Synthesis, Resolution, and Absolute Stereochemistry of (1*R*,2*S*)-(+)-*cis*-1-Methoxycarbonyl-2-methylcyclobutane

John E. Baldwin* and Richard C. Burrell

Department of Chemistry, Syracuse University, Syracuse, New York 13244

jbaldwin@syr.edu

Received June 23, 2000

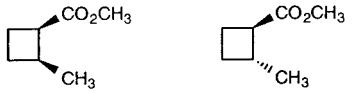
Racemic *cis*-1-methoxycarbonyl-2-methylcyclobutane uncontaminated with the trans isomer was prepared efficiently in five steps; the corresponding amides from (*R*)-(−)-phenylglycinol were separated. An X-ray crystallographic structure determination of the amide from (+)-*cis*-1-methoxycarbonyl-2-methylcyclobutane showed that it was of (1*R*,2*S*) absolute stereochemistry, a revision of configurational assignment.

Introduction

The stereochemical characteristics of thermal rearrangements converting vinylcyclopropanes into cyclopentenes have been investigated in great detail for nearly 25 years, and by now this simplest of 1,3-carbon sigmatropic shifts and the closely associated thermal stereomutations of vinylcyclopropanes are reasonably well understood.[1,2] The stereochemical evidence relating to reaction stereochemistry for vinylcyclobutanes isomerizing to cyclohexenes is much less thoroughly developed. There are valuable studies that have served to reveal some aspects of reaction stereochemistry,[3−5] but there seems to be no case for which the relative participation of each of all four possible stereochemically distinct modes of 1,3-shift have been ferreted out through suitable kinetic work. The major technical problems impeding such work are associated with the propensity of substituted vinylcyclobutanes to suffer thermal stereomutations as well as fragmentations to olefins and dienes at rates comparable to or even faster than rates of isomerization to substituted cyclohexenes.

In preparation for a thorough kinetic study of the thermal stereomutations of the four 1-(*E*)-propenyl-2-methylcyclobutanes to the seven isomeric 3,4- and 3,6-dimethylcyclohexenes, a practical synthetic route to one or both enantiomers of *cis*-1-methoxycarbonyl-2-methylcyclobutane having high and well-defined enantiomeric excess (ee) was sought. A few additional steps were expected to provide samples of cis and trans isomers 1-(*E*)-propenyl-2-methylcyclobutane of the same ee and of known relative stereochemistry. Sure knowledge of the absolute stereochemistry of one enantiomer of the ester would then provide assignments of absolute stereochemistry for the cis and trans hydrocarbon substrates destined for detailed kinetic studies of the thermal stereomutation, fragmentation, and isomerization reactions they would be expected to show.

This report describes two syntheses of racemic *cis*-1-methoxycarbonyl-2-methylcyclobutane ((±)-**1**), the second affording the cis ester free of the trans isomer ((±)-**2**); a resolution providing both enantiomers of *cis*-1-methoxycarbonyl-2-methylcyclobutane of high ee; and a rigorous determination of absolute stereochemistry for these enantiomers, one which prompts revisions of earlier assignments.



(±)-1 (±)-2

Results

The first preparation of (±)-**1** employed conventional malonic ester chemistry (Scheme 1).[3,6] 1,3-Dibromobutane and diethyl malonate were condensed to provide diethyl 2-methylcyclobutane-1,1-dicarboxylate (**3**) which, through hydrolysis and thermal decarboxylation, led to a mixture of cis and trans isomers of 2-methylcyclobu-

(1) (a) Andrews, G. D.; Baldwin, J. E. *J. Am. Chem. Soc.* **1976**, *98*, 6705−6706. (b) Baldwin, J. E.; Villarica, K. A.; Freedberg, D. I.; Anet, F. A. L. *J. Am. Chem. Soc.* **1994**, *116*, 10845−10846. (c) Baldwin, J. E. In *The Chemistry of the Cyclopropyl Group*; Rappoport, Z., Ed.; Wiley: Chichester, 1995; Vol. 2, pp 469−494. (d) Baldwin, J. E. *J. Comput. Chem.* **1998**, *19*, 222−231, and references therein. (e) Baldwin, J. E.; Bonacorsi, S. J.; Burrell, R. C. *J. Org. Chem.* **1998**, *63*, 4721−4725. (f) Baldwin, J. E.; Burrell, R. C. *J. Org. Chem.* **1999**, *64*, 3567−3571. (g) Baldwin, J. E.; Shukla, R. *J. Am. Chem. Soc.* **1999**, *121*, 11018−11019.

(2) (a) Davidson, E. R.; Gajewski, J. J. *J. Am. Chem. Soc.* **1997**, *119*, 10543−10544. (b) Houk, K. N.; Nendel, M.; Wiest, O.; Storer, J. W. *J. Am. Chem. Soc.* **1997**, *119*, 10545−10546. (c) Doubleday: C.; Nendel, M.; Houk, K. N.; Thweatt, D.; Page, M. *J. Am. Chem. Soc.* **1999**, *121*, 4720−4721. (d) Nendel, M.; Sperling, D.; Wiest, O.; Houk, K. N. *J. Org. Chem.* **2000**, *65*, 3259−3268.

(3) Jordan, L. M. Ph.D. Dissertation, Yale University, 1974; *Chem. Abstr.* **1975**, *83*, 58218g; *Diss. Abstr. Int. B* **1975**, *35*, 5332−5333. A summary of this work is provided in: Gajewski, J. J. *Hydrocarbon Thermal Isomerizations*; Academic Press: New York, 1981; pp 177−183.

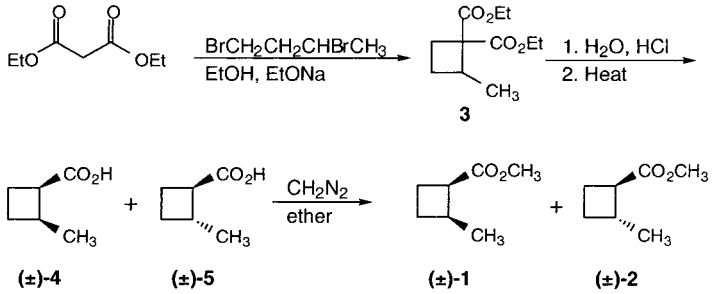
(4) Doering, W. von E.; Mastrocola, A. R. *Tetrahedron* **1981**, *37*, Suppl. 1, 329−344.

(5) (a) Ellis, R. J.; Frey, H. M. *Trans. Faraday Soc.* **1963**, *59*, 2076−2079. (b) Frey, H. M.; Pottinger, R. *J. Chem. Soc., Faraday Trans. 1* **1978**, *74*, 1827−1833. (c) Chickos, J. S.; Frey, H. M. *J. Chem. Soc., Perkin Trans. 2* **1987**, 365−370. (d) Gruseck, U.; Heuschmann, M. *Chem. Ber.* **1990**, *123*, 1911−1926. (e) Lewis, D. K.; Hutchinson, A.; Lever, S. J.; Spaulding, E. L.; Bonacorsi, S. J.; Baldwin, J. E. *Isr. J. Chem.* **1996**, *36*, 233−238. (f) Lewis, D. K.; Charney, D. J.; Kalra, B. L.; Plate, A.-M.; Woodard, M. H.; Cianciosi, S. J.; Baldwin, J. E. *J. Phys. Chem. A* **1997**, *101*, 4097−4102.

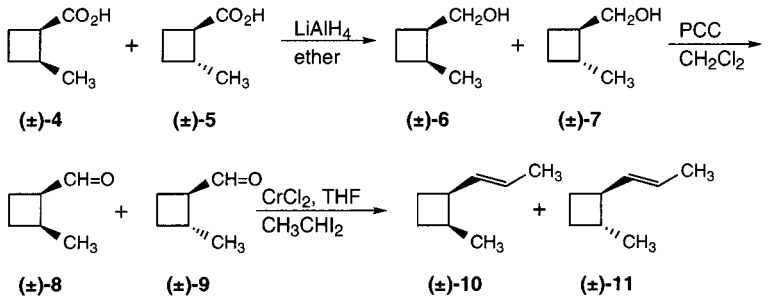
(6) Compare (a) Heisig, G. B.; Stodola, F. H. *Org. Synth.* **1955**, *Coll. Vol. 3*, 213-216. (b) Blomquist, A. T.; Wolinsky, J. *J. Org. Chem.* **1956**, *21*, 1371−1373, and references therein. (c) Cason, J.; Rappaport, H. *Laboratory Test in Organic Chemistry*, 3rd ed.; Prentice Hall: Englewood Cliffs, NJ, 1970; pp 375−378. An alternative procedure based on phase transfer catalysis (Török, B.; Molnár, A. *J. Chem. Soc., Perkin Trans. 1* **1993**, 801−804) did not prove advantageous.

10.1021/jo0009550 CCC: $19.00
Published on Web 09/19/2000

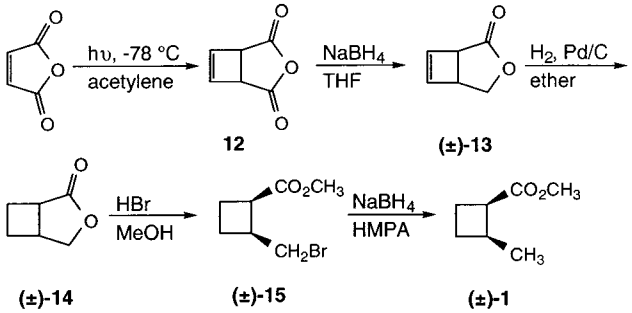
Scheme 1



Scheme 2



Scheme 3

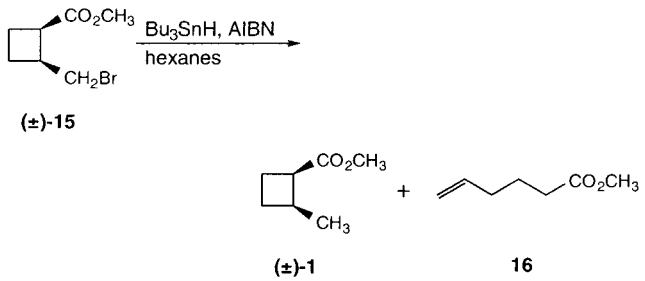


tanecarboxylic acid, (±)-**4** and (±)-**5**. The related methyl esters, (±)-**1** and (±)-**2**, were prepared, separated, and identified through spectra comparisons with data reported in the literature. Both cis and trans esters showed two equal-intensity peaks when analyzed on an octakis-(2,6-di-*O*-pentyl-3-trifluoroacetyl)-γ-cyclodextrin capillary GC column (Astec), thus demonstrating that nonracemic samples of these cis and trans esters could be assayed for ee with convenience and high precision.

The cis and trans acids (±)-**4** and (±)-**5** were converted in three steps (Scheme 2) into the racemic cis and trans forms of 1-(*E*)-propenyl-2-methylcyclobutane, (±)-**10** and (±)-**11**, thus demonstrating synthetic chemistry ready to be applied with optically active acids (or esters) at a later stage of this effort.

The second synthesis of (±)-**1,** which provided it as a single diastereomer, followed the route implemented by Toone and Jones[7] except for one significant modification (Scheme 3).

The sequence of reactions starting from the photochemical cycloaddition of acetylene with maleic anhydride (Scheme 3) proceeded without difficulty to give methyl *cis*-1-methoxy-carbonyl-2-(bromomethyl)cyclobutane, **(±)-15**. Attempts to reduce the bromomethyl function to a methyl group with tri-*n*-butyltin hydride under a variety of conditions gave low yields of the desired product along with substantial amounts of methyl 5-hexenoate (**16**).[8]



Formation of ester **16** under the reaction conditions makes perfect mechanistic sense: similar radical-mediated isomerizations during tri-*n*-butyltin hydride reductions have been reported by many workers.[9] That we were not able to reproduce precisely the reaction conditions which allowed others[7] to realize yields in the conversion of **15** to **1** as high as 97% using Bu_3SnH was a substantial disappointment.

The required reduction was secured with complete suppression of the unwanted isomerization to hexenoate by using $NaBH_4$ in dry HMPA;[10] the conversion of lactone (±)-**14** to distilled (±)-**1** was realized in 50% yield.

The resolution of (±)-**1** was achieved using the functional group transformations of Scheme 4, followed by chromatographic separation of the diastereomeric amides derived from (*R*)-(−)-phenylglycinol, (*R*)-(−)-**18**.

Conversions of the amides **19** and **20** to the corresponding methyl esters afforded (+)-**1**, $[\alpha]_D$ + 58.4, and

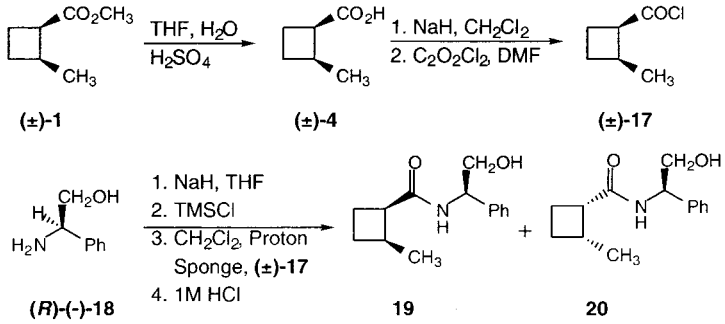
(7) Toone, E. J.; Jones, J. B. *Tetrahedron: Asymmetry* **1991**, *2*, 207−222.

(8) Scarborough, R. M.; Toder, B. H.; Smith, A. B. *J. Am. Chem. Soc.* **1980**, *102*, 3904−3913. The acid is sold by Aldrich.

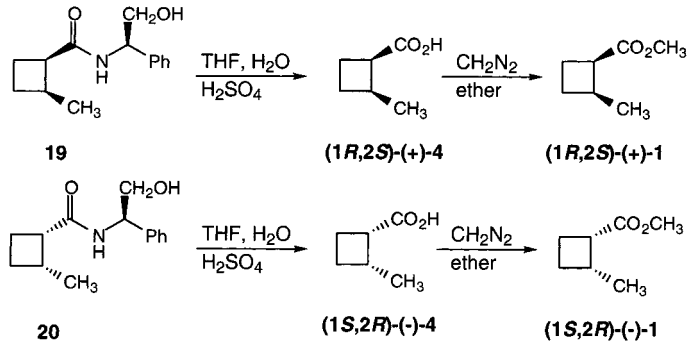
(9) (a) Castaing, M.; Pereyre, M.; Ratier, M.; Blum, P. M.; Davies, A. G. *J. Chem. Soc., Perkin Trans. 2* **1979**, 287−292. (b) Beckwith, A. L. J.; Moad, G. *J. Chem. Soc., Perkin Trans. 2* **1980**, 1083−1092. (c) Maillard, B.; Walton, J. C. *J. Chem. Soc., Perkin Trans. 2* **1985**, 443−450.

(10) Hutchins, R. O.; Kandasamy, D.; Dux, F.; Maryanoff, C. A.; Rotstein, D.; Goldsmith, B.; Burgoyne, W.; Cistone, F.; Dalessandro, J.; Puglis, J. *J. Org. Chem.* **1978**, *43*, 2259−2267.

Scheme 4



Scheme 5



(−)-**1**, $[\alpha]_D$ −62.8, each of 99% enantiomeric excess by GC on the octakis(2,6-di-*O*-pentyl-3-trifluoroacetyl)-γ-cyclodextrin column. The assignments of absolute stereochemistry evident in Schemes 4 and 5 anticipate the structural evidence introduced below.

One difficulty initially plagued the HPLC separation of the diastereomeric amides **19** and **20**: the two amides were resolved satisfactorily on a Nucleosil 50-5 column but, in processing some batches of the mixture of amides, a third component eluting close to the two desired diastereomers was seen. Isolation of the unknown soon resolved the riddle: it proved to be the (*R*)-(−)-phenylglycinol derived amide of (2*Z*,4*E*)-hexadienoic acid.[11] Traces of lactone (±)-**13** apparently remained unreduced in some hydrogenation runs (Scheme 3); as material was carried through the further steps of Scheme 3, the functional group transformations presumably occurred unexceptionally to convert (±)-**13** into *cis*-1-methoxycarbonyl-2-methyl-3-cyclobutene. This cyclobutene contaminant might then have isomerized thermally quite facilely in conrotatory fashion, with the cis disposed methyl and methoxycarbonyl groups dictating the sense of conrotation in the expected "torquoselective" fashion.[12]

The initially alarming "third amide" component apparent in some early separations as the chromatographic eluant was monitored with an ultraviolet detector was registered by a detector response greatly exaggerating its relative concentration, thanks to the relatively high extinction coefficient of the 2,4-hexadienamide chromophore.

For the projected investigation of reaction stereochemistry of the vinylcyclobutane to cyclohexene rearrangement of the four 1-(*E*)-propenyl-2-methylcyclobutanes there could be no uncertainty on assignments of absolute sterechemistry for these reactants, just as there could be no doubts about stereochemistry for the seven possible dimethylcyclohexene products.[13] The assignments of absolute stereochemistry for the enantiomers of **1** were made rigorously through an X-ray crystallographic structure determination for the (*R*)−(−)-phenylglycinol derived amide related to the dextrorotatory ester, (+)-**1**.[14] The X-ray structure for amide **19** defined the relative configurations of all chiral centers and hence the absolute stereochemistry of the molecule. This structure provided sure assignments of absolute stereochemistry for esters (1*R*,2*S*)-(+)-**1** and (1*S*,2*R*)-(−)-**1**.[14]

Discussion and Conclusions

A rotation of $[\alpha]_D$ +22.4 had been reported for one enantiomer of **1** believed to be of quite high ee and of (1*S*,2*R*) stereochemistry.[7] The discrepancy between $[\alpha]_D$ +22.4 and our specific rotation for (+)-**1,** $[\alpha]_D$ +58.4, was large enough to prompt serious concerns and contributed to the decision to check absolute stereochemistry through crystallography. Now (+)-**1** is known to be of (1*R*,2*S*) stereochemistry,[14] so more than the absolute magnitudes of two rotations is at stake.

The correct assignment for (1*R*,2*S*)-(+)-**1** is of some importance, for the compound and several closely related structures have been used to infer reaction stereochemistry for several enzyme-catalyzed hydrolyses and oxidations of considerable synthetic importance. These issues, now that they are clearly evident, will no doubt be soon

(11) (a) Sato, T.; Tsunekawa, H.; Kohama, H.; Fujisawa, T. *Chem. Lett.* **1986**, 1553−1556. (b) Lewis, F. D.; Howard, D. K.; Barancyk, S. V.; Oxman, J. D. *J. Am. Chem. Soc.* **1986**, *108*, 3016−3023.

(12) (a) Hayes, R.; Ingham, S.; Saengchantara, S. T.; Wallace, T. W. *Tetrahedron Lett.* **1991**, *32*, 2953−2954. (b) Binns, F.; Hayes, R.; Ingham, S.; Saengchantara, S. T.; Turner, R. W.; Wallace, T. W. *Tetrahedron* **1992**, *48*, 515−530. (c) Niwayama, S.; Houk, K. N. *Tetrahedron Lett.* **1992**, *33*, 883−886, and references therein.

(13) Baldwin, J. E.; Burrell, R. C. *J. Org. Chem.* **2000**, *65*, 7145−7150.

(14) Alexander, J. S.; Baldwin, J. E.; Burrell, R. C.; Ruhlandt-Senge, K. *Chem. Commun.*, submitted.

resolved. The maze of reported structural interconversions relating (+)-**1** with other molecules is complicated and convoluted; the mere definition of absolute stereochemistry for (1*R*,2*S*)-(+)-**1** does not by itself lead to fully satisfactory and consistent reinterpretations of all accounts in the literature, but some readings of the data do seem more plausible than others.[14] In particular, we believe the (+) isomer of *cis*-3-oxabicyclo-[3.2.0]heptan-2-one is indeed (1*S*,5*R*)-**14**.[15]

For the immediate purposes of this work, the essential stereochemical point is that a great hazard has been avoided. To have relied on the assignment of absolute stereochemistry (1*S*,2*R*) for (+)-**1** provided by the literature[7] would have led to reversed configurational asssignments for the four 1-(*E*)-propenyl-2-methylcyclobutanes and hence to erroneous inferences on the stereochemistry of the thermal reactions converting them into mixtures of seven dimethylcyclohexenes.

With absolute stereochemistry assignments now secure, for both a key synthetic intermediate, (1*R*,2*S*)-(+)-**1**, which may be converted readily into (1*R*,2*S*)-**10** and (1*S*,2*S*)-**11**, and for the six chiral 3,4- and 3,6-dimethylcyclohexenes,[13] the stage is set for synthetic, kinetic, and analytical work which should unveil the stereochemical complexities and preferences characteristic of the thermal vinylcyclobutane-to-cyclohexene isomerizations of the four 1-(*E*)-propenyl-2-methylcyclobutanes.

Experimental Section

***cis*-2-Methylcyclobutanecarboxylic acid** ((±)-**4**) and ***trans*-2-methylcyclobutanecarboxylic acid** ((±)-**5**) were prepared from 1,3-dibromobutane and diethyl malonate.[6] A sample of the intermediate diester **3** (bp 95−115 °C (15 mm), lit.[6b] bp 70−72.5 °C (1.0 mm)) was purified by preparative GC (1-m, 10% SE−30, 110 °C): ^{1}H NMR δ 4.08−4.30 (m, 4 H), 3.05−3.20 (m, 1 H), 2.58−2.72 (m, 1 H), 1.98−2.18 (m, 2 H), 1.60−1.76 (m, 1 H), 1.20−1.32 (m, 6 H), 1.05 (d, J = 7.14 Hz, 3 H); MS *m*/*z* (rel intensity) 214 (1, M$^+$), 185 (4), 173 (32), 169 (30), 160 (14), 140 (12), 127 (100), 122 (46), 113 (16), 99 (48), 67 (22), 55 (17), 41 (25), 29 (81).

Hydrolysis and decarboxylation of **3** led to distilled (±)-**4** and (±)-**5**, collected as a clear oil. Analytical GC showed this material to be a 40:60 mixture of cis acid (±)-**4** and trans acid (±)-**5**. Both were isolated in pure form through preparative GC (1-m, 17% Carbowax, 165 °C). (±)-**4:** ^{1}H NMR δ 3.19−3.31 (m, 1 H), 2.22−2.90 (m, 1 H), 2.27−2.41 (m, 1 H), 1.94−2.22 (m, 2 H), 1.58−1.72 (m, 1 H), 1.12 (d, J = 7.13 Hz, 3 H) (compare ref 7); ^{13}C NMR δ 180.3, 41.7, 32.8, 26.2, 19.9, 16.9; MS *m*/*z* (rel intensity) 114 (1, M$^+$), 99 (8), 86 (11), 73 (100), 68 (26), 55 (30), 42 (45), 41 (40), 39 (32). (±)-**5**: ^{1}H NMR δ 2.53−2.75 (m, 2 H), 1.96−2.21 (m, 3 H), 1.48−1.63 (m, 1 H), 1.14 (d, J = 6.59 Hz, 3 H); ^{13}C NMR δ 180.2, 45.4, 35.3, 26.4, 21.1, 21.1; MS *m*/*z* (rel intensity) 114 (2, M$^+$), 99 (8), 85 (60), 73 (100), 68 (32), 55 (43), 42 (72), 41 (65), 39 (57).

***cis*-1-Methoxycarbonyl-2-methylcyclobutane** ((±)-**1**) and ***trans*-1-methoxycarbonyl-2-methylcyclobutane** ((±)-**2**) were prepared from the mixture of acids (±)-**4** and (±)-**5** through a conventional esterification with diazomethane in ether. A 40:60 mixture of cis/trans isomers was obtained according to analytical GC. They were separated and purified by preparative GC (1-m, 17% Carbowax, 85 °C). (±)-**1**: ^{1}H NMR δ 3.69 (s, 3 H), 3.15−3.27 (m, 1 H), 2.67−2.84 (m, 1 H), 2.29−2.43 (m, 1 H), 1.93−2.20 (m, 2 H), 1.55−1.70 (m, 1 H), 1.03 (d, J = 7.13 Hz, 3 H) (compare ref 3, 7, and 16); ^{13}C NMR δ 174.6, 51.2, 41.7, 32.8, 26.3, 20.2, 17.0; MS *m*/*z* (rel intensity) 128 (2, M$^+$), 113 (10), 97 (12), 87 (100), 69 (43), 55 (73), 41 (55). (±)-**2**: ^{1}H NMR δ 3.67 (s, 3 H), 2.48−2.71 (m, 2 H), 1.94−2.18 (m, 3 H), 1.45−1.61 (m, 1 H), 1.12 (d, J = 6.59 Hz, 3 H) (compare ref 3 and 16); ^{13}C NMR δ 175.4, 51.5, 45.6, 35.1, 26.4, 21.3, 21.2; MS *m*/*z* (rel intensity) 128 (3, M$^+$), 113 (15), 97 (19), 87 (100), 69 (64), 55 (55), 41 (54).

***cis*-2-Methylcyclobutanemethanol** ((±)-**6**) and ***trans*-2-methylcyclobutanemethanol** ((±)-**7**)**.** A 40:60 mixture (1.5 g, 13.2 mmol) of acids (±)-**4** and (±)-**5** in ether (10 mL) was added dropwise to a suspension of $LiAlH_4$ (0.5 g, 13.2 mmol) in ether (60 mL) at 0 °C.[16] The mixture was warmed to room temperature and stirred for 24 h under argon. At that time, the flask was fitted with a reflux condenser and the solution was refluxed for 1.5 h. The solution was cooled to 0 °C and carefully quenched with water (10 mL). The organic layer was removed and the aqueous layer was acidified with 2 N HCl (50 mL). The aqueous layer was then extracted with ether (4 × 40 mL). The combined organic material was dried ($MgSO_4$), filtered, and concentrated by distillation. The residue was purified by column chromatography (silica gel, hexanes:ethyl acetate, 1:9) to give 1.1 g (84%) of *cis*-2-methylcyclobutanemethanol ((±)-**6**) and *trans*-2-methylcyclobutane-methanol ((±)-**7**) as a 40:60 mixture according to analytical GC. Separation of the isomers in pure form was done with preparative GC (1-m, 17% Carbowax, 100 °C). For (±)-**6**:^{1}H NMR δ 3.86−3.72 (m, 1 H), 3.56−3.69 (m, 1 H), 2.42−2.63 (m, 2 H), 1.91−2.17 (m, 2 H), 1.46−1.73 (m, 2 H), 1.11 (br s, 1 H), 1.04 (d, J = 6.86 Hz, 3 H) (compare ref 16); ^{13}C NMR δ 63.6, 39.3, 30.9, 26.5, 21.3, 15.6; MS *m*/*z* (rel intensity) 82 (11), 72 (9), 67 (42), 57 (100), 41 (55), 39 (42). For (±)-**7**: ^{1}H NMR δ 3.60 (br s, 2 H), 1.87−2.18 (m, 4 H), 1.39−1.65 (m, 2 H), 1.47 (br s, 1 H), 1.07 (d, J = 6.31 Hz, 3 H) (compare ref 16); ^{13}C NMR δ 66.7, 45.4, 33.4, 26.4, 21.2, 21.0; MS *m*/*z* (rel intensity) 82 (13), 72 (12), 67 (47), 57 (100), 41 (58), 39 (42).

***cis*-2-Methylcyclobutanecarboxaldehyde ((±)-8) and *trans*-2-Methylcyclobutanecarboxaldehyde ((±)-9).**[17] To a 100-mL flask were added PCC[18] (2.0 g, 9.2 mmol) and dry CH_2Cl_2 (40 mL). A 40:60 mixture (0.6 g, 6.1 mmol) of (±)-**6** and (±)-**7** in CH_2Cl_2 (10 mL) was added dropwise to the PCC solution over 5 h. The reaction mixture was stirred for an additional 2 h at room temperature and then diluted with 40 mL of ether. The brown suspension was filtered through Florisil. The black tar that remained in the flask was washed with ether (3 × 30 mL), the washings were filtered through Florisil, and the Florisil was washed with ether (60 mL). The combined ethereal material was concentrated by distillation to give (±)-**8** and (±)-**9** (0.54 g, 93%, cis/trans 40:60) as a 30% solution in ether according to analytical GC. The aldehydes were separated and purified through preparative GC (1-m, 17% Carbowax, 78 °C). (±)-**8**: ^{1}H NMR δ 9.87 (d, J = 2.47 Hz, 1 H), 3.14−3.27 (m, 1 H), 2.81−2.99 (m, 1 H), 2.35−2.50 (m, 1 H), 2.14−2.28 (m, 1 H), 1.91−2.05 (m, 1 H), 1.58−1.70 (m, 1 H), 1.13 (d, J = 7.13 Hz, 3 H); ^{13}C NMR δ 204.7, 48.8, 33.6, 27.0, 18.0, 17.2; MS *m*/*z* (rel intensity) 98 (2, M$^+$), 83 (23), 69 (58), 57 (92), 55 (44), 42 (71), 41 (100), 39 (69). (±)-**9**: ^{1}H NMR δ 9.70 (d, J = 2.47 Hz, 1 H), 2.54−2.82 (m, 2 H), 1.94−2.20 (m, 3 H), 1.55−1.73 (m, 1 H), 1.16 (d, J = 6.59 Hz, 3 H); ^{13}C NMR δ 196.4, 47.2, 25.8, 20.2, 14.9, 12.1; MS *m*/*z* (rel intensity) 98 (4, M$^+$), 83 (20), 69 (66), 57 (64), 55 (36), 42 (62), 41 (100), 39 (60).

1,1-Diiodoethane was prepared following a literature procedure.[19] The two-step sequence afforded distilled material of bp 60−61 °C (12 mm) (lit.[19] bp 60−61 °C (12 mm)): ^{1}H NMR δ 5.22 (qd, J = 6.58, 1.10 Hz, 1 H), 2.92 (dd, J = 6.58, 1.10 Hz, 3 H) (compare ref 20); ^{13}C NMR δ 38.9, −39.3; MS *m*/*z* (rel intensity) 282 (40, M$^+$), 254 (16), 155 (100), 127 (51).

(15) Jakovac, I. J.; Goodbrand, H. B.; Lok, K. P.; Jones, J. B. *J. Am. Chem. Soc.* **1982**, *104*, 4659−4665.

(16) Hill, E. A.; Chen, A. T.; Doughty, A. *J. Am. Chem. Soc.* **1976**, *98*, 167−170.

(17) Kazanskii, B. A.; Lukina, M. Yu. *Dokl. Akad. Nauk SSSR* **1954**, *94*, 887−889; *Chem. Abstr.* **1955**, *49*, 3030i.

(18) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647−2650.

(19) Friedrich, E. C.; Falling, S. N.; Lyons, D. E. *Synth. Commun.* **1975**, *5*, 33−36.

(20) Neuman, R. C.; Rahm, M. L. *J. Org. Chem.* **1966**, *31*, 1857−1859.

***cis*-(*E*)-Propenyl-2-methylcyclobutane ((±)-10) and *trans*-(*E*)-propenyl-2-methylcyclobutane ((±)-11).**[3,21] To a flame-dried 250-mL round-bottomed flask were added anhydrous $CrCl_2$ (Aldrich, 95%; 5.4 g, 44 mmol) and dry THF (100 mL).[22,23] To the green suspension were added a mixture of aldehydes (±)-**8** and (±)-**9** (0.54 g, 5.6 mmol) and 1,1-diiodoethane (3.2 g, 11.2 mmol) in 18 mL of dry THF. The mixture was stirred for 24 h under argon at room temperature. The olive green solution was quenched with water (200 mL). The dark green aqueous layer was extracted with pentane (4 × 50 mL), and the combined organic material was washed with water (4 × 50 mL), dried ($MgSO_4$), filtered, and concentrated by distillation to give 521 mg (86%, *E*/*Z* 14:1, cis/trans 40:60) of the propenyl-2-methylcyclobutanes as a 7% solution in pentane according to analytical GC. The dominant *E* isomers were separated and obtained in pure form through preparative GC (2.3-m, 20% *ββ*′- oxydipropionitrile (ODPN), 48 °C). (±)-**10**: ^{1}H NMR δ 5.58 (dd, J = 15.37, 7.68 Hz, 1 H), 5.37 (dq, J = 15.37, 6.31 Hz, 1 H), 2.85−2.99 (m, 1 H), 2,38−2.54 (m, 1 H), 1.80−2.12 (m, 3 H), 1.68 (d, J = 6.31 Hz, 3 H), 1.36−1.50 (m, 1 H), 0.96 (d, J = 7.14 Hz, 3 H) (compare ref 3); ^{13}C NMR δ 132.5, 124.6, 40.5, 33.8, 26.3, 24.6, 18.0, 16.4; MS *m*/*z* (rel intensity) 110 (2, M^+), 95 (2), 82 (11), 68 (100), 67 (84), 53 (24), 39 (36). (±)-**11**: ^{1}H NMR δ 5.48 (dd, J = 15.10, 6.86 Hz, 1 H), 5.35 (dq, 15.10, 6.04 Hz, 1 H), 2.24−2.38 (m, 1 H), 1.83−2.13 (m, 3 H), 1.57−1.69 (m, 4 H), 1.32−1.47 (m, 1 H), 1.01 (d, J = 6.59 Hz, 3 H) (compare ref 3); ^{13}C NMR δ 135.4, 123.1, 46.6, 38.0, 26.8, 25.2, 20.4, 17.9; MS *m*/*z* (rel intensity) 110 (3, M^+), 95 (6), 82 (17), 68 (100), 67 (97), 53 (29), 39 (40).

***cis*-3-Cyclobutene-1,2-dicarboxylic anhydride (12)** was prepared from maleic anhydride and acelylene in a 1-L Dewar photochemical reactor following Bloomfield and Owsley.[24] Recrystallization of the crude product from ether gave **12** as white crystals: mp 89−90 °C (lit.[12b] mp 89.5−90 °C); ^{1}H NMR δ 6.49 (d, J = 0.55 Hz, 2 H), 4.05 (d, J = 0.55 Hz, 2 H) (compare ref 12b); ^{13}C NMR δ 167.7, 139.4, 47.7; MS *m*/*z* (rel intensity) 120 (1, M^+), 105 (4), 80 (20), 52 (100).

3-Oxabicyclo[3.2.0]hept-6-en-2-one ((±)-13). Reduction of anhydride **12** with $NaBH_4$ followed by a conventional workup afforded the crude lactone (±)-**13**.[25] Purification by chromatography on silica gel (CH_2Cl_2:ether 98:2) gave 3-oxabicyclo[3.2.0]hept-6-en-2-one (±)-**13**[25,26] as a clear oil (82% yield). A small sample of (±)-**13** was purified by preparative GC (1-m, 10% SE-30, 110 °C): ^{1}H NMR δ 6.31−6.39 (m, 2 H), 4.25−4.36 (m, 2 H), 3.58−3.68 (m, 2 H) (compare ref 25 and 26); ^{13}C NMR δ 175.3, 141.6, 139.2, 68.0, 46.6, 41.9 (compare ref 25); MS *m*/*z* (rel intensity) 110 (34, M^+), 66 (100), 65 (100), 52 (63), 40 (74), 39 (71).

3-Oxabicyclo[3.2.0]heptan-2-one ((±)-14). Catalytic hydrogenation of lactone **(±)-13** (6.23, 55.6 mmol) in ether (70 mL) over 10% Pd/C (≈300 mg) with vigorous stirring for 4 h gave complete reduction, according to analytical GC. The mixture was filtered and concentrated to give a clear oil. Purification on silica gel (CH_2Cl_2:ether, 98:2) gave 3-oxabicyclo-[3.2.0]heptan-2-one (±)-**14**[7,15] as a clear oil (5.63 g, 50.3 mmol, 89%). A small sample of **(±)-14** was further purified by preparative GC (1-m, 10% SE−30, 145 °C): ^{1}H NMR δ 4.32−4.40 (m, 1 H), 4.21−4.28 (m, 1 H), 3.06−3.25 (m, 2 H), 2.34−2.64 (m, 2 H), 2.04−2.23 (m, 2 H) (compare ref 7 and 15); ^{13}C NMR δ 180.8, 74.1, 38.1, 34.3, 25.3, 23.3; MS *m*/*z* (rel intensity) 112 (15, M^+), 85 (10), 67 (100), 55 (48), 53 (41), 39 (49).

***cis*-1-Methoxycarbonyl-2-methylcyclobutane ((±)-1).** To a 100-mL flask were added lactone (±)-**14** (1.17 g, 10.4 mmol) and dry methanol (30 mL). The flask was cooled to −78 °C and anhydrous HBr was bubbled in slowly for 15 min.[7] The reaction mixture was warmed to room temperature and stirred for 3 h. The process of cooling the mixture and bubbling in anhydrous HBr was repeated until the reaction was judged complete by analytical GC. The reaction mixture was then transferred to a separatory funnel, diluted with water (75 mL), and extracted with ether (5 × 25 mL). The combined organic material was then washed with water (2 × 25 mL), dried ($MgSO_4$), filtered, and concentrated to give 1.43 g of the crude *cis*-1-methoxycarbonyl-2-(bromomethyl)-cyclobutane ((±)-**15**):[7] MS *m*/*z* (rel intensity) 127 (51), 95 (34), 87 (70), 67 (54), 55 (68), 41 (100), 39 (60).

To a 100-mL flask were added crude (±)-**15** (1.43 g, 6.9 mmol) and dry HMPA (30 mL).[10] The flask was cooled to 0 °C, and $NaBH_4$ (0.52 g, 18.8 mmol) was added. The mixture was stirred at 0 °C under argon for 1 h and then for 2 h at room temperature. The reaction mixture was cooled to 0 °C and then cautiously quenched with 2 N HCl (30 mL). The contents of the flask were transferred to a separatory funnel, diluted with water (40 mL), and extracted with ether (4 × 25 mL). The combined organic material was washed with water (3 × 25 mL), dried ($MgSO_4$), filtered, and concentrated by distillation. The brown oil that remained was Kugelrohr distilled at 100 mm and 80 °C to give *cis*-1-methoxycarbonyl-2-methylcyclobutane, (±)-**1**,[7] as a clear oil (0.67 g, 5.2 mmol, 50% for the two steps). A small sample of (±)-**1** was further purified by preparative gas chromatography (1-m, 10% SE-30, 80 °C): ^{1}H NMR δ 3.69 (s, 3 H), 3.15−3.27 (m, 1 H), 2.67−2.84 (m, 1 H), 2.29−2.43 (m, 1 H), 1.93−2.20 (m, 2 H), 1.55−1.70 (m, 1 H), 1.03 (d, J = 7.13 Hz, 3 H) (compare ref 3, 7, and 16); ^{13}C NMR δ 174.6, 51.2, 41.7, 32.8, 26.3, 20.2, 17.0; MS *m*/*z* (rel intensity) 128 (2, M^+), 113 (10), 97 (12), 87 (100), 69 (43), 55 (73), 41 (55).

***cis*-2-Methylcyclobutanecarboxylic Acid ((±)-4).** Hydrolysis of ester (±)-**1** (420 mg, 3.3 mmol) in water (20 mL), THF (12 mL), and concentrated H_2SO_4 (2 mL) at reflux for 23 h, followed by a conventional workup, isolation, and Kugelrohr distillation at 80−90 °C (2 mm) gave *cis*-2-methylcyclobutanecarboxylic acid, (±)-**4**,[7] as a clear oil (340 mg, 3.0 mmol, 91%). A small sample of **(±)-4** was further purified by preparative GC (1-m, 17% Carbowax, 140 °C): ^{1}H NMR δ 3.19−3.31 (m, 1 H), 2.22−2.90 (m, 1 H), 2.27−2.41 (m, 1 H), 1.94−2.22 (m, 2 H), 1.58−1.72 (m, 1 H), 1.12 (d, J = 7.13 Hz, 3 H) (compare ref 7); ^{13}C NMR δ 180.3, 41.7, 32.8, 26.2, 19.9, 16.9; MS *m*/*z* (rel intensity) 114 (1, M^+), 99 (8), 86 (11), 73 (100), 68 (26), 55 (30), 42 (45), 41 (40), 39 (32.

Amides 19 and 20. To a 100-mL flask was added a 60% dispersion of NaH (160 mg, 4.0 mmol) in mineral oil. The oil was removed by washing the solid three times with pentane. To the dry solid at 0 °C was added *cis*-2-methylcyclobutanecarboxylic acid ((±)-**4**) (456 mg, 4.0 mmol) in CH_2Cl_2 (30 mL). The mixture was warmed to room temperature and stirred under argon for 15 min. To the white suspension at 0 °C were added DMF (three drops) and oxalyl chloride (524 mg, 4.12 mmol, 0.36 mL). The mixture was then stirred for 30 min at 0 °C and 2 h at room temperature. Analytical GC showed complete conversion of acid (±)-**4** to acid chloride (±)-**17**.

To another 100-mL flask was added a 60% dispersion of NaH (176 mg, 4.4 mmol) in mineral oil. The oil was removed by washing the solid three times with pentane. To the dry solid was added dry THF (30 mL). The flask was cooled to −78 °C and (*R*)-(−)-phenylglycinol **(18)** (604 mg, 4.4 mmol) was added. The mixture was warmed to room temperature and stirred under argon for 15 min. At that time the flask was cooled to −78 °C and TMSCl (480 mg, 4.4 mmol, 0.56 mL) was added via a syringe. The mixture was warmed to room temperature and stirred for 2 h. The solvent was then removed under reduced pressure and CH_2Cl_2 (30 mL) and 1,8-bis(dimethylamino)naphthalene Proton Sponge; 1.2 g, 5.6 mmol) were added to the TMS-protected alcohol. The flask was cooled to −78 °C and the acid chloride **(±)-17** was added dropwise over 30 min. The mixture was allowed to warm slowly to room temperature and it was stirred for an additional 4 h. At that time, 2 N HCl (25 mL) was added and the acidic solution was

(21) Bartlett, P. D.; Schueller, K. E. *J. Am. Chem. Soc.* **1968**, *90*, 6071−6077.
(22) Okazoe, T.; Takai, K.; Utimoto, K. *J. Am. Chem. Soc.* **1987**, *109*, 951−953.
(23) Getty, S. J.; Berson, J. A. *J. Am. Chem. Soc.* **1991**, *113*, 4607−4621.
(24) Bloomfield, J. J.; Owsley, D. C. *Organic Photochemical Syntheses*; Wiley: New York, 1976; Vol 2, pp 36−40.
(25) Mévellec, L.; Evers, M.; Huet, F. *Tetrahedron* **1996**, *52*, 15103−15116.
(26) Binns, F.; Hayes, R.; Hodgetts, K. J.; Saengchantara, S. T.; Wallace, T. W.; Wallis C. J. *Tetrahedron* **1996**, *52*, 3631−3658.

stirred vigorously for 1 h. The contents of the flask were transferred to a separatory funnel, the aqueous layer was removed, and the organic layer was washed with 2 N HCl (2 × 20 mL). The combined aqueous material was back-extracted with CH_2Cl_2 (20 mL). The combined organic material was washed with saturated $NaHCO_3$ (20 mL), dried ($MgSO_4$), filtered, and concentrated to give 760 mg of an off white solid. Column chromatrography (silica gel, ethyl acetate/hexanes, 60:40) gave 700 mg of **19** and **20** as a white solid. It was dissolved in 35 mL of ethyl acetate:isooctane (65:35).

The amides **19** and **20** were separated by preparative HPLC using a Machery-Nagel 20-mm × 25-cm Nucleosil 50-5 column with ethyl acetate:isooctane (65:35) at a flow of 16 mL/min and a Rainin system based on two Rainin Rabbit HBX pumping units with a Gilson 112 UV/VIS detector inferfaced with an Apple Macintosh Plus computer. Three fractions were collected with a combined weight of 600 mg (Fr 1 270 mg, Fr 2 100 mg, Fr 3 230 mg, 64% yield). Fraction 2 was chromatographed again. Fraction 1 contained 300 mg of pure amide **19**: ^{1}H NMR δ 7.24−7.40 (m, 5 H), 6.15 (br d, J = 6.32 Hz, 1 H, NH), 5.01−5.12 (m, 1 H), 3.76−3.93 (m, 2 H), 3.17 (br t, J = 5.49 Hz, 1 H, OH), 3.01−3.13 (m, 1 H), 2.62−2.80 (m, 1 H), 2.26−2.42 (m, 1 H), 1.83−2.20 (m, 2 H), 1.54−1.69 (m, 1 H), 1.10 (d, J = 7.13 Hz, 3 H); ^{13}C NMR δ 173.8, 139.2, 128.8, 127.8, 126.7, 66.7, 55.9, 42.9, 32.7, 26.1, 20.1, 16.5; mp 138−139 °C. Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.06; H, 8.21; N, 6.01. Found: C, 72.29; H, 8.44; N, 5.89. The structure of **19** was established by X-ray crystallography.[14] Fraction 3 contained amide **20** and a small amount of amide **19** (3%); it was chromatrographed a second time to give 295 mg of pure amide **20**: ^{1}H NMR δ 7.24−7.39 (m, 5 H), 6.16 (br d, J = 6.58 Hz, 1 H, NH), 5.12−5.20 (m, 1 H), 3.80−3.88 (m, 2 H), 3.39 (br t, J = 5.76 Hz, 1 H, OH), 3.04−3.16 (m, 1 H), 2.61−2.79 (m, 1 H), 2.28−2.43 (m, 1 H), 1.91−2.18 (m, 2 H), 1.53−1.67 (m, 1 H), 0.99 (d, J = 7.14 Hz, 3 H); ^{13}C NMR δ 174.1, 139.2, 128.8, 127.8, 126.8, 66.7, 56.0, 43.0, 32.9, 26.1, 20.2, 16.5; mp 140−141 °C. Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.06; H, 8.21; N, 6.01. Found: C, 72.25; H, 8.47; N, 5.88.

(+)-*cis*-1-Methoxycarbonyl-2-methylcyclobutane ((1*R*,2*S*)-(+)-1). To a 25-mL round-bottomed flask were added chiral amide **19** (40 mg, 0.17 mmol; fraction 1 above), water (4 mL), THF (3 mL), and concentrated H_2SO_4 (0.3 mL). The mixture was stirred for 48 h at 75 °C. The mixture was then diluted with water (5 mL) and the aqueous layer was extracted with ether (6 × 10 mL). The combined organic material was dried ($MgSO_4$), filtered and concentrated by distillation. A sample purified by preparative GC (1-m 17% Carbowax column; 170 °C) gave (1*R*,2*S*)-(+)-**4**; $[\alpha]_D$ +91 (*c* 0.12, $CHCl_3$). The acid was treated with CH_2N_2 (5 mL) and then allowed to stand at room temperature for 12 h. The solution was concentrated by distillation to give (+)-*cis*-1-methoxycarbonyl-2-methylcyclobutane, (1*R*,2*S*)-(+)-**1**, of better than 99% ee by GC on a 10-m G-TA γ-cyclodextrin (octakis(2,6-di-*O*-pentyl-3-trifluoroacetyl)-γ-cyclodextrin) column (Astec). A small sample was further purified by preparative gas chromatography (1.5-m, 10% SE−30, 60 °C): (1*R*,2*S*)-(+)-**1** had a specific rotation $[\alpha]_D$ +58 (*c* 0.25, $CHCl_3$).

(−)-*cis*-1-Methoxycarbonyl-2-methylcyclobutane((1*S*,2*R*)-(−)-1). Amide **20** (40 mg, 0.17 mmol, fraction 3) was hydrolyzed as described above to give *cis*-2-methylcyclobutanecarboxylic acid **(1*S*,2*R*)−(−)-4**; a preparative GC purified sample had $[\alpha]_D$ −88 (*c* 0.28, $CHCl_3$). The acid was treated with ethereal CH_2N_2 and then allowed to stand at room temperature for 12 h. The solution was concentrated by distillation to give (1*S*,2*R*)-(−)-**1**, of better than 99% ee by chiral GC. A small sample of (1*S*,2*R*)-(−)-**1**, further purified by preparative GC, had $[\alpha]_D$ −63 (*c* 0.26, $CHCl_3$).

Acknowledgment. We thank the National Science Foundation for supporting this work through grants CHE-9532016 and CHE-9902184.

Supporting Information Available: Copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0009550