a [1,3] carbon sigmatropic shift, or isomeric pentadienes through one or another [1,2] hydrogen shift, or stereomutation products, different stereochemical versions of the reactant as the bond initially cleaved reverted to a mixture of deuterium-labeled vinylcyclopropanes.[4] Substituted vinylcyclopropanes typically react through at least these three types of processes characteristic of the parent hydrocarbon. Some, such as *cis*-2-methyl-1-vinylcyclopropane, have access to another mode of structural isomerization.[5]

The thermal chemistry of vinylcyclopropane received fresh attention as soon as theory-based considerations published in 1969 raised the possibility that diradical intermediates might not be involved in vinylcyclopropane-to-cyclopentene isomerizations.[6] The stereochemical preferences for [1,3] carbon shifts

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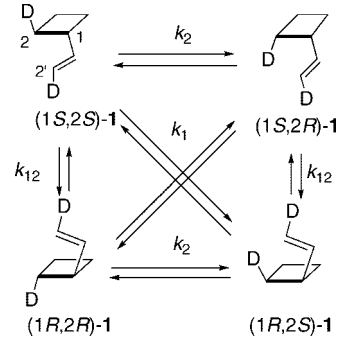
involved in vinylcyclopropane-to-cyclopentene isomerizations were given particular scrutiny. A mechanistic formulation involving transient diradical intermediates was discounted in favor of an alternative mechanistic representation conforming to generalizations postulated through orbital symmetry theory. Years later and after considerable experimental effort contributed sufficient evidence, it became clear that this mechanistic interpretation was not sound.[7] It became generally recognized that vinylcyclopropanes were converted through thermal activation to conformationally flexible diradical intermediates, which in turn could react further through [1,3] carbon shifts, [1,2] hydrogen migrations, or stereomutations to give cyclopentenes, pentadienes, or stereomutation products.[8] Orbital symmetry theory, so powerfully applicable in many cases, proved to be not relevant to the thermal reactions of vinylcyclopropanes.

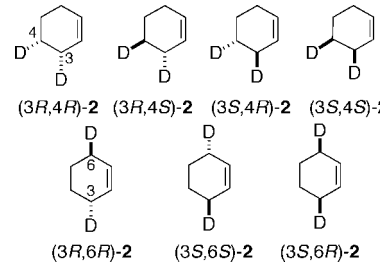
These types of reactions of vinylcyclopropane and the diradical intermediates involved have by now been repeatedly investigated by advanced computational methods. Most impressively, the reaction stereochemistry of the conversion of vinylcyclopropane labeled only with deuterium atoms as stereochemical markers to give deuterium-labeled isomers of cyclopentene determined experimentally[9] has been modeled using a theory-derived potential energy surface[10] and reaction dynamics calculations.[11] The agreement between experimental and theory-based estimations of the relative significance of the four possible stereochemical paths for the [1,3] carbon shifts could hardly be better.

The first demonstration of a simple monocyclic vinylcyclobutane reacting through a [1,3] carbon shift to form a cyclohexene product, the conversion of 2-propenylcyclobutane to 1-methylcyclohexene reported in 1963,[12] introduced obvious questions as to the similarities and differences that might be seen in the reactions of vinylcyclopropanes and vinylcyclobutanes. Given the considerable efforts expended toward defining and understanding the thermal reactions of vinylcyclopropanes, one might imagine that the reactions of vinylcyclobutane and various substituted vinylcyclobutanes would by now have been studied and clarified in a good number of cases. There are, however, only a few. Thermal isomerization studies of chiral 2-methyl- and 2-cyano-1-(*E*)-propenylcyclobutanes leading to stereomutations and to isomeric 3,4-dimethylcyclohexenes[13] or 3-methyl-4-cyanocyclohexenes[14] have demonstrated that all possible stereochemical paths for the [1,3] carbon shifts participate and thermochemically favored rather than orbital symmetry allowed paths are dominant. A less complete study, following the stereomutations of *cis*- and *trans*-1-(*E*)-propenyl-2-*d*-cyclobutanes and competitive structural isomerizations leading to 3-methyl-4-*d*-cyclohexenes, demonstrated that stereomutations and [1,3] carbon shift reactions took place at comparable rates and the isomerizations to 3-methyl-4-*d*-cyclohexenes occurred through "allowed" and "forbidden" stereochemical paths in a 63:37 ratio.[15]

SCHEME 1. Thermal Stereomutations Interconverting the Four Isomers of 2,2′-d_2-Vinylcyclobutane



SCHEME 2. Thermal 3,4- and 3,6-d_2-Cyclohexene Products Derived from [1,3] Sigmatropic Shifts of the Labeled Vinylcyclobutanes Presented in Scheme 1



The stereochemical characteristics of the rearrangement of vinylcyclobutane itself to form cyclohexene have not been reported, a glaring deficiency since an experimental determination of the behavior of the C_6H_{10} parent system would provide the best opportunity for meaningful comparisons with theory-based predictions. The complexities that would need to be overcome to attain this objective are easy enough to envisage but so far they have seemed too intractable to pursue. A similar roadblock to progress is evident in theory-based approaches: serious calculations on the [1,3] carbon shift process leading from vinylcyclobutane to cyclohexene have been done and published, but no predictions of reaction stereochemistry have been made.[16]

To move ahead toward overcoming this mechanistic conundrum, we have focused attention on the most difficult problem posed by such a stereochemical quest: to gain every unique rate constant for gas-phase thermal reactions at a constant temperature for all [1,3] carbon shifts governing these reactions of chiral 2,2′-d_2-labeled vinylcyclobutanes (**1**). By convention, d_0-**1** is unlabeled vinylcyclobutane and *d*-**1** is a monodeuterium-labeled isotopomer of vinylcyclobutane; **1** designates d_2-labeled vinylcyclobutanes, with each specific one named through modifiers as necessary. The same convention applies to other structural sets, as exemplified in Schemes 1 and 2.

One can imagine synthesizing with fair efficiency and high enantiomeric purity one or another of the 2,2′-d_2-vinylcyclobutanes (**1**) to be used as reactants in gas-phase kinetic studies (Scheme 1). They would provide stereochemical markers needed

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to follow the stereochemical distinctions associated with stereomutations and [1,3] carbon shift events.

One can think of analytical tools able to follow relative concentrations of all four possible stereoisomers of the 2,2′-d_2-vinylcyclobutanes (**1**) as they evolve over time through stereomutations (Scheme 1). Any one of the four stereoisomers depicted in Scheme 1 could lead to each of the four stereoisomers of 3,4-d_2-cyclohexene, through [1,3] carbon sigmatropic shifts initiated by a C1−C2 bond cleavage. The two (1*S*) and two (1*R*) isomers could give three 3,6-d_2-cyclohexenes, two enantiomers and one meso isomer, through rearrangements involving C1−C4 bond cleavages. Thus thermal reactions starting from any one of the 2,2′-d_2-vinylcyclobutanes would lead to a time-dependent mixture of all four 2,2′-d_2-vinylcyclobutanes (**1**) and a time-dependent mixture of the seven d_2-cyclohexenes (**2**) shown in Scheme 2.

In addition to the various stereoisomers of the 2,2′-d_2-vinylcyclobutanes (Scheme 1) and d_2-cyclohexenes (Scheme 2), there would be additional thermal reaction products derived from fragmentations: mixtures of ethylene, *d*-ethylene, 1-*d*-butadienes, and 1,4-d_2-butadienes.[17] The reactions leading to these fragments could be easily included exactly in the kinetic analysis, and preparative GC could secure each of the two sets of isomers of Schemes 1 and 2 from a thermal reaction mixture. Each set could then be subjected to quantitative analyses, which raises the question of how the required analyses for the individual 3,4-d_2-cyclohexenes in a mixture of seven deuterium-labeled cyclohexenes could be achieved. This challenge has proved nearly intractable.

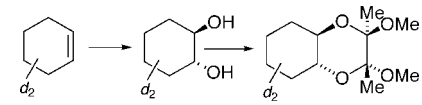
This critical methodological issue had to be resolved before a rational assault on the overall stereochemical and mechanistic goal could be sensibly ventured. There would be no recourse to capillary GC on "chiral" columns, for the structures, differing only by placements of deuterium labels, most probably could not be separated. Although ^{2}H NMR could make some useful distinctions between some diastereomers, it could not distinguish among others and could not separate enantiomers. No plausible analytical method to determine relative concentrations of the four 3,4-d_2-cyclohexenes in reaction mixtures of all seven d_2-cyclohexenes (Scheme 2) was discernible, for some time.

This severe methodological roadblock was eventually overcome, as described below, thus opening a direct path to the immediate objective, an experimental determination of the stereochemistry of the thermal conversion of vinylcyclobutane to cyclohexene, and introducing a new analytical means of valuable potential applicability in certain other mechanistic and stereochemical investigations.

Results and Discussion

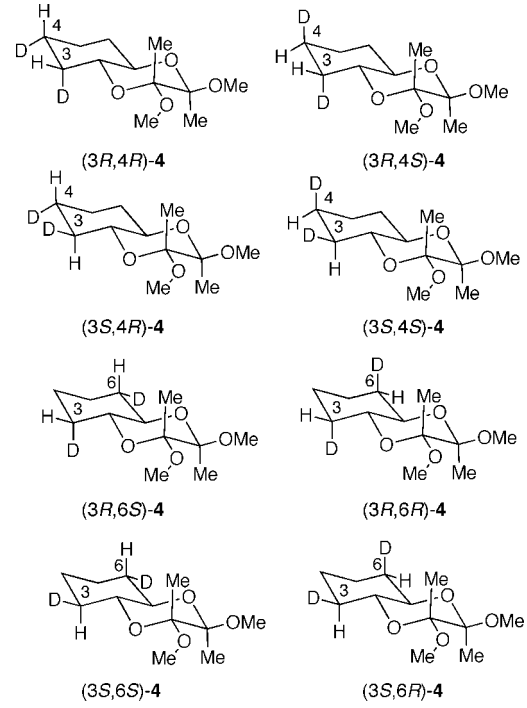
Structural Modification of d_2-Cyclohexenes (2). Initial conceptual strategies for progressing toward a competent analytical tactic were based on converting the mixture of d_2-cyclohexenes (Scheme 2) to a mixture of substituted cyclohexanes that would provide conformational stability and chirality. One could imagine, for instance, converting a mixture of the seven d_2-cyclohexenes **2** to the corresponding eight (1*R*,2*R*)-*trans*-1,2-dihydroxycyclohexanes (**3**)[18] (Scheme 3) and then further to afford the related d_2-labeled 1,2-diacetals **4** (Scheme 4) prepared from the diols using 2,3-butanedione and trimethyl orthoformate.[19]

SCHEME 3. (1*R*,2*R*)-*trans*-1,2-Dihydroxycyclohexanes (3) and Butane-2,3-dione Derived Diacetals (4) from d_2-Cyclohexenes (2)



2 **3** **4**

SCHEME 4. Butane-2,3-diacetals 4 from (1*R*,2*R*)-*trans*-1,2-Dihydroxy-3,4- and -3,6-d_2-Cyclohexanes



The eight d_2-labeled diacetals **4** thusly prepared would then be used to find a suitable analytical method for quantitatively analyzing the four 3,4-d_2 isomers in the presence of the four 3,6-d_2 isomers. For clarity in Scheme 4, and below, the carbon numbering convention adopted follows the standard numbering convention used for the d_2-cyclohexenes, rather than the formally correct option. For the d_0-bicyclic, the alternative would be (2*R*,3*R*,4a*S*,8a*S*)-octahydro-2,3-dimethoxy-2,3-dimethyl-1,4-benzodioxin. This compound is a well-known solid (mp 77 °C); an X-ray structure has been determined, providing its geometrical details.[20]

The d_0-diacetal (d_0-**4**) was made simply from *trans*-1,2-cyclohexanediol utilizing 2,3-butanedione and trimethyl orthoformate.[19] A mixture of 3,4- and 3,6-d_2-analogs, which could be made from **2** through thermal reactions of **1**, was prepared through a short two-step reaction sequence. Addition of DBr generated in situ from CH_3COBr in CH_3OD to 1,3-cyclohexadiene gave both 3-Br-4-*d*-cyclohexenes and 3-Br-6-*d*-cyclohexenes.[21] Reduction of that mixture with $NaBD_3CN$ in the

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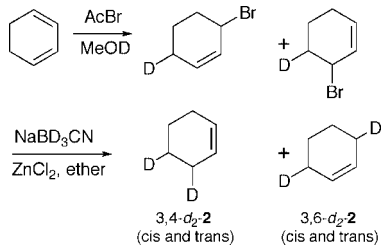
SCHEME 5. Preparations of 3,4-d_2-2 and 3,6-d_2-2 Cyclohexenes



presence of $ZnCl_2$[22] provided a mixture of 3,4-d_2-**2** and 3,6-d_2-**2** isomers (Scheme 5). These d_2-labeled cyclohexenes were oxidized[23] using potassium peroxymonosulfate ("oxone") to afford the *trans*-diols **3**, which were then converted as a mixture to the d_2-diacetals **4**.[19]

Quantitative Analysis of Isomeric Butane-2,3-diacetals 4 Approached by NMR Methods. Various 2D NMR correlation spectroscopic methods were initially imagined to allow one to gain quantitative analytical data that would define stereochemistry for the eight isomers of **4**, especially since the axial and equatorial hydrogens at C3 and C4 are characterized by distinct multiplets: *eq*-C3-H at δ 1.74, *eq*-C4-H at 1.67, *ax*-C3-H at 1.30, and *ax*-C4-H at 1.20 ppm. The methyl groups partially overlapping with *ax*- C3-H absorptions were easily taken out of the way by making the butane-2,3-diacetals from d_6-labeled butane-2,3-dione. While the literature reports examples of ^{2}H− ^{2}H COSY NMR and ^{13}C relayed ^{2} H− ^{2}H COSY 2D experiments and secure definitions of stereochemistry for deuterium labels in methylene groups through a variety of ^{2}H-decoupled proton/carbon NMR shift correlation spectroscopic methods, experimentation using such approaches led nowhere. Various attempts to exploit ^{1}H− ^{2}H NMR correlation spectroscopy[24] and ^{13}C− ^{1}H HSQC plots failed to afford useful outcomes. The extensive overlapping absorptions contributed by the isomeric d_2-labeled diacetals **4** could not be deciphered. There may well be 2D NMR approaches that could have solved this analytical problem, but they eluded our persistent attempts to recognize even one. To gain similar stereochemical information based on ^{2}H NMR was not possible, for the stereochemically distinct $^3J_{^2H-^2H}$ coupling constants in chair cyclohexane systems would have been too small to be seen, and stereochemically specific deuterium-induced chemical shift perturbations on a vicinal hydrogen also proved wanting.[25]

Finally, a direct and readily exercised NMR method was introduced and found to be well suited to meet the challenge posed by the objective. It relied on deuterium-induced perturbations on ^{13}C chemical shifts, perturbations that have considerable stereochemical sensitivity, to carry the day.[26]

Deuterium Perturbations of ^{13}C Chemical Shifts in Cyclohexanes. The analytical problem was resolved by extending published work and by exercising a novel NMR method. Günther and Joseph-Nathan and their collaborators in 1984 reported stereospecific intrinsic ^{2}H/^{1}H isotope effects on ^{13}C chemical shifts on *tert*-butylcyclohexane and cyclohexane.[27] The data they obtained are summarized in Tables 1 and 2.

TABLE 1. Deuterium-Induced Upfield Perturbations, $\Delta\delta$ (ppb), on ^{13}C Chemical Shifts in 1-*d*-4-*tert*-Butylcyclohexane

$\Delta\delta$	C1-D axial	C1-D equatorial	difference	average
$^1\Delta\delta$, at C1	442.2	392.4	48.9	
$^2\Delta\delta$, at C2	98.6	106.2	−7.6	102.4
$^3\Delta\delta$, at C3	14.7	37.7	−23.0	26.2

TABLE 2. Deuterium-Induced Upfield Perturbations, $\Delta\delta$ (ppb), on ^{13}C Chemical Shifts in Cyclohexane

$\Delta\delta$	C1-D axial	C1-D equatorial	difference	average
$^1\Delta\delta$, at C1	444.9[a]	398.4[a]	46.5	
$^2\Delta\delta$, at C2				103.7[b]
$^3\Delta\delta$, at C3				24.9[b]

[a] Recorded at − 80 °C. [b] Recorded at rt.

The data secured for the *tert*-butylcyclohexane system revealed that the one-bond ^{13}C-D perturbation $^1\Delta\delta$ values were the largest, and the axial disposition of D provided the larger of the two. The two-bond and three-bond perturbations, $^2\Delta\delta$ and $^3\Delta\delta$, were larger for equatorial D substituents. The difference favoring the equatorial D $^3\Delta\delta$ perturbation was especially pronounced. The equatorial D-C-C-^{13}C geometry involved is approximately planar and zigzag, facilitating that $^3\Delta\delta$ upfield shift at C3.

The corresponding data for *d*-cyclohexane were less complete; the $^2\Delta\delta$ and $^3\Delta\delta$ values were determined at rt, and the axial and equatorial dispositions of the label were averaged through rapid chair-chair conformational interconversions (Table 2). These averaged values are comparable to the averaged values calculated for the same entries in Table 1. The less than perfect congruence of the cyclohexane rings of the unsubstituted and the *tert*-butyl-substituted structures is reflected in modestly different $\Delta\delta$ values. Hence, for any particular system, such as the butane-2,3-diacetals of Scheme 4, the values of deuterium-induced perturbations on ^{13}C absorptions would have to be determined. Values specific for cyclohexane and for *tert*-butylcyclohexane could approximate or provide guidance for the $\Delta\delta$ values appropriate for applications to the butane-2,3-diacetals of Scheme 4 but would not be quantitatively reliable. They would have to be found experimentally.

The NMR experiments run by Günther and Joseph-Nathan[27] were recorded at 100.61 MHz using broadband ^{1}H decoupling and a ^{2}H lock. The alternative adopted here was to obtain ^{13}C spectra with simultaneous proton and deuterium broadband decoupling.

^{13}C {^{1}H,^{2}H} NMR Spectroscopy. All ^{13}C spectra were acquired at 30 °C with a 600 MHz ^{1}H frequency, 150.9 MHz ^{13}C frequency NMR spectrometer equipped with a 5-mm triple resonance z-gradient probe using $CDCl_3$ as the solvent and spectral widths of 18 000 Hz (120 ppm). The ^{13}C spectra were acquired by decoupling both ^{1}H and ^{2}H simultaneously using inverse-gated WALTZ16 decoupling sequences to obtain completely decoupled ^{13}C absorptions. The ^{2}H decoupling made use of the third channel through the lock switch. The ^{2}H decoupler frequency was set on resonance at ∼2.0 ppm; a 300-ms 90°

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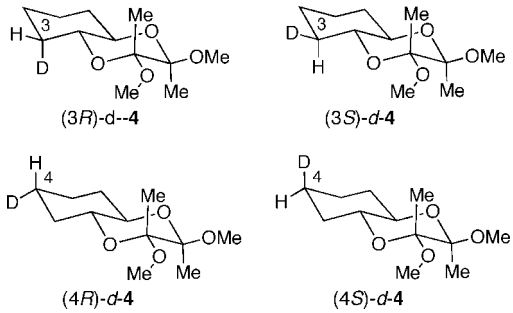
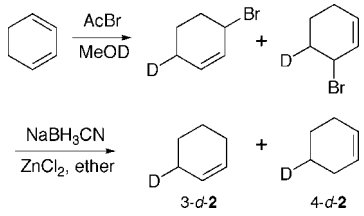
(27) Aydin, R.; Wesener, J. R.; Günther, H. *J. Org. Chem.* **1984**, *49*, 3845–3847.

SCHEME 6. Butane-2,3-diacetals from (1*R*,2*R*)-*trans*-1,2-Dihydroxy-3-*d*- and -4-*d*-Cyclohexanes



SCHEME 7. Preparations of 3-*d*-2 and 4-*d*-2 Cyclohexenes



pulse was used to limit power through the lock channel. The system was locked during the recycle delay, and then the lock was turned off during the acquisition time. To obtain quantitative data the {^{1}H,^{2}H} decoupled ^{13}C spectra were acquired with 15 s relaxation delays, 90° pulse angle, and 2 s acquisition time. The number of collected points was 70 k; 1536 scans were averaged per spectrum. The spectra were processed with 256 K with no window function applied.

Deuterium Isotopic Perturbations ($\Delta\delta$) on ^{13}C Chemical Shifts in 3-*d*- and 4-*d*-Labeled Butane-2,3-diacetals. Determinations of $\Delta\delta$ values for C3 and C4 deuterium-isotope perturbations on ^{13}C chemical shifts depended on making and then studying the four *d*-**4** isomers shown in Scheme 6. These $\Delta\delta$ values could then be used to predict chemical shifts for spectra secured for the d_2-diacetals of Scheme 4 and to see whether stereochemical assignments could be unambiguously made.

The diacetals of Scheme 6 were prepared as racemates but are shown as though each were a butane-2,3-diacetal prepared from a (1*R*,2*R*)-*trans*-1,2-dihydroxycyclohexane. This serves to clarify the presentation of the work, without compromising at all the proof-of-principal objective being pursued. The synthetic route used in Scheme 5 was employed again, replacing $NaBD_3CN$ with $NaBH_3CN$. Overall yields of the product mixtures, realized in Scheme 5 and Scheme 7, were 43% from cyclohexadiene to *trans*-diols and 95% to convert them to the diacetals **4**.

The mixture of four *d*-labeled diacetals (Scheme 6) was used to define deuterium-substituent perturbations of ^{13}C chemical shifts, to gain parameters comparable to those summarized for 1-*d*-4-*tert*-butylcyclohexane and *d*-cyclohexane presented in Tables 1 and 2. The C3 and C4 ^{13}C δ values for d_0-diacetals were recorded at values near 29.3 and 24.0 ppm, with minor variations from run to run. For all of the shift perturbations recorded in Tables 3 and 4 and in spectra later recorded for the mixture of d_2-diacetals of Scheme 4, upfield $\Delta\delta$ shifts of ^{13}C were determined by calculating differences between absorptions observed for C3 or C4 of the *d*-labeled (or d_2-labeled) diacetals and for the d_0-diacetal, the internal chemical shift reference. Under broadband decoupling of both ^{1}H and ^{2}H spins, the ^{13}C absorptions could be observed and identified. Without both decoupling conditions, the spectra were too complex to interpret with confidence. Spectra for the ^{13}C3 and ^{13}C4 regions of the NMR absorptions for *d*-4 diacetals are shown in Figures 1 and 2. The peaks of significance are clearly defined, though some minor contributions to the spectrum presumably from minor contaminations of the sample by d_2-impurities, artifacts of the synthetic sequence employed, are evident. The tabulated $\Delta\delta$ perturbations are shown in Tables 3 and 4.

TABLE 3. Deuterium-Induced Upfield Perturbations, $\Delta\delta$ (ppb), on ^{13}C3 Chemical Shifts in Butane-2,3-diacetals of (1*R*,2*R*)-*trans*-1,2-Dihydroxy-3-*d*- and -4-*d*-cyclohexanes

$\Delta\delta$	D axial	D equatorial	difference	average
$^1\Delta$, at C3	383	353	30	
$^2\Delta$, at C3	91	97	−6	94
$^3\Delta$, at C3	19	28	−9	23.5

TABLE 4. Deuterium-Induced Upfield Perturbations, $\Delta\delta$ (ppb), on ^{13}C4 Chemical Shifts in Butane-2,3-diacetals of (1*R*,2*R*)-*trans*-1,2-Dihydroxy-3-*d*- and -4-*d*-cyclohexanes

$\Delta\delta$	D axial	D equatorial	difference	average
$^1\Delta$, at C4	397	343	54	
$^2\Delta$, at C3, C5	92[a]	102[b]	−10	97[c]
$^3\Delta$, at C6	20	34	−14	27

[a] One absorption of the four contributors, ascribed to the influence of an axial D at C3 or C5. [b] One composite absorption of three contributors, ascribed to a superposition of absorptions influenced by an axial D at C3 or C5 and to axial and equatorial D at C3 or C5. See text. [c] An unweighted average of the two $^2\Delta$ values recorded.

While the spectra associated with absorptions for C3 in Figure 1 and the $\Delta\delta$ values in Table 3 may all be assigned, following the precedents recorded in Tables 1 and 2, the peaks for $^2\Delta$ deuterium perturbations at C4 (Table 4) are not well resolved. The axial and equatorial perturbations are contributed from both adjacent C-D influences. The averages of all four are in the neighborhood of 100 ppb. The axial/equatorial difference for one pair, the axial and equatorial D perturbations at C3 or at C5, are about 10 ppb, whereas for the other pair, at C5 or C3, the difference is very small, and they come together as part of the larger composite evident in Figure 2 near 102 ppb.

Predicted and Observed $\Delta\delta$ ^{13}C Deuterium Perturbations for Diacetals 4. What would one anticipate, given this data, for ^{13}C $\Delta\delta$ deuterium perturbations for the d_2-diacetals of Scheme 4? These parameters would be expected to be projected by simply summing contributions for both deuterium atoms in each system.[28] The projections would be dependent on the position and axial or equatorial disposition of each deuterium label in each stereoisomer. These predictions are summarized in Table 5.

According to these projections, based on the data summarized in Table 3, the ^{13}C3 NMR {^{1}H,^{2}H} decoupled absorptions for the mixture of the isomeric diacetals **4** should show only six signals. The more intense pair of peaks at 353 and 383 ppb reflect the 3,6-d_2-diacetals, for the labels contribute independent $^1\Delta$ isotopic perturbations at C3 and at C6. An *ax*-C3-D and an *ax*-C6-D will each contribute to the 383 ppb perturbation; an isomer with an *ax*-C3-D and an *eq*-C6-D, or vice versa, will have peaks of half the intensity at 383 and 353 ppb. The perturbations contribute individually, not additively. Within Table 5, the $^1\Delta$ isotopic perturbations at C3 and at C6 are labeled

(28) See, inter alia: Anet, F. A. L.; O'Leary, D. J. *Tetrahedron Lett.* **1989**, *30*, 2755–2758.

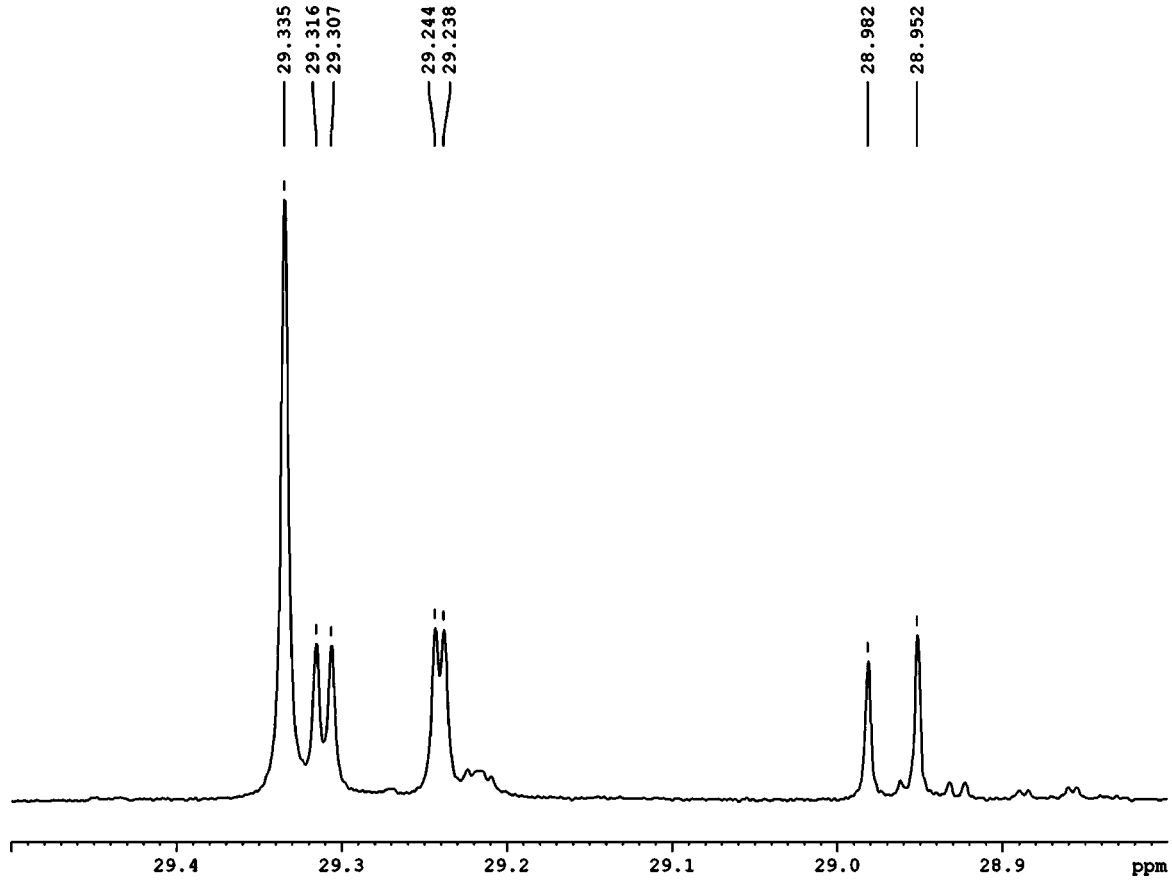


FIGURE 1. ^{13}C3 {^{1}H,^{2}H} region of the NMR spectrum for the *d*-**4** diacetals of Scheme 6. The recorded chemical shifts are as given. The corresponding $\Delta\delta$ values, relative to the absorption for the d_0-**4** internal standard, at δ 29.335, are upfield by 19, 28, 91, 97, 353, and 383 ppb.

with both contributions, using the symbol "&" to emphasize an "and" rather than a "sum" of perturbations. The 3,4-d_2 isomers of **4** have a predicted pattern of four lines of equal intensities at 444, 450, 474, and 480 ppb. These values are listed in the "sum (ppb)" column of entries following "$^1\Delta$ (ppb)" and "$^2\Delta$ (ppb)" values for each of the four 3,4-d_2-isomers. The data under "$^3\Delta$ (ppb)" contribute nothing to the prediction for d_2-**4** structures but are convenient reminders of the experimental $^3\Delta$ perturbations found in Figure 1 and Table 3.

The experimental spectrum for C3 absorptions for the mixture of d_2-labeled isomers of Scheme 4, shown in Figure 3, validates these predictions. The chemical shift perturbations lead to observed ^{13}C3 absorptions at 19 and 29 ppb, comparable to the 19 and 28 ppb values for axial and equatorial D in a $^3\Delta$ relationship to a C3 lacking a deuterium label. The sample has some *d*-**4** component having D at C5 and none at C3. The most intense peaks are seen at 353 and 383 ppb, in accord with the predicted values. The four absorptions at higher field, recorded at 444, 449, 474, and 478 ppb, are in fair agreement with predictions of 444, 450, 474, and 480 ppb. All of the predicted ^{13}C3 $\Delta\delta$ perturbations for the d_2-isomers **4** are in close agreement.

Predicting and then determining chemical shift perturbations at C4, one has to recall the lack of clarity for $^2\Delta\delta$ effects in Table 4. The predictions for the four isomeric 3,4-d_2-isomers of **4** summarized in Table 6 are of special importance.

The ^{13}C4 region of the observed NMR spectrum for the d_2-labeled diacetals (Figure 4) exhibits a pair of peaks at 20 and 33 ppb, a $^3\Delta$ contribution from some *d*-labeled diacetal having D at C6 but not elsewhere. These follow a complex of lines ranging from 92 to 136 ppb. One might surmise that this outcome would be dominated by contributions from $^2\Delta$ perturbations at C4 from D at C3 (92 and 102 ppb) and from $^3\Delta$ perturbations at C6 (20 and 34 ppb). The combinations would lead to predictions of 112, 123, 125, and 136 ppb. An additional component could be contributed by some *d*-diacetal component in the mixture having D at C3 or at C5 ($^2\Delta \approx 102$ for both epimers) but not elsewhere. Additional absorptions could then be expected at $\Delta\delta$ values of 92 and 102 ppb, completing a set of predicted absorptions at 92, 102, 112, 123, 125, and 136 ppb. The complex of lines are observed at 92, 103, 112, 123, and 136 ppb, very close to the values rationalized through the predictions just detailed.

The four-peak pattern predicted in Table 6 relates to diacetals labeled in both C3 and C4. To be in this region the labeled diacetals must be shifted upfield by a $^1\Delta$ perturbation (343 or 397 ppb) and a $^2\Delta$ perturbation (92 and 102 ppb). Any *d*-acetals introduced through synthetic imperfections will not contribute to the 435, 445, 489, and 499 ppb pattern, for they are defined by the $^1\Delta$ perturbations by deuterium at C4 and by the two possible $^2\Delta$ upfield shift contributions provided by axial and equatorial deuterium substitutents at C3. The experimental pattern is seen at 435, 446, 489, and 500 ppb (Figure 4), confirming the $^2\Delta$ assignment to the D-C3 perturbations.

An unambiguous assignments of $^2\Delta$ perturbations from the NMR data secured with mixtures of *d*-diacetals was not accessible (Table 4). Combinations of $^2\Delta$ perturbations of 92 and 102 ppb and of $^1\Delta\delta$ perturbations of 343 and 397 ppb are totally consistent with the experimentally observed spectrum showing absorptions at 435, 446, 489, and 500 ppb (Figure 4).

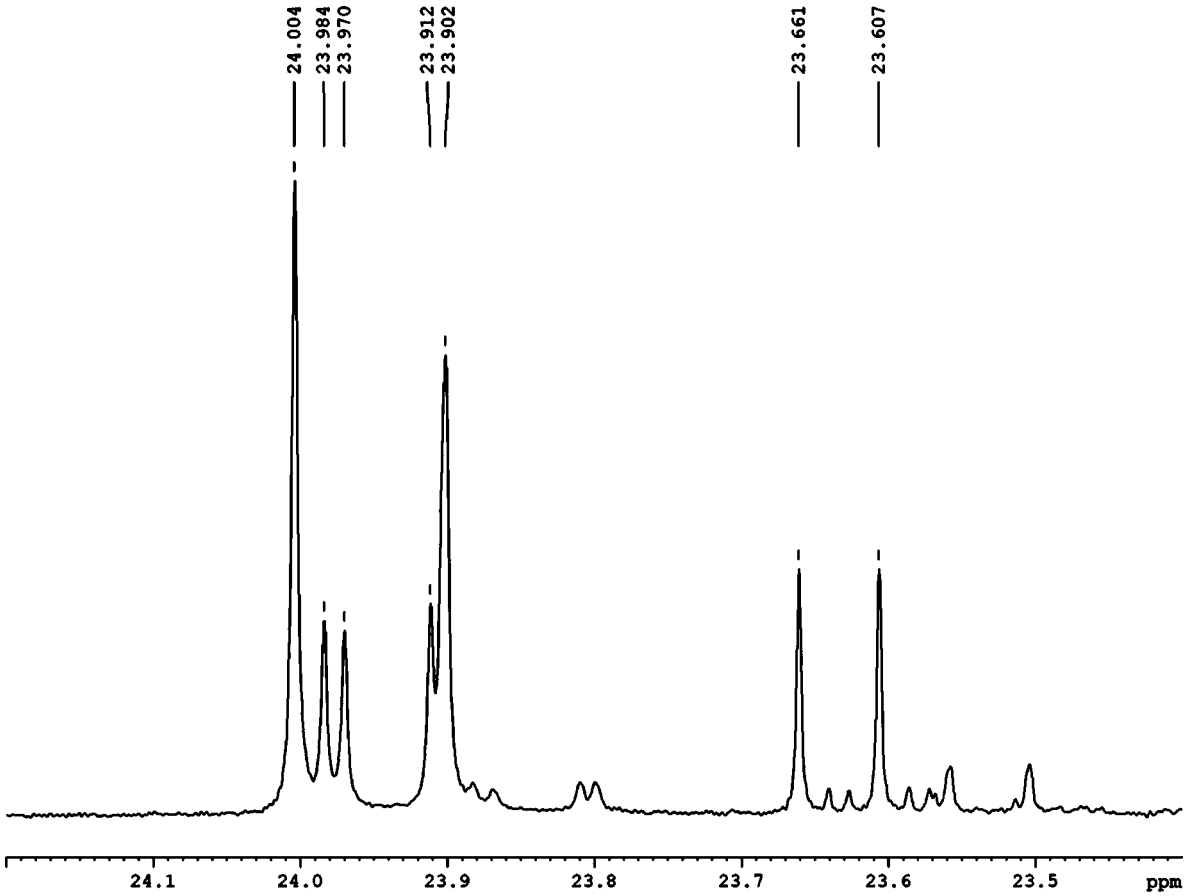


FIGURE 2. ^{13}C4 {^{1}H,^{2}H} region of the NMR spectrum for the *d*-**4** diacetals of Scheme 5. The recorded chemical shifts are as given. The corresponding $\Delta\delta$ values, relative to the absorption for the d_0-**4** internal standard, at δ 24.004, are upfield by 20, 34, 92, 102, 343, and 397 ppb.

TABLE 5. Calculated Deuterium-Induced Upfield Perturbations on ^{13}C3 Chemical Shifts in Butane-2,3-diacetals Derived from (1*R*,2*R*)-*trans*-1,2-Dihydroxy-3,4- and -3,6-d_2-cyclohexanes

isomer	$^{1}\Delta$ (ppb)	$^{2}\Delta$ (ppb)	sum (ppb)	$^{3}\Delta$ (ppb)
(3*R*,4*R*)-**4**	383	97	480	28
(3*R*,4*S*)-**4**	383	91	474	19
(3*S*,4*R*)-**4**	353	97	450	28
(3*S*,4*S*)-**4**	353	91	444	19
(3*R*,6*S*)-**4**	383 & 353			
(3*R*,6*R*)-**4**	383 & 383			
(3*S*,6*S*)-**4**	353 & 353			
(3*S*,6*R*)-**4**	353 & 383			

The stereochemical assignments for specific absorptions observed in ^{13}C {^{1}H,^{2}H} spectra are intrinsic to the predictions, for each is based on stereochemically sensitive dispositions of deuterium labels at C3 and C4. In the ^{13}C3 region of the spectrum of **4** the stereochemical assignments to specific isomers, in increasing order of upfield shifts, are (3*S*,4*S*)-**4** at 444, (3*S*,4*R*)-**4** at 449, (3*R*,4*S*)-**4** at 474, and (3*R*,4*R*)-**4** at 478 ppb (Figure 3). In the ^{13}C4 region of the spectrum of **4** the isomers are (3*R*,4*S*)-**4** at 435, (3*S*,4*S*)-**4** at 446, (3*R*,4*R*)-**4** at 489, and (3*S*,4*R*)-**4** at 500 ppb (Figure 4). This spectroscopic approach applied to a mixture of 3,4- and 3,6-d_2-labeled butane-2,3-diacetals from (1*R*,2*R*)-*trans*-1,2-dihydroxy-3,4- and -3,6-d_2-cyclohexanes could quantify the relevant proportions of all four stereoisomeric 3,4-d_2 products without interference from absorptions derived from 3,6-d_2 components of a reaction mixture from thermal reactions of chiral 2,2′-d_2-vinylcyclobutanes. The agreements between predicted and observed $\Delta\delta$ perturbations as functions of stereochemistry are remarkably satisfactory.

The four ^{13}C3 absorptions at 29.15−29.05 ppm display a somewhat more intense inner pair of peaks (Figure 3), while the four peaks seen in the ^{13}C4 23.85−23.7 ppm region show slightly more intense absorptions for the outer pair (Figure 4). In both regions, the more intense absorptions correspond to the (3*S*,4*R*)-**4** and (3*R*,4*S*)-**4** stereoisomers. Both of these stereoisomers stem from *trans*-3,4-d_2-cyclohexenes (see Scheme 4). The two-step synthetic sequence leading from 1,3-cyclohexadiene to the 3,4- and 3,6-d_2-cyclohexenes provided a slight preference in favor of *trans* over *cis* 3,4-d_2 diastereomers. Were a specific stereoisomer of **1** synthesized and thermally converted to isomers **2** and then on to **3** and finally to a mixture of **4**, there would be no comparable bias in absorption intensities. Only 3,4-d_2-diacetals would be evident in the 435, 446, 489, and 500 ppb pattern of absorptions, and the time-weighted relative mole fraction of each of the four isomers **1** would be known at each reaction time and properly managed during the necessary data reduction.

Conclusions

The remarkably simple ^{13}C {^{1}H,^{2}H} NMR method, which sought a complete answer when applied to the stereochemical problem engaged in this study, achieved its immediate goal. An experimentally practicable approach to define the stereochemical characteristics of suitably deuterium-labeled vinylcyclobutanes to the corresponding cyclohexenes is now at hand,

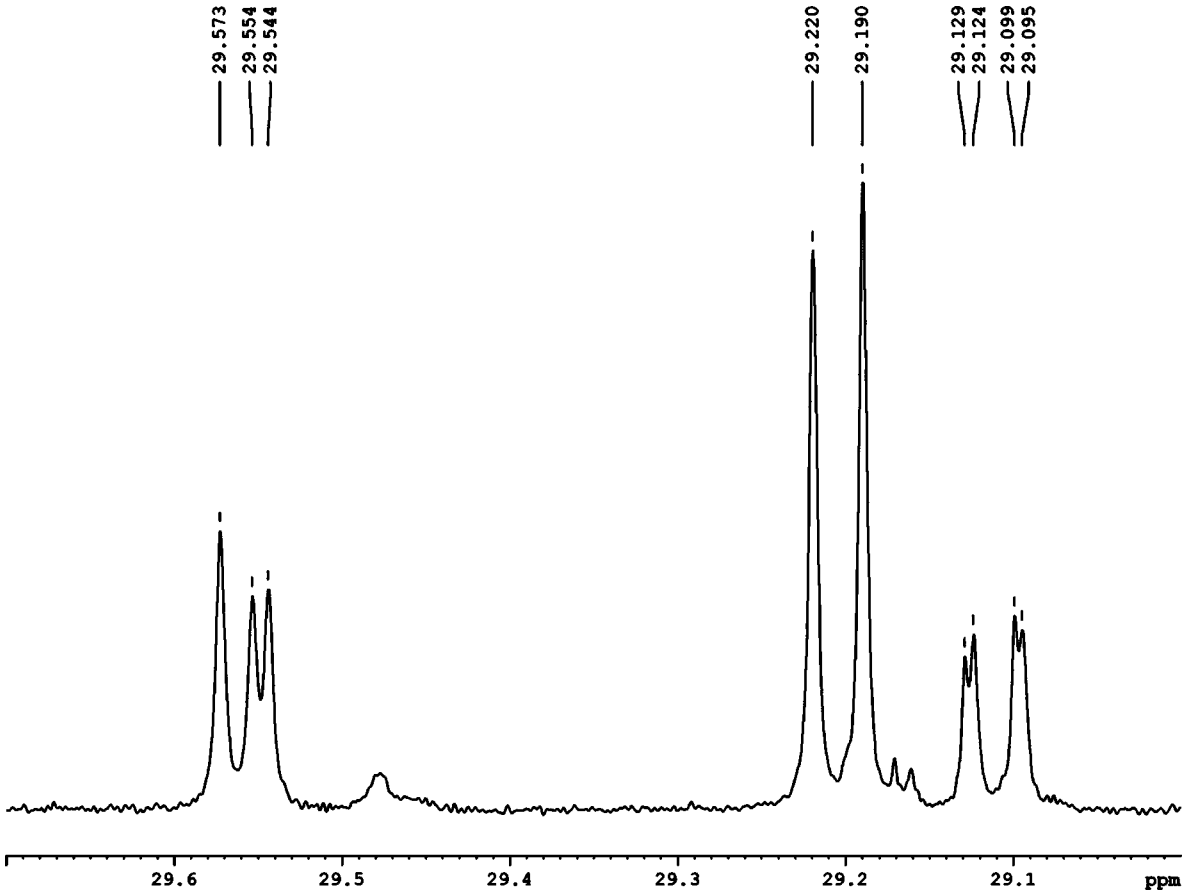


FIGURE 3. ^{13}C3 {^{1}H,^{2}H} region of the NMR spectrum for the diacetals **4** of Scheme 4. The recorded chemical shifts are as given. The corresponding $\Delta\delta$ values, relative to the absorption for the d_0-**4** internal standard, at δ 29.573, are upfield by 19, 29, 353, 383, 444, 449, 474, and 478 ppb.

TABLE 6. Calculated Deuterium-Induced Upfield Perturbations on ^{13}C4 Chemical Shifts in Butane-2,3-diacetals Derived from (1*R*,2*R*)-*trans*-1,2-Dihydroxy-3,4- and -3,6-d_2-cyclohexanes

isomer	$^1\Delta$ (ppb)	$^2\Delta$ (ppb)	sum (ppb)
(3*R*,4*R*)-**4**	397	92	489
(3*R*,4*S*)-**4**	343	92	435
(3*S*,4*R*)-**4**	397	102	499
(3*S*,4*S*)-**4**	343	102	445

and the requisite early and more easily envisaged stages of that overall task have now been engaged. This novel NMR method is not restricted to this particular application. It could be easily and effectively applied to defining the relative proportions of the four isomers of the same diacetal considered here labeled with deuterium at C3 and C5, a case of 1,3- rather than 1,2-d_2 substitutions. Another hypothetical case easily anticipated would be a quantitative analysis of a mixture of the three 1,4-d_2-butadienes, formed for instance through the thermal isomerization of *exo*,*exo*-2,4-d_2-bicyclo[1.1.0]butane.[29] The isomeric 1,5-d_2-penta-1,4-dienes could also be quantitatively resolved through ^{13}C {^{1}H,^{2}H} NMR spectroscopy, enabling a telling stereochemistry study of the thermal reaction of *cis*-2,3-d_2-bicyclo-[2.1.0]pentane to 1,5-d_2-penta-1,4-dienes, products from minor competitive isomerization paths from the bicyclic system.[30] Numerous other applications will no doubt be found to be useful once the method is exercised with different structural variations and research objectives.

(29) Wiberg, K. B.; Lavanish, J. M. *J. Am. Chem. Soc.* **1966**, *88*, 5272–5275.

(30) Steel, C.; Zand, R.; Hurwitz, P.; Cohen, S. G. *J. Am. Chem. Soc.* **1964**, *88*, 679–684.

Experimental Section

General Methods. Synthetic procedures described in the literature for preparing d_0-versions of *d*- and d_2-labeled cyclohexenes *d*-**2** and **2**, *trans*-diols *d*-**3** and **3**, and butane-2,3-diacetals *d*-**4** and **4** were adopted with only minor adjustments. Labeled cyclohexene intermediates were analyzed by capillary GC to test for homogeneity and to compare with unlabeled analogs. The diols and diacetals were purified by column chromatography, and structural identities were confirmed by GCMS and NMR spectroscopy.

3- and 4-*d*-Cyclohexenes (*d*-2). Methyl alcohol-OD (CH_3OD, 1.3 mL, 31.5 mmol) followed by 1,3-cyclohexadiene (2.4 g, 30 mmol) was added to a solution of acetyl bromide (2.4 mL, 31.5 mmol) in CH_2Cl_2 (150 mL) at 0 °C.[21] The reaction mixture was protected from light and stirred overnight at rt and then quenched with saturated aq $NaHCO_3$ (50 mL). The aqueous and organic phases were separated, and the latter was washed with 10% aq $NaHCO_3$ (2 × 50 mL) and brine (2 × 50 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to give a mixture of *d*-labeled 3-bromocyclohexenes (4.9 g, 2.95 mmol, 99%). About half of this crude synthetic intermediate (2.43 g, 15 mmol) was added in one portion to a stirred suspension of anhydrous $NaBH_3CN$ (1 g, 15 mmol) and anhydrous $ZnCl_2$ (1 g, 7.5 mmol) in ether (50 mL).[22] Analysis of the reaction mixture after 30 min by GCMS showed complete disappearance of the starting material. The unreacted reducing agent was quenched with 10% aq $NaHCO_3$ (50 mL), and the layers were separated. The ethereal solution was washed with brine (2 × 50 mL) and then used in the oxidation to give the *trans*-

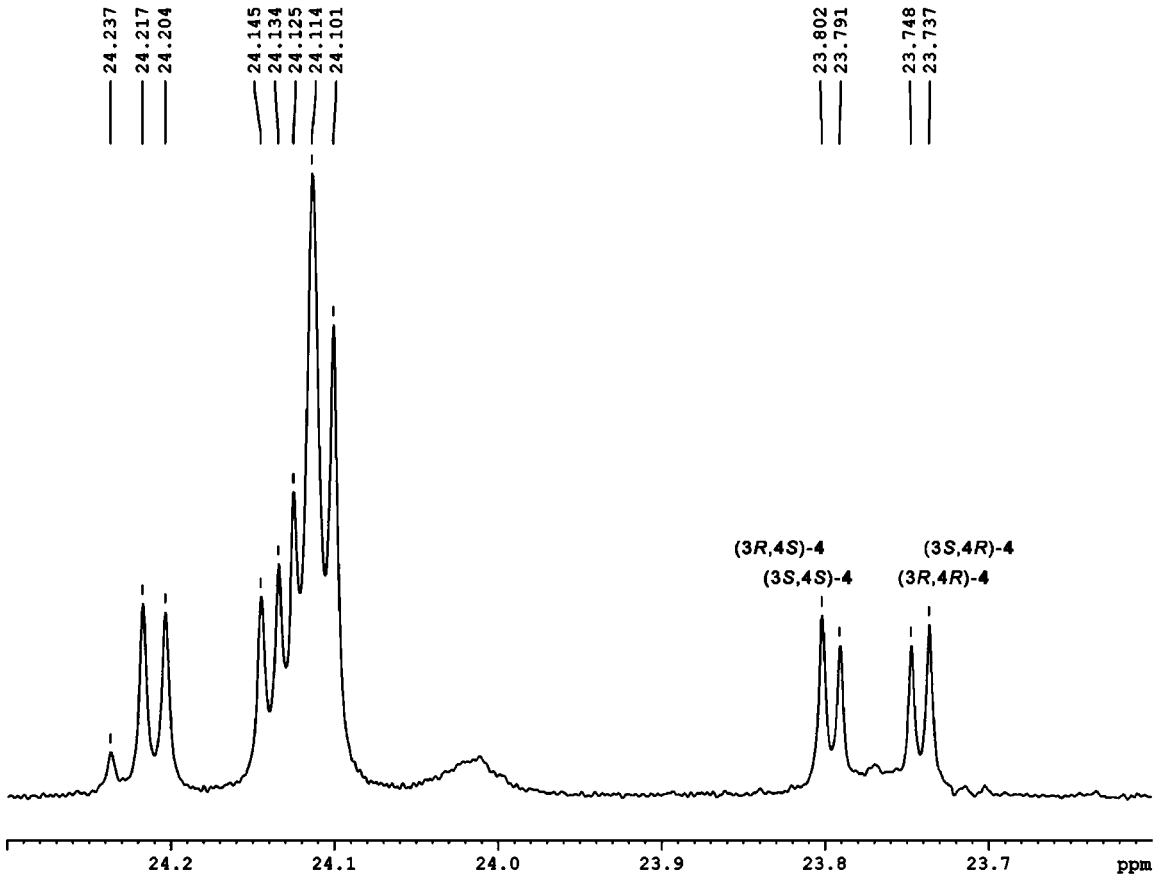


FIGURE 4. ^{13}C4 {^{1}H,^{2}H} region of the NMR spectrum for the **4** diacetals of Scheme 4. The recorded chemical shifts are as given. The $\Delta\delta$ values, relative to the absorption for the d_0-**4** internal standard, at δ 24.237, are upfield by 20, 33, 92, 103, 112, 123, 136, 435, 446, 489, and 500 ppb.

1,2-diols detailed below. Formation of the mixture of *d*-cyclohexenes (**2**) was confirmed by means of GC.

3,4- and 3,6-*d*-Cyclohexenes (2). The procedure followed to prepare 3-*d*- and 4-*d*-**2** from *d*-labeled 3-bromocyclohexenes, but using $NaBD_3CN$ instead of $NaBH_3CN$, gave **2**. The d_2-labeled cyclohexenes and cyclohexene had identical GC retention times.

3- and 4-*d*-Cyclohexane-*trans*-1,2-diols (*d*-3). An ethereal solution of the 3- and 4-*d*-cyclohexenes (*d*-**2**) prepared above was diluted with acetone (100 mL), and an aqueous solution of oxone (50 mL, 15.37 g, 25 mmol) was added at once.[23] The reaction mixture was stirred vigorously at rt overnight and then concentrated under reduced pressure. The residue containing the desired diol and inorganic salts was washed thoroughly with acetone; the acetone solution obtained was concentrated in vacuo. Column chromatography of the concentrate (EtOAc/hexane 3:1) afforded a mixture of 3- and 4-*d*-cyclohexane-*trans*-1,2-diols (*d*-**3**) (740 mg, 6.4 mmol) in 43% yield overall from 1,3-cyclohexadiene. ^{1}H NMR (acetone-d_6): δ 1.24 (m, 3−4H), 1.64 (m, 1−2H), 1.96 (m, 1−2H), 3.25 (m, 2H), 3.81 (m, 2H). ^{13}C NMR: δ 24.5 (split), 33.1 (split), 75.3.

3,4- and 3,6-d_2-Cyclohexane-*trans*-1,2-diols (3). *trans*-1,2-Diols **3** were prepared from **2** following the oxidation procedure described immediately above. ^{1}H NMR ($CDCl_3$): δ 1.26 (m, 3−4H), 1.7 (m, 1−2H), 1.96 (m, 1−2H), 3.06 (m, 2H), 3.35 (m, 2H). ^{13}C NMR: δ 24.7 (split), 33.3 (split), 76.2.

3- and 4-*d*-Butane-2,3-diacetals (*d*-4). Camphorsulfonic acid ($\sim$ 25 mg) was added to a solution of *d*-**3** (590 mg, 5 mmol), 2,3-butanedione (0.5 mL, 5.5 mmol), and trimethyl-orthoformate (2.7 mL, 25 mmol) in methanol (10 mL). The reaction mixture was heated to reflux for 3 h, cooled to rt, and neutralized with triethylamine (1 mL). All volatiles were removed under reduced pressure, and the residue was purified by chromatography (silica gel) to afford diacetal *d*-**4** in 95% yield (1.1 g, 4.8 mmol). ^{1}H NMR ($CDCl_3$): δ 1.21 (s, 6H), 1.29 (m, 3−4H), 1.73 (m, 3−4H), 3.19 (s, 6H), 3.39 (m, 2H). ^{2}H NMR: δ 1.21, 1.29, 1.67, 1.73 (1:1:1:1). ^{13}C NMR: δ 17.7, $\sim$24.5 (split), $\sim$30.0 (split), 47.1, 71.8, 99.5.

3,4- and 3,6-d_2-Butane-2,3-diacetals (4). Diacetals **4** were prepared in the same manner, from **3**. ^{1}H NMR ($CDCl_3$): δ 1.21 (s, 6H), 1.29 (m, 3−4H), 1.73 (m, 3−4H), 3.19 (s, 6H), 3.39 (m, 2H). ^{2}H NMR: δ 1.20, 1.30, 1.67, 1.74 (1:3:1:3). ^{13}C NMR: δ 17.7, 24.5, 30.0, 47.1, 71.8, 99.5.

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