An Enantioselective Method for Reductive Alkylation of Aromatic Carboxylic Acid Derivatives. Examination of the Factors That Provide Stereoselectivity

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Abstract: Birch reduction of the L-prolinol-derived benzoxazepinone **1a** gave amide enolate **16** and alkylation of **16** at −78 °C with a variety of alkyl halides afforded products of α-alkylation with good to excellent diastereoselectivity, e.g., **16a–g**. Reductive alkylation studies of benzoxazepinones **1b–d** and **6a,b** provided information on the effects of aromatic ring substitution and changes in the structure of the chiral auxiliary on the regio- and diastereoselectivities of enolate alkylation. Most noteworthy is the observation that reductive methylation of the (*S*)-2-methylprolinol derived benzoxazepinone **6b** gave γ-alkylated **24** as a 4:1 mixture of diastereoisomers in 80% yield. Reductive methylation of 2-methoxybenzamide **2a**, the acyclic variant of **1a**, gave **28a** and the corresponding diastereoisomer **55** in a ratio of 260:1. Other alkyl halides gave α-alkylation products, **28b–e**, with comparable diastereoselectivities, while protonation of the enolate **27** with excess NH_4Cl at −78 °C gave **29** as a 4:1 mixture of diastereoisomers in 92% yield. Treatment of **29** with *n*-BuLi in THF at −78 °C regenerated enolate **27**. Several solvent and temperature effects on the stereoselectivity of alkylation of **27** were observed, the most remarkable of which was the reversal of the sense of alkylation to favor **55** over **28a** (>99:1) when the enolate was warmed to 25 °C in THF prior to methylation (MeI) at −78 °C. ^1H NMR characterization of enolates **26a**, **26b**, **63a**, and **27** enabled an assignment of *Z* configuration to enolates **27** and **62b**. Chemical reactivity studies with modified substrates **2b–e**, **5a–c**, **7a,b**, **10a–d**, and **32** and two-dimensional NMR data were used to develop models for the structure of enolate **27** in various environments; e.g., **57–59**. Reductive alkylation of 2-methylbenzamide **32** gave **33** with >99:1 diastereoselectivity. The unique value of the chiral auxiliary L-prolinol was demonstrated by reductive methylations of the (*S*)-2-methylprolinol and *dl*-2-(hydroxymethyl)piperidine derivatives **7a**, **7b**, **5b**, and **5c**, which gave α-alkylated products **53a**, **53b**, **54a**, and **56b** without significant stereocontrol.

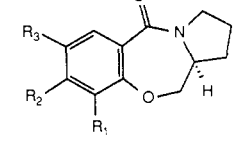
In a series of recent papers we described chemistry that facilitates the conversion of 2-alkoxy-, 2-amino-, 2-alkyl-, and 2-arylbenzoic acid derivatives into a variety of enantiomerically pure chiral cyclohexanes.[2] The key step in the process involves an alkylation or protonation of a chiral amide enolate that is produced by Birch reduction of the aryl nucleus. This chemistry should find wide application in organic synthesis; in fact, we have already described enantioselective total syntheses of (−)-longifolene,[2b] (+)-sibirine,[2d] (+)-nitramine,[2d] (−)-isonitramine,[2d] (+)-pumiliotoxin-C,[2e] and (+)-perhydro 219A.[2g]

We now report a detailed examination of the factors that control the stereoselectivity of alkylation of chiral amide enolates generated from Birch reduction of 2-alkoxy- and 2-methylbenzoic acid derivatives. Information pertaining to (1) enolate structure, (2) the importance of potential chelation sites, (3) the effect of substituents near the enolate alkylation center, and (4) the role of reaction solvent, temperature, and concentration in alkylation stereoselectivity is presented.

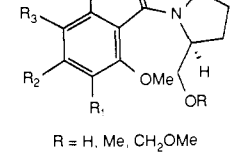
Results and Discussion

Background. The Birch reduction and reductive alkylation of aromatic compounds has been one of the most widely used methods for transformation of these substrates into alicyclic derivatives. Excellent reviews of experimental procedures and applications to organic synthesis are available.[3]

Our initial interest in the reductive alkylation of benzoic acid derivatives was focused on the development of new methods for construction of 2,4- and 2,5-cyclohexadien-1-ones.[4-6] An early attempt at the preparation of optically active 2,4-cyclohexadien-1-ones by the reductive alkylation of a *d*-menthol-derived anisic ester failed to give any diastereoselectivity in the alkylation step.[5] The impressive diastereoselectivities obtained by several research groups for alkylations of prolinol-derived amide enolates and related systems[7] inspired an examination of the reductive alkylations of benzoxazepinone **1a**[2a] and, subsequently, the acyclic variant **2a**.[2c] Excellent diastereoselectivities were observed for



1a, $R_1 = R_2 = R_3 = H$
b, $R_1 = Me$, $R_2 = R_3 = H$
c, $R_2 = Me$, $R_1 = R_3 = H$
d, $R_3 = Me$, $R_1 = R_2 = H$



R = H, Me, CH_2OMe

2a, $R_1 = R_2 = R_3 = R_4 = H$
b, $R_1 = Me$, $R_2 = R_3 = R_4 = H$
c, $R_2 = Me$, $R_1 = R_3 = R_4 = H$
d, $R_3 = Me$; $R_1 = R_2 = R_4 = H$
e, $R_4 = Me$, $R_1 = R_2 = R_3 = H$

reductive alkylation of these substrates, but even more remarkable was the observation that the sense of stereoselection from **2a** was opposite to that obtained from **1a**. These early results appeared to be of great practical value in that a single chiral auxiliary, L-prolinol (**11**), depending on the mode of attachment to the aromatic substrate, provided alkylated products of high enantiomeric purity in both *R* and *S* configurations.

(1) Sterling-Winthrop Fellowship for Graduate Studies, 1986-7.
(2) (a) Schultz, A. G.; Sundararaman, P. *Tetrahedron Lett.* **1984**, *25*, 4591. (b) Schultz, A. G.; Puig, S. *J. Org. Chem.* **1985**, *50*, 915. (c) Schultz, A. G.; Sundararaman, P.; Macielag, M.; Lavieri, F. P.; Welch, M. *Tetrahedron Lett.* **1985**, *26*, 4575. (d) McCloskey, P. J.; Schultz, A. G. *Heterocycles* **1987**, *25*, 437. (e) Schultz, A. G.; McCloskey, P. J.; Court, J. J. *J. Am. Chem. Soc.* **1987**, *109*, 6493. (f) Schultz, A. G.; Macielag, M.; Podhorez, D. E.; Suhadolnik, J. C.; Kullnig, R. K. *J. Org. Chem.* **1988**, *53*, 2456. (g) McCloskey, P. J.; Schultz, A. G. *J. Org. Chem.* **1988**, *53*, 1380.
(3) Hook, J. M.; Mander, L. N. *Nat. Prod. Rep.* **1986**, *3*, 35 and reviews cited therein.
(4) Schultz, A. G.; Dittami, J. P. *Tetrahedron Lett.* **1983**, *24*, 1369.
(5) Schultz, A. G.; Dittami, J. P.; Lavieri, F. P.; Salowey, C.; Sundararaman, P.; Szymula, M. B. *J. Org. Chem.* **1984**, *49*, 4429.
(6) (a) Schultz, A. G.; Lavieri, F. P.; Macielag, M. *Tetrahedron Lett.* **1986**, *27*, 1481. (b) Schultz, A. G.; Lavieri, F. P.; Macielag, M.; Plummer, M. *J. Am. Chem. Soc.* **1987**, *109*, 3991.
(7) (a) Evans, D. A. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic: New York, 1984; Vol. 3, pp 1-110. (b) Takacs, J. M. Ph.D. Thesis, California Institute of Technology, 1981. (c) Enders, D.; Kipphardt, H. *Nachr. Chem. Tech. Lab.* **1985**, *33*, 882.

0002-7863/88/1510-7828$01.50/0

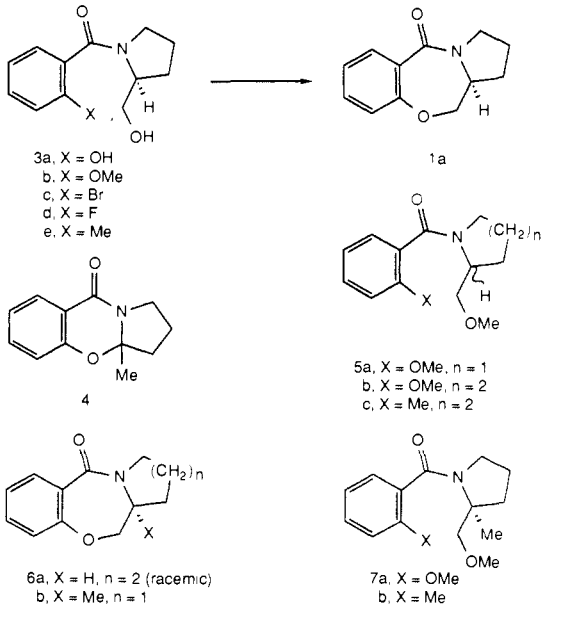
Preparation of Substrates for Reductive Alkylation Studies. Aryl amides **2a–e** were prepared by N-acylation of L-prolinol with the appropriate aroyl chloride. Subsequent O-alkylation of **2a–e** with MeI or $MeOCH_2Cl$ provided the opportunity to test the effect of the group R on the diastereoselectivity of reductive alkylation; e.g., **2a–e**, R = H, Me, CH_2OMe.

Benzoxazepinone **1a** was prepared by several methods. The first procedure involved intermediate **3a**, which was obtained in ca. quantitative yield by DCC coupling of 2-hydroxybenzoic acid with L-proline. Cyclization of **3a** occurred in ~80% overall yield by use of Mitsunobu reaction conditions.[8] Other methods of cyclization resulted in varying amounts of benzoxazinone **4**, presumably formed by elimination to the enamide and intramolecular phenol–olefin addition. For example, benzoxazinone **4** was obtained in 73% yield from treatment of the chloromethyl derivative of **3a** with potassium carbonate in acetone.

More convenient preparations of **1a**, free of benzoxazinone **4**, involve cyclizations of the 2-methoxy derivative **3b**[2c] and the 2-bromo derivative **3c**[9] in DMF with sodium hydride at 120 °C. The 2-fluoro substituent is a considerably better leaving group in aromatic nucleophilic substitution reactions (S_NAr).[10] As a result, cyclization of **3d** occurred at 25 °C, and crystalline **1a** was obtained in 88% isolated yield without the need for chromatographic purification.[9] Thus, 2-fluorobenzoyl derivatives are the preferred substrates for preparation of benzoxazepinones. However, because of the availability of starting materials, methyl-substituted benzoxazepinones **1b–d** were prepared by cyclization of the corresponding 3-, 4-, and 5-methyl-substituted 2-methoxybenzamides.

Several modified aroyl substrates were prepared during the course of investigation of the stereoselectivity of reductive alkylation. Racemic derivative **5a** was obtained by acylation of *dl*-prolinol with 2-methoxybenzoyl chloride. Acylations of *dl*-2-(hydroxymethyl)piperidine with 2-methoxybenzoyl chloride and 2-methylbenzoyl chloride gave the corresponding racemic amides **5b** and **5c**. Racemic benzoxazepinone **6a** also was prepared.

Seebach and co-workers have described a technique for the preparation of α-substituted proline derivatives, with "self-reproduction of chirality" of the original amino acid.[11] Using this method, we prepared (*S*)-2-methylproline and converted it to the benzoxazepinone **6b** and benzamides **7a** and **7b**.



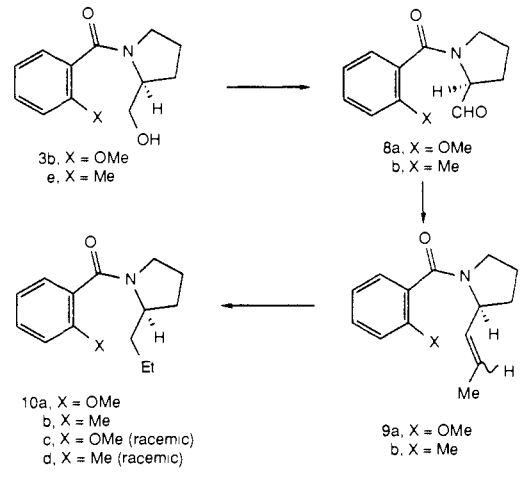
(8) Mitsunobu, O. *Synthesis* **1981**, 1 and references cited therein.

(9) For a study of the cyclization and bimolecular cyclization of **3c**, **3d**, and related substrates, see: Schultz, A. G.; Pinto, D. J. P.; Welch, M.; Kullnig, R. K. *J. Org. Chem.* **1988**, *53*, 1372.

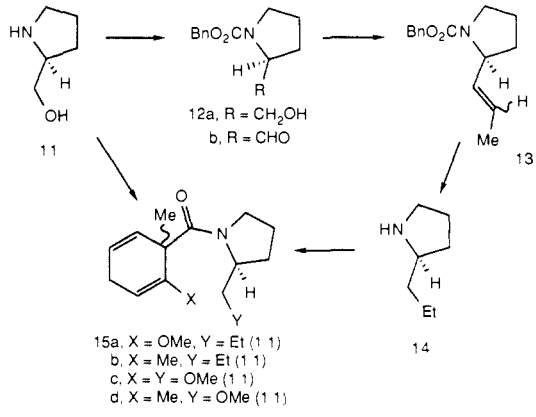
(10) March, J. *Advanced Organic Chemistry*, 3rd ed.; Wiley: New York, 1985; Chapter 13.

(11) Seebach, D.; Boes, M.; Naef, R.; Schweizer, W. B. *J. Am. Chem. Soc.* **1983**, *105*, 5390.

Scheme I



Scheme II



Scheme I outlines the conversions of benzamides **3b** and **3e** to **10a** and **10b**. Swern oxidation[12] of **3b** and **3e** gave aldehydes **8a** and **8b**, and these were treated with ethylenetriphenylphosphorane to give **9a** and **9b** as mixtures of olefin isomers. Hydrogenation of **9a** and **9b** gave **10a** and **10b**. Both sequences were repeated starting with *dl*-prolinol to give samples of racemic amides **10c** and **10d**. Although it was not possible to directly determine the enantiomeric purity of **10a** and **10b** by chiral ^1H NMR shift analyses, subsequent studies (vide infra) indicated that some epimerization had occurred (~90:10 mixtures of enantiomers) during synthesis of **10a** and **10b**.

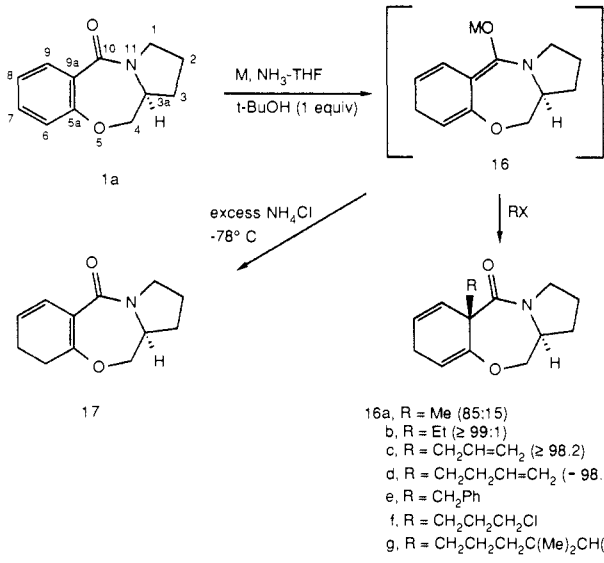
An analysis of the diastereoselectivity of reductive alkylation of **2a**, **32**, **10a**, and **10b** required the preparation of 1:1 diastereoisomeric mixtures of **15a–d** (Scheme II). L-Prolinol (**11**) was converted to the *N*-(benzyloxy)carbonyl derivative **12a**, from which aldehyde **12b** was obtained by Swern oxidation.[12] Condensation of **12b** with ethylenetriphenylphosphorane and hydrogenation (hydrogenolysis) of the resulting mixtures of olefin isomers **13** provided pyrrolidine **14**. Acylations of **14** with the carboxylic acids derived from racemic 6-carbomethoxy-1-methoxy-6-methyl-1,4-cyclohexadiene[13] and 6-carbomethoxy-1,6-dimethyl-1,4-cyclohexadiene provided **15a** and **15b**, respectively. Acylations of L-prolinol (**11**) with these same carboxylic acids, followed by O-methylation of the resulting amido alcohols gave **15c** and **15d**.

Reductive Alkylations of Benzoxazepinones. Birch reduction of **1a** at −78 °C with alkali metals in NH_3–THF solution in the presence of 1 equiv of *tert*-butyl alcohol and alkylation of the resulting amide enolate **16** at −78 °C with methyl iodide gave **16a** in 67% isolated yield (Scheme III), together with the diastereoisomer **18** and the product of γ-alkylation **19** (~3%). The diastereoselectivity of α-alkylation was determined to be 85:15,

(12) Mancuso, A. J.; Huang, S. L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.

(13) Hook, J. M.; Mander, L. N.; Woolias, M. *Tetrahedron Lett.* **1982**, *23*, 1095.

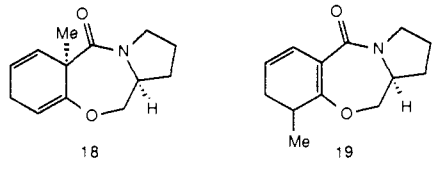
Scheme III



1a 16 17

16a, R = Me (85:15)
b, R = Et (≥ 99:1)
c, R = $CH_2CH{=}CH_2$ (≥ 98:2)
d, R = $CH_2CH_2CH{=}CH_2$ (~ 98:2)
e, R = CH_2Ph
f, R = $CH_2CH_2CH_2Cl$
g, R = $CH_2CH_2CH_2C(Me)_2CH(OMe)_2$

while γ-alkylation produced a single diastereoisomer of undetermined configuration at C(6).[14]



18 19

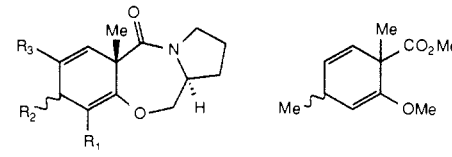
The diastereoselectivity for reductive methylation of **1a** was independent of the alkali metal (Li, Na, K) used in the reduction step. Alkylations of enolate **16** with alkyl halides more sterically demanding than methyl iodide gave diastereoselectivities in excess of 98:2. Ethyl iodide provided **16b** in 82% isolated yield. Allyl bromide (75% yield for **16c**), benzyl bromide (73%), and even homoallylic halides (4-bromo-1-butene, 89%)[15] gave α-alkylated products with excellent diastereoselectivities. Functionalized alkyl halides also are effective as demonstrated by the conversion of **1a** to **16f** (91%; an intermediate in nitramine alkaloid total syntheses)[2d] and to **16g** (96%; an intermediate in the longifolene total synthesis).[2b]

Protonation of the potassium enolate **16** at −78 °C with excess NH_4Cl gave the product of γ-protonation, **17**, in 73% isolated yield. The α-protonated isomer also was observed (20%; ^1H NMR analysis of the crude reaction mixture), but this material could not be isolated by attempted chromatographic separation of the reaction mixture. On the basis of parallel studies with the protonation of the enolate generated from Birch reduction of **2a** (vide infra), we expected to obtain mainly α-protonated material from **16**. Presumably, equilibration between α- and γ-protonated products occurs during quenching of enolate **16**; however, we cannot eliminate the distinct possibility that kinetic protonation[16] occurs predominately at C(6) rather than C(9a).

Regeneration of enolate **16** from **17** was accomplished by treatment with lithium diisopropylamide in THF solution. Methylation in the ammonia-free and *tert*-butyl alcohol free environment provided **16a** and its diastereoisomer **18** in yield and stereoselectivity (90:10 favoring **16a**) comparable to that obtained from Birch reduction–methylation of **1a** (85:15). Evaporative removal of ammonia from Birch reduction of **1a** followed by methylation of **16** in residual THF at −78 °C also did not produce a significant change in product distribution. While not obvious at this stage of the discussion, the absence of solvent effects on the reactivity of **16** is interesting in light of solvent and temperature studies to be considered in the context of reductive alkylation of amide **2a**.

A tentative assignment of stereochemical configuration to the series **16a–d** was initially based on NOE studies with a derivative of **16a**.[2a] Subsequently, an assignment for the entire series **16a–g** was unambiguously made by conversion of **16g** to (−)-longifolene[2b] and an X-ray structure determination of a derivative of **16a**.[17] This information permitted the confident assignment of absolute stereochemical configuration to the nitramine alkaloids, for which only relative configuration had been reported.[2d]

Reductive methylation of the 6- and 8-methylbenzoxazepinones **1b** and **1d** using potassium and methyl iodide afforded **20a** and **20c** with diastereoselectivities (85:15) comparable to that of **1a**. The four diastereoisomers obtained from the 7-methyl derivative **1c** indicated that protonation at C(7) occurred with little stereoselectivity.[18] Similar results had been obtained with methyl 2-methoxy-4-methylbenzoate, which gave a 1.3:1 mixture of diastereoisomers **21**.[5] On the basis of more detailed analysis of the 4-methyl analogue **2c** (vide infra), it is concluded that the two major diastereoisomers of **20** have the methyl at C(9a) in the β configuration. Furthermore, because reductive methylation of **1a** proceeded with the lowest diastereoselectivity of the alkyl halides examined, we believe that alkylation of the enolates derived from **1b–d** with other alkyl halides will occur with diastereoselectivities ≥98:2.[19]



20a, R_1 = Me, R_2 = R_3 = H (85:15)
b, R_2 = Me; R_1 = R_3 = H (1:4.5:6:1)
c, R_3 = Me; R_1 = R_2 = H (85:15)

21 (1:3:1)

Experiments with modified benzoxazepinones **6a** and **6b** revealed some noteworthy effects of variation of the chiral auxiliary on reaction regio- and stereoselectivity.[20] The value of the chiral pyrrolidine ring was demonstrated by reductive methylation of *dl*-**6a**, which gave the α-methylated product as a 2:1 mixture of diastereoisomers. The major isomer (shown as **22**, racemic mixture) was obtained in 36% isolated yield by flash chromatography of the reaction mixture on silica gel. In contrast to the reductive methylation of **1a**, which gave only a small amount of γ-alkylated material (**19**, 3%), **6a** gave **23** as a 3:1 mixture of diastereoisomers in 34% yield. Quantitative analysis of the reaction mixture was performed by VPC methods and GC–MS in which all four components were clearly resolved; however, the minor α-alkylated diastereoisomer and **23** could not be separated by preparative techniques.

Reductive methylation of the (*S*)-2-methylprolinol-derived benzoxazepinone **6b** gave γ-alkylated **24** as a 4:1 mixture of diastereoisomers (~80%). These products were obtained as crystalline materials and were fully characterized, but the products of α-alkylation (**25**, 18%) could not be separated.

(14) The analogous γ-alkylation (methyl iodide) of the enolate derived from Birch reduction of 1,2,3,10,11,11a-hexahydro-5*H*-pyrrolo[2,1-*c*][1,4]-benzodiazepine-5,11-dione was found to occur at C(9) exclusively from the β-face (see ref 2e).

(15) This result is in contrast to that obtained from reaction of homoallylic halides with enolates described in ref 2e.

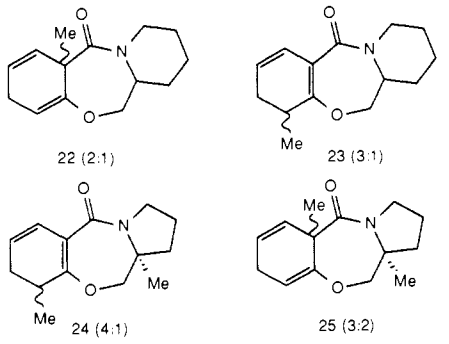
(16) Zimmerman, H. E. *Acc. Chem. Res.* **1987**, *20*, 263.

(17) Unpublished results of Dr. James P. Springer, Merck, Sharp and Dohme Research Laboratories, Rahway, NJ. We thank Dr. Springer for the X-ray crystallographic studies.

(18) One possibility for control of stereochemical configuration at C(7) that was considered involves a protonation (stereoselective?) at C(9a) of the initial radical anion derived from metal reduction of **1c**, a subsequent electron transfer to give the diallylically stabilized carbanion at C(7), and a suprafacial 1,4-hydrogen migration from C(9a) to C(7) to give the 7-methyl analogue of enolate **16**. However, the absence of stereocontrol at C(7) in the conversion of **1c** into **20b** precludes any statement concerning the likelihood of this mechanistic possibility.

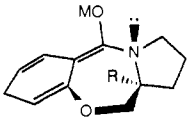
(19) For prior observations concerning the effect of alkyl halide size on the stereoselectivity of enolate alkylation, see: Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737 and references cited therein.

(20) For the effects of substituents attached to the chiral auxiliary prolinol on the stereoselectivities of propionamide alkylations (see ref 7b).



The excellent diastereoselectivities observed with **1a**, especially when compared to the previously mentioned *d*-menthol-derived anisic ester, which failed to give any stereoselection on reductive alkylation, deserves some additional comment. Seebach, Dunitz, and co-workers[21] have found from X-ray crystallographic analysis of amide lithium enolates that, in the solid state, the nitrogen atom is highly pyramidalized. We feel that the stereoselectivities of alkylation discussed in this paper are tied directly to the configurations of the enolate nitrogen atom. In fact, the 1,4-asymmetric induction represented by alkylation of enolate **16** [C(9a)–C(3a)] might be more properly considered to be a case of 1,3-asymmetric induction [(9a)–N(11)].[22]

A three-dimensional representation of enolate **16** is shown as structure **26a**. Dreiding stereomodels suggest that the trans ring fusion defined by the electron pair on the nitrogen atom and the hydrogen atom at C(3a) produces relatively little ring strain. The β-face of **26a** appears to be the most exposed, and, stereoelectronic issues aside,[23] preferential alkylation from this face would be expected. Furthermore, as the alkyl halide becomes more sterically demanding, the degree of selectivity should increase.

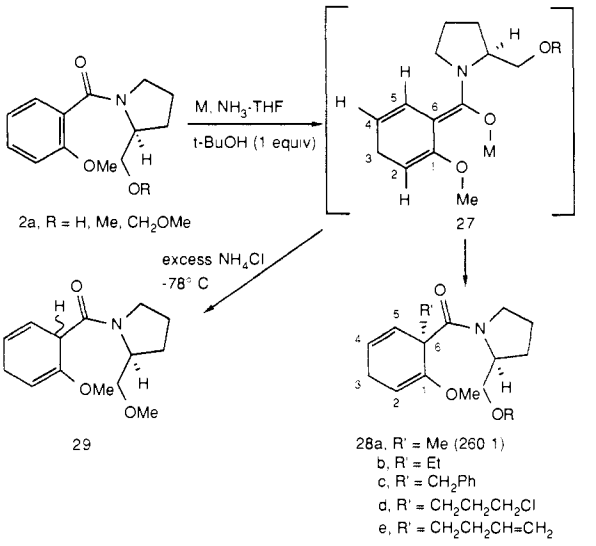


26a, R = H
b, R = Me

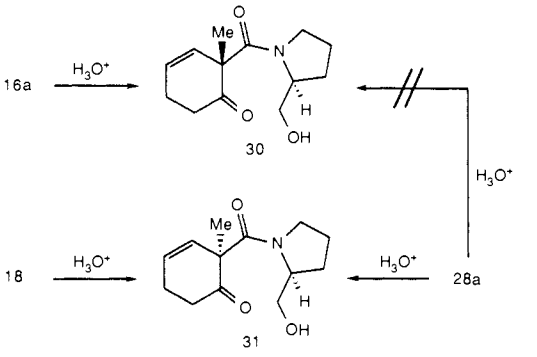
The methyl group at C(3a) in **26b** was expected to provide a shield for the α-face of the enolate and give increased diastereoselectivity for methylation relative to that obtained with **26a** (85:15). Instead, stereoselectivity of α-alkylation of the enolate derived from **6b** deteriorated, and γ-alkylation became the predominant reaction pathway. Models suggest that **26b** is destabilized because of a transannular interaction between C(9a) and the methyl group at C(3a). An inversion of configuration at N(11) would alleviate this interaction, but now the enolate experiences an unfavorable 1,3-steric interaction involving C(1) and methyl iodide approaching C(9a). With both faces of the enolate shielded at C(9a), alkylation occurs predominantly at the relatively unhindered C(6).

It should be noted that γ-alkylation of lithium dienolates[24] and cuprated lithium dienolates[25] derived from unsaturated amides have been previously observed.[26] Although the regioselectivity of alkylation of copper enolates derived from amides of type **17** has not been examined, this modification might provide a means for obtaining γ-alkylation products with enantioselective control.

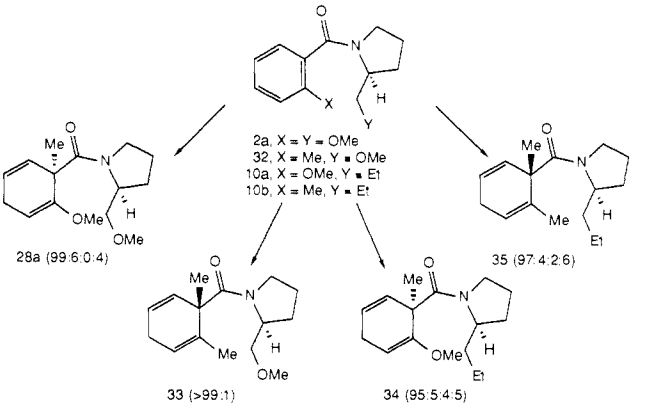
Scheme IV



Scheme V



Scheme VI



Reductive Alkylations of Chiral Benzamides. Birch reduction of **2a** (R = H, Me, or CH_2OMe) as described for **1a** followed by alkylation with methyl iodide at −78 °C gave **28a** and the corresponding diastereoisomer (e.g., **55**) in a ratio of 260:1 (Scheme IV). Alkylation at −33 °C resulted in a slightly decreased stereocontrol (170:1). The diastereoselectivity was found to be independent of the substituent attached to the prolinol oxygen atom[20] and, as with **1a**, the alkali metal used in the reduction step. Chromatography on silica gel provided **28a** in 82–85% yields.[27]

(21) (a) Bauer, W.; Laube, T.; Seebach, D. *Chem. Ber.* **1985**, *118*, 764. (b) Laube, T.; Dunitz, J. D.; Seebach, D. *Helv. Chim. Acta* **1985**, *68*, 1373.

(22) For examples of prior recognition of the importance of the pyramidal nature of the nitrogen atom in alkylations of chiral chelated lithioenamines, amide enolates, and related systems, see: (a) Meyers, A. I.; Williams, D. R.; Druelinger, M. *J. Am. Chem. Soc.* **1976**, *98*, 3032. (b) Hashimoto, S.; Koga, K. *Tetrahedron Lett.* **1978**, 573. (c) Kümin, A. Ph.D. Thesis, Eidgenössischen Technischen Hochschule, 1979. (d) Reference 7b.

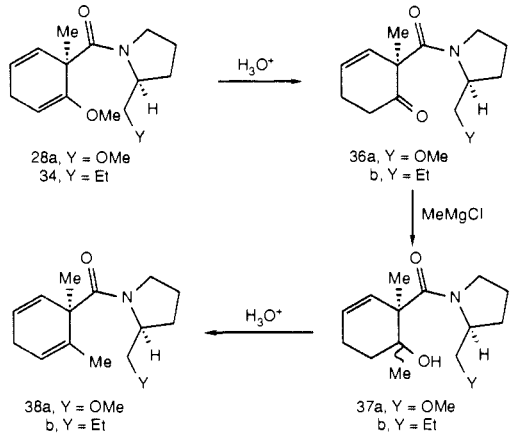
(23) For impressive examples of stereocontrolled bicyclic γ-lactam enolate alkylations and an amination, see: (a) Magnus, P.; Gallagher, T.; Brown, P.; Huffman, J. C. *J. Am. Chem. Soc.* **1984**, *106*, 2105. (b) Meyers, A. I.; Haue, M.; Garland, R. *J. Am. Chem. Soc.* **1984**, *106*, 1146. (c) Baldwin, J. E.; Adlington, R. M.; Jones, R. H.; Schofield, C. J.; Zaracostas, C.; Greengrass, C. W. *J. Chem. Soc., Chem. Commun.* **1985**, 194.

(24) Wu, A.; Snieckus, V. *Tetrahedron Lett.* **1975**, 2057.

(25) Majewski, M.; Mpango, G. B.; Thomas, M. T.; Wu, A.; Snieckus, V. *J. Org. Chem.* **1981**, *46*, 2029.

(26) For the analogous γ-alkylation of copper enolates derived from α,β-unsaturated acids and esters, see: (a) Savu, P. M.; Katzenellenbogen, J. A. *J. Org. Chem.* **1981**, *46*, 239. (b) Ibuka, T.; Aoyagi, T.; Yoneda, F. *J. Chem. Soc., Chem. Commun.* **1985**, 1452.

Scheme VII



Reduction of **2a** (R = H) with lithium gave ~50% of 2-methoxybenzaldehyde. Amide group reductions occur not only with **2a** (R = H), but also *N*,*N*-dimethylbenzamide,[28] *N*,*N*-dimethyl-2-methoxybenzamide, and the 2-methoxybenzamide derived from pyrrolidine. Functional group reduction in **2a** (R = H) can be avoided by the utilization of potassium; subsequent methylation gives **28a** (R = Me) in 83% yield. Exchange of the potassium enolate with excess LiBr and methylation affords **28a** (R = Me) in 71% yield.

The diastereomeric composition of the products of reductive methylation of **2a** (R = Me) was determined by comparison to **15c** obtained as shown in Scheme II. The diastereomeric nature of **15c** (1:1) and **28a** (260:1) was apparent from ^{1}H NMR spectral (200 MHz), GC–MS, and flame ionization GC analyses. These analytical techniques (utilizing **15a**, **15b**, and **15d**) also were used to determine the diastereoselectivities of other reductive alkylations.

Stereochemical configuration of **28a** was deduced by chemical interconversions. Acid-catalyzed hydrolysis of **16a** gave cyclohexenone **30** (oil), while the corresponding minor diastereomer **18** (R = Me) was converted to **31** (mp 98–99 °C). Hydrolysis of **28a** (R = CH_2OMe) gave **31** (mp 98–99 °C) rather than **30** (Scheme V).

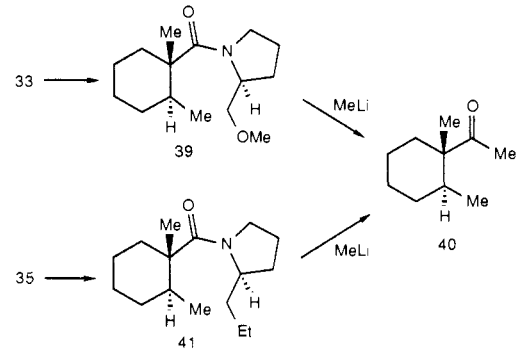
Alkylation of enolate **27** (M = K, R = Me or CH_2OMe) with ethyl iodide, benzyl bromide, 1-bromo-3-chloropropane,[2d] and 4-bromo-1-butene gave **28b–e** in 70–88% yields. A diastereomeric excess of 260:1 was determined for **28b**, but for **28c–e**, the second diastereoisomer was not detected. It is presumed that the diastereoselectivities are comparable to that for formation of **28a** and **28b**; however, the lower limit of detection of the second diastereoisomer in these experiments was estimated to be 2%.

The contrasting reactivities of enolates **16** and **27** were thought to be a result of opposite enolate geometries. An opportunity for chelation of the methoxy group with the alkali metal cation might provide stabilization of **27** relative to the geometric isomer resembling the configurationally locked enolate **16**. A second potential chelation site in **27** is the oxygen atom on the prolinol residue. Reductive alkylations of amides **2a**, **32**, **10a**, and **10b** were performed under identical conditions (K, MeI, ~0.02 M enolate) in order to test the importance of chelation effects on the sense and degree of asymmetric induction (Scheme VI).

Reductive methylation of **32** to give **33** occurred with asymmetric induction opposite to that of enolate **27** with greater than 99:1 selectivity. The effect of the oxygen atom on the prolinol residue was found to be small, but measurable; e.g., **10a** → **34** (95.5:4.5). Reductive methylation of **10b** gave **35** with the same sense of asymmetric induction as observed for formation of **33** but with decreased selectivity (97.4:2.6).

Enol ether **28a** was converted to **38a** by (1) acid-catalyzed enol ether hydrolysis to give **36a**, (2) methyl Grignard addition to **36a** and (3) acid-catalyzed dehydration of the resulting carbinol **37a**

Scheme VIII

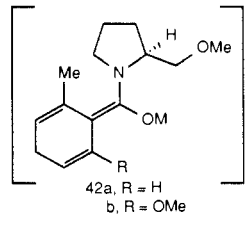


(Scheme VII, ~70% overall yield). ^{1}H NMR and GC–MS data, along with quantitative GC analysis, demonstrated that **38a** corresponds to the minor diastereoisomer obtained from **32**. An analogous procedure was used to establish the configuration of the major isomer, **34**, obtained from reductive methylation of **10a** (Scheme VII).

The constitution of **33**, the major product resulting from reductive methylation of **32**, was determined as shown in Scheme VIII. Amide-directed hydrogenation[29] with the homogeneous catalyst/solvent system $[Ir(cod)py(PCy_3)]PF_6/CH_2Cl_2$[30] gave **39** in 96% yield. Reaction of **39** with MeLi in THF first at 0 °C and then with warming to room temperature provided the methyl ketone **40** in 73% yield ($[\alpha]^{27}_D$ +5.84°). The same series of reactions proceeding from **35** afforded **40**. The reaction of MeLi with amides **39** and **41**, while enabling an important analytical process in the present context, constitutes a synthetically useful method for disposal of chiral auxiliaries unactivated for hydrolytic removal by a neighboring hydroxyl group.[31] Alkyllithium addition also has been effective for removal of the prolinol residue from substrates that are unstable to aqueous acid hydrolysis and in cases for which the amide to ketone conversion is synthetically attractive.[2f]

The optical rotation of **40** obtained from **35** ($[\alpha]^{23}_D$ +4.75° compared to $[\alpha]^{27}_D$ +5.84° for **40** obtained from **33**) revealed that racemization had occurred during preparation of the modified chiral substrates **10a** and **10b** (Scheme I). Preparation of authentic, racemic **40** by a literature procedure[32] and chiral ^{1}H NMR shift studies indicated that **40** obtained from **35** was a 90:10 mixture of enantiomers, requiring that **10a** and **10b** also were 90:10 mixtures of enantiomers. However, reductive alkylations with racemic **10c** and **10d** as well as **5a** demonstrated that alkylation stereoselectivities do not depend on enantiomeric composition of the starting benzamide.

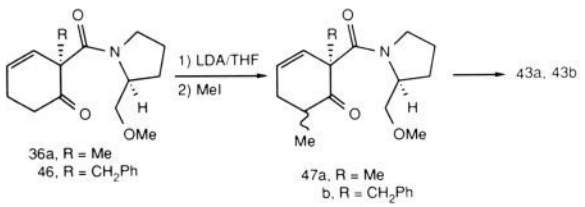
Additional Substituent and Structural Effects. Mechanistic Considerations. The data collected to this stage suggested that enolate **27** is the species undergoing alkylation to give **28** and enolate **42a** is the precursor of **33**. The predominant direction of approach of the alkyl halide to both enolates would be toward the α-face of C(6). Chelation of the alkali metal with the neighboring methoxy group might be responsible for the geometrical preference shown in **27**, while the vinyl methyl group in **42a** might more favorably reside distant from the enolate oxygen



atom. Although the substituted nitrogen atom in **42a** appears to

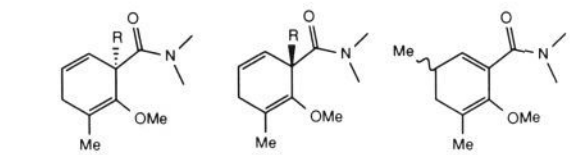
(27) The experimental procedure for preparation of **28a** (R = CH_2OMe) is described in ref 6b.
(28) Schultz, A. G.; Macielag, M. *J. Org. Chem.* **1986**, *51*, 4983.
(29) Schultz, A. G.; McCloskey, P. J. *J. Org. Chem.* **1985**, *50*, 5905.
(30) Crabtree, R. H.; Felkin, H.; Fellebeen-Khan, T.; Morris, G. E. *J. Organomet. Chem.* **1979**, *168*, 183.
(31) Phillips, A. P.; Baltzly, R. *J. Am. Chem. Soc.* **1947**, *69*, 200.
(32) Stork, G.; Borowitz, I. J. *J. Am. Chem. Soc.* **1960**, *82*, 4307.

Scheme IX



be the larger group, the drawing is somewhat deceiving in that enolate aggregates[33] may be the reacting species (vide infra) and, therefore, substituent M could be very large. The absence of an observable effect of a change in metal (Li, Na, K) on the diastereoselectivity of alkylation of enolate **27** is not particularly surprising in light of literature studies.[34]

The next experiments examined the effect of aromatic ring substituents on the diastereoselectivity of reductive methylation. It was reasoned that if the C(1) methoxy group in enolate **27** is involved in chelation with the alkali metal,[35] then placement of a methyl group at C(2) might disrupt chelation[36] and result in altered enolate reactivity. In fact, the 2-methoxy-3-methylbenzoic acid derivative **2b** (R = Me) gave predominantly **44a** (the product of inverted α-alkylation), diastereoisomer **43a**, and γ'-alkylated **45**. Yields for these products are shown, and the figures in parentheses correspond to the analogous product yields for the parent case **2a**. As with **2a**, the distribution of products from **2b** was independent of the alkali metal (Li or K) used in the Birch reduction step.



The ratio of diastereoisomers of γ'-alkylated material **45** was determined to be 42:1. Although the relative configuration of the major isomer has not been established, this result is of interest because of the particularly high 1,6-asymmetric induction.[37]

Reductive benzylation of **2b** (R = Me) gave **43b** and **44b** in a ratio of 1:178; crystalline **44** could be obtained in 75% isolated yield after flash chromatography of the reaction mixture on silica gel. The remarkable degree of regio- and diastereoselectivity obtained for enolate benzylation relative to methylation is suggestive of some special directing effect of the benzyl group. Perhaps coordination between the π-electrons of the aryl ring and the intermediate enolate[38,39] places the benzyl bromide in the proper orientation for alkylation at C(6). Relative configurations

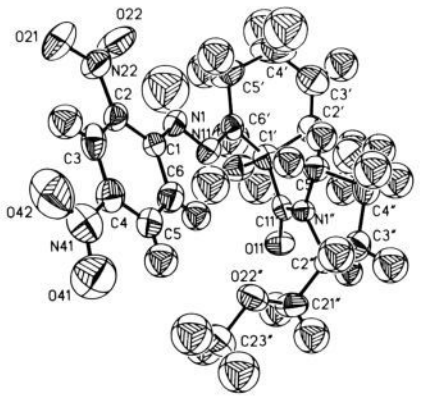
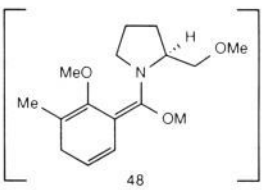


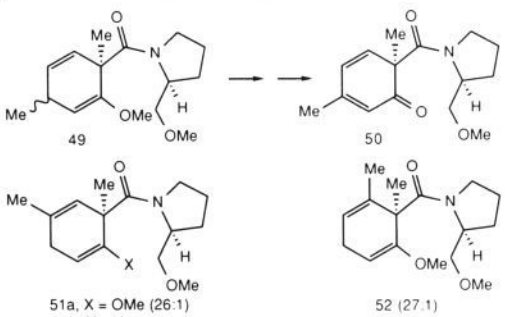
Figure 1. Molecular structure of the (2,4-dinitrophenyl)hydrazine derivative of **52**.

of **43a** and **43b** (and by implication **44a** and **44b**) were related to **28a** and **28c** via enones **36a** and **46** (Scheme IX).

Stereoelectronic considerations appear to provide a satisfactory explanation of the dramatic effect of the methyl substituent on the reductive alkylation of **2b** compared to **2a**. The low-energy conformation of a methoxy group with two ortho neighbors should be out of the plane of the aromatic ring,[36b] probably with a Ar–O–C dihedral angle of ~90°.[40] The methoxy group with only one ortho neighbor experiences restricted rotation in the plane of the ring with the carbon atom of the methoxy group turned away from the neighboring substituent. The second arrangement is compatible with chelation, but the first is not. Thus, the geometry of the enolate generated from **2b** might be that shown in structure **48**. As with enolates **27**, **42a**, and **42b**, the predominant direction of approach of the alkyl halide to C(6) of enolate **48** would be toward the α-face.



The 4-methyl analogue **2c** gave a 2:1 mixture of α-alkylated products **49** (76% isolated yield) and 5% of 2-methoxy-4-methylbenzaldehyde.[28] Cyclohexadienes **49** were determined to be diastereoisomeric at C(3) by conversion to a single 2,4-cyclohexadien-1-one **50**. The 5-methyl analogue **2d** gave **51a** and its diastereomer in a ratio of 26:1 (82% yield). Absolute configuration at C(6) of **49** was assumed to be the same as that of the major isomer **28a** obtained from **2a**. Absolute configuration at C(6) of **51a** was determined by (1) enol ether hydrolysis to the cyclohexenone, (2) ketone carbonyl group reduction, and (3) elimination of the resulting alcohol to give 1,4-cyclohexadiene **51b**. This material was identical with the product obtained from an analogous conversion of **44a** to **51b**.



(33) (a) Jackman, L. M.; Lange, B. C. *Tetrahedron* **1977**, *33*, 2737. (b) Jackman, L. M.; Szeverenyi, N. M. *J. Am. Chem. Soc.* **1978**, *99*, 4954. (c) Jackman, L. M.; Lange, B. C. *J. Am. Chem. Soc.* **1981**, *103*, 4494.

(34) For small changes in alkylation diastereoselectivity of lithium and sodium enolates of chiral imide substrates, for which intramolecular chelation has been suggested, see eq 52 in ref 7a, page 89. Other effects of a change in alkali metal cation on chiral recognition have been observed: Pearson, A. J.; Yoon, J. *J. Chem. Soc., Chem. Commun.* **1986**, 1467. For an example of an absence of an effect of a change in alkali metal, see: Kawanami, Y.; Ito, Y.; Kitagawa, T.; Taniguchi, Y.; Katsuki, T.; Yamaguchi, M. *Tetrahedron Lett.* **1984**, *25*, 857.

(35) Klumpp, G. W.; Sinnige, M. J. *Tetrahedron Lett.* **1986**, *27*, 2247.

(36) (a) Burton, G. W.; Ingold, K. U. *Acc. Chem. Res.* **1986**, *19*, 194. (b) Jardon, P. W.; Vickery, E. H.; Pahler, L. F.; Pourahmady, N.; Mains, G. J.; Eisenbraun, E. J. *J. Org. Chem.* **1984**, *49*, 2130.

(37) We are not aware of any precedent for such high levels of 1,6-asymmetric induction in alkylations of open enolate systems. For examples of macrocyclic stereocontrol, see: (a) Still, W. C.; Galynker, I. *Tetrahedron* **1981**, *37*, 3981. (b) Still, W. C.; Novak, V. J. *J. Am. Chem. Soc.* **1984**, *106*, 1148.

(38) Posner, G. H.; Lentz, C. M. *J. Am. Chem. Soc.* **1979**, *101*, 934.

(39) For a possible charge-transfer interaction between the π-system of an aromatic ring and an amide enolate, see: Heathcock, C. H.; Henderson, M. A.; Oare, D. A.; Sanner, M. A. *J. Org. Chem.* **1985**, *50*, 3019.

(40) Burton, G. W.; LePage, Y.; Gabe, E. J.; Ingold, K. U. *J. Am. Chem. Soc.* **1980**, *102*, 7791.

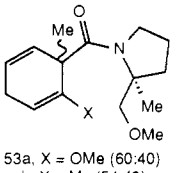
Table I. Stereoselectivity and Regioselectivity of Alkylation of Enolate **27** with Methyl Iodide

entry	method of enolate generation	enolate treatment	alkylation temp, °C	distribution of **28a** and **55**	% yield, **28a + 55**	% yield, **56**
1	*a*	none	−78	260:1	85	*e*
2	*a*	warm to −33 °C	−33	170:1	77	*e*
3	*a*	warm to 25 °C with loss of NH_3; readd NH_3 at −78 °C	−78	3:1	61	*e*
4	*a*	warm to 25 °C with loss of NH_3; recool to −78 °C	−78	<1:99	80	*e*
5	*b*	none	−78	~1:1	86	*e*
6	*b*	add NH_3 at −78 °C	−33	86:1	46[f]	*e*
7	*b*	warm to 25 °C; add NH_3 at −78 °C	−78	1.5:1	88	*e*
8	*b*	warm to 0 °C; recool to −78 °C	−78	1:4	82	*e*
9	*b*	warm to 25 °C; recool to −78 °C	−78	<1:99	94	*e*
10	*c*	none	−78	1:2	60	25
11	*c*	warm to 25 °C; recool to −78 °C	−78	<1:99	82	*e*
12	*d*	none	−78	<1:99	71	*e*
13	*b*	add HMPA (1.6 equiv) at −78 °C	−78	1:9	82	*e*
14	*b*	add HMPA (1.6 equiv) at 0 °C	−78	<1:99	80	*e*

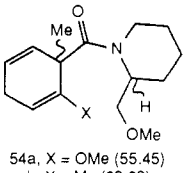
[a] Birch reduction of **2a** in NH_3–THF with 1 equiv of *t*-BuOH at −78 °C. [b] Deprotonation of **29** in THF with *n*-BuLi at −78 °C. [c] Deprotonation of **29** in THF with LDA at −78 °C. [d] Deprotonation of **29** in THF–hexamethylphosphoramide (HMPA) (1.6 equiv) with *n*-BuLi at −78 °C. [e] None detected by ^1H NMR spectral and GC analyses. [f] 30% of **29** recovered in this experiment.

If the proposed geometries of enolates **27** and **42a** are correct, then substitution of a methoxy group for a hydrogen atom in **42a** as shown in **42b** would not be expected to alter the geometry of the enolate or the sense of asymmetric induction on reaction of the enolate with methyl iodide. In accord with this line of reasoning, the 6-methyl analogue **2e** gave a 27:1 mixture of α-alkylation products (95% yield) favoring diastereoisomer **52**. Relative configuration of this substance was determined by X-ray crystallographic analysis of the (2,4-dinitrophenyl)hydrazine derivative, the molecular structure of which is shown in Figure 1.

In dramatic contrast to the excellent stereoselectivities observed for reductive methylation of **2a**, **32**, **10a**, and **10b** (Scheme VI), **7a** and **7b** gave α-alkylated products **53a** and **53b** (85–87% yields) with virtually no stereoselectivity. These results are interpreted



53a, X = OMe (60:40)
b, X = Me (54:46)



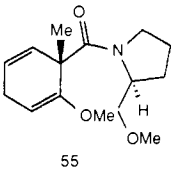
54a, X = OMe (55:45)
b, X = Me (68:32)

to be a consequence of a dissipation of the steric effects of the pyrrolidine ring side chain in **7a** and **7b** by the spatially demanding methyl substituent. It is noteworthy that ~80% γ-alkylated **24** was obtained from reductive methylation of the (*S*)-2-methylprolinol derived benzoxazepinone **6b**, but little, if any, γ-alkylation of **7a** was observed.

Reductive methylation of the *dl*-2-(hydroxymethyl)piperidine derivatives **5b** and **5c** also occurred without significant stereocontrol to give **54a** and **54b** (84–89% yields). This behavior is striking in light of the 260:1 diastereoselectivity obtained from **2a**. The preference for a substituent on a chair piperidine ring to be in an equatorial conformation may be responsible for the inability of the methoxymethyl side chain in enolates generated from **5b** and **5c** to block one face of C(6) more than the other.

Solvent and Temperature Effects on the Stereoselectivity of Alkylation of Enolate 27. Reaction of enolate **27** with excess NH_4Cl at −78 °C produced α-protonated **29** as a 4:1 mixture of diastereoisomers. Flash column chromatography on silica gel afforded **29** in 92% yield, *uncontaminated by the α,β-unsaturated isomer analogous to* ***17***. This reproducibly clean conversion provided an opportunity to examine the behavior of the enolate generated from **29** under a variety of experimental conditions.

Treatment of **29** with *n*-BuLi in THF at −78 °C resulted in α-deprotonation to give enolate **27** rather than carbonyl addition. Addition of ammonia to the enolate maintained at −78 °C in quantities sufficient to mimic the conditions of Birch reduction of **2a** (~10:1 volume distribution of NH_3 to THF) and alkylation at −33 °C with methyl iodide gave **28a** and its diastereoisomer **55** in a ratio of 86:1 (Table I, entry 6). The stereoselectivity of this modification compares favorably to that from **2a** at −33 °C (170:1, entry 2), indicating that *tert*-butyl alcohol in the Birch process has little if any effect on the stereoselectivity of enolate alkylation.[41a]



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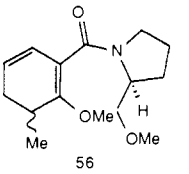


56

In contrast to the reactivity of the enolate in ammonia, methylation in THF at −78 °C gives a 1:1 mixture of **28a** and **55** (entry 5). If the enolate in THF is allowed to warm to 0 °C, recooled to −78 °C, and alkylated with methyl iodide, then **28a** and **55** are formed in a distribution of 1:4 (entry 8). *Warming the enolate in THF to 25 °C and alkylation with methyl iodide at −78 °C gives* ***55*** *with greater than 99:1 selectivity* (entry 9). The same pattern of reactivity vs temperature is observed when diethyl ether is used in place of THF. Diastereoisomer **55** also is the only product observed when ammonia is removed from the Birch reduced **2a** (entry 4). This is accomplished by allowing the reaction mixture to warm to 25 °C; the enolate in residual THF is recooled to −78 °C, and methyl iodide is added.

In considering the dramatic effect of ammonia on the stereoselectivity of alkylation of enolate **27**,[41b] we cite the pioneering work of Laube, Dunitz, and Seebach[21b] who have isolated and characterized by X-ray diffraction studies the dimeric *N,N*-dimethylpropionamide lithium *Z*-enolate as a complex with the lithium-chelating diamine *N,N,N'*-trimethylethylenediamine (TriMEDA). Two salient features of the complex are (1) the highly pyramidalized nitrogen atom of the enolate and (2) the presence of a six-membered ring complex involving chelation of the enolate lithium cation with the NHMe group of TriMEDA as well as a hydrogen atom bridge to the amide nitrogen atom. We now consider a series of experiments that are suggestive of an analogous role for ammonia and diisopropylamine as amide enolate chelating agents.

(41) (a) For examples of the effects of alkoxide salts on the diastereoselectivities of enolate condensation reactions, see: Seebach, D. *Proceedings of the R. A. Welch Foundation Conference on Chemical Research XXVII*, Houston, November 7–9, 1983. (b) Liquid ammonia has been shown to be effective in reducing proton transfer during alkylation of lithium enolates of cyclohexanones. With corresponding sodium and potassium enolates, alkylation and enolate equilibration proceed at comparable rates: Binkley, E. S.; Heathcock, C. H. *J. Org. Chem.* **1975**, *40*, 2156. (c) For the effects of HMPA on enolate reactions and aggregation, see: Fataftah, Z. A.; Kopka, I. E.; Rathke, M. W. *J. Am. Chem. Soc.* **1980**, *102*, 3959. Amstutz, R.; Schweizer, W. B.; Seebach, D.; Dunitz, J. D. *Helv. Chim. Acta* **1981**, *64*, 2617. Seebach, D.; Amstutz, R.; Dunitz, J. D. *Helv. Chim. Acta* **1981**, *64*, 2622.

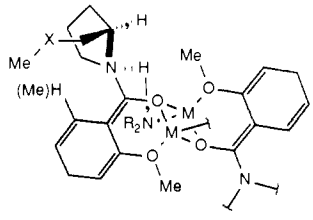
Deprotonation of **29** in THF with lithium diisopropylamide (LDA) at −78 °C and methylation at −78 °C gave **28a** and **55** in a 1:2 ratio in only 60% yield (entry 10) and, for the first time, significant quantities of the product of γ-alkylation, **56** (25%). However, if the enolate from **29** and LDA is allowed to warm to 25 °C and recooled to −78 °C prior to addition of methyl iodide, the γ-alkylated **56** is absent from the reaction mixture and **55** is obtained in 82% yield with >99:1 stereoselectivity (entry 11).

These data indicate that "kinetic enolates" generated by *n*-BuLi and LDA deprotonation at −78 °C react differently at −78 °C, but both relax to enolates with identical reactivities at higher temperature. Recall that addition of ammonia at −78 °C to the enolate generated by deprotonation of **29** with *n*-BuLi and alkylation with methyl iodide successfully reproduced the stereoselectivity of the Birch process. But, what would be the effect on alkylation stereoselectivity if this same enolate were allowed to equilibrate prior to addition of ammonia and methyl iodide? *Addition of 30 mL of ammonia to the enolate in THF that had previously been warmed to 25 °C and alkylation with methyl iodide at −78 °C gave an 88% yield of a 1.5:1 mixture of* ***28a*** *and* ***55*** (entry 7). A similar loss of stereoselectivity was observed when (1) ammonia was removed from the Birch reduction of **2a** at temperatures up to 25 °C, (2) an equivalent amount of ammonia was readded, and (3) methylation was performed at −78 °C (entry 3). Thus a "kinetic enolate" also is generated from Birch reduction of **2a**, but this enolate cannot equilibrate in ammonia when the temperature is maintained at −78 °C.

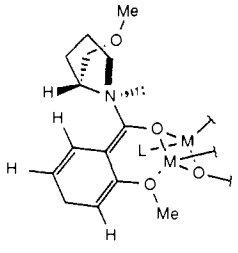
The effect of hexamethylphosphoramide (HMPA) on the stereoselectivity of alkylation also was examined (entries 12–14). In contrast to ammonia, HMPA promotes formation of diastereoisomer **55** (cf. entries **5** and **6** vs **5** and **13**, **14**). HMPA behaves as if it were an enolate relaxant (entries **5** vs **12** and **8**, **9** vs **13**); however, the precise role of HMPA as an enolate modifier remains to be defined.

Proposed Models for the Stereoselectivity of Alkylation of Enolate 27. The enolate that is produced from Birch reduction of **2a** under conditions of kinetic control (Table I, entry 1) may be a solvated dimeric aggregate as shown in **57a**. Chelation of the alkali metal M by the ring methoxy group[42a] and complexation (solvation) of the enolate with ammonia[21b] are proposed. The ammonia bridge in **57a** restricts rotational freedom of the pyrrolidine ring and results in blockage of the β-face of the enolate by the side chain of the chiral auxiliary; alkylation would be expected to occur from the relatively unhindered α-face of the enolate (Table I, entry 1). This same type of enolate aggregate is proposed to account for the stereoselectivity observed for alkylation of the 1-methoxy-5-methyl-substituted enolate **42b**.

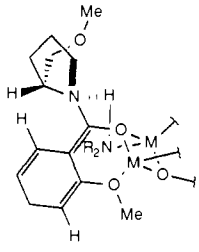
Removal of ammonia from the reaction mixture containing the solvated enolate with warming to 25 °C would allow rotation about the C–N bond and inversion of configuration at nitrogen of the chiral auxiliary to give dimeric enolate **58**. This relaxed arrangement appears to have the side chain of the chiral auxiliary in the least congested environment that is available away from the β-face of the enolate. A new ligand L, presumably a molecule of THF (or diethyl ether), would be at the coordination site formerly occupied by ammonia. The steric effects of the THF coordinated to the alkali metal and the removal of β-facial obstruction would work in concert to direct alkylation to the β-face of the enolate (entry 4). Stereoelectronic effects[23,43] (in the absence of hydrogen bonding from ammonia) also may operate to direct



57a, R = H, X = O, CH_2
b, R = i-Pr



58



59a, R = H
b, R = i-Pr

alkylation to the β-face of **58** antiperiplanar to the electron pair on the nitrogen atom of the chiral auxiliary.

Deprotonation of **29** with LDA at −78 °C could result in the formation of dimeric enolate complex **57b**,[42b] in which an isopropyl group of the amine ligand should provide some concealment of the α-face of the enolate. This model is compatible with a near-complete loss of stereoselectivity of α-alkylation (both faces of the enolate are hindered) and a shift of reactivity toward substantial γ-alkylation of **60b** (entry 10).

How do enolates generated by *n*-BuLi and LDA deprotonation of **29** at −78 °C relax at 25 °C to species that give **55** with >99:1 stereoselectivity? (1) Enolate geometrical isomerization, (2) temperature-dependent aggregation effects,[44] and (3) C–N bond rotation coupled with inversion of configuration at the nitrogen atom have been considered. We believe that enolate geometrical isomerization can be excluded from further consideration on the basis of literature observations[45] and because ^{1}H NMR spectral data (vide infra) obtained from lithium and potassium enolates generated from **29** and **2a** under a variety of conditions suggest the presence of only one geometrical isomer. Furthermore, successive addition of quantities of phenyl mercuric chloride[46] in THF-d_8 to an NMR tube containing the "kinetic lithium enolate" produced no change in the ^{1}H NMR spectrum.

The irreversible changes in the reactivity of enolates generated by deprotonation of **29** appear to be closely related to the changes that occur on removal of ammonia from the enolate **57a**. Treatment of **29** with *n*-BuLi at −78 °C may generate a dimeric enolate that has the chiral auxiliary in a conformation similar to that shown in **57**.[45] We suggest that there is a substantial barrier to conversion of this enolate to enolate **58**. Steric interactions between the side chain of the chiral auxiliary and the methoxy substituent of the enolate neighbor preclude C–N bond rotation without nitrogen inversion.

The free energy of activation for the inversion of the nitrogen atom in *N*-methylpyrrolidine has been found to be ~8 kcal/mol.[47a] However, the combined enolate C–N bond rotation and nitrogen

(42) (a) It has been shown that the lithium enolate of *o*-methoxyacetophenone in THF solution exists primarily as a dimer. Internal solvation of the lithium cation by the methoxy substituent was proposed to account for differences in aggregation between lithium and cesium enolates: Kaufman, M. J.; Streitwieser, A., Jr. *J. Am. Chem. Soc.* **1987**, *109*, 6092. (b) The X-ray crystallographic characterization of a lithium ketone enolate–lithium diisopropylamide complex, which shows a seven-membered chelate ring composed of the enolate oxygen atom, a lithium atom and a silyl ether oxygen atom, has been reported: Williard, P. G.; Hintze, M. J. *J. Am. Chem. Soc.* **1987**, *109*, 5539. See footnote 4 in this paper for reference to work suggesting the existence of aggregates of enolates and amide bases in solution.

(43) Deslongchamps, P. In *Stereoelectronic Effects in Organic Chemistry*; Pergamon: New York, 1983; Chapter 4.

(44) Jackman, L. M.; Szevernyi, N. *J. Am. Chem. Soc.* **1977**, *99*, 4954.

(45) In a study of ketone lithium enolates in 1,2-dimethoxyethane, equilibration between geometrical isomers did not occur by changes in temperature: House, H. O.; Trost, B. M. *J. Org. Chem.* **1965**, *30*, 2502.

(46) Ketone, aldehyde and ester enolates have been shown to undergo geometrical equilibration with catalytic phenylmercuric chloride: Spears, G. W.; Caufield, C. E.; Still, C. W. *J. Org. Chem.* **1987**, *52*, 1226.

(47) (a) Lambert, J. B.; Oliver, W. L., Jr. *J. Am. Chem. Soc.* **1969**, *91*, 7774. (b) For an example of the isolation of a configurationally stable "invertomer" of an acyclic trivalent nitrogen compound, *N*-[(trichloromethyl)sulfonyl-*N*-(1-phenylethyl)benzenesulfonamide, see: Raban, M.; Kenney, G. W. J., Jr.; Moldowan, J. M.; Jones, F. B., Jr. *J. Am. Chem. Soc.* **1968**, *90*, 2985. Although the free energy of activation for the inversion process in this compound was estimated to be 17.2 kcal/mol at 68 °C, exchange of the trichloromethyl for a *p*-tolyl group lowers $\Delta G^{\ddagger}$ to ~12.3 kcal/mol.

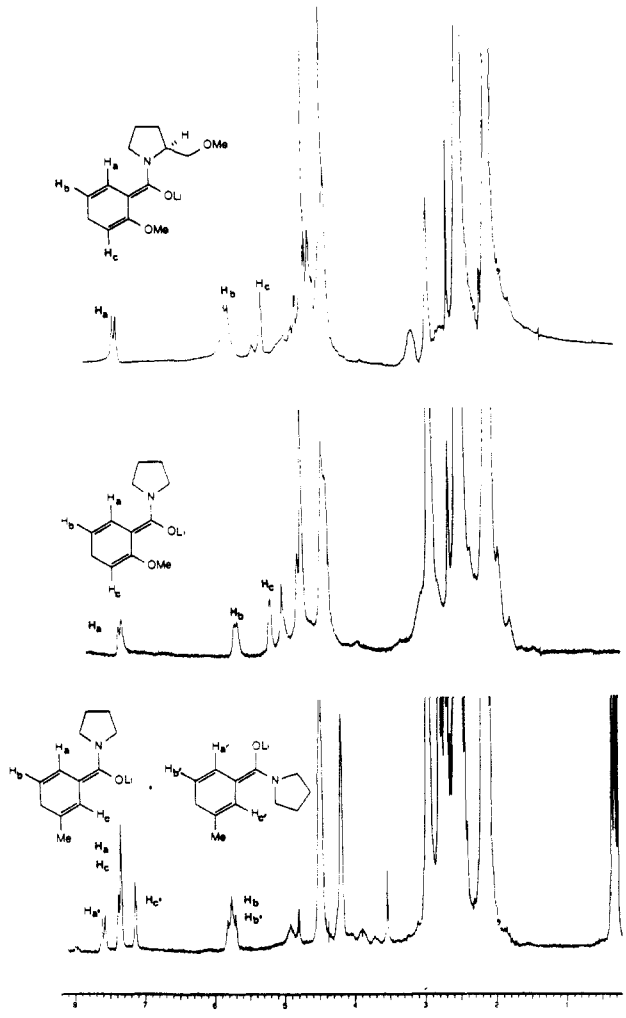


Figure 2. ^{1}H NMR spectra of lithium enolates **27** (top), **62b** (middle), and the *E* and *Z* mixture **62a** and **63a** (bottom) recorded in THF-d_8 at 25 °C.

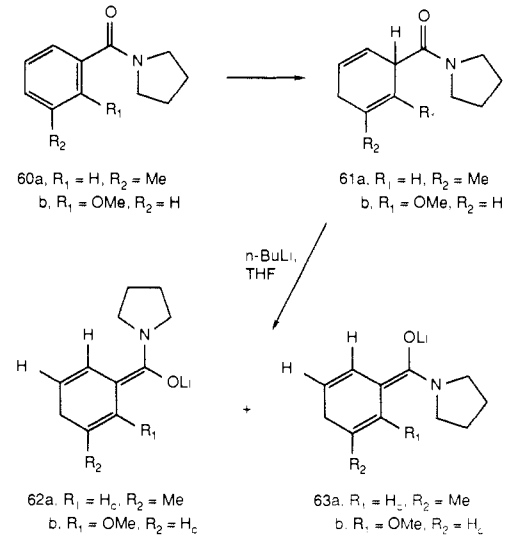
atom inversion within the confines of the dimeric enolate may have a $\Delta G^{\ddagger}$ substantially higher than 8 kcal/mol.[47b] At −78 °C, the process of enolate relaxation may be slow on the time scale of the alkylation reaction.

The dimeric enolate obtained by deprotonation of **29** with *n*-BuLi and maintained at −78 °C provides no stereoselectivity on methylation at −78 °C (entry 5) possibly because stereoelectronic effects of the uncoordinated nitrogen electron pair are working in opposition to the steric effects of the prolinol side chain. A THF ligand (THF in place of ammonia shown in **57a**) also would tend to offset the effects of the prolinol side chain. Complexation with added ammonia produces **57a** (entry 6), but warming the enolate in THF to 25 °C would allow relaxation to **58** (entry 9). Addition of ammonia to **58** might result in ligand exchange to give the enolate complex **59a**. Without the blocking ligand (THF) found in **58**, this new enolate complex shows virtually no stereoselection on methylation (entry 7).

Warming **57b** to 25 °C apparently results in dissociation of the diisopropylamine and enolate relaxation to give **58**. Reassociation of diisopropylamine with **58** would produce **59b**. This enolate complex, by virtue of a blocking *N*-isopropyl group, gives predominately **55** on methylation (entry 11).

NMR Studies with 27 and Related Enolates. Deprotonation of **29** with *n*-BuLi in THF-d_8 at −78 °C gave a solution of enolate that was stable in the temperature range of −78 to 25 °C. A complex ^{1}H NMR spectrum was observed at −78 °C, but warming the enolate to 25 °C resulted in a simplification of the spectrum. The appearance of the resonances due to the vinyl protons H_a, H_b, and H_c from the sample at 25 °C (Figure 2) suggested the presence of a single geometrical isomer. The temperature-dependent NMR effect was reversible and the original spectrum was reproduced on cooling to −78 °C. As expected, alkylation of the NMR sample maintained at −78 °C with MeI gave an approximately 1:1 mixture of **28a** and **55**, but the sample warmed to 25 °C gave **55** in 80% yield with >99:1 stereoselectivity.

Scheme X



The reversible spectral changes, while interesting, do not elucidate the sources of irreversible, temperature-dependent changes in the enolate that affect alkylation stereoselectivity. For the present, the important finding is that *a single enolate geometrical isomer is responsible for the >99:1 stereoselectivity of alkylation in THF.*

The configuration of enolate **27** was determined by the study of model systems (Scheme X). Birch reduction of the 3-methylbenzamide **60a** gave the α-protonated **61a**, which, when reacted with *n*-BuLi in THF-d_8, gave an approximately 60:40 distribution of enolate geometrical isomers. The ^{1}H NMR spectrum of the enolate mixture (Figure 2) displays two sets of doublets for H_a, two singlets for H_c (one singlet overlapping a doublet for H_a in the same molecule), and a poorly resolved multiplet incorporating both H_b resonances. Two-dimensional NOE studies (Figure 3) provided an assignment of resonances belonging to each isomer. In the major isomer, **62a**, an NOE was observed between H_a and the pyrrolidine ring protons, but no NOE was detected between H_c and the pyrrolidine ring. Complementary data were recorded for the minor geometrical isomer **63a**. The moderate downfield shifts of H_a in **63a** relative to H_a in **62a** (0.23 ppm) and H_c in **62a** relative to H_c in **63a** (0.21 ppm) presumably are the result of deshielding effects of the enolate oxygen atom.

A similar set of experiments was carried out with the 2-methoxybenzamide **60b** (Scheme X). As expected, the ^{1}H NMR spectrum of the enolate generated from **61b** revealed the presence of only one geometrical isomer (Figure 2), and this has been assigned the *Z* configuration **62b** on the basis of the chemical shift for H_a in **62b** relative to H_a in **62a**. These resonances are virtually superimposable when measured downfield from resonances due to proteated THF in the samples. The ^{1}H NMR spectrum of the enolate generated by deprotonation of **29**, when compared to that of **62b**, allows a definitive assignment of *Z* configuration to **27**.[48]

In contrast to the straightforward two-dimensional NOE experiments described for **62a**, enolate **27** showed enhancements not only for H_a and the pyrrolidine ring protons, but also for the vinyl methoxy group and the pyrrolidine ring protons. This observation provides support for the dimeric enolate model **58**, in which the

(48) (a) For prior NMR spectroscopic studies of the lithium enolate derived from *N,N*-dimethylacetamide, see: Woodbury, R. P. Ph.D. Thesis, Michigan State University, 1976. (b) ^{1}H NMR data have been reported for the isomeric products of O-silylation of the lithium enolates produced from deprotonation of *N,N*-diethylpropionamide. ^{13}C NMR studies of the lithium enolate of pyrrolidylpropionamide suggested the presence of a single isomer, but an assignment of enolate configuration was not reported (see ref 7b).

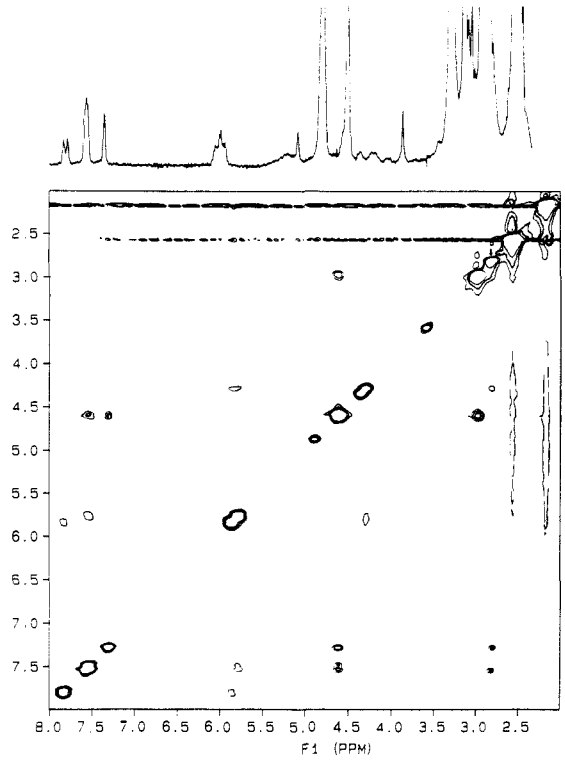


Figure 3. Two-dimensional phase-sensitive NOESY spectrum of **62a** and **63a**; all cross-peaks are phased downward and the diagonal peaks are upward. The pulse sequence described by D. J. States, R. A. Haberborn, and D. J. Ruben (*J. Magn. Reson.* **1982**, *48*, 286–292) was used.

chiral auxiliary is approximately equidistant from H_a on one enolate monomeric unit and the vinyl methoxy group on the other.[49] The geometry of the dimer is more easily appreciated in modification **57**.

Conclusion

This paper has focused on the many factors that operate to control the stereoselectivity of the reductive alkylation of chiral 2-methoxy and related benzamides. Chemical reactivity and ^1H NMR data have provided the framework for the formulation of models of the intermediates involved in the alkylation step. The remarkable effects of ammonia and diisopropylamine on the stereoselectivity of amide enolate alkylations uncovered in this study should find application in other electrophile–enolate systems. The exceptional quality of stereocontrol exhibited by the chiral auxiliary L-prolinol and the availability of either enantiomeric series of 6-alkyl-1-methoxy-1,4-cyclohexadienes by solvent and temperature modifications highlight the synthetic utility of the process.

Experimental Section

General Procedure for Preparation of Substituted [2′-(Hydroxymethyl)pyrrolidinyl]benzamides. (*S*)-2-Methyl-1-[[2′-(hydroxymethyl)-pyrrolidinyl]carbonyl]benzene (3e). 2-Methylbenzoyl chloride (1.55 g, 10.0 mmol) in dry CH_2Cl_2 (10 mL) was added to a stirred solution of L-prolinol (1.10 g, 11.0 mmol) and triethylamine (1.46 g, 14.4 mmol) in dry CH_2Cl_2 (25 mL) at 0 °C. After the addition of the acid chloride was complete, the reaction mixture was warmed to room temperature and stirred for 4 h. A solution of 5% HCl (50 mL) was added to the reaction mixture, and the mixture was extracted with chloroform (3 × 50 mL). The extracts were combined and washed with saturated sodium bicarbonate solution (50 mL) and brine (50 mL). The organic layer was dried over magnesium sulfate, and solvent was removed in vacuo. Flash chromatography (silica gel, ethyl acetate–hexane, 4:1) provided **3e** (2.15 g, 98%) as an off-white solid. The analytical sample was prepared by recrystallization from ether: mp 66–69 °C; ^1H NMR ($CDCl_3$) δ 1.52–2.00 (m, 3 H), 2.06 (m, 1 H), 2.32 (s, 3 H), 3.20 (m, 2 H), 3.77 (m, 2 H), 4.40 (m, 1 H), 5.15 (m, 1 H, exchangeable with D_2O), 7.18–7.36 (m, 4 H); IR (KBr) 3600–3100 (br), 1600, 1420 cm^{-1}; $[\alpha]^{20}_D$ −64.1° (*c* 1.20, $CHCl_3$); CI-MS, *m/z* (relative intensity) 220 ($M^+ + 1$, 100). Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.81. Found: C, 71.20; H, 7.72.

General Procedure for Preparation of Substituted Benzoxazepinones. Preparation of (3a*S*)-2,3,3a,4-Tetrahydro-1*H*,1*H*-pyrrolo[2,1-c]benzoxazepin-10-one (1a). Method C. A solution of **3d** (350 mg, 1.5 mmol) and sodium hydride (108 mg, 4.5 mmol) in DMF (20 mL) was stirred at room temperature for 18 h. The DMF was removed in vacuo. H_2O (15 mL) was added to the residue, and the mixture was extracted with chloroform (3 × 30 mL). The extracts were combined and dried over magnesium sulfate. Solvent was removed in vacuo, and crystallization with diethyl ether–pentane afforded **1a** (246 mg, 88%): ^1H NMR ($CDCl_3$) δ 1.66 (m, 1 H), 1.86 (m, 2 H), 2.16 (m, 1 H), 3.78 (t, *J* = 6 Hz, 2 H), 3.86 (m, 1 H), 4.08 (t, *J* = 8 Hz, 1 H), 4.38 (dd, *J* = 8 Hz, *J* = 1 Hz, 1 H), 7.0 (d, *J* = 6 Hz, 1 H), 7.3 (t, *J* = 6 Hz, 1 H), 7.4 (t, *J* = 6 Hz, 1 H), 8.60 (dd, *J* = 6 Hz, *J* = 1 Hz, 1 H); IR ($CHCl_3$) 1620 cm^{-1}; CI-MS, *m/z* (relative intensity) 204 ($M^+ + 1$, 100). Anal. Calcd for $C_{12}H_{13}NO_2$: C, 70.92; H, 6.89. Found: C, 71.09; H, 6.46.

General Procedure for Preparation of Substituted, Hydroxyl-Protected [2′-(Hydroxymethyl)pyrrolidinyl]benzamides. (*S*)-2-Methyl-1-[[2′-(methoxymethyl)pyrrolidinyl]carbonyl]benzene (32). A solution of **3e** (0.33 g, 1.5 mmol), sodium hydride (48 mg, 2.0 mmol), and methyl iodide (0.71 g, 5 mmol) in THF (5 mL) was stirred at reflux for 18 h. The THF was removed in vacuo, and the residue was dissolved in chloroform. The chloroform solution was washed with 10% HCl (10 mL) and brine (10 mL) and then dried over magnesium sulfate. Removal of the solvent in vacuo gave a yellow oil. Flash column chromatography (silica gel, ethyl acetate–hexane, 3:2) afforded **32** (0.34 g, 98%) as a colorless oil: ^1H NMR ($CDCl_3$) (mixture of rotational isomers) δ 1.64–2.08 (m, 4 H), 2.10, 2.11 (2 s, 3 H), 3.00–3.18 (m, 2 H), 3.08, 3.39 (2 s, 3 H), 3.68 (m, 2 H), 4.43 (m, 1 H), 7.14–7.30 (m, 4 H); IR (film) 2970, 1620, 1600 cm^{-1}; $[\alpha]^{23}_D$ −92.5° (*c* 1.53, $CHCl_3$); CI-MS, *m/z* (relative intensity) 234 ($M^+ + 1$, 100), 202 (7), 142 (15), 119 (12). Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21. Found: C, 71.90; H, 8.27.

General Procedure for Preparation of Substituted (2′-Formylpyrrolidinyl)benzamides. Preparation of (*S*)-2-Methyl-1-[(2′-formylpyrrolidinyl)carbonyl]benzene (8b). To a stirred solution of oxalyl chloride (0.42 g, 3.3 mmol) in dry CH_2Cl_2 (7.5 mL) was added dimethyl sulfoxide (0.52 g, 6.6 mmol) in CH_2Cl_2 (1.5 mL) at −60 °C. The reaction mixture was stirred for 2 min, and a solution of **3e** (0.66 g, 3.0 mmol) in CH_2Cl_2 (3.0 mL) was added via a syringe. After 15 min, triethylamine (1.52 g, 15 mmol) was added, and the reaction mixture was stirred for 5 min at −60 °C and then allowed to warm to 20 °C. Water (20 mL) was added, and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were washed with 1% HCl (20 mL), saturated sodium bicarbonate solution (20 mL), and brine (20 mL) and then dried over anhydrous sodium sulfate. Removal of solvent in vacuo afforded a yellow oil. Flash column chromatography (silica gel, ethyl acetate–hexane, 3:2) gave **8b** (0.57 g, 88%) as a colorless solid. The analytical sample was prepared by recrystallization from CH_2Cl_2–hexane: mp 62–64 °C; ^1H NMR ($CDCl_3$) (mixture of rotational isomers) δ 1.82–1.99 (m, 2 H), 2.02–2.26 (m, 2 H), 2.31, 2.37 (2 s, 3 H), 3.23–3.36, 3.75–3.89 (2 m, 2 H), 4.13, 4.73 (2 m, 1 H), 7.21–7.38 (m, 4 H), 9.27, 9.76 (2 d, *J* = 1 Hz, 1 H); IR ($CHCl_3$) 2995, 1728, 1622 cm^{-1}; $[\alpha]^{25}_D$ −77.3° (*c* 0.98, CH_3OH); CI-MS, *m/z* (relative intensity) 218 ($M^+ + 1$, 100), 126 (8), 119 (29). Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.87; H, 6.96. Found: C, 71.73; H, 7.01.

General Procedure for Preparation of Substituted [2′-(1-Propenyl)-pyrrolidinyl]benzamides. (*S*)-(*E*)- and (*S*)-(*Z*)-2-Methyl-1-[[2′-(1-propenyl)pyrrolidinyl]carbonyl]benzene (9b). To a stirred suspension of ethyltriphenylphosphonium iodide (6.82 g, 15.8 mmol) in dry THF (42 mL) at 0 °C was added *n*-butyllithium (10.2 mL, 15.8 mmol, 1.55 M solution in hexane). After 1 h at 20 °C, a solution of **8b** (3.44 g, 15.8 mmol) in THF (42 mL) was added. The resulting slurry was stirred at 20 °C for 18 h, brine (100 mL) was added, and the aqueous mixture was extracted with chloroform (3 × 100 mL). The combined organic extracts were washed with water (100 mL) and brine (100 mL) and then dried over anhydrous magnesium sulfate. Removal of solvents in vacuo afforded a yellow oil. Flash column chromatography (silica gel, hexane–ethyl acetate, 4:1) gave **9b** (2.56 g, 71%) as a colorless oil: ^1H NMR ($CDCl_3$) (mixture of isomers) δ 0.81, 1.42, 1.80 (3 d, *J* = 6 Hz, 3 H), 1.58–1.78 (m, 2 H), 1.84–2.13 (m, 2 H), 2.02, 2.03, 2.09 (3 s, 3 H), 3.05–3.22, 3.58–3.85 (2 m, 2 H), 3.94, 4.38, 4.78 (3 m, 1 H), 4.96–5.66 (m, 2 H), 7.07–7.24 (m, 4 H); IR (film) 3015, 1625, 1600, 1440 cm^{-1}; $[\alpha]^{21}_D$ +42.6° (*c* 1.25, CH_3OH); CI-MS, *m/z* (relative intensity) 230

(49) Both syn and anti forms of the dimeric enolate have been considered. The anti arrangement shown in **57** appears best suited for complexation with ammonia. However, molecular models show that both syn and anti forms are compatible with the NOE experiments.

($M^+ + 1$, 100), 138 (16). Anal. Calcd for $C_{15}H_{19}NO$: C, 78.56; H, 8.35. Found: C, 78.37; H, 8.27.

General Procedure for Preparation of Substituted [2′-(1-Propyl)-pyrrolidinyl]benzamides. (*S*)-2-Methyl-1-[[2′-(1-propyl)pyrrolidinyl]-carbonyl]benzene (10b). A solution of **9b** (2.57 g, 11.2 mmol) in ethanol (20 mL) containing 5% palladium on carbon (255 mg, 1 mol %) was stirred under an atmosphere of hydrogen at 20 °C for 18 h. Filtration through Celite and concentration of the reaction mixture by removal of solvent in vacuo, followed by flash column chromatography (silica gel, ethyl acetate–hexane, 1:3) gave **10b** (2.48 g, 96%) as a colorless oil: ^{1}H NMR ($CDCl_3$) (mixture of rotational isomers) δ 0.55, 0.96 (2 t, J = 7 Hz, 3 H), 1.06–1.50 (m, 3 H), 1.62–2.08 (m, 5 H), 2.28, 2.30 (2 s, 3 H), 3.08–3.14, 3.50–3.62 (2 m, 2 H), 3.76, 4.26 (2 m, 1 H), 7.16–7.26 (m, 4 H); IR (film) 3060, 1620, 1600, 1485, 1405 cm^{-1}; $[\alpha]^{25}_D$ – 82.3° (*c* 0.75, CH_3OH); CI-MS, *m/z* (relative intensity) 232 ($M^+ + 1$, 100), 140 (18). Anal. Calcd for $C_{15}H_{21}NO$: C, 77.88; H, 9.15. Found: C, 77.92; H, 9.03.

Preparation of (2′*S*,6*R*)-1-Methoxy-6-methyl-6-[[2′-(methoxymethyl)pyrrolidinyl]carbonyl]-1,4-cyclohexadiene (28a). A solution of **2a** (0.25 g, 1.0 mmol) in dry THF (5 mL) and *tert*-butyl alcohol (74 mg, 1.0 mmol) was cooled to –78 °C. Liquid ammonia (60 mL, predried over sodium amide and then distilled) was added to the reaction mixture. Potassium (86 mg, 2.2 equiv) was added to the stirred solution in small pieces. Methyl iodide (0.28 g, 2.0 mmol) was added, and the resulting yellow solution was stirred for 1 h at –78 °C. After addition of NH_4Cl (~0.5 g), the mixture was warmed slowly to room temperature while the ammonia was removed with a stream of nitrogen. Brine (~20 mL) was added, and the mixture was extracted with chloroform (3 × 20 mL). The combined organic extracts were washed with 10% sodium thiosulate (20 mL), water (20 mL), and brine (20 mL) and then dried over anhydrous magnesium sulfate. Removal of solvents in vacuo provided the crude product as a 260:1 mixture of diastereomers (GC analysis). Flash chromatography (silica gel, ethyl acetate–hexane, 3:2) gave **28a** (0.23 g, 85%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.42 (s, 3 H), 1.68–2.00 (m, 4 H), 2.73–3.01 (m, 2 H), 3.22–3.38 (m, overlapping s at 3.36, 5 H), 3.53 (s, 3 H), 3.60–3.68 (m, 2 H), 4.32 (m, 1 H), 4.67 (t, J = 3 Hz, 1 H), 5.53 (dt, J = 9 Hz, 2 Hz, 1 H), 5.77 (m, 1 H); ^{1}H NMR (C_6D_6) δ 1.41 (m, 1 H), 1.53–1.84 (m, overlapping s at 1.77, 6 H), 2.54 (d, J = 22 Hz, 1 H), 2.67 (d, J = 22 Hz, 1 H), 3.05–3.30 (m, 1 H), 3.15 (s, 3 H), 3.21 (s, 3 H), 3.44–3.64 (m, 2 H), 3.71 (dd, J = 10 Hz, J = 2 Hz, 1 H), 4.36 (t, J = 3 Hz, 1 H), 4.51 (m, 1 H), 5.53 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 24.8, 26.3, 26.4, 46.2, 48.1, 49.0, 57.9, 58.7, 71.9, 90.5, 123.9, 128.6, 155.8, 170.6; IR (film) 2970, 1680, 1630, 1445 cm^{-1}; CI-MS, *m/z* (relative intensity) 266 ($M^+ + 1$, 89), 234 (14), 142 (100); GC (150 °C for 2 min, 2 °C/min) t_R (percent) 33.72 (99.6), 34.66 min (0.4).

General Procedures for Preparation of 1-Methoxy-6-(pyrrolidinylcarbonyl)-1,4-cyclohexadienes. (2′*S*)-1-Methoxy-6-[[2′-(methoxymethyl)pyrrolidinyl]carbonyl]-1,4-cyclohexadiene (29). To a solution of **2a** (1.0 g, 4 mmol) and *tert*-butyl alcohol (0.39 mL, 4 mmol) in dry THF (5 mL) was added liquid ammonia (50 mL, predried over sodium amide and then distilled) at –78 °C. Potassium (343 mg, 8.8 mmol) was added at –78 °C until a blue coloration was maintained. The enolate was quenched with solid NH_4Cl at –78 °C. The ammonia was removed, and water (30 mL) was added to the reaction mixture. The aqueous mixture was extracted with methylene chloride (3 × 100 mL). The extracts were combined and washed with 10% HCl (100 mL), saturated $NaHCO_3$ solution (100 mL), and brine (100 mL). The organic layer was dried over magnesium sulfate, and solvent was removed in vacuo to give **29** as a 4:1 mixture of diastereomers. Flash column chromatography (silica gel, ethyl acetate–hexane, 4:1) afforded **29** (926 mg, 92%): ^{1}H NMR ($CDCl_3$) δ 1.93 (m, 5 H), 2.84 (dd, J = 6 Hz, J = 3 Hz, 2 H), 3.20–4.04 (m with 2 overlapping s at 3.33 and 3.55, 10 H), 4.30 (m, 1 H), 4.83 (t, J = 1 Hz, 1 H), 5.62 (dt, J_d = 8 Hz, J_t = 1 Hz, 1 H), 5.88 (d, J = 4 Hz, 1 H); IR (film) 1625 cm^{-1}; CI-MS, *m/z* (relative intensity) 252 ($m^+ + 1$, 100); GC (160 °C for 2 min, 2 °C/min) t_R (percent) 14.14 (82.5), 15.44 min (17.5).

(2′*S*,6*R*)- and (2′*S*,6*S*)-1-Methoxy-2,6-dimethyl-6-[[2′-(methoxymethyl)pyrrolidinyl]carbonyl]-1,4-cyclohexadiene (43a and 44a) and (2′*S*)-2-methoxy-1,5-dimethyl-3-[[2′-(methoxymethyl)pyrrolidinyl]-carbonyl]-1,3-cyclohexadiene (45) were prepared from **2b** (130 mg, 0.5 mmol) as described for **28a** as a 70:30 mixture of regioisomers **44a** and **43a** (70%; 5:1 mixture of diastereomers) and **45** (30%; 42:1 mixture of diastereomers). Flash column chromatography (silica gel, ethyl acetate–hexane, 1:1) gave **44a** and **43a** (86 mg, 61%) as a 5:1 mixture of diastereromers: ^{1}H NMR ($CDCl_3$) (mixture of diastereomers) δ 1.40 (s, 3 H), 1.64 (s, 3 H), 1.80 (m, 4 H), 2.60, 2.80 (dd, J = 20, 10 Hz, 2 H), 3.30 (s, 3 H), 3.40 (m, 2 H), 3.58 (m, 2 H), 3.59 (s, 3 H), 4.28 (m, 1 H), 5.42 (dt, J_d = 8 Hz, J_t = 2 Hz, 1 H), 5.66 (dt, J_d = 8 Hz, J_t = 2 Hz, 1 H); IR (film) 1618 cm^{-1}; CI-MS, *m/z* (relative intensity) 280 ($M^+ + 1$, 100); GC (220 °C for 2 min, 2 °C/min) t_R (percent) 8.84 (52.7), 9.44 min (10.6). Compound **45** (36 mg, 26%) was obtained as a 42:1 mixture of diastereomers: ^{1}H NMR ($CDCl_3$) (mixture of diastereomers) δ 1.02, 1.03 (2 d, J = 6 Hz, 3 H), 1.76, 1.80 (2 s, 3 H), 2.92 (m, 4 H), 3.25 (2 m, 2 H), 3.20–3.65 (m with 2 overlapping s at 3.39 and 3.52, 11 H), 3.98, 4.28 (2 br s, 1 H), 5.74, 5.76 (2 d, J = 8 Hz, 1 H); IR (film) 1610 cm^{-1}; CI-MS, *m/z* (relative intensity) 280 ($M^+ + 1$, 100); GC (220 °C for 2 min, 2 °C/min) t_R (percent) 10.86 (97.7), 12.53 min (2.3).

(2′*S*,6*S*)-1-Methoxy-2-methyl-6-benzyl-6-[[2′-(methoxymethyl)-pyrrolidinyl]carbonyl]-1,4-cyclohexadiene (44b) was prepared from **2b** (263 mg, 1.0 mmol) as described for **28a** as a 178:1 mixture of diastereomers. Flash column chromatography (silica gel, hexane–ethyl acetate, 1:1) gave **44b** (266 mg, 75%) as a colorless solid: mp 106–110 °C; ^{1}H NMR ($CDCl_3$) δ 1.53 (s, 3 H), 1.88 (m, 5 H), 2.26 (br d, J = 10 Hz, 1 H), 2.92 (d, J = 7 Hz, 1 H), 3.30–3.78 (m with 2 overlapping s at 3.38 and 3.59, 11 H), 4.35 (m, 1 H), 5.39 (dt, J_d = 8 Hz, J_t = 0.5 Hz, 1 H), 5.56 (dt, J_d = 8 Hz, J_t = 1 Hz, 1 H), 7.13 (m, 5 H); IR ($CHCl_3$) 1620 cm^{-1}; CI-MS, *m/z* (relative intensity) 356 ($M^+ + 1$, 25), 142 (100); GC (210 °C for 2 min, 4 °C/min) t_R (percent) 20.39 (99.4), 21.51 min (0.6). Anal. Calcd for $C_{22}H_{29}NO_3$: C, 74.33; H, 8.22. Found: C, 74.13; H, 8.20.

General Procedure for Preparation of 1-Methyl-6-(pyrrolidinylcarbonyl)-1,4-cyclohexadienes. (2′*S*,6*S*)-1,6-Dimethyl-6-[[2′-(metboxymethyl]pyrrolidinyl]carbonyl]-1,4-cyclohexadiene (33). A solution of **32** (0.25 g, 1.0 mmol) in dry THF (5 mL) and *tert*-butyl alcohol (74 mg, 1.0 mmol) was cooled to –78 °C. Ammonia (60 mL, predried over sodium amide and then distilled) was added to the reaction mixture. Potassium (86 mg, 2.2 mmol) was added to the stirred solution in small pieces. Methyl iodide (0.12 mL, 2.0 mmol) was added, and the resulting yellow solution was stirred for 1 h at –78 °C. After addition of NH_4Cl (0.5 g), ammonia was removed and water (10 mL) was added to the reaction mixture. The mixture was extracted with CH_2Cl_2 (3 × 10 mL). The extracts were combined and washed with 10% HCl (10 mL), saturated $NaHCO_3$ solution (10 mL), and brine (10 mL). The organic layer was dried over $MgSO_4$, and solvent was removed in vacuo to give the crude product as a >99:1 mixture of diastereomers. Flash column chromatography (silica gel, ethyl acetate–hexane, 1:1) gave **33** (0.22 g, 90%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.36 (s, 3 H), 1.66 (d, J = 2 Hz, 3 H), 1.68–2.02 (m, 4 H), 2.60–2.86 (m, 2 H), 3.32–3.50 (m, overlapping s at 3.38, 6 H), 3.63 (dd, J = 9 Hz, 3 Hz, 1 H), 4.35 (m, 1 H), 5.53 (m, 1 H), 5.59 (dt, J = 10 Hz, 2 Hz, 1 H), 5.81 (m, 1 H); ^{1}H NMR (C_6D_6) δ 1.20–1.44 (m, 1 H), 1.46–1.83 (m, overlapping s at 1.58; d, J = 2 Hz at 1.62, 9 H), 2.28–2.58 (m, 2 H), 3.16 (s, 3 H), 3.36 (m, 2 H), 3.48 (dd, J = 10 Hz, 9 Hz, 1 H), 3.63 (dd, J = 10 Hz, 3 Hz, 1 H), 4.48 (m, 1 H), 5.28 (m, 1 H), 5.54 (m, 1 H), 5.64 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 19.2, 25.0, 26.0, 26.8, 27.0, 46.7, 48.4, 57.9, 59.0, 72.3, 120.4, 123.3, 129.9, 133.9, 172.1; IR (film) 2995, 2935, 2880, 2820, 1610, 1400, 1380 cm^{-1}; $[\alpha]^{25}_D$ –53.1° (*c* 0.96, CH_3OH); CI-MS, *m/z* (relative intensity) 250 ($M^+ + 1$, 100), 142 (33); GC (140 °C for 2 min, 2 °C/min) t_R (percent) 28.66 min (only one peak was observed).

General Procedure for Preparation of Pyrrolo[2,1-*c*][1,3 and 1,4]-benzoxepin-10-ones. (3a*S*)-2,3,3a,4,6,7-Hexahydro-1*H*,10*H*-pyrrolo-[2,1-*c*][1,4]benzoxazepin-10-one (17). Potassium (0.51 g, 13 mmol) was added to a stirred solution of **1a** (1.2 g, 6.0 mmol) and *tert*-butyl alcohol (0.58 mL, 6.0 mmol) in dry THF (8 mL) and liquid NH_3 (75 mL, predried over sodium amide and then distilled) at –78 °C. The blue color of the solution was maintained for 10 min, and solid ammonium chloride was added. The ammonia was removed by slow evaporation, and the resulting THF solution was partitioned between H_2O and CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL), and the extracts were combined, washed with brine (50 mL), and dried over $MgSO_4$. Solvent was removed in vacuo to give a pale yellow solid. Flash column chromatography (silica gel, ethyl acetate–methanol, 10:1) gave **17** (800 mg, 73%) as a colorless solid: mp 76 °C; ^{1}H NMR ($CDCl_3$) δ 1.66–2.44 (m, 8 H), 3.40–3.94 (m, 4 H), 4.37 (d, J = 6 Hz, 1 H), 5.60 (dt, J_d = 6 Hz, J_t = 2 Hz, 1 H), 6.70 (d, J = 6 Hz, 1 H); IR (film) 2960, 1600, 1435 cm^{-1}; CI-MS, *m/z* (relative intensity) 206 ($M^+ + 1$, 100).

(3a*S*,9a*S*)-9a-Methyl-2,3,3a,4,7,9a-Hexahydro-1*H*,10*H*-pyrrolo[2,1-*c*][1,4]benzoxazepin-10-one (16a), 18, and (3a*S*)-6-Methyl-2,3,3a,4,6,7-Hexahydro-1*H*,10*H*-pyrrolo[1,4]benzoxazepin-10-one (19). Ammonia (70 mL, dried over sodium amide) was distilled into a solution of **1a** (203 mg, 1 mmol) and *tert*-butyl alcohol (74 mg, 1 mmol) in dry THF (5 mL) at –78 °C. Potassium (100 mg, 2.2 mmol) was added to the stirred solution at –78 °C, and after 20 min, methyl iodide (290 mg, 2.0 mmol) was added and stirring was continued at –78 °C for 1 h. Ammonia was removed by slow evaporation, and the reaction mixture was quenched with solid NH_4Cl at –33 °C. Brine (10 mL) was added, and the mixture was extracted with chloroform (3 × 10 mL). The combined extracts were washed with 10% sodium thiosulfate solution (30 mL) and brine (30 mL) and then dried over $MgSO_4$. Solvent was removed in vacuo, and flash column chromatography (silica gel, ethyl acetate–methylene chlo-

ride, 1:4) gave **16a** (148 mg, 67%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.51 (s, 3 H), 1.55 (m, 3 H), 2.02 (m, 1 H), 2.78 (m, 2 H), 3.56 (dd, J = 8 Hz, J = 6 Hz, 2 H), 3.88 (dd, J = 10.5 Hz, J = 10 Hz, 1 H), 4.13 (dd, J = 10 Hz, J = 2 Hz, 1 H), 4.25 (m, 1 H), 5.42 (m, 1 H), 5.70 (m, 1 H), 6.02 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 22.50 (t), 26.83 (t), 27.26 (q), 29.57 (t), 48.03 (s), 48.24 (t), 73.47 (t), 110.75 (d), 122.26 (d), 131.67 (d), 151.11 (s), 172.99 (s); GC-CIMS, t_R (percent) m/z (relative intensity) 6.33 min (85%) 220 (M^+ + 1, 100). Compound **18** also was isolated (18 mg, 8%): mp 116–117 °C; ^{1}H NMR ($CDCl_3$) δ 1.51 (s, 3 H), 1.82 (m, 3 H), 2.10 (m, 1 H), 2.74 (m, 2 H), 3.39 (dd, J = 8 Hz, 6 Hz, 2 H), 3.78 (m, 1 H), 4.23 (dd, J = 10 Hz, 2 Hz, 2 H), 5.46 (t, J = 2 Hz, 1 H), 5.74 (dt, J_d = 10 Hz, J_t = 2 Hz, 1 H), 5.94 (dt, J_d = 10 Hz, J_t = 2 Hz, 1 H); IR (KBr) 2980, 1670, 1620, 1410 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 22.31 (t), 23.39 (q), 26.90 (t), 30.17 (t), 47.90 (s), 49.07 (t), 58.18 (d), 111.07 (d), 120.62 (d), 131.87 (d), 152.43 (s), 173.60 (s); GC–CI–MS t_R (percent) m/z (relative intensity) 6.36 min (15%) 220 (M^+ + 1, 100). Compound **19** also was isolated (6.2 mg, 3%): ^{1}H NMR ($CDCl_3$) δ 1.03 (d, J = 8 Hz, 3 H), 1.60 (m, 1 H), 1.87 (m, 4 H), 2.36 (m, 1 H), 3.50 (m, 1 H), 3.75 (m, 2 H), 3.88 (m, 2 H), 4.38 (m, 1 H), 5.62 (m, 1 H), 6.70 (m, 1 H); IR (film) 2940, 1600, 1430 cm^{-1}; GC–CI–MS t_R (percent) m/z (relative intensity) 6.82 min (3%) 220 (M^+ + 1, 100).

General Procedure for Preparation of 2-Substituted 3-Cyclohexen-1-ones and 3-Substituted 2-Cyclohexen-1-ones. (2′*S*,2*R*)-2-Methyl-2-[[2′-(methoxymethyl)pyrrolidinyl]carbonyl]-3-cyclohexen-1-one (36a). To a stirred solution of **28a** (0.19 g, 0.72 mmol) in methanol (4 mL) was added 10% hydrochloric acid (1 mL) at 20 °C. After 24 h at room temperature, the reaction mixture was neutralized by adding concentrated sodium bicarbonate (5 mL). The aqueous mixture was extracted with ethyl acetate (3 × 10 mL), and the combined organic extracts were washed with brine (10 mL) and dried over anhydrous magnesium sulfate. Removal of solvents in vacuo followed by flash chromatography (silica gel, ethyl acetate–hexane, 3:2) gave **36a** (0.16 g, 87%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.44 (s, 3 H), 1.69–1.99 (m, 4 H), 2.40–2.78 (m, 4 H), 3.07 (m, 1 H), 3.22–3.40 (m, overlapping s at 3.36, 5 H), 3.69 (dd, J = 10 Hz, 3 Hz, 1 H), 4.27 (m, 1 H), 5.67 (br d, J = 10 Hz, 1 H), 5.96 (dt, J = 10 Hz, 2 Hz, 1 H); IR (film) 2975, 2928, 2882, 2826, 1700, 1627, 1445, 1398, 1378 cm^{-1}; $[\alpha]^{22}_D$ −68.8° (c 1.89, CH_3OH); CI-MS, m/z (relative intensity) 252 (M^+ + 1, 100), 220 (12), 142 (24). Anal. Calcd for $C_{14}H_{21}NO_3$: C, 66.91; H, 8.42. Found: C, 66.75; H, 8.21.

(2′*S*,2*S*)-2-Methyl-2-[[2′-(hydroxymethyl)pyrrolidinyl]carbonyl]-3-cyclohexen-1-one (30) was prepared from **16a** (64 mg, 0.22 mmol) as described for **36a**. Flash column chromatography (silica gel, ethyl acetate) gave **30** (69 mg, 63%) as a colorless oil; ^{1}H NMR ($CDCl_3$) δ 1.44–1.61 (m, overlapping s at 1.51, 4 H), 1.68–1.92 (m, 2 H), 2.07 (m, 1 H), 2.47–2.83 (m, 4 H), 3.15 (m, 1 H), 3.28 (m, 1 H), 3.52–3.76 (m, 2 H), 4.37 (m, 1 H), 4.62 (dd, J = 7 Hz, 3 Hz, 1 H), 5.76 (br d, J = 10 Hz, 1 H), 6.01 (dt, J = 10 Hz, 3 Hz, 1 H); IR (film) 3700–3100 (br), 2975, 2930, 2875, 1702, 1615, 1440, 1403 cm^{-1}; CI–MS, m/z (relative intensity) 238 (M^+ + 1, 100), 220 (8), 128 (20).

(2*R*,2′*S*)-2-Methyl-2-[(2′-propylpyrrolidinyl)carbonyl]-3-cyclohexen-1-one (36b) was prepared from **34** (263 mg, 1.0 mmol) as described for **36a**. Flash column chromatography (silica gel, hexane–ethyl acetate, 2:1) gave **36b** as a colorless solid. The analytical sample was prepared by recrystallization from hexane: mp 49–51 °C; ^{1}H NMR ($CDCl_3$) δ 0.94 (t, J = 8 Hz, 3 H), 1.20–1.38 (m, 3 H), 1.46 (s, 3 H), 1.57–1.97 (m, 5 H), 2.50–2.70 (m, 4 H), 3.08 (m, 1 H), 3.34 (m, 1 H), 4.11 (m, 1 H), 5.71 (br d, J = 10 Hz, 1 H), 5.97 (dt, J = 10 Hz, 3 Hz, 1 H); IR ($CHCl_3$) 3020, 2995, 2959, 2923, 2864, 1704, 1610, 1440, 1405, 1378, 1360 cm^{-1}; $[\alpha]^{27}_D$ −87.8° (c 0.58, $CHCl_3$); CI-MS, m/z (relative intensity) 250 (M^+ + 1, 93), 140 (100). Anal. Calcd for $C_{15}H_{23}NO_2$: C, 72.25; H, 9.30. Found: C, 72.27; H, 9.16.

(2′*S*,2*S*)-2,6-Dimethyl-2-[[2′-(methoxymethyl)pyrrolidinyl]carbonyl]-3-cyclohexen-1-one was prepared from **44a** (400 mg, 1.4 mmol) as described for **36a**. Flash column chromatography (silica gel, ethyl acetate–hexane, 1:1) gave the title compound (320 mg, 86%) as a 3:2 mixture of diastereomers; ^{1}H NMR ($CDCl_3$) (mixture of isomers) δ 1.16 (d, J = 3 Hz, 3 H), 1.44 (s, 3 H), 1.66–2.06 (m, 5 H), 2.56–3.02 (m, 4 H), 3.34 (s, 3 H), 3.53 (m, 2 H), 4.28 (br m, 1 H), 5.72 (dd, J = 2 Hz, 0.5 Hz, 1 H), 5.84 (dt, J_d = 2 Hz, J_t = 1 Hz, 1 H); IR (film) 1628, 1705 cm^{-1}; CI-MS, m/z (relative intensity) 266 (M^+ + 1, 100), 142 (65). Anal. Calcd for $C_{15}H_{23}NO_3$: C, 67.89; H, 8.73. Found: C, 67.78; H, 8.79.

(2′*S*,2*R*)-2,4-Dimethyl-2-[[2′-(methoxymethyl)pyrrolidinyl]carbonyl]-3-cyclohexen-1-one was prepared from **51a** (964 mg, 3.6 mmol) as described for **36a**. Flash column chromatography (silica gel, ethyl acetate–hexane, 4:1) gave the title compound (732 mg, 81%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.40 (s, 3 H), 1.62–2.04 (m with overlapping s at 1.80, 7 H), 2.24–2.78 (m, 4 H), 2.98–3.48 (m with overlapping s at 3.34, 6 H), 3.64 (dd, J = 3 Hz, 1 Hz, 1 H), 4.24 (br s, 1 H), 5.38 (s, 1 H); IR (film) 1705, 1630 cm^{-1}; GC–CI-MS: t_R (percent) m/z (relative intensity) 8.74 min (7) 266 (M^+ + 1, 100), 142 (62); 8.93 min (93) 266 (M^+ + 1, 100), 142 (74). Anal. Calcd for $C_{15}H_{23}NO_3$: C, 67.89; H, 8.73. Found: C, 67.77; H, 8.74.

(2′*S*)-3,6-Dimethyl-6-[[2′-(methoxymethyl)pyrrolidinyl]carbonyl]-2-cyclohexen-1-one and (2′*S*)-2,5-dimethyl-2-[[2′-(methoxymethyl)-pyrrolidinyl]carbonyl]-3-cyclohexen-1-one, prepared from **49** (200 mg, 0.7 mmol) as described for **36a**, gave (2′*S*)-2,5-dimethyl-2-[[2′-(methoxymethyl)pyrrolidinyl]carbonyl]-3-cyclohexen-1-one (168 mg, 90%) as a yellow oil: ^{1}H NMR ($CDCl_3$) (mixture of diastereomers) δ 1.10 (2 overlapping d, J = 3 Hz, 3 H), 1.40, 1.48 (2 s, 3 H), 1.60–2.14 (m, 4 H), 2.20–2.46 (m, 1 H), 2.52–2.90 (m, 2 H), 2.92–3.14 (m, 1 H), 3.20–3.86 (m with 2 overlapping s at 3.38 and 3.40, 6 H), 4.30 (br s, 1 H), 5.52–5.92 (m, 2 H); IR (film) 1705, 1625 cm^{-1}; CI-MS, m/z (relative intensity) 266 (M^+ + 1, 100), 220 (16.07), 142 (15.86). Further purification of the yellow oil by flash column chromatography (silica gel, ethyl acetate–hexane, 1:1) resulted in a 1:1 mixture of (2′*S*)-2,5-dimethyl-2-[[2′-(methoxymethyl)pyrrolidinyl]carbonyl]-3-cyclohexen-1-one (67 mg, 36%) and (2′*S*)-3,6-dimethyl-6-[[2′-(methoxymethyl)-pyrrolidinyl]carbonyl]-2-cyclohexen-1-one (78 mg, 42%): ^{1}H NMR ($CDCl_3$) δ 1.35 (s, 3 H), 1.64–2.04 (m with overlapping s at 1.94, 8 H), 2.10–2.64 (m, 3 H), 3.04–3.50 (m with overlapping s at 3.36, 6 H), 3.61 (dd, J = 3 Hz, 1 Hz, 1 H), 4.27 (br s, 1 H), 5.89 (br s, 1 H); IR (film) 1660, 1625 cm^{-1}; GC–CI-MS t_R (percent) 8.48 min (25) m/z (relative intensity) 266 (M^+ + 1, 100), 8.57 min (25) 266 (M^+ + 1, 100), 8.64 min (50), 266 (M^+ + 1, 100). Anal. Calcd for $C_{15}H_{23}NO_3$: C, 67.89; H, 8.73. Found: C, 67.74; H, 8.71.

General Procedure for Hydrogenation of 1,4-Cyclohexadienes.[29] (1*S*,2*S*,2′*S*)-1,2-Dimethyl-1-[(2′-propylpyrrolidinyl)carbonyl]cyclohexane (41). A solution of **35** (0.12 g, 0.50 mmol) in dry methylene chloride (4 mL) containing $[Ir(cod)PyPCy_3]PF_6$ (40 mg, 10 mol %) was stirred under an atmosphere of hydrogen at 20 °C for 6 h. Solvents were removed in vacuo, and the residue was triturated with dry ethyl ether. The solid was removed by filtration, and the filtrates were concentrated in vacuo to provide a yellow oil. Flash chromatography (silica gel, ethyl acetate-hexane, 1:4) gave **41** (0.12 g, 93%) as a colorless oil (single diastereomer): ^{1}H NMR ($CDCl_3$) δ 0.61 (d, J = 8 Hz, 3 H), 0.87 (t, J = 7 Hz, 3 H), 1.09 (s, 3 H), 1.16–1.36 (m, 5 H), 1.40–1.62 (m, 7 H), 1.65–1.92 (m, 4 H), 2.30 (m, 1 H), 3.43 (m, 1 H), 3.65 (m, 1 H), 4.17 (m, 1 H); IR (film) 2952, 2920, 2860, 1608, 1447, 1360 cm^{-1}; $[\alpha]^{29}_D$ −18.9° (c 1.45, CH_3OH); CI-MS, m/z (relative intensity) 252 (M^+ + 1, 100), 140 (11), 111 (19). Anal. Calcd for $C_{16}H_{29}NO$: C, 76.44; H, 11.63. Found: C, 76.55; H, 11.58.

General Procedure for Preparation of Methyl Ketones. (1*S*,2*S*)-1,2-Dimethyl-1-acetylcyclohexane (40) from 39. To a stirred solution of **39** (0.25 g, 1.0 mmol) in THF (5 mL) at 0 °C was added methyllithium (2.14 mL, 3.0 mmol, 1.4 M solution in ether). The resulting solution was stirred at 0 °C for 1 h and at room temperature for 2 h. The reaction mixture was quenched by addition of saturated ammonium chloride solution (10 mL), and the aqueous mixture was extracted with ether (3 × 10 mL). The combined organic extracts were washed with brine (10 mL) and dried over anhydrous magnesium sulfate. Removal of solvents in vacuo followed by flash chromatography (silica gel, hexane–diethyl ether, 10:1) gave **40** (89.1 mg, 58%) as a colorless liquid: ^{1}H NMR ($CDCl_3$) δ 0.66 (d, J = 7 Hz, 3 H), 0.98 (s, 3 H), 1.10–1.68 (m, 8 H), 1.94 (m, 1 H), 2.08 (s, 3 H); IR ($CHCl_3$) 2940, 2860, 1685, 1450, 1350 cm^{-1}; $[\alpha]^{27}_D$ +5.8° (c 1.78, Et_2O); CI-MS, m/z (relative intensity) 155 (M^+ + 1, 100), 97 (50). Anal. Calcd for $C_{10}H_{18}O$: C, 77.87; H, 11.76. Found: C, 78.03; H, 11.70.

The enantiomeric purity of **40** was determined by observation of the ^{1}H NMR spectrum in the presence of the chiral shift reagent tris[3-[(heptafluoropropyl)hydroxymethylene]-*d*-camphorato]europium(III). Addition of several aliquots of $Eu(hfc)_3$ to a solution of racemic **40** in $CDCl_3$ caused the singlet at 2.08 (methyl group) to separate into two equivalent singlets. Under the same conditions, the resonance for nonracemic **40** appeared as one singlet.

General Procedure for Preparation of 1-Hydroxycyclohex-3-enes. (2′*S*,2*R*)-1,2-Dimethyl-1-hydroxy-2-[[2′-(methoxymethyl)pyrrolidinyl]-carbonyl]cyclohex-3-ene (37a). To a stirred solution of **36a** (60 mg, 0.24 mmol) in dry THF (1 mL) was added methylmagnesium bromide (96 μL, 3 M solution in ether, 0.29 mmol) via syringe at 0 °C. The cooling bath was removed, and the resulting pale yellow solution was stirred at room temperature for 10 h. The reaction mixture was quenched by addition of saturated ammonium chloride solution (3 mL), and the aqueous mixture was extracted with chloforom (3 × 5 mL). The combined organic extracts were washed with brine (2 × 5 mL) and dried over anhydrous magnesium sulfate. Removal of solvents in vacuo provided a pale yellow oil. Flash chromatography (silica gel, methylene chloride–ethyl acetate, 4:1) gave **37a** (54 mg, 84%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.10–1.28 (m, 2 H), 1.40 (s, 3 H), 1.59 (s, 3 H),

1.74–2.02 (m, 5 H), 2.09–2.20 (m, 2 H), 3.35 (br s, overlapping m at 3.42, 5 H), 3.56–3.76 (m, 2 H), 4.15 (m, 1 H), 5.58 (m, 1 H), 5.97 (m, 1 H); IR (film) 3650–3150 (br), 3020, 2965, 2930, 2880, 1580, 1445, 1370, 1330 cm^{-1}; CI-MS, *m/z* (relative intensity) 268 ($M^+ + 1$, 100), 250 (43), 142 (32). Anal. Calcd for $C_{15}H_{25}NO_3$: C, 67.38; H, 9.43. Found: C, 67.31; H, 9.86.

(2′*S*,2*R*)-1,2-Dimethyl-1-hydroxy-2-[[2′-(1-propyl)pyrrolidinyl]carbonyl]cyclohex-3-ene (37b) was prepared from **36b** in 82% yield as described for **37a**. Flash column chromatography (silica gel, hexane–ethyl acetate, 1:1) gave **37b** as a colorless oil: ^1H NMR ($CDCl_3$) δ 0.94 (t, J = 8 Hz, 3 H), 1.08–1.38 (m, overlapping br s at 1.26, 7 H), 1.41 (s, 3 H), 1.54 (m, 1 H), 1.66–2.03 (m, 6 H), 2.10–2.20 (m, 2 H), 3.48–3.78 (m, 2 H), 4.16, 4.52 (2 m, 1 H), 5.61 (m, 1 H), 6.00 (dt, J = 10 Hz, 2 Hz, 1 H); IR (film) 3600–3150 (br), 3020, 2960, 2930, 2865, 1580, 1460, 1440, 1408, 1380 cm^{-1}; CI-MS, *m/z* (relative intensity) 266 ($M^+ + 1$, 100), 248 (60), 140 (97). Anal. Calcd for $C_{16}H_{27}NO_2$: C, 72.41; H, 10.25. Found: C, 72.32; H, 10.16.

(2′*S*,2*S*)-2,6-Dimethyl-1-hydroxy-2-[[2′-(methoxymethyl)-pyrrolidinyl]carbonyl]cyclohex-3-ene. To a stirred solution of (2′*S*,2*S*)-2,6-dimethyl-2-[[2′-(methoxymethyl)pyrrolidinyl]carbonyl]-3-cyclohex-1-one (1.1 g, 4.1 mmol) in EtOH (25 mL) was added sodium borohydride (0.252 g, 6.6 mmol) at 0 °C. The reaction mixture was slowly warmed to room temperature and stirred for 4 h. The excess sodium borohydride was quenched with 10% HCl solution, and the ethanol was removed in vacuo. The residue was partitioned between CH_2Cl_2 and H_2O and extracted with CH_2Cl_2 (3 × 50 mL). The combined extracts were dried over magnesium sulfate, and solvent was removed in vacuo to give a pale yellow oil, which solidified on standing. Flash column chromatography (silica gel, ethyl acetate–hexane, 4:1) gave the title compound (961 mg, 87%) as oily crystals: ^1H NMR ($CDCl_3$) (mixture of diastereomers) δ 1.06 (d, J = 3 Hz, 3 H), 1.28 (s, 3 H), 1.60–2.30 (m, 8 H), 2.92–3.22 (m, 2 H), 3.26–3.72 (m with overlapping s at 3.30, 5 H), 3.72–4.08 (m, 1 H), 4.36 (br s, 1 H), 5.52–5.96 (2 m, 2 H); IR ($CHCl_3$) 3330, 2905, 1590 cm^{-1}; CI-MS, *m/z* (relative intensity) 268 ($M^+ + 1$, 90), 250 (21), 142 (32), 120 (100). Anal. Calcd for $C_{15}H_{25}NO_3$: C, 67.38; H, 9.42. Found: C, 67.45; H, 9.31.

(2′*S*,2*R*)-2,4-Dimethyl-1-hydroxy-2-[[2′-(methoxymethyl)-pyrrolidinyl]carbonyl]cyclohex-3-ene was prepared from (2′*S*,2*R*)-2,4-dimethyl-2-[[2′-(methoxymethyl)pyrrolidinyl]carbonyl]-3-cyclohex-1-one (300 mg, 1.1 mmol) as described for (2′*S*,2*S*)-2,6-dimethyl-1-hydroxy-2-[[2′-(methoxymethyl)pyrrolidinyl]carbonyl]cyclohex-3-ene. Recrystallization from ether–pentane gave the title compound (251 mg, 94%) as a colorless solid: mp 102–108 °C; ^1H NMR ($CDCl_3$) (3:2 mixture of diastereomers) δ 1.28, 1.38 (2 s, 3 H), 1.69 (br s, 3 H), 1.70–2.16 (m, 8 H), 3.33 (s, 3 H), 3.40–3.80 (m, 5 H), 4.13 (dd, J = 6 Hz, 1 Hz, 1 H), 4.32 (br s, 1 H), 5.38, 5.46 (2 br s, 1 H); IR ($CHCl_3$) 3400, 2925, 1588 cm^{-1}; CI-MS, *m/z* (relative intensity) 268 ($M^+ + 1$, 100), 250 (22), 142 (32), 116 (48). Anal. Calcd for $C_{15}H_{25}NO_3$: C, 67.38; H, 9.42. Found: C, 67.22; H, 9.51.

General Procedure for Dehydration of Alcohols. (2′*S*,6*R*)-1,6-Dimethyl-6-[[2′-(methoxymethyl)pyrrolidinyl]carbonyl]-1,4-cyclohexadiene (38a). To a stirred solution of **37a** (40 mg, 0.15 mmol) in methanol (1 mL) was added concentrated hydrochloric acid (100 μL). The resulting solution was heated at reflux for 6 h. After being cooled to room temperature, the reaction mixture was neutralized by addition of saturated sodium bicarbonate (2 mL). Most of the methanol was removed in vacuo, and the aqueous mixture was extracted with ethyl acetate (3 × 5 mL). The combined organic extracts were washed with brine (5 mL) and dried over anhydrous magnesium sulfate. Removal of solvents in vacuo followed by flash chromatography (silica gel, hexane–ethyl acetate, 2:1) gave **38a** (34 mg, 91%) as a colorless solid. The analytical sample was prepared by recrystallization from hexane: mp 54–56 °C; ^1H NMR ($CDCl_3$) δ 1.34 (s, 3 H), 1.66 (d, J = 2 Hz, 3 H), 1.76–1.96 (m, 4 H), 2.58–2.86 (m, 2 H), 3.29 (m, 1 H), 3.34 (s, 3 H), 3.41–3.70 (m, 3 H), 4.14 (m, 1 H), 5.50 (m, 1 H), 5.57 (dt, J = 10 Hz, 2 Hz, 1 H), 5.78 (m, 1 H); IR ($CHCl_3$) 2990, 2935, 2880, 2820, 1605, 1445, 1402, 1380 cm^{-1}; $[\alpha]^{25}_D$ −52.9° (*c* 1.21, CH_3OH); CI-MS, *m/z* (relative intensity) 250 ($M^+ + 1$, 100), 142 (17); GC (140 °C for 2 min, 2 °C/min) t_R 29.46 min. GC co-injection of **38a** from this reaction with **33** derived from reductive alkylation of **32**: GC (140 °C for 2 min, 2 °C/min) t_R (percent) 27.76 (43.3), 29.33 min (54.5). Anal. Calcd for $C_{15}H_{23}NO_2$: C, 72.25; H, 9.30. Found: C, 71.99; H, 9.41.

(2′*S*,6*R*)-1,6-Dimethyl-6-[[2′-(1-propyl)pyrrolidinyl]carbonyl]-1,4-cyclohexadiene (38b). Prepared from **37b** in 88% yield as described for **38a**. Flash column chromatography (silica gel, hexane–ethyl acetate, 2:1) gave **38b** as a colorless oil: ^1H NMR ($CDCl_3$) δ 0.91 (t, J = 8 Hz, 3 H), 1.04–1.40 (m, overlapping s at 1.32, 6 H), 1.50–1.94 (m, overlapping d at 1.68, J = 2 Hz, 8 H), 2.56–2.84 (m, 2 H), 3.28 (m, 1 H), 3.64 (m, 1 H), 4.12 (m, 1 H), 5.50 (m, 1 H), 5.56 (dt, J = 10 Hz, 2 Hz, 1 H), 5.76 (m, 1 H); IR (film) 3020, 2955, 2920, 2860, 1610, 1435, 1392, 1375 cm^{-1}; $[\alpha]^{25}_D$ −34.1° (*c* 0.30, CH_3OH); CI-MS, *m/z* (relative intensity) 248 ($M^+ + 1$, 100), 140 (61); GC (140 °C for 2 min, 2 °C/min) t_R 35.80 min. GC co-injection of **38b** derived from this reaction with **35** derived from reductive alkylation of **10b**: GC (150 °C for 2 min, 2 °C/min) t_R (percent) 21.28 (53.63), 23.00 min (45.53).

General Procedure for Methylation of β-Keto Amides. (2′*S*,2*R*)-2,6-Dimethyl-2-[[2′-(methoxymethyl)pyrrolidinyl]carbonyl]-3-cyclohexen-1-one (47a). A solution of lithium diisopropylamide (3.3 mmol, 1.6 equiv) was prepared by addition of *n*-butyllithium (1.52 mL, 3.3 mmol, 2.16 M in hexanes) to diisopropylamine (0.47 mL, 3.3 mmol) in THF (5 mL) at 0 °C. The solution was stirred at 0 °C for 20 min and then cooled to −78 °C. The LDA solution was slowly added to a solution of **36a** (500 mg, 2.0 mmol) in THF (5 mL) at −78 °C. The reaction mixture was stirred at −78 °C for ~20 min, and methyl iodide (0.074 mL, 1.2 mmol) was added. The reaction mixture was slowly warmed to room temperature and stirred for 1 h. A 10% HCl solution (2 mL) was added, and the THF was removed in vacuo. The residue was partitioned between H_2O and CH_2Cl_2 and extracted with CH_2Cl_2 (3 × 50 mL). The combined extracts were dried over $MgSO_4$, and solvent was removed in vacuo to give a dark yellow oil. Flash column chromatography (silica gel, ethyl acetate–hexane, 4:1) gave **47a** (291 mg, 55%): ^1H NMR ($CDCl_3$) (mixture of diastereomers) δ 1.08 (d, J = 3 Hz, 3 H), 1.36 (s, 3 H), 1.60–2.0 (m, 4 H), 2.01–2.21 (m, 1 H), 2.58–2.72 (m, 2 H), 3.22–3.42 (m with overlapping s at 3.32, 6 H), 3.54 (dd, J = 3 Hz, 1 Hz, 1 H), 4.26 (br s, 1 H), 5.70 (d, J = 6 Hz, 1 H), 5.82 (dt, J_d = 6 Hz, J_t = 1 Hz, 1 H); IR (film) 2950, 1705, 1625 cm^{-1}; CI-MS, *m/z* (relative intensity) 266 ($M^+ + 1$, 100), 234 (14.89), 142 (53.84). Anal. Calcd for $C_{15}H_{23}NO_3$: C, 67.89; H, 8.73. Found: C, 67.78; H, 8.79.

General Procedure for Preparation of Enol Ethers from β-Keto Amides. (2′*S*,6*R*)-1-Methoxy-2,6-dimethyl-6-[[2′-[(methoxymethyl)pyrrolidinyl]carbonyl]-1,4-cyclohexadiene (43a). To a stirred solution of **47a** (200 mg, 0.75 mmol) in methanol (3 mL) and trimethylorthoformate (3 mL) was added concentrated sulfuric acid (3 drops) at room temperature. The reaction mixture was stirred at room temperature for 18 h, and saturated $NaHCO_3$ solution (~5 mL) was added. Methanol was removed in vacuo, and the resulting residue was partitioned between H_2O and CH_2Cl_2 and extracted with CH_2Cl_2 (3 × 50 mL). The combined extracts were dried over $MgSO_4$, and solvent was removed in vacuo to give a dark yellow oil. Flash column chromatography (silica gel, ethyl acetate–hexane, 4:1) gave **43a** (160 mg, 76%) as a pale yellow oil: ^1H NMR ($CDCl_3$) δ 1.44 (s, 3 H), 1.67–2.06 (m with overlapping s at 1.71, 7 H), 2.69 (dd, J = 20, 10 Hz, 2 H), 3.20–3.62 (m with two overlapping s at 3.34 and 3.62, 9 H), 3.71 (dd, J = 4 Hz, 1 Hz, 1 H), 4.36 (br m, 1 H), 5.48 (dt, J = 6 Hz, 1 Hz, 1 H), 5.66 (dt, J = 6 Hz, 1 Hz, 1 H); GC (180 °C for 2 min, 2 °C/min) t_R 17.63 min. GC co-injection with **43a** and **44a** (5:1 mixture of diastereomers) derived from reductive alkylation of **2b**: GC (180 °C for 2 min, 2 °C/min) t_R (percent) 16.23 (14.93), 17.52 (15.87); GC of **43a** and **44a** derived from **2b**: GC (180 °C for 2 min, 2 °C/min) t_R (percent) 16.29 (25.72), 17.52 min (5.26).

(2′*S*,6*R*)-1-Methoxy-2-methyl-6-benzyl-6-[[2′-(methoxymethyl)-pyrrolidinyl]carbonyl]-1,4-cyclohexadiene (43b) was prepared from **47b** (263 mg, 1.0 mmol) as described for **43a**. Purification of the crude reaction mixture by flash column chromatography (silica gel, hexane–ethyl acetate, 1:1) gave **43b** (266 mg, 76%) as a colorless solid: mp 106–110 °C; ^1H NMR ($CDCl_3$) δ 1.53 (s, 3 H), 1.88 (m, 5 H), 2.26 (br d, J = 10 Hz, 1 H), 2.92 (d, J = 7 Hz, 1 H), 3.30–3.78 (m with overlapping s at 3.38 and 3.59, 11 H), 4.35 (m, 1 H), 5.39 (dt, J_d = 8 Hz, J_t = 0.5 Hz, 1 H), 5.56 (dt, J_d = 8 Hz, J_t = 1 Hz, 1 H), 7.13 (m, 5 H); IR ($CHCl_3$) 1620 cm^{-1}; CI-MS, *m/z* (relative intensity) 356 ($M^+ + 1$, 25), 142 (100); GC (210 °C for 2 min, 4 °C/min) t_R (percent) 20.39 (99.4), 21.51 min (0.56). Anal. Calcd for $C_{22}H_{29}NO_3$: C, 74.33; H, 8.22. Found: C, 74.13; H, 8.20.

(2′*S*,6*S*)-1-Methoxy-6-methyl-6-[[2′-(methoxymethyl)pyrrolidinyl]carbonyl]-1,4-cyclohexadiene (55). *n*-Butyllithium (0.68 mL, 1.1 mmol, 1.6 M in hexanes) was added to THF (20 mL), and a solution of **29** (251 mg, 1.0 mmol) in THF (10 mL) was added at −78 °C. The reaction mixture was stirred at −78 °C for ~5 min, the cooling bath was removed, and the reaction mixture was allowed to warm to room temperature. Stirring was continued at room temperature for 30 min, and then the reaction mixture was recooled to −78 °C. After 30 min at −78 °C, methyl iodide (0.186 mL, 3.0 mmol) was added. Stirring was continued at −78 °C for 30 min, and then water (5 mL) was added. The reaction mixture was slowly warmed to room temperature, after which solvents were removed in vacuo. The residue was partitioned between H_2O and CH_2Cl_2, and the water layer was extracted with CH_2Cl_2 (3 × 100 mL). The combined extracts were washed with sodium thiosulfate solution (100 mL) and brine (100 mL) and dried over $MgSO_4$. Solvent was removed in vacuo to give **55** (249 mg, 94%) as a single diastereomer: ^1H NMR ($CDCl_3$) δ 1.42 (s, 3 H), 1.68–2.00 (m, 4 H), 2.71–2.98 (m, 2 H), 3.20–3.40 (m with overlapping s at 3.35, 5 H), 3.51 (s, 3 H), 3.62–3.70

(m, 2 H), 4.32 (m, 1 H), 4.67 (t, J = 3 Hz, 1 H), 5.53 (dt, J_d = 9 Hz, J_t = 3 Hz, 1 H), 5.77 (m, 1 H); GC (150 °C for 2 min, 2 °C/min) t_R time 13.00 min. GC co-injection of **55** and **28a**: component (t_R, min) **28a** (12.41), **58** (13.08).

(2′*S*)-1-Methoxy-6-methyl-2-[[2′-(methoxymethyl)pyrrolidinyl]-carbonyl]-1,4-cyclohexadiene (56). To a stirred solution of diisopropylamine (0.16 mL, 1.1 mmol) in THF (15 mL) was added *n*-butyllithium (0.44 mL, 1.1 mmol, 2.5 M in hexanes) at −78 °C. The mixture was warmed to 0 °C and stirred at 0 °C for ~20 min and then cooled to −78 °C. A solution of **29** (251 mg, 1.0 mmol) in THF (15 mL) was added, and stirring was continued at −78 °C for ~20 min, after which methyl iodide (0.124 mL, 2.0 mmol) was added. After the mixture was stirred at −78 °C for 30 min, water (5.0 mL) was added, the reaction mixture was warmed to room temperature, and solvent was removed in vacuo. The residue was dissolved in CH_2Cl_2 (30 mL) and washed with 10% sodium thiosulfate solution (30 mL) and brine (30 mL). The organic layer was dried over $MgSO_4$, solvent was removed in vacuo, and flash column chromatography gave a mixture of **55** and **28a** (135 mg, 60%, 2:1) and **56** (56 mg, 25%). **56**: ^{1}H NMR ($CDCl_3$) (mixture of diastereomers) δ 1.08 (2 overlapping d, J = 3 Hz, 3 H), 1.60–2.20 (m, 6 H), 2.40–2.62 (m, 1 H), 3.14–3.88 (m with overlapping s at 3.32, 3.38, 3.76, 3.78, 10 H), 4.32 (m, 1 H), 5.50 (m, 1 H), 5.90 (dd, J = 6 Hz, J = 1 Hz, 1 H); IR (film) 1625 cm^{-1}; CIMS, m/z (relative intensity) 266 (M^+ + 1, 90), 142 (100).

Preparation of Lithium and Potassium Amide Enolates for NMR Experiments. Lithium Enolate of 1-Methoxy-6-(pyrrolidinylcarbonyl)-1,4-cyclohexadiene (62b). *n*-Butyllithium (0.15 mL, 0.3 mmol, 2.5M in hexanes) was added to a 5-mm NMR tube fitted with a rubber septum. The solvent was removed at room temperature in vacuo, after which the tube was cooled to −78 °C and THF-d_8 (0.25 mL) was added. The addition of a solution of **61b** (50 mg, 0.24 mmol) in THF-d_8 (0.25 mL) to the *n*-butyllithium solution at −78 °C produced an immediate dark-orange coloration. NMR data were collected over a range of temperatures; ^{1}H NMR (THF-d_8, 25 °C) 1.85–3.50 (m, 4 H, THF, hexane), 4.31–4.85 (m, 2 H), 4.89–5.21 (m with overlapping s at 4.89, 7 H), 5.31 (br s, 1 H), 5.89 (m, 1 H), 7.45 (d, J = 5 Hz, 1 H). Methyl iodide (0.03 mL, 0.48 mmol) was added to the NMR tube at −78 °C after the spectral data were recorded. The usual workup provided 1-methoxy-6-methyl-6-(pyrrolidinylcarbonyl)-1,4-cyclohexadiene (44 mg, 83%).

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Registry No. 1a, 94225-47-5; **1b**, 115512-72-6; **1c**, 115512-73-7; **1d**, 115512-74-8; **2a** (R = Me), 102069-84-1; **2a** (R = CH_2OMe), 115512-61-3; **2b** (R = H), 115512-66-8; **2b** (R = Me), 115512-79-3; **2c** (R = H), 115512-67-9; **2c** (R = Me), 115512-80-6; **2d** (R = H), 115512-68-0; **2d** (R = Me), 115512-81-7; **2e** (R = H), 115512-69-1; **2e** (R = CH_2OMe), 115512-82-8; **3b**, 102069-83-0; *dl*-**3b**, 115588-34-6; **3b** (2′-methyl derivative), 115512-62-4; **3c**, 111904-55-3; **3d**, 111904-56-4; **3d** (2′-methyl derivative), 115512-64-6; *dl*-**3d** (piperidinyl homologue), 115512-65-7; **3e**, 115512-57-7; **3e** (2′-methyl derivative), 115512-59-9; *dl*-**3e**, 115588-33-5; *dl*-**5a**, 115588-36-8; *dl*-**5b**, 115512-77-1; *dl*-**5b** (2′-alcohol), 115512-63-5; *dl*-**5c**, 115512-76-0; *dl*-**5c** (2′-alcohol), 115512-60-2; *dl*-**6a**, 115512-71-5; **6b**, 115512-70-4; **7a**, 115512-78-2; **7b**, 115512-75-9; **8a**, 115512-84-0; *dl*-**8a**, 115588-38-0; **8b**, 115512-83-9; *dl*-**8b**, 115588-37-9; (*S*)-(*E*)-**9a**, 115512-87-3; (*S*)-(*Z*)-**9a**, 115512-88-4; *dl*-(*E*)-**9a**, 115588-41-5; *dl*-(*Z*)-**9a**, 115588-42-6; (*S*)-(*E*)-**9b**, 115512-85-1; (*S*)-(*Z*)-**9b**, 115512-86-2; *dl*-(*E*)-**9b**, 115588-39-1; *dl*-(*Z*)-**9b**, 115588-40-4; **10a**, 115512-90-8; **10b**, 115512-89-5; *dl*-**10c**, 115588-44-8; *dl*-**10d**, 115588-43-7; **11**, 23356-96-9; *dl*-**11**, 10200-26-7; **12a**, 6216-63-3; **12b**, 71461-30-8; (*E*)-**13**, 115513-36-5; (*Z*)-**13**, 115513-37-6; **14**, 86661-34-9; **16a**, 94225-48-6; **16b**, 94225-49-7; **16c**, 94225-50-0; (9a*R*)-**16c**, 115588-54-0; **16d**, 94225-51-1; (9a*R*)-**16d**, 115588-55-1; **16e**, 115513-43-4; **17**, 115512-98-6; **18**, 94292-51-0; **19**, 94225-52-2; (9a*S*)-**20a**, 115513-48-9; (9a*R*)-**20a**, 115588-60-8; **20b** (isomer 1), 115513-49-0; **20b** (isomer 2), 115588-61-9; **20b** (isomer 3), 115588-62-0; **20b** (isomer 4), 115588-63-1; (9a*S*)-**20c**, 115513-50-3; (9a*R*)-**20c**, 115588-64-2; *dl-cis*-**22**, 115588-59-5; *dl-trans*-**22**, 115588-58-4; *dl-cis*-**23**, 115513-47-8; *dl-trans*-**23**, 115513-46-7; (6*S*)-**24**, 115513-45-6; (6*R*)-**24**, 115588-57-3; (9a*S*)-**25**, 115513-44-5; (9a*R*)-**25**, 115588-56-2; **27** (R = Me; M = Li), 115513-35-4; **28a** (R = H), 102069-86-3; (6*S*)-**28a** (R = H), 115513-40-1; **28a** (R = Me), 102069-87-4; *dl*-**28a** (R = Me), 115588-45-9; **28b** (R = Me), 115512-99-7; (6*S*)-**28b** (R = Me), 115513-00-3; **28c** (R = Me), 115513-01-4; **28e** (R = CH_2OMe), 115513-02-5; (6*R*)-**29**, 115512-91-9; (6*S*)-**29**, 115512-92-0; **30**, 102069-90-9; **31**, 102069-91-0; **32**, 102069-92-1; **33**, 102131-11-3; **33** (2′-*O*-(CH_2OMe) derivative), 115513-13-8; **33** (2′-alcohol), 115513-42-3; **34**, 115513-07-0; (6*S*)-**34**, 115533-25-0; *dl*-(*R**,*R**)-**34**, 115648-27-6; *dl*-(*R**,*S**)-**34**, 115588-46-0; **35**, 115513-16-1; (6*R*)-**35**, 115513-17-2; **36a**, 115513-20-7; **36b**, 115513-21-8; **37a**, 115513-28-5; **37b**, 115513-29-6; **38a**, 102131-12-4; **38a** (Y = OH), 115513-41-2; **38b**, 115513-17-2; **39**, 115588-35-7; **40**, 115588-50-6; *dl*-**40**, 115513-27-4; **41**, 115513-26-3; **43a**, 115512-93-1; **43b**, 115512-97-5; **44a**, 115533-24-9; **44a** (ketone, isomer 1), 115513-22-9; **44a** (ketone, isomer 2), 115588-48-2; **44b**, 115512-96-4; (5*R*)-**45**, 115512-94-2; (5*S*)-**45**, 115512-95-3; **46**, 115513-58-1; (6*R*)-**47a**, 115588-53-9; (6*S*)-**47a**, 115588-52-8; (6*R*)-**47b**, 115588-65-3; (6*S*)-**47b**, 115513-59-2; (3*R*)-**49**, 115588-47-1; (3*S*)-**49**, 115513-08-1; **49** (ketone, isomer 1), 115513-24-1; **49** (ketone, isomer 2), 115588-49-3; **49** (6-bromo ketone, dimethyl ketal), 115513-60-5; **50**, 115513-62-7; **50** (dimethyl ketal), 115513-61-6; **51a**, 115513-09-2; (6*S*)-**51a**, 115513-10-5; **51a** (ketone), 115513-23-0; **51b**, 115513-56-9; (6*R*)-**51b**, 115513-57-0; **52**, 115513-51-4; (6*S*)-**52**, 115513-52-5; **52** (ketone), 115513-53-6; **52** (ketone, 2,4-dinitrophenylhydrazone), 115513-54-7; (6*R*)-**53a**, 115513-14-9; (6*S*)-**53a**, 115513-15-0; (6*R*)-**53b**, 115513-03-6; (6*S*)-**53b**, 115513-04-7; *dl*-(*R**,*R**)-**54a**, 115513-05-8; *dl*-(*R**,*S**)-**54a**, 115513-06-9; *dl*-(*R**,*R**)-**54b**, 115513-18-3; *dl*-(*R**,*S**)-**54b**, 115513-19-4; **55**, 102069-89-6; (6*R*)-**56**, 115513-63-8; (6*S*)-**56**, 115533-26-1; **61a**, 115513-34-3; **61b**, 115513-32-1; **62a**, 115513-65-0; **62b**, 115513-64-9; 2-MeC_6H_4COCl, 933-88-0; 2-$MeOC_6H_4COCl$, 21615-34-9; 2-FC_6H_4COCl, 393-52-2; 2-BrC_6H_4COCl, 7154-66-7; 2-MeO-3-MeC_6H_3COCl, 22256-43-5; 2-MeO-4-MeC_6H_3COCl, 51671-69-3; 2-MeO-5-MeC_6H_3COCl, 25045-35-6; 2-MeO-6-MeC_6H_3COCl, 50463-84-8; 2-MeO-4-MeC_6H_3CHO, 57415-35-7; (2′*S*,6*R*)-3,6-dimethyl-6-[[2′-(methoxymethyl)-1-pyrrolidinyl]carbonyl]-2-cyclohexen-1-one, 115513-25-2; 2,6-dimethyl-1-hydroxy-2-[[2′-(methoxymethyl)-1-pyrrolidinyl]carbonyl]-2-cyclohexen-1-one, 115513-30-9; (2′*S*,1*S*,2*R*)-2,4-dimethyl-1-hydroxy-2-[[2′-(methoxymethyl)-1-pyrrolidinyl]-carbonyl]cyclohex-3-ene, 115513-31-0; (2′*S*,1*R*,2*R*)-2,4-dimethyl-1-hydroxy-2-[[2′-(methoxymethyl)-1-pyrrolidinyl]carbonyl]cyclohex-3-one, 115588-51-7; *dl*-1-methoxy-6-methyl-6-(1-pyrrolidinylcarbonyl)-1,4-cyclohexadiene, 115513-33-2; (*S*)-2-methyl-2-pyrrolidinemethanol, 115512-58-8; *dl*-2-piperidinemethanol, 2554-59-8; (2′*S*,6*S*)-1-methyl-6-ethyl-6-[[2′-(methoxymethyl)-1-pyrrolidinyl]carbonyl]-1,4-cyclohexadiene, 115513-11-6; (2′*S*,6*R*)-1-methyl-6-ethyl-6-[[2′-(methoxymethyl)-1-pyrrolidinyl]carbonyl]-1,4-cyclohexadiene, 115513-12-7; *dl*-1-methoxy-6-methyl-6-(carbomethoxy)-1,4-cyclohexadiene, 108417-50-1; *dl*-1-methoxy-6-methyl-6-carboxy-1,4-cyclohexadiene, 102069-93-2; *dl*-1,6-dimethyl-6-(carbomethoxy)-1,4-cyclohexadiene, 115513-38-7; *dl*-1,6-dimethyl-6-carboxy-1,4-cyclohexadiene, 115513-39-8; *dl-trans*-1,2-dimethyl-1-(carbomethoxy)cyclohexane, 115513-55-8.

Supplementary Material Available: Tables of crystal structure data, atomic coordinates, bond lengths, bond angles, anistropic parameters, and hydrogen atom coordinates for the 2,4-dinitrophenylhydrazone derivative of **52** and experimental procedures for compounds discussed in the text but not described in the Experimental Section (47 pages). Ordering information is given on any current masthead page.