On the Stereochemistry of Diaryl-Substituted Cyclohexanones Formed by Michael Reactions. Trans to Cis Isomerization of Their Ketals under Basic Conditions

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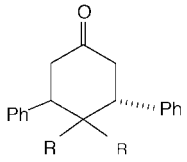
The stereochemistry of C-1-substituted 2,6-diphenylcyclohexan-4-ones **1**−**3** prepared by Michael reactions has been investigated. While preparations of these compounds have been reported over the past 70 years, in many instances the correct stereochemistry at C-2 (6) and, in some instances at C-1, was uncertain. We show here that in one case in which two identical substituents (CN) are present at C-1, it is possible to isomerize the initially formed trans isomer **1d** to the cis isomer **3f**. When a cyano group and a dissimilar substituent are present at C-1, the initially formed trans isomer may be isomerized to the cis compound. The stereochemistry is vertified by NMR spectroscopy and by X-ray analysis. Reaction of the ethylene ketals (**4** and **5**) of these ketones with KOH in DMSO at elevated temperatures gives rise to cis products, and deuterium-labeling studies demonstrated the acidity of the benzylic hydrogen at C-2 (6). Isomerization was evident since the trans ketal **4a** and the cis ketal **4b** gave the same amide **6a**. ^{1}H and ^{13}C NMR spectra provided conclusive evidence for the cis → trans rearrangement.

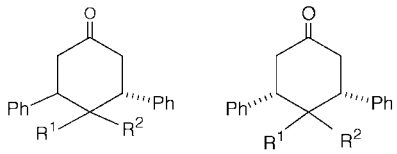
The Michael reaction of 1,5-diaryl-1,4-pentadien-3-ones with active methylene compounds has long been employed to prepare highly substituted cyclohexanones. The products of these reactions are of interest in terms of their stereochemistry and as starting materials for the synthesis of compounds with possible biological activity.[1] The assignment of stereochemistry in some of these Michael products has been uncertain or, in some cases, incorrect.

When $R^1 = R^2$ in the methylene compound and Ar = Ph, the product may exist as a trans (dl) or cis (meso) isomer. When $R^1 \neq R^2$, a trans isomer (dl) or two meso compounds (cis) are possible. The uncertainty regarding the stereochemistry in a Michael product is exemplified by the case $R^1 = R^2 = CO_2Me$ (**1a**). We recently resolved



1a, R=CO_2Me
b, R=CO_2t-Bu
c, R=CO_2Et
d, R=CN

this question by X-ray crystallography, which showed that **1a** is the trans isomer.[2] When $R^1 = R^2 = CO_2$-*t*-Bu (**1b**), only the trans isomer is formed;[3] the same result is found when $R^1 = R^2 = CO_2$ Et (**1c**).[4] When $R^1 = R^2 =$ CN (**1d**), the initially formed Michael product has been alternately reported as unspecified[5] and as cis.[6] X-ray analysis of **1d** shows unambiguously that this is the trans isomer. When $R^1 \neq R^2$, the initially formed isomer (trans) may often be converted into one of the cis isomers **2**. For example, the trans Michael products **2a**, **2b**, **2c**, and **2d** have been reported to be converted by base (or acid) into the cis isomers **3a**,[7,8] **3b**,[9] **3c**,[5] and **3d**.[8,10]



2 **3**

a, R^1=CN, R^2=CO_2Et
b, R^1=CN, R^2=CO_2Me
c, R^1=CN, R^2=Ph
d, R^1=CN, R^2=$CONH_2$
e, R^1=CN, R^2=CO_2t-Bu
3f, R^1=R^2=CN
3g, R^1=H, R^2=$CONH_2$

The literature suggests that when $R^1 = R^2$ the thermodynamically stable isomer is the trans (dl), whereas when $R^1 \neq R^2$, one of the two possible meso isomers is

(1) (a) Rele, D. N.; Baskaran, S.; Korde, S. S.; Vora, J. D.; Trivedi, G. K. *Indian J. Chem., Sect. B* **1996**, *35B*, 431. (b) Reddy, D. B.; Padmavathi, V.; Reddy, M. M. *Indian J. Chem., Sect. B* **1992**, *31B*, 407. (c) Reddy, D. B.; Padmavathi, V.; Reddy, P. V. R. *Indian J. Chem., Sect. B* **1992**, *31B*, 774.

(2) Rowland, A. T.; Winemiller, M. D.; Sabat, M. *Tetrahedron Lett.* **1997**, *38*, 1287.

(3) Coutlangus, M. L.; Filla, S. A.; Rowland, A. T. *J. Chem. Educ.* **1989**, *66*, 520.

(4) Kohler, E. P.; Dewey, C. S. *J. Am. Chem. Soc.* **1924**, *46*, 1267.

(5) Kingsbury, C. A.; Jordan, M. E. *J. Chem. Soc., Perkin Trans. 2* **1977**, 364.

(6) Otto, H.-H.; Triepel, J.; Schmelz, H.; Meyer-Schaar, J. *Arch. Pharm. (Weinheim, Ger.)* **1976**, *309*, 786.

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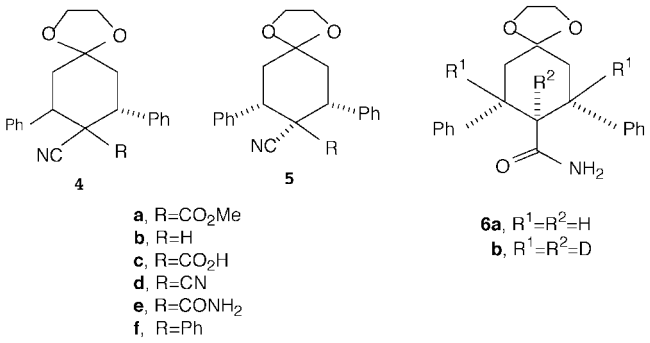
the most stable compound. We find that reaction of dibenzalacetone with *tert*-butyl cyanoacetate gives the trans compound **2e**, which is isomerized to the cis compound **3e** by treatment with NaOH in EtOH. X-ray crystallography shows that the ester group occupies the equatorial position on the chair, providing conclusive evidence for the position of substituents at C-1. Kingsbury[5] used C−H coupling constants to conclude that the cyano group in the cyano ester **3b** is axial, not equatorial as was reported earlier.[11] It thus appears that the cyano group occupies an axial position in the cis isomers **3**.

As indicated previously, only the trans isomers of compounds **1** are known. Since the cis compounds **3** demand an axial orientation of the linear cyano group, the bulky substituent at C-1 apparently cannot be accommodated in the axial position. The cis dicyano ketone **3f**, however, does not suffer from the same restrictions. We have found that the trans isomer **1d** is readily converted to **3f** by treatment with Triton B in EtOH at room temperature. Mention is made of **3f** in a footnote in an earlier publication[8] with no supporting data. The trans phenyl ketone **2c** was not isomerized to the cis compound **3c** by treatment with Triton B; **3c** was obtained by hydrolysis of the cis ketal **5f** (vide infra).

Each of the cis isomers **3a**−**f** exhibits a deceptively simple AMX pattern (d of d, t, d of d) for the cyclohexane ring protons,[3,5,7] whereas the trans isomers **1a**−**d** and **2a**−**e** show complicated patterns for the related protons (see also the Experimental Section). Since a meso isomer posseses a σ through C-1/C-4, ^{13}C NMR analysis easily differentiates this compound from its trans precursor.

We investigated the reactions with base of the ethylene ketals of several Michael ketones in order to determine if the trans → cis conversion would occur without the complication of a retrograde reaction that takes place with the free ketone.[12] The base system was a heterogeneous mixture of concd aqueous KOH in DMSO at temperatures ranging from room temperature to 150 °C.

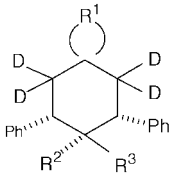
When the cis cyano ketal **5a** was reacted at ∼150 °C for 4 h, the amide **6a** was isolated in 80% yield. The reaction involved saponification of the ester, decarboxylation, and partial hydrolysis of the nitrile. The ^{13}C NMR and other spectral data substantiate the structure and stereochemistry of **6a**; X-ray analysis verifies the amide group in an equatorial position. Hydrolysis of the ketal group in **6a** gave the keto amide **3g**. Under the reaction conditions used for **5a**, the trans cyano ketal **4a** gave the *same* amide **6a**, indicating an inversion of configuration at C-2 (C-6) at some point in the sequence. When the ketal **4a** was treated with KOD/D_2O in DMSO-d_6 at ∼150 °C, the amide **6b** was obtained in which the C-1, C-2, and C-6 hydrogens were replaced by deuterium as shown in the ^{13}C NMR spectrum by the disappearance of the C-1 signal (54.5) and very weak peaks due to C-2 and C-6 (44.2). The ^{1}H NMR spectrum also indicated the absence of the corresponding hydrogen signals. To verify the lack of acidity of the C-3 and C-5 methylene hydrogens under the basic conditions of the reaction, the



a, R=CO_2Me
b, R=H
c, R=CO_2H
d, R=CN
e, R=$CONH_2$
f, R=Ph

6a, R^1=R^2=H
b, R^1=R^2=D

3,3,5,5-tetradeuterio derivative (**7**) of the cis ketal **3b** was prepared, converted to its ethylene ketal (**7b**), and treated with KOH/H_2O in DMSO at 150 °C. The spectral data of the resulting amide (**7c**) indicated complete retention of the C-3 and C-5 deuterium atoms.



7a, R^1 = O , R^2=CN, R^3=CO_2Me

b, R^1 = O,O-ethylene , R^2=CN, R^3 = CO_2Me

c, R^1 = O,O-ethylene , R^2=H, R^3 = $CONH_2$

The reaction of the trans ketal **4a** with base was conducted at lower temperatures in order to see if the isomerization would occur under milder conditions. At steam bath temperature for 18 min, **4a** underwent saponification and loss of CO_2 to give the known[7] trans nitrile **4b** with retention of configuration. At rt, the trans cyano ester **4a** underwent saponification in 1 h to give the trans cyano acid **4c**. The cis cyano ester **5a** required a higher temperature (∼90 °C) for saponification to the cis cyano acid **5c**, apparently due to steric hindrance of the equatorial ester group imposed by the flanking aromatic rings.

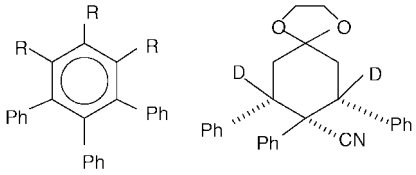
The results of the saponification reactions indicate that the base abstracts a benzylic proton from C-2 (C-6) at elevated temperatures from the mono cyano intermediate to generate a carbanion that may be reprotonated to give the more stable cis isomers.

The cis → trans isomerization was tested with other ketals. The ketal (**4d**) of the trans dicyano ketone **1d** was treated at 150 °C for 5 h to give the amide **6a** obtained previously. In like fashion, both the trans cyano amido ketal (**4e**) and the isomeric cis compound **5e** gave the ketal amide **6a** upon reaction with base at 150 °C. In each of these cases, the saponification of the preexisting amide group leads to the same cyano intermediate formed from **4a**, **5a**, and **4d** under the basic conditions.

A somewhat different result was obtained when the trans phenyl ketal (**4f**) of the ketone **2c** was saponified at 150 °C. The product mixture was separated cleanly by chromatography to give 1,2,3-triphenylbenzene (**8a**) and the cis phenyl ketal (**5f**). The ketal **5f** was identified by its spectra and by hydrolysis to the known[5,13] ketone **3c**. The aromatic product **8a** was identical to that

(7) Rowland, A. T.; Gill, B. C. *J. Org. Chem.* **1988**, *53*, 434.
(8) Ahmed, M. G.; Ahmed, S. A.; Rasul, G.; Bakar, M. H. *J. Bangladesh Chem. Soc.* **1988**, *1*, 45.
(9) Kohler, E. P.; Helmkamp, R. W. *J. Am. Chem. Soc.* **1924**, *46*, 1018.
(10) Otto, H.-H. *Monatsh. Chem.* **1978**, *109*, 681.
(11) Otto, H.-H. *Arch. Pharm. (Weinheim, Ger.)* **1972**, *305*, 913.
(12) Rowland, A. T.; Hohneker, J. A.; McDaniel, K. F.; Moore, D. S. *J. Org. Chem.* **1982**, *47*, 301.
(13) Helmkamp, R. W.; Tanghe, L. J.; Plati, J. T. *J. Am. Chem. Soc.* **1940**, *62*, 3215.

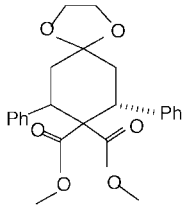
produced by an Ullmann reaction;[14] the spectra of **8a** were identical to those of the commercially available material (Aldrich 27,677-4). The production of ketal **5f** further illustrates the acidity of the C-2(6) benzylic hydrogens in type **4** compounds. No amide was detected in this case, presumably due to hindrance by the C-1 phenyl group to saponification of the nitrile. When the reaction of **4f** was conducted with KOD/D_2O in DMSO-d_6, the 4,5,6-trideuterated derivative (**8b**) of **8a** was obtained accompanied by the dideuterated cis phenyl ketal **9**. When the cis phenyl ketal **5f** was heated with base in DMSO at 150 °C, only starting material was recovered. It thus appears that the trans compound **4f** but not the isomeric **5f** has C-2 (6) hydrogens acidic enough to initiate the aromatization reaction. This observation is being investigated further.



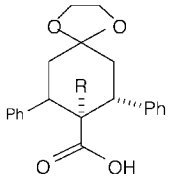
8 a, R=H
b, R=D

9

The 4-deoxy relative (**11**) of the ketone **3b** was studied. Clemmensen reduction of **3b** gave a mixture of the unsaturated cyano ester (**10**) and <10% of the saturated ester **11**. Catalytic hydrogenation of **10** gave pure **11** that, after heating with KOH/H_2O in DMSO at 146 °C and chromatography of the crude product, gave the cis amide **12a**. When the saponification was conducted in DMSO-d_6 with KOD/D_2O at 150 °C, the amide **12b** was obtained. The ^{13}C NMR spectrum of **12b** indicated the absence of the C-1 signal (δ 55.1) and the dimunition of the C-2(6) signal at δ 47.0, again reflecting the lesser acidity of the benzylic hydrogens in cis isomers. Reaction of ester **11** with base in DMSO at ~100 °C gave the cyano acid **12c**, illustrating the stability of the carboxylate anion in the cis cyano compounds relative to the trans isomers (cf. **4a** → **4b**).

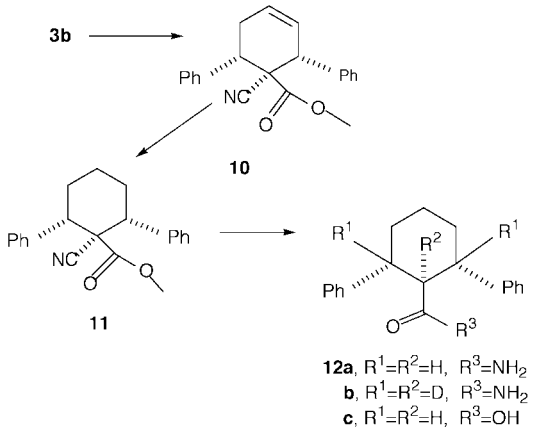


13



14a, R=H
b, R=D

The behavior of the ketal diester **13** toward the basic medium was examined. It had been shown previously[12] that **13** undergoes decarbalkoxylation to give a monoester.[15] Unlike the other examples discussed above, the product of saponification−decarboxylation before acidification should be the monoanion of the ketal acid **14**. The formation of the anion should inhibit the abstraction of a benzylic hydrogen from C-2(6) to give a doubly charged intermediate; therefore, no configuration change (cis → trans) was anticipated. Reaction of the diester **13** with KOH/H_2O in DMSO at 120 °C for 20 min (or 150 °C for 7 h) gave the trans ketal monoacid **14** as predicted. When the reaction was conducted in DMSO-d_6, ^{13}C and ^1H NMR analysis showed that only the C-1 hydrogen in **14** had been replaced by deuterium as was anticipated by reaction of the intermediate carbanion of the initially formed monoester with hydrogen (or deuterium). Protonation at C-1 followed by saponification of the remaining ester then generates the salt of **14** with no benzylic hydrogen abstraction.



12a, R^1=R^2=H, R^3=NH_2
b, R^1=R^2=D, R^3=NH_2
c, R^1=R^2=H, R^3=OH

The results of this investigation illustrate the advantage that may be taken of the acidity of benzylic hydrogens in the trans isomers to facilitate isomerization to cis isomers. Work is in progress on relatives of **4f** to determine if the production of substituted benzenes of type **8** from the appropriate ketals may be a general and efficient synthesis.

Experimental Section

General Methods. Basic procedures have been noted elsewhere.[7,12] ^1H NMR and ^{13}C NMR spectra were recorded at 80.13 and 20.15 MHz, respectively, in the indicated solvents. Signals in ^{13}C NMR spectra were assigned from BB and DEPT techniques. Coupling constants (*J*) are given in Hz. Some IR spectra were obtained on disposable polyethylene cards (PEC).[16] The general procedure for reactions of ketals with base in DMSO was as follows: To a magnetically stirred mixture of the compound in DMSO heated to ca. 100 °C was added the KOH/H_2O solution. The temperature of the bath was then raised to ±2 °C of the indicated value for the specified time. The cooled reaction mixture was diluted with H_2O, and the precipitate was collected, washed with H_2O, and recrystallized. The procedure for the preparation of the ethylene ketals has been given elsewhere.[7] The principal author has deposited atomic coordinates for compounds **1d**, **3e**, **3f**, and **6a** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained on request from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK. "Drops" in the following procedures were measured from 14.5-cm Pasteur pipets.

***tert*-Butyl 1-Cyano-2(e),6(a)-diphenyl-4-oxocyclohexane-1-carboxylate (2e).** To a magnetically stirred suspension of 10.002 g (42.69 mmol) of dibenzalacetone in 150 mL of MeOH was added 7.00 mL (48 mmol) of *tert*-butyl cyanoacetate and 25 drops of a 25% NaOMe−MeOH solution. A heavy precipitate formed within 2 min as the dibenzalacetone dissolved. After 10 min, the mixture was cooled, collected by filtration, and washed with cold MeOH. The solid was warmed

(14) Ozasa, S.; Fujioka, Y.; Kikutake, J.; Ibuki, E. *Chem. Pharm. Bull.* **1983**, *31*, 1572.

(15) The decarbalkoxylation of **13** was erroneously believed[12] to involve a rearrangement of cis to trans with respect to the phenyl groups. We now know that the diester **13** is the trans isomer.[2]

(16) Wigman, L. S.; Hart, E. E.; Gombatz, C. *J. Chem. Educ.* **1996**, *73*, 677.

in 40 mL of acetone to dissolve unreacted dibenzalacetone, cooled to 0 °C, and collected to give 11.094 g (69%) of **2e**: mp 184−185 °C dec; IR ($CHCl_3$) 2245, 1725 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.03 (s, 9 H), 2.61−3.35 (m, 4 H), 3.88−4.10 (m, 2 H), 7.29−7.32 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 27.3, 41.8, 42.7, 43.0, 47.2, 56.1, 84.6, 119.0, 128.4, 128.7, 129.0, 136.9, 137.6, 165.3, 201.4. Anal. Calcd for $C_{24}H_{25}NO_3$: C, 76.77; H, 6.71; N, 3.73. Found: C, 76.55; H, 6.57; N, 3.65.

***tert*-Butyl 1(a)-Cyano-2(e),6(e)-diphenyl-4-oxocyclohexane-1(e)-carboxylate (3e).** To a magnetically stirred suspension of 1.112 g (2.962 mmol) of the trans *tert*-butyl ester **2e** in 225 mL of 95% EtOH at room temperature was added 15 drops of freshly prepared 10% NaOH (aq) solution. An additional five drops of the base were added after 25 min, and the mixture was stirred for a further 75 min. The colorless solution was diluted with 225 mL of water and the product gradually coagulated upon cooling. The powder was collected, washed with water, and taken up in $CHCl_3$. The dried solution was concentrated and diluted with MeOH to give 795 mg of **3e**: mp 221−223 °C dec; IR ($CHCl_3$) 2245, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.93 (s, 9 H), 2.70 (d of d, J = 14.4, 3.2, 2 H), 3.26 (t, J = 14.4, 2 H), 3.68 (d of d, J = 14.4, 3.2, 2 H), 7.36 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 27.2, 44.0, 49.5, 59.1, 84.3, 116.6, 128.4, 128.6, 128.7, 136.6, 165.2, 203.7. Anal. Calcd for $C_{24}H_{25}NO_3$: C, 76.77; H, 6.71; N, 3.73. Found: C, 76.27, 76.48; H, 6.73, 6.85; N, 3.70. An additional 158 mg of **3e** was obtained by concentrating the mother liquor: mp 221−223 °C dec; total yield, 86%.

Isomerization of 1d to 2(e),6(e)-Diphenyl-4-oxocyclohexane-1,1-dicarbonitrile (3f). To a magnetically stirred solution of 1.548 g (5.15 mmol) of the trans dicyano ketone **1d**[7] in 460 mL of 100% EtOH at room temperature was added 12 drops of Triton B. After 1.1 h, 24 drops of glacial HOAc were added to the pinkish colored solution. The mixture was allowed to evaporate to dryness overnight, and the residue was chromatographed on 25 g of neutral alumina. Elution with 60 mL of acetone gave a colorless fraction, which was concentrated to ~8 mL and diluted with petroleum ether to give 1.322 g (85%) of **3f**, mp 210−211 °C. Recrystallization from acetone−ethyl ether gave the following data: mp 211.5−212.5 °C; IR ($CHCl_3$) 1715 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.77 (d, br legs, J = 14.4, ~2, 2 H), 3.26 (t, J = 14.4, 2 H), 3.62 (d of d, J = 14.4, 2.4, 2 H), 7.44 (s, 10 H); ^{13} C NMR ($CDCl_3$) δ 43.0,47.9, 50.2, 112.4, 113.5, 128.3, 129.3, 129.7, 135.2, 202.6. Anal. Calcd for $C_{20}H_{16}N_2O$: C, 79.98; H, 5.37; N, 9.33. Found: C, 79.76, 79.50; H, 5.60, 5.49; N, 9.47.

Attempted Isomerization of the Trans Triphenyl Ketone 2c. To a magnetically stirred solution of 1.009 g (2.87 mmol) of **2c**[13] in 300 mL of 100% EtOH at ~55 °C was added 12 drops of Triton B. After 13 h, the solution was acidified with 24 drops of glacial HOAc, and the solvent was evaporated with air and low heat. The residue was recrystallized from acetone−MeOH to give 720 mg of starting material (**2c**): mp 190−191.5 °C; ^1H NMR identical to the starting material.

Methyl 1(a)-Cyano-2(e)6(e)-diphenyl-4,4-(ethylenedioxy)cyclohexane-1(e)-carboxylate (5a). A mixture of 19.7 g (59.1 mmol) of the cis oxo ester **3b**,[9] 15 mL (270 mmol) of ethylene glycol, and 0.82 g of TSA in 300 mL of benzene was boiled for 4 h. The dried solution was concentrated to 50 mL and then diluted with 80 mL of ethyl ether. The ketal **5a** (16.8 g) gradually separated as large chunks of colorless crystals: mp 156−158 °C; IR ($CHCl_3$) 2245, 1740, 1250 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.99 (br d of d, J = 13.6, 3.2, 2 H), 2.53 (t, J = 13.6, 2 H), 3.25 (s, 3 H), 3.72 (d of d, J = 13.6, 3.2, 2 H), 3.99 (s, 4 H), 7.32 (s, 10 H); ^{13}C NMR ($CDCl_3$) δ 37.4, 47.5, 52.6, 60.0, 64.7, 107.2, 116.1, 128.1, 128.2, 128.5, 137.9, 167.8. Anal. Calcd for $C_{23}H_{23}NO_4$: C, 73.19; H, 6.14; N, 3.71. Found: C, 73.56, 73.38; H, 6.38, 6.22; N, 3.65.

Concentration of the mother liquor and additon of petroleum ether gave an additional 4.2 g of **5a**: mp 156−157 °C; total yield, 94%.

Reaction of the Cis Methyl Ester 5a with Base. A mixture of 2.520 g (6.68 mmol) of **5a**, 26 mL of DMSO, and 2.6 g (39 mmol) of KOH in 2 mL of H_2O was heated at 148 °C for 4 h. The product was dissolved in hot acetone, filtered through cotton to remove some gelatinous material, and concentrated to give 1.198 g of **2(e),6(e)-diphenyl-4,4-(ethylenedioxy)cyclohexane-1(e)-carboxamide (6a)** as white plates: mp 234−237 °C; IR (PEC) 3480, 3360, 1670, 1605 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.77−1.90 (m, 4 H), 2.58−3.31 (m, 3 H), 3.90 (t, $J \cong$ 2.4, 4 H), 6.08 (br s, 1 H), 6.59 (br s, 1 H), 7.23 (s, 10 H); ^{13}C NMR (DMSO-d_6) δ 41.9, 44.2, 54.5, 63.6, 63.9, 107.4, 126.0, 127.6, 127.9, 143.4, 173.6. Anal. Calcd for $C_{21}H_{23}NO_3$: C, 74.75; H, 6.87; N, 4.15. Found: C, 74.96; H, 6.88; N, 4.20.

Concentration of the mother liquor gave two additional crops of **6a**: 377 mg (mp 234.5−237 °C) and 224 mg (mp 233−236.5 °C): total yield, 80%.

2(e),6(e)-Diphenyl-4-oxocyclohexane-1(e)-carboxamide (3g). A mixture of 1.039 g (3.08 mmol) of the cis amide **6a**, 4 mL of H_2O, and 14 drops of concd HCl in 25 mL of acetone was heated under reflux for 1 h. The warm mixture was diluted with 21 mL of H_2O and cooled, and the precipitate was collected and washed with 1:1 acetone−H_2O to give 781 mg (86%) of **3g** as glistening colorless plates: mp 308−313 °C dec, with slight softening at ~304 °C; IR (PEC) 3455, 3130, 1693, 1665 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.25−2.40 (m, 2 H), 2.76−3.20 (m, 5 H), 6.27 (br s, 1 H), 6.84 (br s, 1 H), 7.31 (br s, 10 H); ^{13}C NMR (DMSO-d_6) δ 46.3, 47.8, 54.0, 126.3, 127.4, 128.0, 142.3, 172.7, 207.4. Anal. Calcd for $C_{19}H_{19}NO_2$: C, 77.79; H, 6.53; N, 4.78. Found: C, 77.79; H, 6.50; N, 4.93.

Reaction of the Trans Methyl Ester 4a with Base. A mixture of 2.485 g (6.58 mmol) of **4a**,[7] 26 mL of DMSO, and 2.6 g (39 mmol) of KOH in 2 mL of H_2O was heated at 148 °C for 4 h. Recrystallization of the crude product from acetone gave 1.178 g of the amide **6a**, mp 234.5−237 °C. Concentration of the mother liquor gave two additional crops of **6a**: 401 mg (mp 230−236 °C) and 146 mg (mp 233−237 °C); total yield, 78%. Spectra of this product were identical in all respects to the amide obtained from the cis methyl ester **5a**.

Reaction of the Trans Methyl Ester 4a in DMSO-d_6. A mixture of 1.018 g (2.697 mmol) of **4a**, 10 g of DMSO-d_6, and 1.5 mL of a 40% KOD/D_2O solution was heated at 150 °C for 4.2 h. The slightly cooled mixture was diluted with 30 mL of D_2O, and the resulting precipitate was isolated in the usual manner. Recrystallization from acetone gave 399 mg of **1(a),2(a),6(a)-Trideuterio-2(e),6(e)-diphenyl-4,4-(ethylenedioxy)cyclohexane-1(e)-carboxamide (6b):** mp 234.5−238 °C; ^1H NMR (DMSO-d_6) δ 1.82 (m, 4 H), 3.89 (t, J = 3.2, 4 H), 6.07 (br s, 0.5 H), 6.57 (br s, 0.5 H), 7.23 (s, 10 H); ^{13}C NMR (DMSO-d_6) δ 41.9, 63.7, 64.0, 107.6, 126.1, 127.7, 128.0, 143.5, 173.6. Two more crops of **6b** were isolated from the mother liquor: 176 mg (mp 232.5−235.5 °C) and 81 mg (mp 233.5−235.5 °C); total yield, 71%.

Methyl 1(a)-Cyano-2(e),6(e)-diphenyl-3,3,5,5-tetradeuterio-4-oxocyclohexane-1(e)-carboxylate (7a). To a magnetically stirred solution of 4.750 g (14.25 mmol) of the cis methyl ester **3b**[9] in 70 mL of MeOD was added 7 drops of a 25% NaOMe−MeOH solution. After 30 min at room temperature, the solution was distributed between ether and water. The layers were separated, and the aqueous phase was extracted twice with ether. The combined ether extracts were washed three times with water, dried, concentrated, and diluted with petroleum ether to yield 4.536 g (94%) of **7a**: mp 147−148 °C; ^1H NMR ($CDCl_3$) δ 3.22 (s, 3 H), 3.73 (s, 2 H), 7.33 (s, 10 H); ^{13}C NMR ($CDCl_3$) δ 49.1, 52.8, 59.4, 115.8, 127.8, 128.6, 128.7, 136.4, 166.9, 204.4.

Methyl 1(a)-Cyano-3,3,5,5-tetradeuterio-2(e),6(e)-diphenyl-4,4-(ethylenedioxy)cyclohexane-1(e)-carboxylate (7b). A mixture of 2.00 mL (36 mmol) of ethylene glycol, 197 mg of TSA, 16 mL of D_2O, and 80 mL of benzene was boiled until (2 h) 16 mL of an aqueous phase was collected in the sidearm.[7] To the benzene phase was added 2.001 g (5.93 mmol) of the tetradeuterio ketone **7a** and 20 mL additional benzene. The mixture was boiled for 3 h and then worked up in the usual manner.[7] Crystallization from ethyl ether gave 2.091 g (92%) of **7b**: mp 156.5−158 °C; ^1H NMR (DMSO-d_6) δ 3.35 (s, 3 H), 3.64 (s, 2H), 3.96 (s, 4 H), 7.30 (s, 10 H); ^{13}C NMR (DMSO-d_6) δ 46.6, 52.6, 60.0, 64.3, 106.2, 115.7, 127.7, 128.1, 128.5, 137.8, 167.3.

Reaction of the Tetradeuterio Ketal 7b with Base. A mixture of 397 mg (1.04 mmol) of **7b**, 5 mL of DMSO, and 0.30 g (4.6 mmol) of KOH in 0.5 mL of H_2O was heated at 149 °C for 4 h. Recrystallization of the crude product from CH_2Cl_2−petroleum ether gave 239 mg (67%) of **2(e),6(e)-diphenyl-3,3,5,5-tetradeuterio-4,4-(ethylenedioxy)cyclohexane-1(e)-carboxamide (7c):** mp 231.5−234 °C; ^{1}H NMR (DMSO-d_6) δ 2.72−3.20 (m, 3 H), 3.90 (t, J = 2.4, 4 H), 6.08 (s, 1 H), 6.59 (s, 1 H), 7.23 (m, 10 H); ^{13}C NMR (DMSO-d_6) δ 44.2, 54.6, 63.7, 64.0, 107.5, 126.1, 127.7, 128.0, 143.5, 173.7.

2(e),6(a)-Diphenyl-4,4-(ethylenedioxy)cyclohexane-1-carbonitrile (4b). A mixture of 1.011 g (2.68 mmol) of the trans cyano ketal **4a**, 10 mL of DMSO, and 0.91 g (14 mmol) of KOH in 1 mL of H_2O was magnetically stirred on a steam bath for 18 min. Dilution with water and filtration gave a white solid that was recrystallized from acetone−MeOH to give 546 mg of **4b**: mp 147.5−149.5 °C (lit.[7] mp 146−148 °C). The ^{1}H NMR spectrum was identical to that reported for **4b**.[7] An additional 83 mg of **4b**, mp 146−147 °C, was recovered from the mother liquor. Total yield, 73%.

1-Cyano-2(e),6(a)-diphenyl-4,4-(ethylenedioxy)cyclohexane-1-carboxylic Acid (4c). A mixture of 1.113 g (2.95 mmol) of the trans methyl ester **4a** in 10 mL of DMSO and 0.75 g (11 mmol) of KOH in 1 mL of H_2O was stirrred magnetically at room temperature for 65 min. The mixture was diluted with 30 mL of water and extracted twice with ether. To the basic aqueous phase was added 3 mL of 6 M HCl and ether. The mixture was shaken and separated, and the aqueous layer was extracted again with ether. The combined organic phases were dried, filtered, and evaporated. The resulting oil was crystallized from CH_2Cl_2−petroleum ether to give 959 mg (89%) of the acid **4c**: mp 194.5−196 °C dec; IR (PEC) 3300−2600, 1740 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.89−2.07 (m, 2 H), 2.33−2.90 (m, 2 H), 3.47−4.02 (m, 6 H), 7.29−7.32 (m, 11 H); ^{13}C NMR (DMSO-d_6) δ 35.0, 35.9, 42.4, 45.7, 57.3, 63.7, 108.7, 119.2, 127.6, 128.0, 128.2, 128.3, 128.4, 137.9, 138.9, 168.3. Anal. Calcd for $C_{22}H_{21}NO_4$: C, 72.71; H, 5.83; N, 3.86. Found: C, 72.57; H, 5.65; N, 3.71.

1(a)-Cyano-2(e),6(e)-diphenyl-4,4-(ethylenedioxy)-cyclohexane-1(e)-carboxylic Acid (5c). To a magnetically stirred solution of 15.045 g (39.86 mmol) of the cis methyl ester **5a** in 134 mL of DMSO at 93 °C was added a solution of 9.95 g (150 mmol) of KOH in 13.3 mL of H_2O. The mixture was stirred at 88 °C for 50 min and then poured into water and filtered to remove a small amount of solid. The cooled filtrate was acidified with 40 mL of 6 M HCl, and the resulting solid was collected, washed with water, and recrystallized from acetone to give 12.891 g (89%) of **5c**: mp 235−239 °C dec; IR 1715 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.94 (d of d, br legs, J = 12.8, 2.9, 2 H), 2.34 (t, J = 12.8, 2 H), 3.60 (d of d, J = 12.8, 3.2, 2 H), 3.95 (s, 4 H), 7.32 (s, 10 H); ^{13}C NMR (DMSO-d_6) 37.2, 46.5, 59.7, 64.2, 106.4, 116.6, 127.9, 128.1, 128.4, 138.2, 168.1. Anal. Calcd for $C_{22}H_{21}NO_4$: C, 72.71; H, 5.83; N, 3.86. Found: C, 72.69; H, 5.66; N, 3.82.

2(e),6(a)-Diphenyl-4,4-(ethylenedioxy)cyclohexane-1,1-dicarbonitrile (4d). A mixture of 1.011 g (3.37 mmol) of the dicyano ketone **1d**, 1.0 mL (18 mmol) of ethylene glycol, and 47 mg of TSA in 20 mL of benzene was boiled for 3 h. The residue obtained by evaporation of the dried solution was crystallized from acetone−MeOH to give 828 mg of **4d** as white needles: mp 146−147.5 °C; IR ($CHCl_3$) 2245, 1135 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.11−2.68 (m, 4 H), 3.65−3.83 (d of d, 2 H), 3.93 (m, 4 H), 7.32−7.56 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 36.0, 45.8, 64.5, 107.4, 114.6, 128.8, 128.9, 136.9. Anal. Calcd for $C_{22}H_{20}N_2O_2$: C, 76.72; H, 5.85; N, 8.14. Found: C, 76.94; H, 5.90; N, 7.93.

Concentration of the mother liquor, followed by the addition of MeOH, gave an additional 188 mg of **4d**: mp 145−146 °C; total yield, 87%.

Reaction of the Trans Dicyano Ketal 4d with Base. A mixture of 1.039 g (3.02 mmol) of **4d**, 10 mL DMSO, and 0.95 g (14 mmol) of KOH in 1 mL of H_2O was heated at 150 °C for 5 h. Recrystallization of the crude product gave 182 mg of the amide **6a** as plates with mp 237−238 °C. Concentration of the mother liquor gave two more crops: 276 mg (mp 234−237 °C) and 146 mg (mp 235−237 °C); total yield, 59%. Spectra of this product were identical to those of the amide **6a** obtained from the cis methyl ester **5a**.

1(a)-Cyano-2(e),6(e)-diphenyl-4,4-(ethylenedioxy)-cyclohexane-1(e)-carboxamide (5e). A mixture of 3.012 g (9.46 mmol) of the cis cyano amide **3d**,[10] 4.0 mL (72 mmol) of ethylene glycol, and 0.20 g of TSA in 70 mL of benzene was boiled for 5.2 h. The neutralized reaction mixture was allowed to evaporate from the aqueous wash. The resulting solid was collected, washed well with water, and recrystallized twice from acetone−MeOH to give 1.900 g (55%) of **5e**: mp 256−258 °C; IR (PEC) 3460, 3370, 3260, 3210, 2220, 1695, 1600, 1155; ^{1}H NMR (DMSO-d_6) δ 1.91 (d of d, br, J = 13.6, ∼3, 2 H), 2.34 (t, J = 13.6, 2 H), 3.66 (br d of d, $J \cong$ 13, 3, 2 H), 3.96 (s, 4 H), 7.03−7.31 (m, 12 H); ^{13}C NMR (DMSO-d_6) δ 37.7, 45.9, 59.7, 64.0, 106.4, 117.5, 127.5, 128.1, 138.5, 166.6. Anal. Calcd for $C_{22}H_{22}N_2O_3$: C, 72.91; H, 6.12; N, 7.73. Found: C, 72.90; H, 5.94; N, 7.60.

1-Cyano-2(e),6(a)-diphenyl-4,4-(ethylenedioxy)cyclohexane-1-carboxamide (4e). A mixture of 4.532 g (14.2 mmol) of the trans cyano amide **2d**,[10] 6 mL (110 mmol) of ethylene glycol, and 0.30 g of TSA in 110 mL of benzene was boiled for 5.7 h. The neutralized reaction mixture was allowed to evaporate from the aqueous wash. The suspended solid was collected, washed with water, and recrystallized from acetone−MeOH. The crude product (4.16 g, mp 204−213 °C) was boiled in acetone, filtered to remove some insoluble material, concentrated, and diluted with MeOH. The ketal **4e** (2.452 g, 48%) separated upon cooling: mp 214−216 °C; IR (PEC) 3450, 3320, 2230, 1695, 1600, 1110 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.72−2.10 (m, 2 H), 2.33−3.00 (m, 2 H), 3.39−4.08 (m, 6 H), 6.64 (s, 1 H), 7.18−7.30 (m, 11 H); ^{13}C NMR (DMSO-d_6) δ 35.4, 36.2, 41.6, 46.2, 56.4, 63.7, 63.8, 108.9, 120.3, 127.5, 128.3, 128.7, 138.3, 139.4, 167.0. Anal. Calcd for $C_{22}H_{22}N_2O_3$: C, 72.91; H, 6.12; N, 7.73. Found: C, 72.87; H, 5.93; N, 7.62.

Reaction of the Trans Cyano Amide 4e with Base. A mixture of 1.038 g (2.86 mmol) of **4e**, 10 mL of DMSO, and 0.97 g (15 mmol) of KOH in 1 mL of H_2O was heated at 150 °C for 4.5 h. The crude product was recrystallized from acetone to give 413 mg of the amide **6a**, mp 236−238 °C. Two additional crops were obtained by concentration of the mother liquor: 187 mg (mp 235−237 °C) and 128 mg (mp 233−235 °C); total yield, 75%. Spectra were identical to those of the amide **6a** produced from the cis methyl ester **5a**.

Reaction of the Cis Cyano Amide 5e with Base. A mixture of 1.002 g (2.76 mmol) of **5e**, 10 mL of DMSO, and 0.91 g (14 mmol) of KOH in 1 mL of H_2O was heated at 150 °C for 5 h. The crude solid was recrystallized from acetone to give 399 mg of the amide **6a**, mp 236−238 °C. Two additional crops were obtained by concentration of the mother liquor: 298 mg (mp 235.5−238 °C) and 46 mg (mp 230−233.5 °C); total yield, 80%. Spectra of this product were identical to those of **6a** obtained from the cis methyl ester **5a**.

1,2(e),6(a)-Triphenyl-4,4-(ethylenedioxy)cyclohexane-1-carbonitrile (4f). A mixture of 15.00 g (42.7 mmol) of the trans triphenyl ketone **2c**,[13] 24 mL (430 mmol) of ethylene glycol, and 1.22 g of TSA in 380 mL of benzene was boiled for 17 h. The oil obtained by evaporation of the benzene was crystallized twice from acetone−MeOH to give 13.12 g of **4f**: mp 136−137 °C; IR ($CHCl_3$) 2245, 1120 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 2.07−2.29 (m, 2 H), 2.50−2.89(m, 2 H), 3.69−4.05 (m, 6 H), 6.99 (s, 5 H), 7.08−7.10 (s, 10 H); ^{13}C NMR ($CDCl_3$) δ 36.4, 38.7, 43.7, 50.0, 54.9, 64.2, 64.4, 109.2, 122.3, 126.8, 127.2, 127.5, 127.7, 127.8, 128.0, 128.5, 129.1, 135.5, 138.6, 139.5. Anal. Calcd for $C_{27}H_{25}NO_2$: C, 82.00; H, 6.37; N, 3.54. Found: C, 81.83; H, 6.66; N, 3.52.

The residues obtained from the mother liquors were recrystallized from acetone−MeOH to give 1.88 g of **4f**: mp 135−137 °C; total yield, 89%.

Reaction of the Trans Triphenyl Cyano Ketal 4f with Base. A mixture of 3.118 g (7.88 mmol) of **4f**, 30 mL of DMSO, and 2.98 g (45 mmol) of KOH in 3 mL of H_2O was heated at 150 °C for 9.5 h. The crude product was chromatographed on 55 g of neutral alumina. Elution with cyclohexane gave 1.119 g of an oil, which crystallized from CH_2Cl_2−MeOH to give

1.038 g of **1,2,3-triphenylbenzene (8a):** mp 160−161 °C (lit.[14] mp 158.4 °C); MS (EI/eV) *m/z* 306.1; ^{1}H NMR ($CDCl_3$) δ 6.89 (m, 5 H), 6.98 (m, 10 H), 7.41 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 125.8, 126.1, 127.1, 127.2, 127.5, 129.5, 129.9, 131.6, 139.2, 139.6, 142.0. The IR, ^{1}H NMR, and ^{13}C NMR spectra were identical to those of commercially available **8a**. The mother liquor deposited an additional 33 mg of **8a**: mp 158−159.5 °C: total yield, 44%.

Elution of the column with 50% CH_2Cl_2−cyclohexane gave 1.366 g of a solid that was recrystallized from CH_2Cl_2−MeOH to give 856 mg of **1(e),2(e),6(e)-triphenyl-4,4-(ethylenedioxy)cyclohexane-1(a)-carbonitrile (5f):** mp 143−144 °C; IR ($CHCl_3$) 2245, 1140 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.09 (d of d, br legs, J = 12.8, ∼3, 2 H), 2.73 (t, J = 12.8, 2 H), 3.71 (d of d, J = 12.8, 3.2, 2 H), 4.02 (s, 4 H), 7.05 (s, 15 H); ^{13}C NMR ($CDCl_3$) δ 39.3, 50.3, 57.1, 64.7, 107.6, 119.2, 127.1, 127.4, 127.6, 128.1, 128.7, 136.3, 138.7. Anal. Calcd for $C_{27}H_{25}NO_2$: C, 82.00; H, 6.37; N, 3.54. Found: C, 81.72; H, 6.39; N, 3.46. An additional 272 mg of **5f** was obtained from the mother liquor: mp 147−148 °C; total yield, 36%. Recrystallization from CH_2Cl_2−MeOH gave mp 152.5−153.5 °C.

Treatment of this ketal (**5f**) with KOH−H_2O in DMSO at 147 °C for 6 h gave only starting material (mp and ^{1}H NMR).

Hydrolysis of the Triphenyl Cis Ketal 5f. A solution of 359 mg (0.908 mmol) of **5f** in 8 mL of acetone containing 1 mL of H_2O and 10 drops of 6 M HCl was heated under reflux for 10 h. (An additional six drops of the acid were added after 7.5 h.) The solution was diluted with water, and the precipitate was collected, washed with water, dried, and recrystallized from CH_2Cl_2−cyclohexane to give 118 mg of **1(e),2(e),6(e)-triphenyl-4-oxocyclohexane-1(a)-carbonitrile (3c)**: mp 213.5−215 °C (lit.[13] mp 213 °C); IR ($CHCl_3$) 2235, 1720 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.80 (d with br legs, J = 12.8, 2 H), 3.49 (t, J = 12.8, 2 H), ∼3.75 overlaps 3.49 signal (m, 2 H), 7.09 ("s", 15 H). These NMR data are in agreement with those reported for **3c**.[5]

Two additional crops of **3c** were obtained by concentration of the mother liquor: 56 mg (mp 212.5−215 °C) and 39 mg (209.5−213 °C); total yield, 67%.

Reaction of the Trans Triphenyl Cyano Ketal 4f with DMSO-d_6. A mixture of 1.503 g (3.80 mmol) of **4f**, 15 g of DMSO-d_6, and 2 mL of a 40% KOD−D_2O solution was heated at 150 °C for 8.5 h. The red-brown colored mixture was diluted with 30 mL of D_2O, cooled overnight, and filtered. The dried solid was chromatographed on 21.5 g of neutral alumina. Elution with cyclohexane gave 550 mg of a solid that was recrystallized from CH_2Cl_2−95% EtOH to yield 486 mg (41%) of **4,5,6-trideuterio-1,2,3-triphenylbenzene (8b):** mp 159.5−160 °C; ^{1}H NMR ($CDCl_3$) δ 6.87−6.90 (m, 5 H), 7.08 (s, 10 H); ^{13}C NMR ($CDCl_3$) δ 125.8, 126.2, 127.2, 127.5, 129.9, 131.7, 139.2 (weak), 139.6, 142.0.

Elution with 50% CH_2Cl_2−cyclohexane gave 365 mg of a foam that crystallized from CH_2Cl_2−MeOH to give 259 mg (17%) of **2(a),6(a)-dideuterio-1(e),2(e),6(e)-triphenyl-4,4-(ethylenedioxy)cyclohexane-1(a)-carbonitrile (9)**: mp 154.5−155 °C; ^{1}H NMR ($CDCl_3$) δ 2.08 (d, J = 12.8, 2 H), 2.72 (d, J = 12.8, 2 H), 4.00 (s, 4 H), 7.05 (s, 15 H); ^{13}C NMR ($CDCl_3$) δ 39.2, 49.9 (v weak t), 57.0, 64.7, 107.8, 119.3, 127.2, 127.5, 127.7, 128.2, 128.7, 136.4, 138.9.

Clemmensen Reduction of the Ketone 3b. A mixture of ZnHg [prepared[17] from 11.00 g (40.5 mmol) of $HgCl_2$ and 50.0 g (0.76 mol) of Zn dust], 15.01 g (45.0 mmol) of the cis cyano ketone **3b**, and 50 mL of concd HCl in 250 mL of 95% EtOH was heated under reflux for 5 h. (After 1.8 h, an additional 40 mL of the acid was added.) The warm mixture was filtered, the ZnHg rinsed with 95% EtOH, and the colorless solution was concentrated to 350 mL. Upon standing overnight at room temperature, 11.73 g (82%) of **methyl 1(a)-cyano-2(e),6(e)-diphenyl-3-cyclohexene-1(e)-carboxylate (10)** precipitated as needles with mp 151.5−153 °C, soften at 150 °C. Recrystallization of a sample from 95% EtOH gave the following data: mp 153.5−155 °C; IR ($CHCl_3$) 2245, 1740, 1655 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.03−3.24 (m, >2 H), 3.25 (s, 3 H), 3.55 (d of d, $J \cong$ 12, 4, 1 H), 4.36 (m, 1 H), 5.78 (d of d, $J \cong$ 10.4, 1.6, 1 H), 6.0 (m, 1 H), 7.30 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 29.9, 47.5, 49.8, 52.6, 57.7, 116.2, 127.1, 127.9, 128.2, 128.3, 128.5, 128.6, 128.8, 138.3, 138.4, 168.2. Anal. Calcd for $C_{21}H_{19}NO_2$: C, 79.47; H, 6.03; N, 4.41. Found: C, 79.43; H, 6.15; N, 4.35. The ^{13}C NMR spectrum displayed trace absorptions corresponding to the saturated cyano ester **11**. These are not listed above.

Methyl 1(a)-Cyano-2(e),6(e)-diphenylcyclohexane-1(e)-carboxylate (11). A solution of 0.82 g (2.6 mmol) of the unsaturated ester **10** in 60 mL of ethyl acetate was hydrogenated in the presence of Pd−C at room temperature for 30 min. After purging, the mixture was filtered and evaporated to dryness. The residue was recrystallized from MeOH to give 0.69 g (83%) of **11** as white plates, mp 141−143 °C. Recrystallization from acetone−MeOH gave the following data: mp 145−146.5 °C; IR ($CHCl_3$) 2240, 1735 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.6−2.55 (m, 6 H), 3.20 (s, 3 H), 3.34 (d of d, J = 12.8 and 3.2, 2 H), 7.30 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 25.8, 28.4, 50.6, 52.3, 60.4, 116.8, 127.9, 128.2, 128.4, 139.4, 168.1. Anal. Calcd for $C_{21}H_{21}NO_2$: C, 78.97; H, 6.63; N, 4.39. Found: C, 78.85; H, 6.52; N, 4.30.

Reaction of the Cis Methyl Ester 11 with Base. A mixture of 815 mg (2.55 mmol) of **11**, 8 mL of DMSO, and 0.85 g (13 mmol) of KOH in 1 mL of H_2O was heated at 146 °C for 5.5 h. The crude product (657 mg) was chromatographed on 15 g of neutral alumina. Elution with 50% CH_2Cl_2−cyclohexane through 100% CH_2Cl_2 gave 602 mg of homogeneous fractions (^{1}H NMR) that were combined and crystallized from CH_2Cl_2−cyclohexane to give 367 mg of **2(e),6(e)-diphenylcyclohexane-1(e)-carboxamide (12a)** as plates: mp 235−236 °C; IR (PEC) 3520, 3400, 1680, 1585 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.66−2.03 (m, 6 H), 2.39 (t, J = 10.4, 1 H), 2.85−3.15 (m, 2 H), 4.47 (br s, 2 H), 7.23 (s, 10 H); ^{13}C NMR (DMSO-d_6) δ 26.3, 34.4, 47.0, 55.1, 125.9, 127.7, 127.9, 144.9, 174.0. Anal. Calcd for $C_{19}H_{21}NO$: C, 81.68; H, 7.58; N, 5.01. Found: C, 81.44, 81.36; H, 7.19, 7.26; N, 4.84, 4.87.

Two additional crops of **12a** were obtained from the mother liquor: 128 mg (mp 235−236 °C) and 51 mg (mp 231−234 °C); total yield, 77%.

Reaction of the Cis Methyl Ester 11 in DMSO-d_6. A mixture of 710 mg (2.22 mmol) of **11**, 7 mL of DMSO-d_6, and 1 mL of a 40% KOD−D_2O solution was heated at 152 °C for 5.5 h. The warm solution was diluted with 30 mL of D_2O, and the precipitate was collected and washed with water. The dried solid was chromatographed on 15 g of neutral alumina. Elution with 60% CH_2Cl_2−cyclohexane and 100% acetonitrile gave 511 mg of a solid that was recrystallized from CH_2Cl_2−cyclohexane to yield 404 mg of **2(e),6(e)-diphenyl-1(a),2(a),6(a)-trideuteriocyclohexane-1(e)-carboxamide (12b)**: mp 235.5−236.5 °C; ^{1}H NMR ($CDCl_3$) δ 1.59−2.03 (m, 6 H), ∼3.0 (trace of signal), 4.45 (br s, 2H), 7.23 (s, 10 H); ^{13}C NMR (DMSO-d_6) δ 26.3, 34.3, 47.0 (weak), 125.9, 127.7, 128.0, 144.9, 174.1. An additional 59 mg of **12b** was recovered from the mother liquor: 59 mg (mp 232−235.5 °C); total yield, 74%.

1(a)-Cyano-2(e),6(e)-cyclohexane-1(e)-carboxylic Acid (12c). A mixture of 819 mg (2.56 mmol) of the cis ester **11**, 8 mL of DMSO, and 0.82 g (12 mmol) of KOH in 1 mL of H_2O was heated at 102 °C for 1.3 h. The warm mixture was diluted with 35 mL of water and then acidified with 5 mL of 6 M HCl. The resulting precipitate was collected, washed with water, and recrystallized from acetone−cyclohexane to give 420 mg of **12c**, mp 251−260 °C dec. The mother liquor deposited an additional 187 mg of **12c**, mp 245−250 °C dec, total yield, 78%. Recrystallization from 100% EtOH gave the following data: mp 250−253 °C dec; IR (PEC) 1710 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.78−2.21 (m, 6 H), 3.29−3.39 (m, 2 H), 7.31 (s, 10 H); ^{13}C NMR (DMSO-d_6) δ 25.2, 28.6, 49.2, 60.0, 117.5, 127.6, 128.2, 128.3, 140.0, 168.3. Anal. Calcd for $C_{20}H_{19}NO_2$: C, 78.66; H, 6.27; N, 4.59. Found: C, 78.66; H, 6.21; N, 4.73.

Reaction of Dimethyl 2(e),6(a)-Diphenyl-4,4-(ethylenedioxy)cyclohexane-1,1-dicarboxylate (13) with Base. A mixture of 1.102 g (2.69 mmol) of **13**,[12] 10 mL of DMSO,

(17) Fieser, L. F.; Fieser, M. *Reagents for Organic Synthesis*; John Wiley: New York, 1967; pp 1287−1288.

and 0.75 g (11 mmol) of KOH in 1 mL of water was heated at 120 °C for 20 min. The mixture was diluted with water, cooled to 0 °C, poured into a separatory funnel with 3 mL of 6 M HCl and ice, and extracted three times with ether. The combined ether phases were washed three times with water, dried, and evaporated to give 876 mg of white solid. Recrystallization from ethyl ether−petroleum ether gave 819 mg (90%) of **2(e),6(a)-diphenyl-4,4-(ethylenedioxy)cyclohexane-1-carboxylic acid (14a)**: mp 164.5−166 °C (lit.[12] mp 165.5−166.5 °C); ^{1}H NMR identical to that reported.[12]

Reaction of the Trans Dimethyl Ester 13 with DMSO-d_6. A mixture of 1.019 g (2.48 mmol) of **13**, 10 g of DMSO-d_6, and 1.0 mL of a 40% NaOD−D_2O solution was heated at 118 °C for 1 h and then cooled, diluted with 15 mL of D_2O, and poured into a mixture of ether, 26 mL of 1 M HCl, and ice. The mixture was shaken, the layers were separated, and the aqueous phase was extracted again with ether. The organic extracts were washed twice with water, dried, and concentrated. Recrystallization of the residue from ether−petroleum ether gave 757 mg (90%) of **1-deuterio-2(e),6(a)-diphenyl-4,4-(ethylenedioxy)cyclohexane-1-carboxylic acid (14b)**: mp 165−166 °C; ^{13}C NMR ($CDCl_3$) δ 36.1, 39.1, 39.8, 40.0, 64.0, 64.2, 109.3, 126.5, 126.7, 127.3, 128.1, 128.3, 128.5, 141.5, 143.9, 178.3.

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Supporting Information Available: ORTEP diagrams for compounds **1d**, **3e**, **3f**, and **6a** (42 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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