triethyl phosphonoacetate (2.4 g, 8 mmol) in toluene (10 mL) with a syringe at 0 °C. After 30 min of stirring, the aldehyde (vide supra) (1.3 g, 6 mmol) was added at 0 °C, the reaction mixture was stirred for 2.5 h at room temperature, and then the mixture was quenched with saturated NH_4Cl solution. Oily materials were extracted with ethyl acetate. After removing the solvent, the crude product obtained was mixed with methanol (15 mL) and *p*-toluenesulfonic acid (10 mg), stirred for 24 h at room temperature, and subsequently worked up. The product was purified by silica gel to give the γ-fluoro-γ-methyl-δ-hydroxy-α,β-unsaturated esters.

Erythro isomer (R = Me): $[\alpha]^{24}_D$ −8.17° (*c* 1.25; MeOH). ^{19}F NMR ($CDCl_3$): 80 (ddqq) ppm. ^1H NMR ($CDCl_3$): δ 1.16 (CH_3CHOH, dd, J_{CH_3-CH} = 6.5, J_{CH_3-F} = 1.2 Hz), 1.30 (CH_3CH_2, t, $J_{CH_3-CH_2}$ = 7.2 Hz), 1.43 (CH_3CF, d, J_{CH_3-F} = 21 Hz), 3.00 (OH), 4.00 (CH, dq, J_{H-F} = 22.6 Hz), 4.16 (CH_3CH_2, q), 5.96 (CH=, d, $J_{H-H_{trans}}$ = 16.5 Hz), 6.86 (=CHCF, dd, J_{H-F} = 21 Hz).

Threo isomer (R = Me): $[\alpha]^{24}_D$ +8.34° (*c* 1.24; MeOH). ^{19}F NMR ($CDCl_3$): 78.5 (ddqq) ppm. ^1H NMR ($CDCl_3$): δ 1.13 (CH_3CHOH, dd, J_{CH_3-CH} = 6.6, J_{CH_3-F} = 1.2 Hz, 1.30 (CH_3CH_2, t, $J_{CH_3-CH_2}$ = 7.2 Hz), 1.45 (CH_3CF, f, J_{CH_3-F} = 22.4 Hz), 3.10 (OH), 4.00 (CH, dq, J_{H-F} = 13.7 Hz), 4.14 (CH_3CH_2, q), 6.00 (=CH, d, $J_{H-H_{trans}}$ = 16.2 Hz), 6.88 (=CHCF, dd, J_{H-F} = 21.6 Hz).

Erythro isomer (R = Ph): $[\alpha]^{24}_D$ +8.00° (*c* 0.92; MeOH). ^{19}F NMR ($CDCl_3$): 76 (ddq) ppm. ^1H NMR ($CDCl_3$): δ 1.20 (CH_3CH_2, t, $J_{CH_3-CH_2}$ = 7.2 Hz), 1.34 (CH_3CF, d, J_{CH_3-F} = 21 Hz), 3.30 (OH), 4.10 (CH_3CH_2, q), 4.97 (CH, d, J_{H-F} = 12 Hz), 5.91 (CH=, d, $J_{H-H_{trans}}$ = 15 Hz), 6.83 (=CHCF, dd, J_{H-F} = 19.5 Hz), 7.20 (Ar H).

Threo isomer (R = Ph): $[\alpha]^{24}_D$ −41.5° (*c* 1.20; MeOH). ^{19}F NMR ($CDCl_3$): 77 (ddq) ppm. ^1H NMR ($CDCl_3$): δ 1.20 (CH_3CH_2, t, $J_{CH_3-CH_2}$ = 7.5 Hz), 1.40 (CH_3CF, d, J_{CH_3-F} = 21.0 Hz), 3.32 (OH), 4.10 (CH_3CH_2, q), 4.67 (CH, d, J_{H-F} = 12.0 Hz), 5.90 (CH=, d, $J_{H-H_{trans}}$ = 15.0 Hz), 6.80 (=CHCF, dd, J_{H-F} = 21.0 Hz), 7.27 (Ar H).

(d) *O*-Carbamates of δ-Hydroxy-α,β-unsaturated Esters. Into a solution of chlorosulfonyl isocyanate (0.87 g, 8 mmol) and methylene chloride (20 mL) was added (−)-δ-hydroxy-α,β-unsaturated ester (4.6 mmol) at −78 °C, and then the mixture was allowed to warm to room temperature. After 30 min of stirring, water was added and then the whole was heated at 70 °C for 5 h. Oily materials were extracted with ethyl acetate, the extract was dried over anhydrous magnesium sulfate, and the solvent was removed. The *O*-carbamate was purified by column chromatography using *n*-hexane–ethyl acetate (5:1).

Erythro isomer (R = Me): $[\alpha]^{24}_D$ +6.36° (*c* 1.09; MeOH). ^{19}F NMR ($CDCl_3$): 81 (ddqq) ppm. ^1H NMR ($CDCl_3$): δ 1.26 (CH_3CHOH, dd, J_{CH_3-CH} = 6.6, J_{CH_3-F} = 1.0 Hz), 1.32 (CH_3CH_2, t, $J_{CH_3-CH_2}$ = 7.0 Hz), 1.45 (CH_3CF, d, J_{CH_3-F} = 21.7 Hz), 4.22 (CH_3CH_2, q), 4.90 (CH, dq, J_{H-F} = 21.4 Hz), 4.98 (NH_2), 6.10 (CH=, d, $J_{H-H_{trans}}$ = 15.9 Hz), 6.90 (=CHCF, dd, J_{H-F} = 20.4 Hz).

Threo isomer (R = Me): $[\alpha]^{24}_D$ +18.9° (*c* 1.12; MeOH). ^{19}F NMR ($CDCl_3$): 79 (ddqq) ppm. ^1H NMR ($CDCl_3$): δ 1.29 (CH_3CHOH, dd, J_{CH_3-H} = 6.6, J_{CH_3-F} = 1.0 Hz), 1.33 (CH_3CH_2, t, $J_{CH_3-CH_2}$ = 7.2 Hz), 1.50 (CH_3CF, d, J_{CH_3-F} = 21.7 Hz), 4.21 (CH_3CH_2, q), 4.91 (CH, dq, J_{H-F} = 12.6 Hz), 5.04 (NH), 6.10 (=CH, d, $J_{H-H_{trans}}$ = 15.9 Hz), 6.90 (=CHCF, dd, J_{H-F} = 20.9 Hz).

Erythro isomer (R = Ph): $[\alpha]^{24}_D$ −10.7° (*c* 1.12; MeOH). ^{19}F NMR ($CDCl_3$): 75.5 (ddq) ppm. ^1H NMR ($CDCl_3$): δ 1.25 (CH_3CH_2, t, $J_{CH_3-CH_2}$ = 7.2 Hz), 1.43 (CH_3CF, d, J_{CH_3-F} = 21.6 Hz), 4.17 (CH_3CH_2, q), 4.96 (NH_2), 5.73 (CH=, d, $J_{H-H_{trans}}$ = 15.6 Hz), 5.95 (CH, d, J_{H-F} = 16.2 Hz), 6.92 (=CHCF, dd, J_{H-F} = 20.3 Hz), 7.31 (Ar H).

Threo isomer (R = Ph): $[\alpha]^{24}_D$ −31.4° (*c* 1.02; MeOH). ^{19}F NMR ($CDCl_3$): 79.5 (ddq) ppm. ^1H NMR ($CDCl_3$): δ 1.26 (CH_3CH_2, t, $J_{CH_3-CH_2}$ = 7.0 Hz), 1.43 (CH_3CF, d, J_{CH_3-F} = 21.5 Hz), 4.17 (NH_2), 6.01 (CH, d, J_{H-F} = 13.2 Hz), 5.71 (CH=, d, $J_{H-H_{trans}}$ = 16.5 Hz), 6.91 (=CHCF, dd, J_{H-F} = 21.5 Hz), 7.34 (Ar H).

(e) Cyclic Carbamate. A mixture of the *O*-carbamate (1 mmol) and potassium *tert*-butoxide (1.1 mmol) in tetrahydrofuran (3 mL) was stirred for 5 min at 0 °C and the mixture was quenched with water. Oily materials were extracted with diethyl ether, and the product was isolated after workup.

Asymmetric Microbial Reduction of Prochiral 2,2-Disubstituted Cycloalkanediones

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Asymmetric microbial reduction of a series of 2,2-disubstituted 1,3-cycloalkanediones with bakers' yeast was examined as an example of an enzyme-catalyzed distinction of a substrate containing two trigonal carbonyl centers with stereoheterotropic faces and one prochiral tetrahedral carbon center where monoreduction generates two chiral centers. Synthetically useful yeast-mediated reductions were achieved for cyclopentanoid and cyclohexanoid diones with a variety of substituents at C2 providing chiral intermediates for enantioselective syntheses. For each case studied, the ketol products had >98% ee, and the hydroxy configuration was consistently of the *S* configuration. For the cyclopentanoids, the major product of yeast reduction was the (2*S*,3*S*) diastereomer, whereas for the cyclohexanoids, the major product was the (2*R*,3*S*) diastereomer. The relative stereoselectivity of the yeast-mediated reduction of each substrate was compared with that of reduction with $NaBH_4$.

The discovery and development of applications of enzyme-catalyzed processes to effect asymmetric reactions on synthetic substrates to provide optically pure intermediates for enantioselective syntheses is an alternative complementary strategy to methods involving resolution of racemates, chiral pool templates, and asymmetric synthetic reagents.[1] The organic chemist can consider microorganisms as a microscopic reaction vessel containing numerous enzymes complete with cofactors that can potentially react with a synthetic substrate. However, most enzymes have specific requirements for substrate binding and catalytic activity that limits the versatility of this approach as compared with a synthetic reagent that offers a wider range of substrate opportunities. This lack of

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(1) For pertinent reviews of this topic, refer to: (a) *Enzymes in Organic Synthesis*; Ciba Foundation Symposium 111; Pitman: London, 1985. (b) Whitesides, G. M.; Wong, C. H. *Aldrichimica Acta* **1983**, *16*, 27. (c) Sih, C. J.; Rosaza, J. P. In *Applications of Biochemical Systems in Organic Chemistry*; Jones, J. B., Sih, C. J., Perlman, D., Eds.; Wiley: New York, 1976; Part I, Chapter III. (d) Kieslich, K. *Microbial Transformations of Chemical Compounds Excluding Steroids and Noncyclic Structures*; G. Thieme Verlag: Stuttgart, 1976.

0022-3263/87/1952-3223$01.50/0

Scheme I. Asymmetric Monoreduction

generality of enzyme-catalyzed processes is exchanged for the following advantages. Enzymes can catalyze chemoselective transformations of multifunctional compounds. Since enzymes provide a chiral environment, asymmetric reactions are common. Enzymatic reactions occur under mild conditions. The use of microorganisms as the source of enzymes for synthetic applications offers the following additional advantages. The microorganism can be cultured, and hence the "biological reagent" is available for small- or large-scale reactions. The enzymes in a microorganism are "stabilized" by virtue of their "natural environment", and no special techniques to supply cofactors or to maintain activity are required, other than keeping the cells viable. The fact that microorganisms contain numerous enzymes provides the opportunity to effect multiple reactions on a given substrate, and this can be both an advantage or disadvantage for a given circumstance. Also, microorganisms contain a bank of inducible enzymes that may be activated in various ways to provide a transformation. Microbial reactions can be influenced by the addition of enzyme inhibitors,[2] cell immobilization,[3] and culture conditions[6q] to the extent of inducing enzyme activity or increasing the selectivity of transformations. Fermentation technology has provided commercial processes for the preparation of pharmaceuticals and other chemicals.[4]

The development of applications of microbial transformations in organic synthesis can proceed with two distinct strategies: (1) *substrate selection*, involving the discovery of new subtrates that undergo enzyme-catalyzed reactions with a given type of microorganism and establishment of the scope and limitations of substrate analogues; (2) *microorganism selection*, involving the screening and selection of microorganisms that will accomplish a desired trasnformation on a given substrate. We utilized the first type of strategy and chose common bakers' yeast (*Saccharomyces cerevisiae*) as the microorganism to study. Bakers' yeast is readily available in a dry active form[5] and is known to contain a variety of enzymes capable of reducing a wide variety of carbonyl-containing compounds. Asymmetric microbial reduction of carbonyl-containing substrates with bakers' yeast is a useful method for obtaining optically active secondary hydroxy compounds, and new examples continue to appear.[6]

The ability of certain enzymes to (1) differentiate stereoheterotropic faces of a trigonal atom such as the carbon of a carbonyl function or (2) distinguish two enantiotopic homomorphic groups attached to a prochiral center can lead to asymmetric transformations resulting in enantiomerically pure products from an achiral substrate. A structure that provides the opportunity for both of these distinctions would be an interesting substrate for investigation. Prochiral 2,2-disubstituted cycloalkanediones offer two trigonal carbonyl centers with stereoheterotopic faces and one prochiral tetrahedral carbon center. Enzyme-catalyzed asymmetric monoreduction of this type of substrate generates two chiral centers (Scheme I). Previous work involving microbial applications for steroid syntheses[7] fully substantiated examples of this type of asymmetric monoreduction with a variety of microorganisms. It was our intent to first establish whether common bakers' yeast could efficiently effect similar reduction of prochiral 2,2-disubstituted cycloalkanediones and then survey the scope of this method for various substrates and identify structural elements that control the stereoselectivity and enantioselectivity of the yeast-mediated reduction.[8] Another objective was to integrate these microbial transformations into synthetic strategies for enantiospecific syntheses of natural product targets.

Results and Discussion

Yeast-Mediated Reduction of 2,2-Disubstituted 1,3-Cyclopentanediones. A variety of readily accessible substrates **2**–**8** derived from 2-methyl-1,3-cyclopentanedione (**1**) were chosen to examine the influence of substrate modifications on the course and stereoselectivity of the enzyme-catalyzed reduction mediated by bakers' yeast. Alkylation of **1** with allyl bromide[9] and propargyl bromide provided the diones **3** and **4**, respectively. Catalytic hydrogenation of **3** gave the propyl dione **2**. The diones **5**–**8** were prepared by alkylation of **1** with excess 3-chloro-2-methylpropene, acrylonitrile, methyl bromoacetate, and methyl acrylate in triethylamine at reflux for 16 h. A standard procedure as given in the Experimental Section was used for the incubation of the diones **2**–**8** in a growing bakers' yeast culture (*S. cerevisiae*) in order to compare differences in enzymatic reduction resulting from the structural variations of the substrates. In each case, the major product of the yeast reduction was the monoreduced ketol product. The results of the yeast-medi-

(2) Lanzilotta, R. P.; Bradley, D. G.; Beard, C. C. *Appl. Microbiol.* **1975**, *29*, 427.

(3) Nakamura, K.; Higaki, M.; Ushio, K.; Oka, S.; Ohno, A. *Tetrahedron Lett.* **1985**, 4213.

(4) (a) Stodola, F. H. *Chemical Transformations by Microorganisms*; Wiley: New York, 1958. (b) Charney, W.; Herzog, H. L. *Microbial Transformations of Steroids*; Academic: New York, 1967. (c) Leuenberger, H. G. W. In *Antibiotics and Other Secondary Metabolites: Biosynthesis and Production*; Academic: New York, 1978.

(5) The type of bakers' yeast used in these studies was Fleischmann's active dry yeast for baking, Standard Brands Inc.

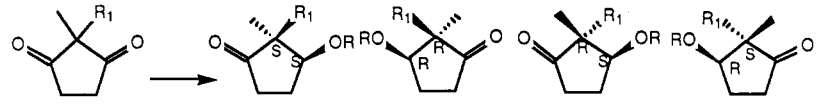
(6) For typical examples of synthetically useful yeast reductions of carbonyl-containing compounds, see: (a) Neuberg, C. *Adv. Carbohyd. Chem.* **1949**, *4*, 75. (b) Lemieux, R. U.; Giguere, J. *Can. J. Chem.* **1951**, *29*, 678. (c) MacLeod, R.; Prosser, H.; Fikentscher, L.; Lanyi, J.; Mosher, H. S. *Biochemistry* **1964**, *3*, 838. (d) Deol, B. S.; Ridley, D. D.; Simpson, G. W. *Aust. J. Chem.* **1976**, *29*, 2459. (e) Akita, H.; Furuichi, A.; Koshiji, H.; Horikoshi, K.; Oishi, T. *Tetrahedron Lett.* **1982**, 4051. (f) Zhou, B.; Gopalan, A. S.; VanMiddlesworth, F.; Shieh, W. R.; Sih, C. J. *J. Am. Chem. Soc.* **1983**, *105*, 5925. (g) Hirama, M.; Shimizu, M.; Iwashita, M. *J. Chem. Soc., Chem. Commun.* **1983**, 599. (h) Zuger, M. F.; Giovannini, F.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 1012. (i) Sih, C. J.; Chen, C.-S. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 570. (j) Seebach, D.; Renaud, P.; Schweizer, W. B.; Zuger, M. F.; Brienne, M. J. *Helv. Chim. Acta* **1984**, *67*, 1843. (k) Nakamura, K.; Ushio, K.; Oka, S.; Ohno, A. *Tetrahedron Lett.* **1984**, *3979*. (l) Fuganti, C.; Grasselli, P.; Gasati, P.; Carmeno, M. *Tetrahedron Lett.* **1985**, 101. (m) Mori, K.; Mori, H.; Sugai, T. *Tetrahedron* **1985**, *41*, 919. (n) Utaka, M.; Watabu, H.; Takeda, A. *Chem. Lett.* **1985**, 1475. (o) Tsuboi, S.; Nishiyama, E.; Utaka, M.; Takeda, A. *Tetrahedron Lett.* **1986**, 1915. (p) Buisson, D.; Azerad, R. *Ibid.* **1986**, 2631. (q) Ushio, K.; Inouye, K.; Nakamura, K.; Oka, S.; Ohno, A. *Ibid.* **1986**, 2657. (r) Nakamura, K.; Miyai, T.; Nozaki, K.; Ushio, K.; Oka, S.; Ohno, A. *Ibid.* **1986**, 3155. (s) Guanti, G.; Banfi, L.; Narisano, E. *Ibid.* **1986**, 3547. (t) Kozikowski, A. P.; Mugrage, B. B.; Li, C. S.; Felder, L. *Ibid.* **1986**, 4817. (u) Fuganti, C.; Grasselli, P.; Seneci, P. F.; Casati, P. *Ibid.* **1986**, *5275*. (v) Hirama, M.; Nakamine, T.; Ito, S. *Ibid.* **1986**, 5281. (w) Itoh, T.; Yonekawa, Y.; Sato, T.; Fujisawa, T. *Ibid.* **1986**, 5405. (x) Kitazume, T.; Nakayama, Y. *J. Org. Chem.* **1986**, *51*, 2795. (y) Seebach, D.; Eberle, M. *Synthesis* **1986**, 37.

(7) Gibian, H.; Kieslich, K.; Koch, H. J.; Kosmol, H.; Rufor, C.; Schroder, E.; Vossing, R. *Tetrahedron Lett.* **1966**, 2321.

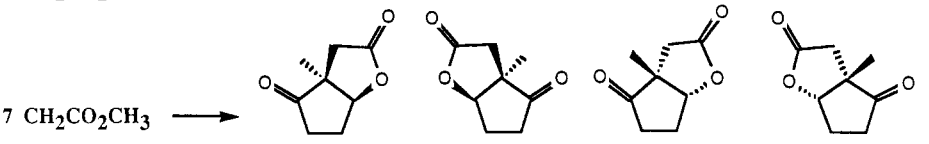
(8) Some aspects of this work have been previously communicated: (a) Brooks, D. W.; Grothaus, P. G.; Irwin, W. L. *J. Org. Chem.* **1982**, *47*, 2820. Note that the structurers for compounds **3**, **6**, and **9** reported in this communication were incorrectly shown, and they should be the corresponding enantiomers with the (2*R*,2*S*) configuration. (b) Brooks, D. W.; Mazdiyasni, H., Chakrabarti, S. *Tetrahedron Lett.* **1984**, 1241.

(9) The procedure reported by Newman, M. S.; Manhart, J. H. *J. Org. Chem.* **1961**, *26*, 2113, was optimized.

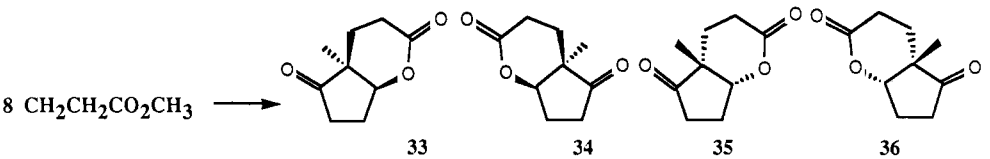
Table I. Reduction of 2,2-Disubstituted 1,3-Cyclopentanediones



R_1				
2 $CH_2CH_2CH_3$	9	10	11	12
3 $CH_2CH{=}CH_2$	13	14	15	16
4 $CH_2C{\equiv}CH$	17	18	19	20
5 $CH_2C(CH_3){=}CH_2$	21	22	23	24
6 $CH_2CH_2C{\equiv}N$	25	26	27	28



7 $CH_2CO_2CH_3$ → 29 30 31 32



8 $CH_2CH_2CO_2CH_3$ → 33 34 35 36

entry	dione	reactn[a]	ketol products (% compn)	yield,[b] %	rec dione, %
1	**2**	A	**9** (100)	60	30
2	**2**	B	**9, 10**; **11, 12** (85, 15)	70	10
3	**3**	A	**13**; **15** (90, 10)	75	15
4	**3**	B	**13, 14**; **15, 16** (75, 25)	75	5
5	**4**	A	**17**; **19** (67, 33)	60	25
6	**4**	B	**17, 18**; **19, 20** (67, 33)	60	10
7	**5**	A	**21** (100)	75	10
8	**5**	B	**21, 22**; **23, 24** (85, 15)	77	5
9	**6**	A	**25**; **27** (96, 4)	71	9
10	**6**	B	**25, 26**; **27, 28** (50, 50)	60	20
11	**7**	A	**29** (100)	9	80
12	**7**	B			
13	**8**	A	**33** (100)	52	25
14	**8**	B	**33, 34**; **35, 36** (90, 10)	59	33

[a] A = bakers' yeast, B = 1 equiv of $NaBH_4$. [b] The yield reported for the yeast reductions is percent of product isolated not subtracting recovered starting material and represents the amount of product isolated with a standard fermentation procedure and not one optimized for that substrate.

Table II. γ Steric Compression Effect in Cyclopentane Ketols

	^{13}C NMR chemical shifts (δ from Me_4Si)							
ketol	**9**	**11**	**13**	**15**	**17**	**19**	**21**	**23**
CH_3	19.2	15.0	19.7	15.0	19.8	15.1	19.9	14.2
CH_2 (C6)	32.3	37.6	34.0	39.8	20.8	24.9	38.1	43.0

ated reductions are summarized in Table I along with the results of reduction of the same diones with 1 equiv of $NaBH_4$ for comparison of relative stereoselectivity.

The enantiomeric composition of the microbial products was determined by analysis of the ^1H NMR spectra of the corresponding (*R*)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA) esters.[10] The corresponding (*R*)-MTPA esters **9a–36a** of the racemic ketols **9–36** derived from $NaBH_4$ reduction were used as control standards. In each case the methyl group at C2 of the MTPA esters was clearly resolved. *For all the examples studied the enantiomeric purity of the microbial products was in excess of 98%.*[11]

The relative configurations of the ketols were apparent by ^{13}C NMR analysis. A substantial shielding was observed for the methyl signal of the minor isomer due to a γ steric compression effect[12] of the syn hydroxyl group. A similar shielding effect was observed for the C6 methylene signal syn to the hydroxyl group for the major isomer. The consistency of this observation is evident for each example as shown in Table II.

Monoreduction of the diones **2–8** can potentially result in a diastereomeric pair of enantiomers. It is interesting to compare the products resulting from enzyme-catalyzed reduction with those of chemical reduction with 1 equiv of sodium borohydride. In general, the yeast-mediated reduction was more stereoselective than sodium borohydride reduction for all the cyclopentanediones studied. For the series propyl, allyl, and propynyl there was a similar trend of decreased stereoselectivity. This may reflect a distinction based on the size of the substituents at C2, R group vs. CH_3. This premise can be used to improve the stereoselectivity as demonstrated for the dione **5** containing a larger methallyl group that is reduced by yeast with complete stereoselectivity, while the corresponding allyl dione **3** gave a 90:10 mixture of diastereomers. The nitrile

(10) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.

(11) A control experiment established a practical limit of detection of 1.5% of diastereomer in the ^1H NMR of (+)-MTPA esters at 470 MHz.

(12) Grant, D. M.; Cheney, B. V. *J. Am. Chem. Soc.* **1967**, *89*, 5315.

6 and ester 8 were also reduced stereoselectively. The ester 7 was a noticeably poorer substrate, being converted to the lactone 29 in only 9% yield under the standard fermentation conditions used. Also, it was interesting to observe that sodium borohydride reduction of ester 7 did not provide any lactone products after aqueous acidic workup. Lactones 31 and 32 are not known, and models indicate they are highly strained and therefore may not be stable as such but rather likely exist in the hydroxy acid form.

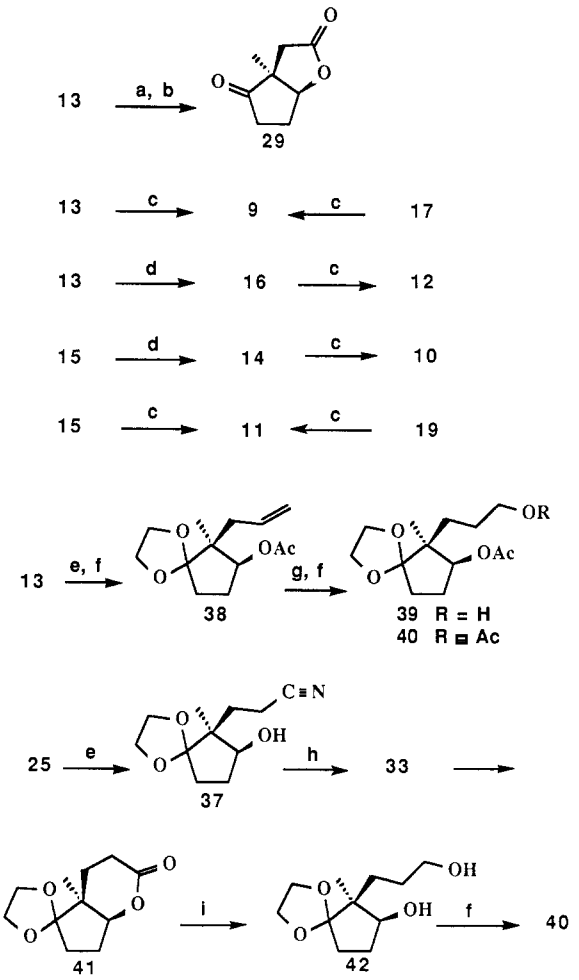
The yield reported in Table I represents the amount of ketol products isolated not subtracting recovered starting material. The conditions of the yeast reduction were kept standard for each substrate in order to observe any effects of structural changes on conversion efficiency. The remaining mass consisted of unreacted dione and small amounts of diol products (<5%). In this study, attempts to optimize various parameters such as temperature, pH, and added nutrients to improve the yeast reduction conversions were not investigated. Yeast reduction for the various cyclopentanediones substrates provided synthetically useful conversions to chiral products except for the ester 7. The diastereomeric ketols could be separated by chromatography on silica gel. From these result it appears that yeast reduction of various 2,2-disubstituted cyclopentanediones has considerable scope for substrate variations at the C2 position.

Determination of Absolute Configuration of Cyclopentanoid Ketols. The absolute configurations of the chiral yeast products were established as outlined in Scheme II and are described as follows. The allyl ketol 13 was transformed to the known (2*S*,3*S*)-lactone 29[13] in 60% overall yield by ozonolysis and subsequent oxidation with Jones' reagent.[14] The ketols 13 and 17 were catalytically hydrogenated to provide 9. After several trial reactions,[15] a suitable method was found to cleanly epimerize the hydroxy group of the allyl ketol 13 that involved treatment of the corresponding tosylate with excess potassium nitrite in dimethylformamide[16] followed by an aqueous workup to provide 16, which was catalytically reduced to 12. Epimerization of 15 by the above procedure gave 14, which was catalytically reduced to 10. Thus, all possible compounds of the enantiomeric diastereomeric pair of monoreduced ketols 9–16 were accessible. The absolute configuration of the ketol 21 was established by subsequent elaboration to the known bicyclo enedione 45.[17]

The previously correlated allyl ketol 13 was converted to the corresponding ketal acetate 38, and hydroboration–oxidation gave the alcohol 39, which was converted to the diacetate 40, the correlation standard. The nitrile 25 was converted to the corresponding ketal 37, which was subjected to saponification, and subsequent acid treatment gave the lactone 33. The lactone 33 was converted to the corresponding ketal 41, and reduction with lithium aluminum hydride gave the diol 42, which was converted to the diacetate 40, thus completing the correlation sequence.

Yeast-Mediated Reduction of 2,2-Disubstituted 1,3-Cyclohexanediones. We further investigated the yeast reduction of an analogous series of substituted cyclohexanediones in order to evaluate the generality of this

Scheme II. Correlation of Absolute Configuration and Interconversions of Cyclopentanoids[a]



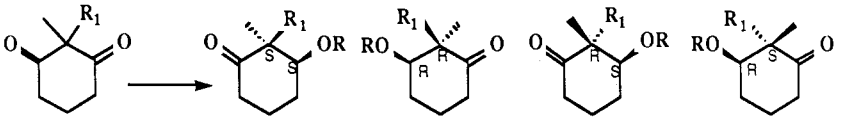
[a] Reagents: (a) O_3, CH_2Cl_2, py, −78 °C; (b) $HCrO_3$, acetone, 0 °C; (c) H_2, ethanol, PtO_2 catalyst; (d) KNO_2, DMF, 85 °C; aqueous HCl; (e) ethylene glycol, trimethyl orthoformate, TsOH catalyst; (f) Ac_2O, py; (g) BH_3/THF; aqueous H_2O_2, NaOH; (h) NaOH; aqueous HCl; (i) $LiAlH_4$, THF.

strategy to provide chiral intermediates for synthesis. A variety of readily accessible substrates 50–55 derived from 2-methyl-1,3-cyclohexanedione (49) were prepared as follows. Alkylation of 49 with allyl bromide and propargyl bromide provided the diones 51 and 52, respectively. Catalytic hydrogenation of 51 gave the propyl dione 60. The diones 53–55 were prepared by alkylation of 49 with excess 3-chloro-2-methylpropene, acrylonitrile, and methyl acrylate in triethylamine at reflux for 16 h. The same standard procedure used for the cyclopentanediones as given in the Experimental Section was used for the incubation of the diones 50–55 with bakers' yeast in order to compare the enzymatic reduction of the two series. The results of the yeast-mediated reductions are summarized in Table III along with the results of reduction of the same diones with 1 equiv of $NaBH_4$ for comparison of relative stereoselectivity.

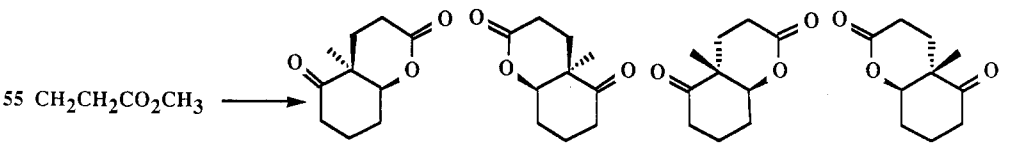
The enantiomeric compositionof the microbial products was determined, as before, by analysis of the ^1H NMR spectra of the corresponding (*R*)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA) esters, and the (*R*)-MTPA esters of the racemic ketols derived from $NaBH_4$ reduction were used as control standards. The methyl group at C2 was clearly resolved for each diastereomeric MTPA derivative. *The enantiomeric purity of the microbial ketol products was consistently >98%.*

(13) Schwarz, S.; Carl, C.; Schick, H. *Z. Chem.* **1978**, *18*, 401.
(14) Bowers, A.; Halsall, T. G.; Jones, E. R. H.; Lemin, A. J. *J. Chem. Soc.* **1953**, 2555.
(15) The following methods gave very low yields of the desired epimeric alcohol: (a) Cooper, E. L.; Yankee, E. W. *J. Am. Chem. Soc.* **1974**, *96*, 5875. (b) Bose, A. K.; Lal, B.; Hoffman, W. A.; Manhas, M. S. *Tetrahedron Lett.* **1973**, 1619.
(16) Raduchel, B. *Synthesis* **1980**, 292.
(17) Brooks, D. W.; Woods, K. W. *J. Org. Chem.* **1987**, *52*, 192.

Table III. Reduction of 2,2-Disubstituted 1,3-Cyclohexanediones



R_1	57	58	59	60
50 $CH_2CH_2CH_3$				
51 $CH_2CH{=}CH_2$	61	62	63	64
52 $CH_2C{\equiv}CH$	65	66	67	68
53 $CH_2C(CH_3){=}CH_2$	69	70	71	72
54 $CH_2CH_2C{\equiv}N$	73	74	75	76



55 $CH_2CH_2CO_2CH_3$

77 78 79 80

entry	dione	reactn[a]	ketol products (% compn)	yield,[b] %	rec dione, %
1	**50**	A	**57**; **59** (22, 78)	80	15
2	**50**	B	**57**, **58**; **59**, **60** (98, 2)	70	10
3	**51**	A	**61**; **63** (45, 55)	80	15
4	**51**	B	**61**, **62**; **63**, **64** (83, 16)	70	10
5	**52**	A	**65**; **67** (27, 73)	75	20
6	**52**	B	**65**, **66**; **67**, **68** (64, 36)	70	15
7	**53**	A	**69**; **71** (40, 60)	49	20
8	**53**	B	**69**, **70**; **71**, **72** (90, 10)	55	30
9	**54**	A	**73**; **75** (30, 70)	49	30
10	**54**	B	**73**, **74**; **75**, **76** (50, 50)	60	20
11	**55**	A	**77**; **79** (35, 65)	20	60
12	**55**	B	**77**, **78**; **79**, **80** (85, 15)	36	35

[a] A = bakers' yeast, B = 1 equiv of $NaBH_4$. [b] The yield reported for the yeast reductions is percent of product isolated not subtracting recovered starting material and represents the amount of product isolated with a standard fermentation procedure and not one optimized for that substrate.

Table IV. γ Steric Compression Effect in Cyclohexane Ketols

	^{13}C NMR chemical shifts (δ from Me_4Si)											
ketol	**57**	**59**	**61**	**63**	**65**	**67**	**69**	**71**	**73**	**75**	**77**	**79**
CH_3	19.0	17.5	20.0	17.6	21.1	17.2	19.5	18.0	19.7	17.1	23.8	16.6
CH_2 (C7)	33.8	38.6	37.7	40.2	22.9	24.7	40.7	43.7	29.3	30.1	23.4	25.9

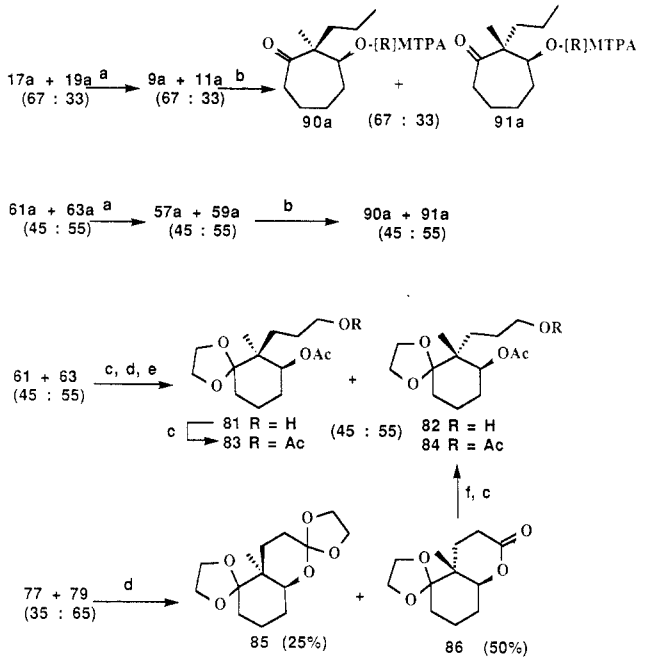
Similar to the cyclopentanoid series, the relative configuration of the cyclohexanoid ketols could be determined by analysis of the ^{13}C NMR spectra on the basis of the observed syn shielding phenomena (γ steric compression) as summarized in Table IV. Unlike the cyclopentanoid series, for the cyclohexanoid series the enzymatic vs. $NaBH_4$ reduction proceeded with different stereoselectivity with respect to the distinction of the substituents at C2. The major diastereomer found in the cyclopentanoid series was (2*S*,3*S*), whereas the major diastereomer in the cyclohexanoid series had the (2*R*,3*S*) configuration. It is interesting to recognize the asymmetric consistency of the yeast reduction in both series to provide only the (*S*)-hydroxy configuration.

Determination of Absolute Configuration of the Cyclohexanoid Ketols. The absolute configuration of the cyclohexanoid yeast products was established as follows (Scheme III). The (*R*)-MTPA esters **9a** and **11a** (67:33), derived from catalytic reduction of **17a** and **19a**, of known absolute configuration were treated with diazomethane and $AlCl_3$ resulting in ring expansion[18] to a mixture of the corresponding cycloheptanoid (*R*)-MTPA esters **90a** and **91a** (67:33), which were used as correlation standards. The reaction rate for ring expansion of the cyclopentanoid system to the cyclohexanoid system was *slower* than further ring expansion of the cyclohexanoid to the cycloheptanoid system. Catalytic reduction of a mixture of the (*R*)-MTPA esters **61a** and **63a** (45:55) gave the corresponding (*R*)-MTPA esters **57a** and **59a** (45:55), which were identical with those of the (*R*)-MTPA esters **57a** and **59a** (22:78) derived from yeast reduction of the dione **50**. Ring expansion of the (*R*)-MTPA esters **61a** and **63a** (45:55) with diazomethane and $AlCl_3$ provided the corresponding cycloheptanoid (*R*)-MTPA esters **90a** and **91a** (45:55), identical by ^1H NMR at 470 MHz to **90a** and **91a** (67:33) derived from the cyclopentanoids **9a** and **11a**. The propynyl ketols **65** and **67** were correlated in a similar fashion by catalytic reduction of the corresponding mixture of MTPA esters **65a** and **67a** (27:73).

The absolute configuration of the lactones **77** and **79** (35:65) was established as follows. As correlation standards, the diacetates **83** and **84** were prepared from the correlated allyl ketols **61** and **63** (45:55) by a sequence of steps involving (1) acetylation of the hydroxy group, (2) ketal formation, and (3) hydroboration–oxidation. The diastereomeric mixture of alcohols **81** and **82** was separated by chromatography, and they were converted to the corresponding diacetates **83** and **84**, respectively. The diastereomeric mixture of lactones **77** and **79** (35:65) was

(18) House, H. O.; Grubbs, E. J.; Gannon, W. F. *J. Am. Chem. Soc.* **1960**, *82*, 4099.

Scheme III. Correlation of Absolute Configuration of Cyclohexanoids[a]

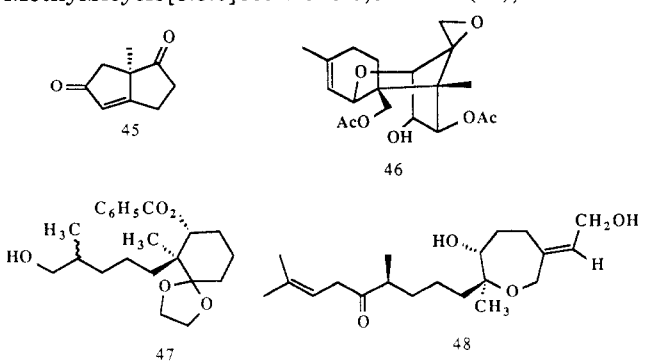


[a] Reagents: (a) H_2, PtO_2 catalyst; (b) CH_2N_2, $AlCl_3$ catalyst, 0 °C; (c) Ac_2O, py; (d) ethylene glycol, trimethyl orthoformate, TsOH catalyst; (e) BH_3/THF; aqueous H_2O_2, NaOH; (f) $LiAlH_4$, THF.

treated with ethylene glycol and *p*-toluenesulfonic acid catalysis to give the ortho ester **85** (25%) and the ketal **86** (50%), which were separated by chromatography. Reduction of **86** with $LiAlH_4$ provided the diol **87**, which was diacetylated to give **84** which showed the same optical rotation and ^1H NMR as **84** prepared from the allyl ketol **63**.

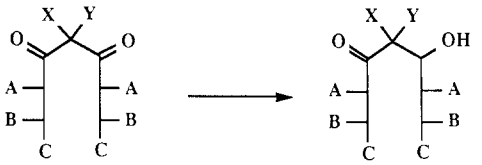
The absolute configuration of the yeast products **69**, **71**, **73**, and **75** were not chemically correlated but were assigned on the basis of analysis of the ^1H NMR chemical shifts of the (*R*)-MTPA esters using the configuration correlation model of Mosher[10] and the MTPA esters of the racemic ketols as controls. In each case, the methyl signal of the (*R*)-MTPA esters of the yeast products was the upfield diastereomer compared with the corresponding (*R*)-MTPA esters of the racemic ketols. According to the correlation model, this implies the (*S*)-hydroxy configuration for the yeast products.

Applications for Enantioselective Synthesis. Applications of these chiral yeast-derived products for enantioselective synthesis have been reported. (*R*)-5-Methylbicyclo[3.3.0]oct-1-ene-3,6-dione (**45**),[19] a useful



(19) (a) Trost, B. M.; Curran, D. P. *J. Am. Chem. Soc.* **1980**, *102*, 5699. (b) Trost, B. M.; Curran, D. P. *Tetrahedron Lett.* **1981**, 4929. Trost, B. M.; Curran, D. P. *J. Am. Chem. Soc.* **1981**, *103*, 7380.

Scheme IV. Asymmetric Monoreduction of Prochiral Diones



building block for fused cyclopentanoid natural products, was prepared from the ketol **13**[8a] and in an improved procedure from ketol **21**.[17] The allyl ketol **13** was also used as a chiral precursor in an enantioselective total synthesis of the trichothecene mycotoxin anguidine (diacetoxyscirpenol **46**).[20] A chiral precursor **47** for the diterpenoid zoapatanol (**48**) was prepared via yeast reduction of a 2,2-disubstituted-1,3-cyclohexanedione.[8b] The keto lactone **29** is also a useful chiral building block.[21]

Yeast reduction of cyclopentane and cyclohexanediones thus appears to be a generally useful method for preparing optically pure ketols with a variety of substituents in the C2 position. Further investigation of the outcome of yeast reduction with increasing ring size to cycloheptanoid and cyclooctanoid systems has been reported.[22] The outcome of the yeast reduction of these prochiral 1,3-dione systems can theoretically provide a pair of enantiomeric diastereomers, but we observed in every case studied an enantioselective preference for the (*S*)-hydroxy configuration and varying degrees of stereoselectivity with respect to distinguishing the substituents at C2, thus resulting in the formation of a mixture of optically pure diastereomers or one product. It is important to realize that the chemist is not limited to the inherent asymmetric preference of the yeast reduction, since the ketol products can be manipulated by simple synthetic procedures to provide any of the four absolute configurations desired. A method to epimerize the hydroxy configuration of the ketols has been illustrated. The conversion of a given ketol to the corresponding enantiomer is accomplished by transposing the hydroxy and keto groups, and this sequence has been previously demonstrated.[8b] From these results we have demonstrated that yeast reduction of 2,2-disubstituted 1,3-cycloalkanediones is a useful and versatile method that can be integrated into synthetic strategies for enantioselective syntheses of natural products. The strategy could be further expanded by designing substrates with *n* prochiral elements as shown in Scheme IV. Asymmetric reduction, microbial or synthetic, of one carbonyl could then generate a product with $n - 1$ chiral centers.

Experimental Section

All experiments requiring anhydrous conditions were conducted under a dry nitrogen atmosphere. Reactions were performed at room temperature unless indicated otherwise and stirred with a magnetically driven stir bar. Reactions were monitored by thin-layer chromatography (TLC) on precoated silica gel 60 F-254 plates (0.25 mm) or gas chromatography (6 ft, 10% SE-30 on 80–100-mesh Chromosorb W). The plates were visualized by spraying or dipping with a *p*-anisaldehyde solution (1350 mL of ethanol, 50 mL of concentrated H_2SO_4, 15 mL of glacial acid acid, 37 mL of *p*-anisaldehyde) or a phosphomolybdic acid solution (5% in methanol) followed by heating the plate (125–150 °C).

(20) Brooks, D. W.; Grothaus, P. G.; Mazdiyasni, H. *J. Am. Chem. Soc.* **1983**, *105*, 4472.

(21) Schwarz, S.; Truckenbrodt, G.; Meyer, M.; Zepter, R.; Weber, G.; Carl, C.; Wentzke, M.; Schick, H.; Welzel, H.-P. *J. Prakt. Chem.* **1981**, *323*, 729.

(22) Brooks, D. W.; Mazdiyasni, H.; Sallay, P. *J. Org. Chem.* **1985**, *50*, 3411.

Chromatography was performed with 230–400-mesh silica gel. Solvents were evaporated on a rotary evaporator at aspirator pressure (ca. 20 mm). Nuclear magnetic resonance (NMR) spectra were acquired on a Perkin-Elmer R-32, Nicolet 470-MHz, or Varian XL-200 NMR spectrometer. Chemical shifts are reported (δ) downfield relative to tetramethylsilane as standard. Mass spectra were obtained via electron impact (EI) or chemical ionization (CI) with a Finnigan 4171 spectrometer. Optical rotations were measured with a Rudolph Research Autopol III at 23 °C and are expressed as $[\alpha]_D$ (concentration in grams/100 mL, solvent).

General Procedure for Catalytic Hydrogenation. A Brown automatic gasimeter was used to introduce H_2 (generated by adding an aqueous 1 M solution of $NaBH_4$ to a 50% aqueous solution of acetic acid) to a solution of olefin in ethanol containing 1–5 mol % PtO_2. The reaction was monitored by gas chromatography or TLC. After about 2–4 h, the reaction was complete and the solution was filtered through Celite and evaporated to give the product.

2-Methyl-2-propyl-1,3-cyclopentanedione (2): prepared by catalytic hydrogenation of **3** by the general procedure given; 98% yield; bp 65 °C (2 mm); ^{1}H NMR ($CDCl_3$, 90 MHz) δ 0.84 (3 H, t, J = 7 Hz, CH_3), 1.08 (3 H, s, CH_3), 1.15–1.75 (4 H, m), 2.73 (4 H, br s); ^{13}C NMR ($CDCl_3$, 20 MHz) δ 14.3 (CH_3), 18.1 (CH_2), 19.1 (CH_3), 35.3 ($2CH_2$), 38.2 (CH_2), 56.8 (C), 216.6 (2 C=O); MS, m/e M^+ 154. Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 69.95; H, 9.25.

2-Methyl-2-(3-propenyl)-1,3-cyclopentadienone (3).[9] To a solution of **1** (35 g, 0.3 mol) in 1 M NaOH (300 mL) was added 3-bromopropene (50 mL, 0.6 mol). The reaction was stirred for 24 h after which the mixture was extracted with CH_2Cl_2 (3 × 100 mL), and the organic phase was washed with aqueous saturated NaCl, dried over $MgSO_4$, filtered, and evaporated. The crude product was distilled to yield dione **3**: 39 g, 85%, bp 65 °C (2 mm); ^{1}H NMR ($CDCl_3$, 90 MHz) δ 1.1 (3 H, s, CH_3), 2.3 (2 H, d, J = 8 Hz), 2.7 (4 H, br s), 4.8–5.2 (2 H, m), 5.3–5.9 (1 H, m); ^{13}C NMR ($CDCl_3$, 20 MHz) δ 18.7 (CH_3), 35.4 ($2CH_2$), 40.1 (CH_2), 56.6 (C), 119.7 (=CH_2), 131.7 (CH=), 215.9 (2 C=O), MS, m/e M^+ 152. Anal. Calcd for $C_9H_{12}O_2$: C, 71.03; H, 7.95. Found: C, 71.12; H, 7.83.

2-Methyl-2-(3-propynyl)-1,3-cyclopentanedione (4). The conditions used to prepare **3** from **1** were duplicated except with 3-bromopropyne (53 mL, 0.6 mol). The crude product was recrystallized from ether in hexane to give dione **4**: 32 g, 70%; mp 69 °C; ^{1}H NMR ($CDCl_3$, 90 MHz) δ 1.20 (3 H, s, CH_3), 2.04 (1 H, t, J = 3 Hz), 2.48 (2 H, d, J = 3 Hz), 3.85 (4 H, br s); ^{13}C NMR ($CDCl_3$, 50.3 MHz) 19.4 (CH_3), 24.3 (CH_2), 35.8 (2 CH_2), 55.3 (C), 70.8 (≡CH), 78.9 (C≡), 215.1 (2 C=O); MS, m/e M^+ 150. Anal. Calcd for $C_9H_{10}O_2$: C, 71.98; H, 6.71. Found: C, 71.75; H, 6.82.

General Preparation for the Preparation of 2,2-Disubstituted 1,3-Cyclopentanediones 5–8. To a solution of 2-methyl-1,3-cyclopentanedione (**1**; 4 g, 0.036 mol) in triethylamine (20 mL) was added 3-chloro-2-methylpropene (for **5**), acrylonitrile (for **6**), methyl bromoacetate (for **7**), or methyl acrylate (for **8**) (0.2 mol), and the mixture was refluxed for 16 h. Dichloromethane (25 mL) was added and the mixture was washed with 1 N HCl (25 mL) and aqueous saturated NaCl (25 mL). The organic extract was dried over $MgSO_4$, and the solvent was evaporated to give crude product, which was purified by distillation or chromatography to afford the corresponding diones 5–8.

2-(2-Methyl-2-propenyl)-2-methyl-1,3-cyclopentanedione (5): purified by distillation; bp 65–70 °C (0.2 mm); yield 5 g 84%; ^{1}H NMR ($CDCl_3$, 470 MHz) δ 1.13 (3 H, s, CH_3), 1.65 (3 H, s, CH_3), 2.42 (2 H, s), 2.75 (4 H, m), 4.55 (1 H, s), 4.80 (1 H, s); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 20.5 (CH_3), 24.0 (CH_3), 35.6 (2 CH_2), 43.7 (CH_2), 57.4 (C), 115.0 (=CH_2), 140.8 (C=), 216.7 (2 CO); MS, m/e M^+ 166. Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.09; H, 8.54.

2-(Cyanoethyl)-2-methyl-1,3-cyclopentanedione (6): purified by distillation; bp 120 °C (0.5 mm); yield 3 g, 50%; ^{1}H NMR ($CDCl_3$, 470 MHz) δ 1.20 (3 H, s, CH_3), 2.05 (2 H, t, J = 7.5 Hz), 2.41 (2 H, t, J = 7.5 Hz), 2.90 (4 H, m); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 12.6 (CH_2), 20.6 (CH_3), 28.2 (CH_2), 34.8 (2 CH_2), 55.2 (C), 118.7 (C≡N), 214.6 (2 C=O); MS, m/e M^+ 165. Anal. Calcd for $C_9H_{11}NO_2$: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.34; H, 6.85; N, 8.39.

2-[(Methoxycarbonyl)methyl]-2-methyl-1,3-cyclopentanedione (7): purified by chromatography (silica gel, 30% ethyl acetate in hexane); yield 5 g, 75%; ^{1}H NMR ($CDCl_3$, 90 MHz) δ 1.1 (3 H, s, CH_3), 2.85 (4 H, s), 2.9 (2 H, s), 3.6 (3 H, s OCH_3); MS, m/e M^+ 184. Anal. Calcd for $C_9H_{12}O_4$: C, 58.69; H, 6.57. Found: C, 58.73; H, 6.55.

2-[(Methoxycarbonyl)ethyl]-2-methyl-1,3-cyclopentanedione (8): purified by chromatography (silica gel, 25% ether in dichloromethane); yield 6 g, 90%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.15 (3 H, s, CH_3), 1.98 (2 H, t, J = 7.5 Hz), 2.30 (2 H, t, J = 7.5 Hz), 2.81 (4 H, s), 3.62 (3 H, s, OCH_3); MS, m/e M^+ 198. Anal. Calcd for $C_{10}H_{14}O_4$: C, 60.60; H, 7.12. Found: C, 60.71; H, 7.05.

2-Methyl-2-propyl-1,3-cyclohexanedione (50): prepared by catalytic hydrogenation of **51** by the general procedure; 98% yield; ^{1}H NMR ($CDCl_3$, 90 MHz) δ 0.9 (3 H, t, J = 7 Hz), 1.0–1.3 (2 H, m), 1.2 (3 H, s, CH_3), 1.7–2.2 (4 H, m), 2.6–2.8 (4 H, m); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 14.4 (CH_3), 17.8 (CH_3), 18.1 (CH_2), 18.8 (CH_2), 38.0 (2 CH_2), 40.0 (CH_2), 65.9 (C), 210.3 (2 C=O); MS, m/e M^+ 168. Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.42; H, 9.48.

2-Methyl-2-(3-propenyl)-1,3-cyclohexanedione (51): prepared from 2-methyl-1,3-cyclohexanedione by the same procedure as used for **3**; 85% yield; ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 14.0 (CH_3), 15.6 (CH_2), 30.48 (2 CH_2), 33.0 (CH_2), 51.8 (C), 94.5 (=CH_2), 105.2 (CH=), 209.0 (2 C=O); MS, m/e M^+ 166. Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.34; H, 8.29.

2-Methyl-2-(3-propynyl)-1,3-cyclohexanedione (52): prepared from 2-methyl-1,3-cyclohexanedione by the same procedure as used for **4**; 70% yield; ^{1}H NMR ($CDCl_3$, 90 MHz) δ 1.3 (3 H, s, CH_3), 1.8–2.5 (4 H, m), 2.6–2.9 (5 H, m); MS, m/e M^+ 164. Anal. Calcd for $C_{10}H_{12}O_2$: C, 73.15; H, 7.37. Found: C, 73.25; H, 7.26.

2-(2-Methyl-2-propenyl)-2-methyl-1,3-cyclohexanedione (53): prepared from 2-methyl-1,3-cyclohexanedione by the same procedure as used for **5**; 85% yield; ^{1}H NMR ($CDCl_3$, 470 MHz) δ 1.25 (3 H, s, CH_3), 1.65 (3 H, s, CH_3), 2.0 (2 H, m), 2.58 (2 H, s), 2.70 (4 H, m), 4.51 (1 H, s); MS, m/e M^+ 180. Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found C, 73.25; H, 8.99.

2-(Cyanoethyl)-2-methyl-1,3-cyclohexanedione (54): prepared from 2-methyl-1,3-cyclohexanedione by the same procedure as used for **6**; 70% yield; ^{1}H NMR ($CDCl_3$, 470 MHz) δ 1.37 (3 H, s, CH_3), 1.87 (1 H, m), 2.11 (1 H, m), 2.20 (2 H, m), 2.28 (2 H, m), 2.65 (2 H, m), 2.80 (2 H, m); MS, m/e M^+ 179. Anal. Calcd for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31; N, 7.82. Found: C, 67.13; H, 7.29; N, 7.78.

2-[(Methoxycarbonyl)ethyl]-2-methyl-1,3-cyclohexanedione (55): prepared from 2-methyl-1,3-cyclohexanedione by the same procedure as used for **8**; 75% yield; ^{1}H NMR ($CDCl_3$, 90 MHz) δ 1.28 (3 H, s, CH_3), 1.8–2.1 (2 H, m), 2.15 (4 H, m), 2.70 (4 H, m), 3.62 (3 H, s, OCH_3); MS, m/e M^+ 212. Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.14; H, 7.69.

General Procedure for the Yeast Reduction of the 2,2-Disubstituted 1,3-Diones. To a solution of D-glucose (15 g) and yeast extract (0.5 g) in distilled water (100 mL) at 35–40 °C was added with stirring dry active bakers' yeast (10 g, Fleischmann's, Standard Brands Inc.). The mixture was stirred open to the air for 30 min, maintaining the temperature between 30 and 35 °C, after which the dione (1 g, neat or dissolved in 1 mL of Me_2SO) was added dropwise over 5 min. The mixture was vigorously stirred open to the air at 23–25 °C for 24 h, then diluted with 150 mL of water, and extracted with dichloromethane (250 mL) in a continuous extractor for 48 h. The organic extract was evaporated to provide a crude product consisting of ketol, unreacted dione, and a trace of diol. The components of the mixture were purified by chromatography on silica gel.

(2*S*,3*S*)-3-Hydroxy-2-methyl-2-propylcyclopentanone (9): purified by chromatography (silica gel, 30% ethyl acetate in hexane); $[\alpha]_D$ +68.7° (c 1.94, $CHCl_3$); IR (neat) 3400 (br s), 1720 cm^{-1} (s); ^{1}H NMR ($CDCl_3$, 470 MHz) δ 0.94 (3 H, t, J = 7.2 Hz, CH_3), 1.00 (3 H, s, CH_3), 1.29 (1 H, m), 1.42 (1 H, m), 1.50 (2 H, m), 1.61 (1 H, br s, OH), 1.95 (1 H, m), 2.16–2.32 (2 H, m), 2.46 (1 H, m), 4.11 (1 H, t, J = 4.5 Hz); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 14.8 (CH_3), 17.1 (CH_2), 19.2 (CH_3), 27.8 (CH_2), 32.3 (CH_2), 34.0 (CH_2), 53.2 (C), 77.6 (CHOH), 221.0 (C=O); MS, m/e M^+ 156. Anal. Calcd for $C_9H_{16}O_2$: C, 69.19; H, 10.32. Found: C, 68.97; H, 10.59.

(2*S*,3*S*)-3-Hydroxy-2-methyl-2-(3-propenyl)cyclopentanone (13): purified by chromatography (silica gel, 30% ethyl acetate in hexane); $[\alpha]_D$ +80.7° (*c* 0.4, $CHCl_3$); IR (neat) 3380 (br s), 3010 (w), 1710 cm^{-1} (s); ^1H NMR ($CDCl_3$, 470 MHz) δ 1.01 (3 H, s, CH_3), 1.78 (1 H, d, J = 3 Hz), 1.97 (1 H, m), 2.16–2.52 (5 H, m), 4.13 (1 H, dd, J = 4, 3 Hz), 5.16 (2 H, m), 5.89 (1 H, m); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 19.7 (CH_3), 27.8 (CH_2), 34.0 (CH_2), 35.4 (CH_2), 53.2 (C), 77.2 (CHOH), 118.1 (=CH_2), 134.4 (CH=), 220.6 (C=O); MS, *m/e* M^+ 154. Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 70.40; H, 9.43.

(2*R*,3*S*)-3-Hydroxy-2-methyl-2-(3-propenyl)cyclopentanone (15): purified by chromatography (silica gel, 30% ethyl acetate in hexane); $[\alpha]_D$ −86.5° (*c* 0.26, $CHCl_3$); IR (neat) 3400 (br m), 3050 cm^{-1} (w), 1730 (s); ^1H NMR ($CDCl_3$, 470 MHz) δ 1.02 (3 H, s, CH_3), 1.69 (1 H, br s, OH), 1.87 (1 H, m), 2.14–2.30 (4 H, m), 2.48 (1 H, m), 4.23 (1 H, t, J = 6.4 Hz), 5.11 (2 H, m), 5.76 (1 H, m); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 15.0 (CH_3), 27.5 (CH_2), 34.9 (CH_2), 39.8 (CH_2), 53.0 (C), 75.4 (CHOH), 118.7 (=CH_2), 133.5 (C=), 219.9 (C=O); MS, *m/e* M^+ 154. Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 70.06; H, 9.40.

(2*S*,3*S*)-3-Hydroxy-2-methyl-2-(3-propynyl)cyclopentanone (17): purified by chromatography (silica gel, 30% ethyl acetate in hexane); $[\alpha]_D$ +195.9° (*c* 0.72, $CHCl_3$); IR (neat) 3400 (br s), 3260 (s), 2100 (w), 1730 cm^{-1} (s); ^1H NMR ($CDCl_3$, 470 MHz) δ 1.13 (3 H, s, CH_3), 2.10–2.11 (2 H, m), 2.04 (1 H, t, J = 2.7 Hz), 2.18–2.28 (1 H, m), 2.33–2.57 (4 H, m), 4.27 (1 H, dd, J = 3.3, 1.0 Hz); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 19.8 (CH_3), 20.8 (CH_2), 27.4 (CH_2), 34.0 (CH_2), 53.2 (C), 70.6 (≡CH), 76.6 (CHOH), 81.1 (C≡), 219.9 (C=O); MS, *m/e* M^+ 152. Anal. Calcd for $C_9H_{12}O_2$: C, 71.03; H, 7.95. Found: C, 70.82; H, 8.11.

(2*R*,3*S*)-3-Hydroxy-2-methyl-2-(3-propynyl)cyclopentanone (19): purified by chromatography (silica gel, 30% ethyl acetate in hexane); $[\alpha]_D$ −138.6° (*c* 0.29, $CHCl_3$); IR (neat) 3450 (br m), 3270 (s), 2100 (w), 1730 cm^{-1} (s); ^1H NMR ($CDCl_3$, 470 MHz) δ 1.08 (3 H, s, CH_3), 1.86 (1 H, m), 2.04 (1 H, m), 2.06 (1 H, t, J = 2.7 Hz), 2.17 (1 H, m), 2.28–2.42 (3 H, m), 2.50 (1 H, m), 4.41 (1 H, dd, J = 6.7, 2.1 Hz); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 15.1 (CH_3), 24.9 (CH_2), 27.1 (CH_2), 35.0 (CH_2), 51.8 (C), 71.1 (≡CH), 75.2 (CHOH), 80.6 (C≡), 218.5 (C=O); MS, *m/e* M^+ 152. Anal. Calcd for $C_9H_{12}O_2$: C, 71.03; H, 7.95. Found: C, 70.99; H, 8.08.

(2*S*,3*S*)-3-Hydroxy-2-(2-methyl-2-propenyl)-2-methylcyclopentanone (21): purified by chromatography (silica gel, 25% ethyl acetate in hexane); $[\alpha]_D$ +99.0° (*c* 7.6, $CHCl_3$); ^1H NMR ($CDCl_3$, 470 MHz) δ 1.00 (3 H, s), 1.80 (3 H, s), 1.9–2.5 (7 H, m), 4.25 (1 H, m), 4.90 (1 H, s), 4.95 (1 H, s); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 19.9 (CH_3), 24.2 (CH_3), 27.9 (CH_2), 33.4 (CH_2), 38.1 (CH_2), 53.5 (C), 77.4 (CHOH), 114.4 (=CH_2), 143.0 (C=), 220.7 (CO); MS, *m/e* M^+ 168. Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.45; H, 9.70.

(2*S*,3*S*)-2-(Cyanoethyl)-3-hydroxy-2-methylcyclopentanone (25): purified by chromatography (silica gel, 10% ethyl acetate in CH_2Cl_2); $[\alpha]_D$ +89.2° (*c* 3.55, $CHCl_3$); ^1H NMR ($CDCl_3$, 470 MHz) δ 1.03 (3 H, s, CH_3), 1.8–2.6 (8 H, m), 4.23 (1 H, m); MS, *m/e* M^+ 167. Anal. Calcd for $C_9H_{13}NO_2$: C, 64.65; H, 7.84. Found: C, 64.78; H, 7.65.

(1*S*,5*S*)-5-Methyl-2-oxabicyclo[3.3.0]octane-3,6-dione (29):[13] purified by chromatography 20% ether in CH_2Cl_2 and recrystallized from ether in hexane; mp 96 °C; $[\alpha]_D$ +94.7° (*c* 0.17, $CHCl_3$); IR ($CHCl_3$) 1790 (s), 1750 cm^{-1} (s); ^1H NMR ($CDCl_3$, 470 MHz) δ 1.27 (3 H, s, CH_3), 2.23 (1 H, m), 2.42–2.54 (3 H, m), 2.53 (1 H, d, J = 18.2 Hz), 2.84 (1 H, d, J = 18.2 Hz), 4.83 (1 H, dd, J = 4.7, 1.0 Hz); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 18.5 (CH_3), 24.8 (CH_2), 34.2 (CH_2), 34.2 (CH_2), 39.1 (CH_2), 52.4 (C), 87.6 (CH), 174.4 (COO), 218.4 (CO); MS, *m/e* M^+ 154. Anal. Calcd for $C_8H_{10}O_3$: C, 62.33; H, 6.54. Found: C, 62.05; H, 6.36.

(1*S*,6,*S*)-6-Methyl-2-oxabicyclo[4.3.0]nonane-3,7-dione (33): purified by chromatography (silica gel, 50% ethyl acetate in hexane); $[\alpha]_D$ +33.9° (*c* 2.5, $CHCl_3$); ^1H NMR ($CDCl_3$, 470 MHz) δ 1.13 (3 H, s, CH_3), 1.80 (1 H, m), 2.10 (1 H, m), 2.40 (4 H, m), 3.65 (2 H, m), 4.65 (1 H, m); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 21.5 (CH_3), 26.2 (CH_2), 27.0 (CH_2), 27.8 (CH_2), 33.9 (CH_2), 48.0 (C), 85.7 (CH), 171.9 (COO), 218.6 (CO); MS, *m/e* M^+ 168. Anal. Calcd for $C_9H_{12}O_3$: C, 64.27; H, 7.19. Found: C, 64.11; H, 7.28.

(1*S*,6*S*)-6-Methyl-2-oxabicyclo[4.3.0]nonane-3,7-dione (33). To a solution of **25** and **27** (96:4; 0.5 g, 3 mmol) in ethylene glycol (0.93 g, 15 mmol) and trimethyl orthoformate (1.1 g, 7.5 mmol) was added *p*-toluenesulfonic acid (0.05 g, 0.3 mmol) with stirring. After 4 h, saturated aqueous $NaHCO_3$ (10 mL) was added, and the mixture was extracted with ether (3 × 10 mL). The combined organic extract was washed with saturated aqueous NaCl, dried over $MgSO_4$, filtered, and evaporated. The crude product was purified by chromatography (silica gel, 50% ether in CH_2Cl_2) to afford **33**: 200 mg, 40%; $[\alpha]_D$ +27.5° (*c* 3.5, $CHCl_3$); other spectra identical with **33** prepared by microbial reduction of **8**.

(2*S*,3*S*)-3-Hydroxy-2-methyl-2-propylcyclohexanone (57): $[\alpha]_D$ +75° (*c* 0.57, $CHCl_3$); ^1H NMR ($CDCl_3$, 470 MHz) δ 0.97 (3 H, t, J = 7.5 Hz, CH_3), 1.02 (1 H, m), 1.18 (3 H, s, CH_3), 1.29 (1 H, m), 1.60 (4 H, m), 1.70 (1 H, m), 1.97 (2 H, m), 2.37 (2 H, m), 3.69 (1 H, dd, J = 8.5, 4 Hz); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 14.9 (CH_3), 16.7 (CH_2), 19.0 (CH_3), 20.7 (CH_2), 28.8 (CH_2), 33.8 (CH_2), 37.7 (CH_2), 54.9 (C), 77.6 (CHOH), 215.4 (C=O); MS, *m/e* M^+ 170. Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66. Found: C, 70.67; H, 10.56.

(2*R*,3*S*)-3-Hydroxy-2-methyl-2-propylcyclohexanone (59): $[\alpha]_D$ −50.9 (*c* 0.54, $CHCl_3$); ^1H NMR ($CDCl_3$, 470 MHz) δ 0.92 (3 H, t, J = 7.5 Hz, CH_3), 1.10 (1 H, m), 1.12 (3 H, s, CH_3), 1.34 (1 H, m), 1.57 (3 H, m), 1.80 (2 H, m), 2.11 (2 H, m), 2.34 (1 H, m), 2.42 (1 H, m), 3.91 (1 H, dd, J = 5.5, 2.5 Hz); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 14.8 (CH_3), 17.3 (CH_2), 17.5 (CH_3), 20.7 (CH_2), 28.2 (CH_2), 37.9 (CH_2), 38.6 (CH_2), 54.5 (C), 76.4 (CHOH), 214.9 (C=O); MS, *m/e* M^+ 170. Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66. Found: C, 70.48; H, 10.71.

(2*S*,3*S*)-3-Hydroxy-2-methyl-2-(3-propenyl)cyclohexanone (61): $[\alpha]_D$ +32° (*c* 0.42, $CHCl_3$); ^1H NMR ($CDCl_3$, 470 MHz) δ 1.19 (3 H, s, CH_3), 1.72 (1 H, m), 1.76 (1 H, br s, OH), 1.90 (1 H, m), 2.05 (2 H, m), 2.41 (4 H, m), 3.81 (1 H, m), 5.10 (2 H, m), 5.78 (1 H, m); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 20.0 (CH_3), 20.6 (CH_2), 28.5 (CH_2), 36.9 (CH_2), 37.7 (CH_2), 54.0 (C), 76.7 (CHOH), 118.0 (=CH_2), 134.2 (CH=), 214.4 (C=O); MS, *m/e* M^+ 168. Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.41; H, 9.45.

(2*R*,3*S*)-3-Hydroxy-2-methyl-2-(3-propenyl)cyclohexanone (63): $[\alpha]_D$ −4.7° (*c* 0.6, $CHCl_3$); ^1H NMR ($CDCl_3$, 470 MHz) δ 1.17 (3 H, s, CH_3), 1.68 (2 H, m), 1.88 (1 H, m), 2.05 (2 H, m), 2.20 (4 H, m), 3.90 (1 H, m), 5.10 (2 H, m), 5.78 (1 H, m); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 17.6 (CH_3), 20.4 (CH_2), 28.5 (CH_2), 37.6 (CH_2), 40.2 (CH_2), 54.5 (C), 75.1 (CHOH), 118.0 (=CH_2), 134.0 (CH=), 214.4 (C=O); MS, *m/e* M^+ 168. Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.43; H, 9.48.

(2*S*,3*S*)-3-Hydroxy-2-methyl-2-(3-propynyl)cyclohexanone (65): $[\alpha]_D$ +9.3° (*c* 5.7, $CHCl_3$); ^1H NMR ($CDCl_3$, 470 MHz) δ 1.28 (3 H, s, CH_3), 1.58 (1 H, m), 1.85 (1 H, m), 2.0–2.5 (7 H, m), 2.70 (1 H, m), 4.21 (1 H, br s); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 20.6 (CH_2), 21.1 (CH_3), 22.9 (CH_2), 28.1 (CH_2), 37.6 (CH_2), 52.4 (C), 71.1 (≡CH), 74.9 (CHOH), 81.1 (C≡), 213.1 (C=O); MS, *m/e* M^+ 166. Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.13; H, 8.56.

(2*R*,3*S*)-3-Hydroxy-2-methyl-2-(3-propynyl)cyclohexanone (67): $[\alpha]_D$ +46.6° (*c* 6.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 470 MHz) δ 1.22 (3 H, s, CH_3), 1.58 (1 H, m), 1.85 (1 H, m), 2.0–2.5 (8 H, m), 4.08 (1 H, dd, J = 7.5, 4 Hz); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 17.2 (CH_3), 20.0 (CH_2), 24.7 (CH_2), 29.0 (CH_2), 37.1 (CH_2), 54.4 (C), 71.2 (≡CH), 74.3 (CHOH), 81.6 (C≡)), 212.0 (C=O); MS, *m/e* M^+ 166. Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.14; H, 8.60.

(2*S*,3*S*)-3-Hydroxy-2-methyl-2-(2-methyl-2-propenyl)-cyclohexanone (69): ^1H NMR ($CDCl_3$, 470 MHz) δ 1.12 (3 H, s, CH_3), 1.64 (3 H, s, CH_3), 1.7–2.1 (4 H, m), 2.35 (2 H, m), 2.50 (2 H, s), 2.55 (1 H, m), 3.64 (1 H, dd, J = 7.5, 4 Hz), 4.70 (1 H, s), 4.84 (1 H, s); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 19.5 (CH_3), 20.9 (CH_2), 24.0 (CH_3), 28.7 (CH_2), 39.4 (CH_2), 40.7 (CH_2), 56.5 (C), 77.6 (CHOH), 114.8 (=CH_2), 142.00 (C=), 214.6 (C=O); MS, *m/e* M^+ 182. Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found: C, 72.43; H, 9.87.

(2*R*,3*S*)-3-Hydroxy-2-methyl-2-(2-methyl-2-propenyl)-cyclohexanone (71): ^1H NMR ($CDCl_3$, 470 MHz) δ 1.08 (3 H, s, CH_3), 1.60 (3 H, s, CH_3), 1.7–2.1 (4 H, m), 2.3–2.5 (5 H, m), 3.85 (1 H, d, J = 6 Hz), 4.70 (1 H, s), 4.84 (1 H, s); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 18.0 (CH_3), 20.7 (CH_2), 24.0 (CH_3), 28.2 (CH_2), 37.7 (CH_2), 43.7 (CH_2), 56.5 (C), 75.9 (CHOH), 115.0 (=CH_2), 147.6 (C=), 214.6 (C=O); MS, *m/e* M^+ 182. Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found: C, 72.54, H, 10.07.

(2S,3S)-2-(Cyanoethyl)-3-hydroxy-2-methylcyclohexanone (73): ^{1}H NMR ($CDCl_3$, 470 MHz) δ 1.35 (3 H, s, CH_3), 1.5–2.5 (11 H, m), 3.80 (1 H, m); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 12.3 (CH_2), 19.7 (CH_3), 20.5 (CH_2), 28.7 (CH_2), 29.3 (CH_2), 37.5 (CH_2), 59.5 (C), 73.4 (CHOH), 120.0 (C≡N), 213.7 (C=O); MS, *m/e* M^+ 181. Anal. Calcd for $C_{10}H_{15}NO_2$: C, 66.27; H, 8.34; N 7.73. Found: C, 66.31; H, 8.39; N, 7.62.

(2R,3S)-2-(Cyanoethyl)-3-hydroxy-2-methylcyclohexanone (75): ^{1}H NMR ($CDCl_3$, 470 MHz) δ 1.30 (3 H, s, CH_3), 1.5–2.5 (11 H, m), 3.90 (1 H, m); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 12.6 (CH_2), 17.1 (CH_3), 20.1 (CH_2), 28.9 (CH_2), 30.1 (CH_2), 37.3 (CH_2), 60.5 (C), 73.4 (CHOH), 120.0 (C≡N), 213.2 (C=O); MS, *m/e* M^+ 181. Anal. Calcd for $C_{10}H_{15}NO_2$: C, 66.27; H, 8.34; N, 7.73. Found: C, 66.19; H, 8.41; N, 7.69.

(1S,6S)-6-Methyl-2-oxabicyclo[4.4.0]decane-3,7-dione (77). ^{1}H NMR ($CDCl_3$, 470 MHz) δ 1.30 (3 H, s, CH_3), 1.5–2.7 (10 H, m), 4.60 (1 H, dd, J = 4, 4 Hz); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 20.1 (CH_2), 23.4 (CH_2), 23.8 (CH_3), 26.4 (CH_2), 26.9 (CH_2), 36.4 (CH_2), 48.3 (C), 81.4 (CH), 170.8 (COO), 210.4 (C=O); MS, *m/e* M^+ 182. Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.92; H, 7.74. Found: C, 65.98; H, 7.65.

(1S,6R)-6-Methyl-2-oxabicyclo[4.4.0]decane-3,7-dione (79): ^{1}H NMR ($CDCl_3$, 470 MHz) δ 1.20 (3 H, s, CH_3), 1.5–2.7 (10 H, m), 4.26 (1 H, dd, J = 7, 4 Hz); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 16.6 (CH_3), 20.3 (CH_2), 25.9 (CH_2), 26.6 (CH_2), 27.5 (CH_2), 37.5 (CH_2), 46.6 (C), 85.4 (CH), 171.2 (COO), 211.5 (C=O); MS, *m/e* M^+ 182. Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.92; H, 7.74. Found: C, 65.81; H, 7.79.

General Procedure for the Preparation of (R)-MTPA Esters. To a stirred solution of ketol (0.3 mmol) in dichloromethane (1 mL) was added pyridine (1 mmol) followed by (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (0.9 mmol), and the mixture was stirred overnight. Ether (10 mL) and water (10 mL) were added, and the layers were separated. The organic phase was washed with 0.1 N HCl (5 mL) and aqueous saturated $NaHCO_3$, dried over $MgSO_4$, filtered, and evaporated to provide the (*R*)-MTPA ester in 90–98% yield. The methyl group at C2 was used to measure enantiomeric purity and diastereomeric composition with the racemic $NaBH_4$ reduction products as control standards. The ^{1}H NMR chemical shift for the methyl signal C2 of the (*R*-MTPA ester is given as follows: **9a**, 1.03; **10a**, 1.04; **11a**, 0.88; **12a**, 0.96; **13a**, 1.01; **14a**, 1.02; **15a**, 0.91; **16a**, 0.98; **17a**, 1.20; **18a**, 1.21; **19a**, 0.95; **20a**, 1.03; **21a**, 0.98; **22a**, 1.02; **23a**, 0.94; **24a**, -; **25a**, 1.14; **26a**, 1.15; **27a**, 0.90; **28a**, 1.00; **57a**, 1.06; **58a**, 1.13; **59a**, 0.95; **60a**, 1.02; **61a**, 1.08; **62a**, 1.16; **63a**, 1.02; **64a**, 1.05; **65a**, 1.34; **66a**, 1.35; **67a**, 1.09; **68a**, 1.11; **69a**, 1.10; **70a**, 1.19; **71a**, 1.05; **72a**, 1.13; **73a**, 1.15; **74a**, 1.22; **75a**, 1.10; **76a**, 1.12.

General Procedure for $NaBH_4$ Reduction of the 2,2-Disubstituted 1,3-Diones. To a solution of dione (1 mmol) in THF (5 mL) was added an aqueous 0.5 M solution of $NaBH_4$ (0.25 mmol). The mixture was stirred for 3 h, water (10 mL) was added, and the pH was adjusted to 2 with 0.5 N HCl. The solution was extracted with ether (2 × 25 mL), and the combined organic extract was washed with aqueous saturated NaCl, dried over $MgSO_4$, filtered, and evaporated to afford a mixture of ketol, dione, and small amount of diol products. The components were purified by chromatography on silica gel.

(1S,5S)-5-Methyl-2-oxabicyclo[3.3.0]octane-3,6-dione (29).[13] A solution of ketol **13** (0.5 g, 3.2 mmol) and pyridine (0.7 mL) in CH_2Cl_2 (10 mL) was cooled to −78 °C, and excess ozone (ozonized oxygen was generated by a Wellsbach Model T-23 ozonizer operating at an oxygen pressure of 8 psi and a flow rate of 0.015 ft^3/min) was bubbled into the solution until the characteristic blue color persisted for 2 min. The mixture was then flushed with nitrogen until it became clear and was allowed to warm to 20 °C. The solution was diluted with CH_2Cl_2 (15 mL) and washed with 0.1 N HCl (2 × 20 mL) and saturated aqueous NaCl. The organic extract was dried over $MgSO_4$, filtered, and evaporated. The crude ozonide was dissolved in acetone (10 mL) and cooled to 0 °C. Jones' reagent[14] was added dropwise with vigorous stirring until the brown-orange color persisted. The excess oxidant was quenched with isopropanyl alcohol. The mixture was filtered through Celite, and the solids were washed with acetone (3 × 10 mL). The filtrate was evaporated, and the residue was purified by chromatography (silica gel, 20% ether in CH_2Cl_2) and recrystallized from ether in hexane: mp 96 °C; other data, identical with that for **29** prepared by microbial reduction of **7**.

General Hydroxy Inversion Procedure. (2S,3R)-3-Hydroxy-2-methyl-2-(3-propenyl)cyclopentanone (16). To a solution of ketol **13** (1.0 g, 6.5 mmol) in pyridine (6.5 mL) was added *p*-toluenesulfonyl chloride (1.5 g, 7.8 mmol), and the mixture was stirred for 64 h. The mixture was diluted with ether (30 mL) and 1 N HCl (20 mL), and the layers were separated. The organic extract was washed with 1 N HCl (3 × 20 mL) and saturated aqueous NaCl, dried over $MgSO_4$, filtered, and evaporated to give the corresponding tosylate (1.7 g, 85%; purified by recrystallization from ether in hexane; mp 44 °C). To a solution of tosylate (1.0 g, 3 mmol) in dimethylformamide (30 mL) was added anhydrous KNO_2 (4 g, 48 mmol), and the mixture was heated at 80 °C with vigorous mechanical stirring for 36 h. The DMF was removed by heating in vacuo (0.5 mm), and the residue was diluted with saturated aqueous NaCl (20 mL) and extracted with CH_2Cl_2 (5 × 10 mL). The combined organic extract was washed with saturated aqueous NaCl (10 mL), dried over $MgSO_4$, filtered, and evaporated. The crude product was purified by chromatography (silica gel, 30% ethyl acetate in hexane) to afford ketol **16**: 0.7 g, 70%; $[\alpha]_D$ +86° (*c* 0.45, $CHCl_3$); other spectral data, identical with that for **15**.

(2S,3S)-3-Acetoxy-2-methyl-2-(3-propenyl)cyclopentanone Ethylene Acetal (38). To a stirred solution of ketol **13** (1.0 g, 6.5 mmol) in pyridine (1.0 g, 13 mmol) was added acetic anhydride (1.0 g, 9.6 mmol). After 16 h, the excess pyridine and acetic anhydride were removed under vacuum. The residue was dissolved in dichloromethane (230 mL) and washed with 1 N HCl (20 mL) and saturated aqueous NaCl. The organic extract was dried over $MgSO_4$, filtered, and evaporated. The crude acetate of **13** was dissolved in ethylene glycol (1.3 g, 25 mmol) and trimethyl orthoformate (1.5 g, 10 mmol), and *p*-toluenesulfonic acid (89 mg, 0.51 mmol) was added. After the mixture was stirred for 16 h, saturated aqueous $NaHCO_3$ (10 mL) was added, and the mixture was extracted with ether (3 × 20 mL). The organic extract was washed with saturated aqueous NaCl (20 mL), dried over $MgSO_4$, filtered, and evaporated. The crude product was purified by chromatography (silica gel, 30% ethyl acetate in hexane) to afford **38**: 0.8 g, 51%; ^{1}H NMR ($CDCl_3$, 90 MHz) δ 1.00 (3 H, s, CH_3), 1.5–2.5 (6 H, m), 2.05 (3 H, s, CH_3), 3.9 (4 H, m), 4.9–5.2 (3 H, m), 5.89 (1 H, m); MS, *m/e* M^+ 240.

(2S,3S)-3-Acetoxy-2-(3-acetoxypropyl)-2-methylcyclopentanone Ethylene Acetal (40). To a stirred solution of **38** (0.8 g, 3.3 mmol) in THF (4 mL) at 0 °C was added BH_3/THF (5 mmol, 5 mL of a 1 M solution in THF). The mixture was stirred for 3 h at 25 °C, after which an aqueous solution of 30% H_2O_2 (1 mL) and 1 N NaOH (1 mL) was added slowly. After 1 h, water (5 mL) was added, and the mixture was extracted with ether (3 × 10 mL). The organic extract was washed with saturated aqueous NaCl, dried over $MgSO_4$, filtered, and evaporated. The residue was dissolved in pyridine (0.8 g, 10 mmol), and acetic anhydride (0.8 g, 8.0 mmol) was added. After 16 h, the excess pyridine and acetic anhydride were removed under vacuum, and the residue was purified by chromatography (silica gel, 20% ether in dichloromethane) to afford **40**: 640 mg, 65%; $[\alpha]_D$ +18.9° (*c* 10, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 470 MHz) δ 1.10 (3 H, s, CH_3), 1.3–2.3 (8 H, m), 2.04 (3 H, s, CH_3), 2.07 (3 H, s, CH_3), 3.80 (2 H, t, J = 7.0 Hz), 3.91 (2 H, t, J = 7.0 Hz), 4.01 (2 H, t, J = 7.0 Hz), 4.90 (1 H, dd, J = 3, 3 Hz); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 19.4 (2 CH_3), 21.0 (CH_3), 23.7 (CH_2), 25.0 (CH_2), 26.0 (CH_2), 32.6 (CH_2), 48.5 (C), 64.4 (CH_2), 65.1 (CH_2), 65.5 (CH_2), 79.9 (CH), 118.3 (C), 170.7 (C=O), 171.2 (C=O); MS, *m/e* M^+ 300. Anal. Calcd for $C_{15}H_{24}O_6$: C, 59.99; H, 8.05.

(1S,6S)-6-Methyl-2-oxabicyclo[4.3.0]nonane-3,7-dione (33) from Ketol 25. To a stirred solution of ketol **25** (0.5 g, 3 mmol) in ethylene glycol (0.9 g, 15 mmol) and trimethyl orthoformate (1.1 g, 75 mmol) was added *p*-toluenesulfonic acid (0.05 g, 0.3 mmol). After 16 h, saturated aqueous $NaHCO_3$ (10 mL) was added, and the mixture was extracted with ether (3 × 10 mL). The organic extract was washed with saturated aqueous NaCl (10 mL), dried over $MgSO_4$, filtered, and evaporated. The crude product was dissolved in methanol (5 mL), a solution of aqueous NaOH (1 g in 1 mL) was added, and the mixture was refluxed 16 h. After cooling to 25 °C, the solution was adjusted to pH 2

with 2 N HCl, and the mixture was extracted with ether/ethyl acetate (1:1, 3 × 10 mL). The organic extract was washed with saturated aqueous NaCl (10 mL), dried over $MgSO_4$, filtered, and evaporated. Purification by chromatography (silica gel, 40% ether in dichloromethane) gave lactone **33**: 220 mg, 40%; $[\alpha]_D$ +27.5° (*c* 3.5, $CHCl_3$); other spectral data, identical with that from **33** prepared by yeast reduction of dione **8**.

(2*S*,3*S*)-3-Acetoxy-2-(3-acetoxypropyl)-2-methylcyclopentanone Ethylene Acetal (40). Lactone **33** was converted to the corresponding ethylene acetal **41** by the procedure used for **38**. To a stirred solution of $LiAlH_4$ (36 mg, 0.94 mmol) in THF (2 mL) at 0 °C was added a solution of lactone **41** (0.1 g, 0.5 mmol) in THF (2 mL). The mixture was stirred for 3 h at 25 °C, after which saturated aqueous ether (5 mL) followed by methanol (1 mL) was added. After 4 h, the solids were filtered and washed with THF (3 × 10 mL). The filtrate was evaporated to provide the crude diol **42**, which was diacetylated by the same procedure as that used for **38**. Purification by chromatography (silica gel, 20% ether in CH_2Cl_2) gave **40**: 80 mg, 53%; $[\alpha]_D$ +17.1° (*c* 4, $CHCl_3$); other spectral data, identical with that for **40** prepared from **38**.

General Procedure for Ring Expansion. (2*S*,3*S*)- and (2*R*,3*S*)-3-[(+)-α-[(Trifluoromethyl)phenyl]acetoxy]-2-methyl-2-propylcycloheptanone (90a, 91a). To a stirred solution of a mixture of MTPA esters **9a** and **11a** (67:33; 0.4 g, 1 mmol) in ether (2 mL) at 0 °C was added a solution of CH_2N_2 (2.1 equiv of 0.5 M CH_2N_2 in ether) followed by anhydrous $AlCl_3$ (10 mg). The mixture was stirred for 1 h, after which solid $NaHCO_3$ (100 mg) was added; the mixture was filtered and evaporated. The crude product was analyzed by ^1H NMR and found to consist of mainly the seven-membered homologues **90a** and **91a**, which were used as correlation standards after purification by chromatography (silica gel, 30% ethyl acetate in hexane). **90a**: ^1H NMR ($CDCl_3$, 470 MHz) δ 0.78 (3 H, t, *J* = 7 Hz, CH_3), 1.08 (3 H, s, CH_3), 1.05–1.80 (9 H, m), 2.17 (1 H, m), 2.34 (1 H, m), 2.60 (1 H, m), 3.55 (3 H, br s, OCH_3), 5.13 (1 H, d, *J* = 8 Hz), 7.40 (3 H, m), 7.55 (2 H, m); MS, *m/e* M^+ 400. **91a**: ^1H NMR ($CDCl_3$, 470 MHz) δ 0.76 (3 H, t, *J* = 7 Hz, CH_3), 1.05 (3 H, s, CH_3), 1.05–1.80 (9 H, m), 2.17 (1 H, m), 2.34 (1 H, m), 2.60 (1 H, m), 3.58 (3 H, br s, OCH_3), 5.38 (1 H, dd, *J* = 9, 2 Hz), 7.40 (3 H, m), 7.55 (2 H, m); MS, *m/e* M^+ 400.

(2*S*,3*S*)- and (2*R*,3*S*)-3-Acetoxy-2-(3-acetoxypropyl)-2-methylcyclohexanone Ethylene Acetal (83, 84). The diacetates **83** and **84** were prepared from ketols **61** and **63** by a sequence of (1) acetylation, (2) ethylene acetal formation, (3) hydroboration–oxidation, (4) separation of the mixture of diastereomeric alcohols **81** and **82** by chromatography (silica gel, 20% ether in dichloromethane), and (5) acetylation, using similar procedures as described for the conversion of ketol **13** to diacetate **40**. **83**: $[\alpha]_D$ +18.5° (*c* 2, $CHCl_3$); ^1H NMR ($CDCl_3$, 470 MHz) δ 0.92 (3 H, s, CH_3), 1.5–1.7 (10 H, m), 2.04 (6 H, s, 2 CH_3), 3.90 (4 H, m), 4.02 (2 H, t, *J* = 7 Hz), 4.91 (1 H, dd, *J* = 4, 4 Hz); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 16.2 (CH_3), 19.1 (CH_2), 21.1 (CH_3), 21.3 (CH_3), 23.8 (CH_2), 25.9 (CH_2), 27.2 (CH_2), 29.7 (CH_2), 45.5 (C), 64.6 (CH_2), 65.2 (CH_2), 65.7 (CH_2), 77.5 (CH), 112.6 (C), 170.5 (COO), 171.2 (COO); MS, *m/e* M^+ 314. Anal. Calcd for $C_{16}H_{26}O_6$: C, 61.16; H, 8.34. Found: C, 61.04; H, 8.47. **84**: $[\alpha]_D$ +27.9° (*c* 2, $CHCl_3$); ^1H NMR ($CDCl_3$, 470 MHz) δ 1.05 (3 H, s, CH_3), 1.4–1.8 (10 H, m), 2.03 (6 H, s, 2 CH_3), 3.92 (6 H, m), 4.89 (1 H, dd, *J* = 3, 5 Hz); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 15.3 (CH_3), 19.0 (CH_2), 21.0 (CH_3), 21.3 (CH_3), 24.4 (CH_2), 26.3 (CH_2), 29.9 (CH_2), 30.0 (CH_2), 45.0 (C), 64.3 (CH_2), 65.0 (CH_2), 66.7 (CH_2), 76.2 (CH), 113.1 (C), 170.5 (COO), 171.2 (COO); MS, *m/e* M^+ 314. Anal. Calcd for $C_{16}H_{26}O_6$: C, 61.16; H, 8.34. Found: C, 61.24; H, 8.12.

(2*S*,3*S*)-6-Methyl-2-oxabicyclo[4.4.0]decane-3,7-dione 3,7-Diethylene Acetal (85) and (2*R*,3*S*)-6-Methyl-2-oxabicyclo[4.4.0]decan-3-one Ethylene Acetal (86). To a solution of lactones **77** and **79** (35:65; 100 mg, 0.5 mmol) in benzene (50 mL) were added ethylene glycol (170 mg, 2.7 mmol) and *p*-toluenesulfonic acid (9 mg, 0.05 mmol). The solution was refluxed for 16 h with azeotropic removal of water. The mixture was cooled to 25 °C, solid $NaHCO_3$ was added, and the solvent was evaporated. The residue was purified by chromatography (silica gel, 10% dichloromethane in ether) to give two products, the ortho ester **85** (33 mg, 25%) and the lactone **86** (57 mg, 50%). **85**: ^1H NMR ($CDCl_3$, 470 MHz) δ 1.08 (3 H, s, CH_3), 1.47 (6 H, m), 1.74 (2 H, m), 2.02 (2 H, m), 3.9 (8 H, m), 4.15 (1 H, m); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 13.4 (CH_3), 19.7 (CH_2), 26.2 (CH_2), 26.6 (CH_2), 28.0 (CH_2), 30.0 (CH_2), 41.7 (C), 63.4 (CH_2), 64.6 (CH_2), 64.9 (CH_2), 65.3 (CH_2), 75.7 (CH), 112.3 (C), 119.2 (C); MS, *m/e* M^+ 270.

(2*R*,3*S*)-3-Acetoxy-2-(3-acetoxypropyl)-2-methylcyclohexanone Ethylene Acetal (84). Lactone **86** was converted to diacetate **84** by a similar procedure of $LiAlH_4$ reduction and acetylation as used for the conversion of **41** to **40**. The diacetate **84** prepared in this manner had $[\alpha]_D$ +27.7° (*c* 10, $CHCl_3$) and other spectral data, identical with that for **84** prepared from **63**.

Synthesis and Resolution of 3-Amino-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-ones

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Two efficient synthetic routes to the 3-amino-1,4-benzodiazepin-2-ones **2** and **3** were developed. The first sequence was carried out in 55–60% overall yield and involves a novel mercuric ion assisted ammonia displacement of the (alkylthio)glycinamide **14** to produce the key intermediate α-aminoglycinamide **15**. The second approach features a practical two-step amination of the parent 1,4-benzodiazepine ring system **24** to afford the title compound **3** in 49% overall yield from 2-aminobenzophenone. The 3-amino-1,4-benzodiazepine **3** was resolved via the separation of the corresponding diastereomeric phenylalanyl amides. The desired (−)-**3** enantiomer was then liberated by use of the Edman degradation.

The ubiquity of the benzodiazepines in the chemical literature is doubtless a consequence of the multifarious biological responses they elicit in animals. The use of this class of compounds as therapeutic agents is not merely confined to the management of anxiety and stress-related conditions as additional novel applications are continuously emerging.[1-3] The recent demonstration that the 5-phenyl-1,4-benzodiazepine ring system can serve as a useful template in the construction of ligands for peptide receptors has imparted further interest in these compounds

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