Diastereo- and Enantiodifferentiation in Indium-Promoted Allylations of 2,3-Azetidinediones in Water. Definition of Long-Range Stereocontrol Elements on π-Facial Selectivity for β-Lactam Synthesis

Leo A. Paquette,*,† Roger R. Rothhaar,† Methvin Isaac,† Lillian M. Rogers,‡ and Robin D. Rogers‡

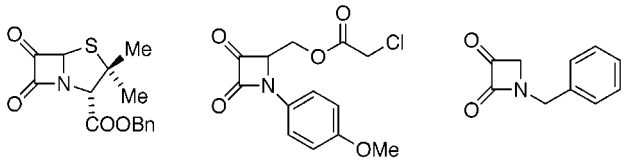
Evans Chemical Laboratories, The Ohio State University, Columbus, Ohio 43210 and the Department of Chemistry, The University of Alabama, Tuscaloosa, Alabama 35487

Received February 27, 1998

The stereochemical course of the reactions of *N*-benzyl-2,3-azetidinedione with six differently functionalized allylic bromides, as promoted by indium metal in 1:1 H_2O−THF, were initially examined. Three of the examples that proved to be usefully stereoselective were subsequently reevaluated in azetidinediones which now carried (*S*)-α-methylbenzyl and (*R*)-α-(1-naphthyl)ethyl residues bonded to nitrogen. These enantiomerically pure building blocks afforded products that differed in the facial sense of organometallic addition to the ketonic carbonyl. Interestingly, the diastereofacial selectivity is directly linked to the *R* or *S* configuration of the exocyclic *N*-amido substituent. Stereochemical assignments to many of the products were based on X-ray crystallographic measurements. In other cases, spectral correlations were used. The global results clearly show that fundamental, yet previously unappreciated, long-range nonbonded steric interactions do control the extent to which competing cyclic transition states operate.

The reaction of carbonyl compounds with allylindium reagents, as generated under aqueous conditions, has rapidly gained recognition as an important, environmentally benign synthetic method.[1] As a consequence of the adoption by these organometallic reagents of cyclic transition states with aldehydes, type I behavior is seen,[2] and high levels of diastereoselectivity are observed unless steric factors contravene.[3,4] These transformations are now also recognized to be subject to chelation control,[5] stereodifferentiation in setting multiple contiguous stereogenic centers,[6] and long-range induction.[7]

At the outset of the present studies,[8] no information was available regarding the stereochemistry of reactions involving 2,3-azetidinediones with allylmetals.[9] The ketonic carbonyl in compounds of this class has previously been recognized to possess heightened electrophilicity. For example, **1** forms a crystalline cyanohydrin,[10] readily undergoes Wittig olefination,[11] and is conveniently receptive to the Peterson olefination[12] and Henry reactions.[13] Analogously, **2** has been reported to undergo the Reformatsky reaction smoothly.[14] Monocyclic 2,3-azetidinediones such as **3** have been prepared by several different methods.[15−17]



1 **2** **3**

The transformations alluded to above form the basis for the preparation of diverse types of biologically active compounds.[18] Recently, **3** has been utilized additionally as a starting material for gaining access to hydantocidin analogues.[19] The modest yields frequently recorded for

† The Ohio State University.

‡ The University of Alabama. To whom queries regarding the crystallographic analyses should be directed.

(1) Reviews: (a) Li, C.-J. *Chem. Rev.* **1993**, *93*, 2023. (b) Lubineau, A.; Augé, J.; Queneau, Y. *Synthesis* **1994**, 741. (c) Li, C.-J. *Tetrahedron* **1996**, *52*, 5643. (d) Paquette, L. A. In *Green Chemistry: Frontiers in Benign Chemical Synthesis and Processing*; Anastas, P., Williamson, T., Eds.; Oxford University Press: New York, 1998.

(2) Roush, W. R. In *Comprehensive Organic Synthesis*; Heathcock, C., Ed.; Pergamon Press: Oxford, 1991; Vol. 2, p 1.

(3) Isaac, M. B.; Chan, T. H. *Tetrahedron Lett.* **1995**, *36*, 8957.

(4) Paquette, L. A.; Mitzel, T. M. *J. Org. Chem.* **1996**, *61*, 8799.

(5) (a) Paquette, L. A.; Mitzel, T. M. *J. Am. Chem. Soc.* **1996**, *118*, 1931. (b) Paquette, L. A.; Lobben, P. C. *J. Am. Chem. Soc.* **1996**, *118*, 1917. (c) Paquette, L. A.; Mitzel, T. M.; Isaac, M. B.; Crasto, C. F.; Schomer, W. W. *J. Org. Chem.* **1997**, *62*, 4293.

(6) Isaac, M. B.; Paquette, L. A. *J. Org. Chem.* **1997**, *62*, 5333.

(7) (a) Maguire, R. J.; Mulzer, J.; Bats, J. W. *J. Org. Chem.* **1996**, *61*, 6936. (b) Paquette, L. A.; Bennett, G. D.; Chhatriwalla, A.; Isaac, M. B. *J. Org. Chem.* **1997**, *62*, 3370. (c) Paquette, L. A.; Bennett, G. D.; Isaac, M. B.; Chhatriwalla, A. *J. Org. Chem.* **1998**, *63*, in press.

(8) Paquette, L. A.; Isaac, M. B. *Heterocycles* **1998**, *47*, 107.

(9) After the initiation of our efforts, a report appeared describing the allylindation of 4-substituted-2,3-azetidinediones in aqueous tetrahydrofurans: Jayaraman, M.; Manhas, M. S.; Bose, A. K. *Tetrahedron Lett.* **1997**, *38*, 709.

(10) Lo, Y. S.; Sheehan, J. C. *J. Org. Chem.* **1975**, *40*, 191.

(11) Sheehan, J. C.; Buku, A.; Chacko, E.; Commons, T. J.; Lo, Y. S.; Ponzi, D. R.; Schwarzel, W. C. *J. Org. Chem.* **1977**, *42*, 4045.

(12) Brenner, D. G. *J. Org. Chem.* **1985**, *50*, 18.

(13) Chandrasekaran, S.; Kluge, A. F.; Edwards, J. A. *J. Org. Chem.* **1977**, *42*, 3972.

(14) Palomo, C.; Aizpurua, J. M.; Lopez, M. C.; Aurrekoetxea, N.; Oiarbide, M. *Tetrahedron Lett.* **1990**, *31*, 6425.

(15) (a) van der Veen, J. M.; Bari, S. S.; Krishnan, L.; Manhas, M. S.; Bose, A. K. *J. Org. Chem.* **1989**, *54*, 5758. (b) Manhas, M. S.; Bari, S. S.; Bhawal, B. M.; Bose, A. K. *Tetrahedron Lett.* **1984**, *25*, 4733. (c) Bose, A. K.; Manhas, M. S.; Chib, J. S.; Chawla, H. P. S.; Dayal, B. *J. Org. Chem.* **1974**, *39*, 2877.

(16) Tufariello, J. J.; Pinto, D. J. P.; Milowsky, A. S.; Reinhardt, D. V. *Tetrahedron Lett.* **1987**, *28*, 5481.

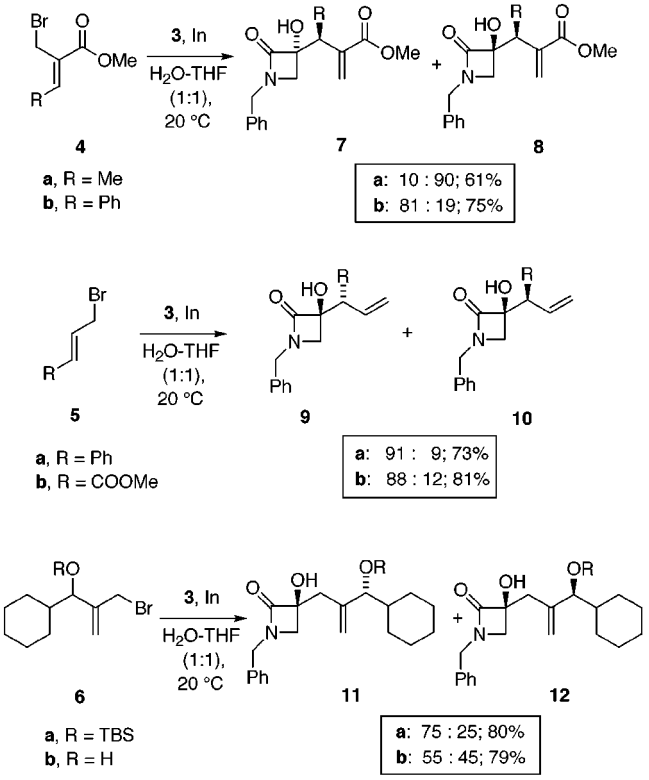
(17) Behrens, C.; Paquette, L. A. *Org. Synth.* **1998**, *75*, 106.

(18) Georg, G., Ed. *The Organic Chemistry of β-Lactams*; VCH: New York, 1992.

(19) Paquette, L. A.; Behrens, C. *Heterocycles* **1997**, *46*, 27.

S0022-3263(98)00372-7 CCC: $15.00
Published on Web 07/10/1998

Scheme 1



the addition of organometallics to **1**−**3** *under anhydrous conditions* have recently been traced to a propensity for enolization, such that proton transfer can become kinetically competitive.[19] This unwanted side reaction can be curtailed in some cases by precomplexation of the azetidinedione with an equivalent of boron trifluoride etherate.[19]

In light of the reduced basicity of allylindium reagents, comparable complications were not anticipated with **3** and analogues thereof in the presence of water. Consequently, the opportunity exists for determining the levels to which the prochiral ketonic carbonyl group in the simplest 2,3-azetidinediones structurally related to **3** is amenable to π-facially selective nucleophilic attack. The essentially planar geometry of the four-membered ring in **3** is seemingly well suited to critical analysis of the stereoselectivity with which two new stereocenters are simultaneously formed during capture of variously substituted allylindium reagents. Beyond that, we anticipated on the basis of those transition state models developed in the preceding context that long-range effects resulting from the presence of chiral substituents on nitrogen would bias the absolute configuration set at these positions in a predictable and useful direction.

Results and Discussion

The *N*-Benzyl Derivative. Experimental Proof of Principle. We have earlier identified the indium reagents derived from allylic bromides **4**−**6** to be useful mechanistic probes and have therefore made recourse to them again in the present context.[4−6] First to be addressed was the diastereoselectivity of their individual reactions with N-benzylazetidinedione **3** (Scheme 1). To guarantee homogeneity throughout this study, all of the coupling reactions were performed in a solvent system consisting of equal amounts of water and tetrahydrofuran. In this way, advantage could simultaneously be taken of the more rapid rates that operate when H_2O is present. Product distributions were determined by ^{1}H NMR integration at 300 MHz (when key signals from individual diastereomers were sufficiently distinctive), by quantitation of the individual diastereomers following chromatographic separation, or by a combination of these methods.

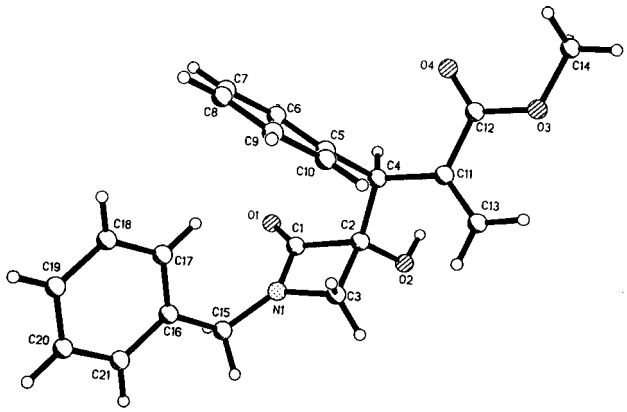


Figure 1. ORTEP diagram of **7b**.

The initial results with **4a**[20] and **4b**[21] proved significant in that stirring with **1** and a suspension of indium powder at room temperature led within 5 h to the complete consumption of reactants, but differently biased product distributions. The stereochemical assignments in these examples rest on spectral correlations and on X-ray crystallographic analyses of **7b** (Figure 1) and analogues of **8a** (see below). Interestingly, a change in the geometry of the allyl bromide as in **5a** and **5b** was not met with a crossover in stereoinduction when R is phenyl. This conclusion is reflected in the predominant formation of **7b** and **9a**. The carbomethoxy substituent does not alter the kinetic dominance with which **9** is formed (ca. 90% for both **a** and **b**). As before, the relative stereochemistries of **9** and **10** were determined by means of a crystal structure determination for **9a**. Where **6a** and **6b**[7] are concerned, the bulky nature of the OTBS substituent is sufficient to favor the formation of **11a**. The near-equitable distribution of **11b** and **12b** can be construed to be the reflection of a mismatch between the steric demands that develop within the indium coordination sphere and internal chelation to the free hydroxyl group. The diastereomers **9** were differentiated from their counterparts **10** on the basis of the chemical shifts and coupling patterns observed for their allylic and vinyl protons. In line with those trends established earlier,[7] the $=CH_2$ singlets in **11a** (δ 5.08 and 5.06 in $CDCl_3$) appear downfield relative to those in **12a** (δ 5.02 and 5.00).

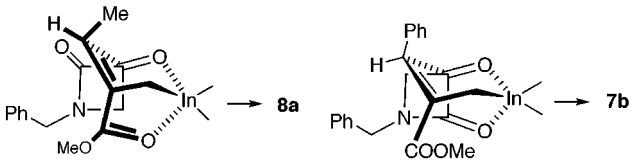
Mechanistic Considerations. Any discussion of the stereoselectivities observed above must take into consideration the fact that an allylindium reagent is capable in principle of coordinating intramolecularly to both carbonyl oxygens of the azetinedione. Furthermore, those organometallics derived from esters **4a**/**4b** and from alcohol **6b** have the added capacity for intramolecular

(20) (a) Goldberg, O.; Drieding, A. S. *Helv. Chim. Acta* **1976**, *59*, 1904. (b) Hoffmann, H. M. R.; Rabe, J. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 795.

(21) (a) Buchholz, R.; Hoffmann, H. M. R. *Helv. Chim. Acta* **1991**, *74*, 1213. (b) Drewes, S. E.; Hoole, R. F. A. *Synth. Commun.* **1985**, *15*, 1067.

chelation. The reaction trajectories defined in Scheme 1 implicate a preference for operation of an interesting array of geometrically defined transition states. In all instances, coordination of the indium to the ketonic carbonyl of the heterocycle provides a quite suitable platform for S_N' delivery of the allyl residue. This requirement is invariant and is the fundamental structural feature that eventuates in CC bond formation.

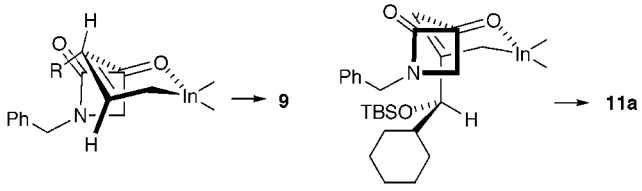
For **4a** to lead predominantly to **8a**, the amide carbonyl cannot be oriented toward the indium atom. The good selectivity seen in this example is believed to reflect secondary chelation to the ester carbonyl as in **A**, al-



A B

though it is not known with certainty whether this added binding indeed operates. The choice by indium of the ester carbonyl as a ligating partner could be enhanced by the placement of an electron-donating methyl group on the β-carbon. That a comparable diastereoselectivity is not seen with **4b** would in turn be consistent with the placement of an electron-withdrawing phenyl substituent at this site. From a purely electronic perspective, the lessened electronic density would diminish the attractiveness of the ester as a coordination site, thereby providing an opportunity for alternative involvement of both azetidinedione carbonyls as in **B**. Indeed, these results clearly show that the substitution pattern in bromides of type **4** is a significant and previously unappreciated variable in determining diastereofacial selectivity.

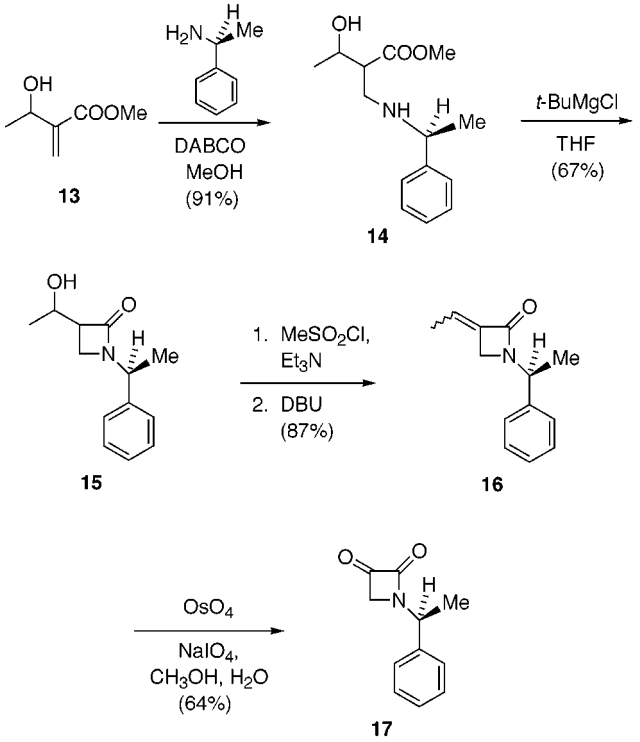
The secondary chelation effects proposed in **A** and **B** are not a necessary condition for effective 1,2-addition since **5a** and **5b** likewise add smoothly and efficiently to **3**. The contrasting *E* double-bond geometry is clearly conducive to the formation of **9** via **C**. From a purely steric viewpoint, it is not surprising that the azetidinedione would prefer to orient itself as in **C** rather than as in **B** relative to the allylindium species. The positioning of an sp^2-hybridized center in close proximity to the R group translates into lessened nonbonding steric interactions. However, the magnitude of this effect cannot be large since bromides **6a** and **6b** are substituted in a manner that should induce a sterically driven reversal



C D

in diastereoselectivity. However, this is not the case, as **11** is the predominant product, presumably formed via **D**. In this model, the tertiary hydrogen needs only to be projected in the direction of the bulky solvated indium center for the relative steric bulk of the cyclohexyl and OTBS substituents to dictate π-facial discrimination. It is reasonable to expect that when the hydroxyl group is

Scheme 2



unprotected as in **6b**, other factors associated with its polarity, size, and binding power grow in importance.

Single Asymmetric Synthesis. Selectivity Involving the (*S*)-α-Methylbenzyl Azetidinedione Reagent. The diastereofacial selectivity in reactions of allylindium reagents **4**−**6** with azetidinedione **3** is determined by the substitution pattern within the metallic species. The transition state models **A**−**D** advanced here to explain the direction of chiral induction share in common the feature of positioning the benzyl substituent on nitrogen in relatively close proximity to one or another component of the indium reagent. As a consequence, we have come to question whether the presence of a stereogenic center α to the nitrogen might influence in a utilitarian way the stereochemical outcome of certain of these coupling reactions. Although these effects are clearly long range, the mandatory cyclic character associated with the structural arrangements in **A**−**D** does not leave matters as distal as first impressions might convey. Beyond this, it is unlikely that N-bonded substituents in azetidinediones flex significantly out of plane. The three-dimensional crystallographic structures illustrated herein collectively reveal this structural characteristic.

The preparation of **17**, the first enantiomerically pure substrate to be examined, is shown in Scheme 2. Michael addition of (*S*)-α-methylbenzylamine to the Baylis−Hillman product **13**[22] led to **14** which was cyclized through the agency of *tert*-butylmagnesium chloride.[16] Following dehydration to provide **16**, oxidative cleavage of the double bond gave **17** in convenient fashion.

Although four products can possibly arise from treatment of **17** with bromide **4a** in the presence of indium, only three were detected and their distribution was 50:41:9. After chromatographic separation, the major constituent was rigorously identified as the "syn" adduct **18a**

(22) Ciganek, E. *Org. React.* **1997**, *51*, 201.

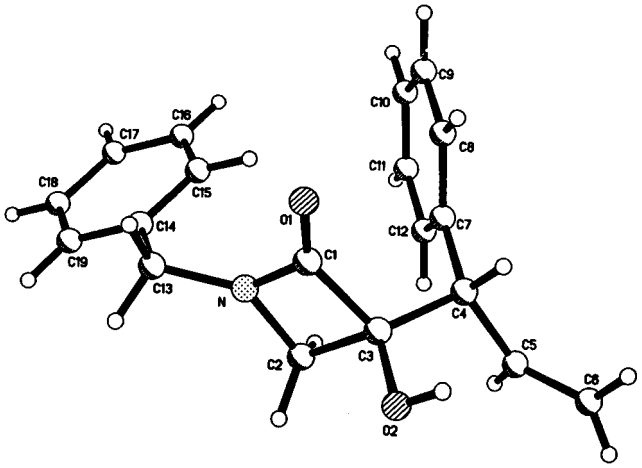


Figure 2. ORTEP diagram of **9a**.

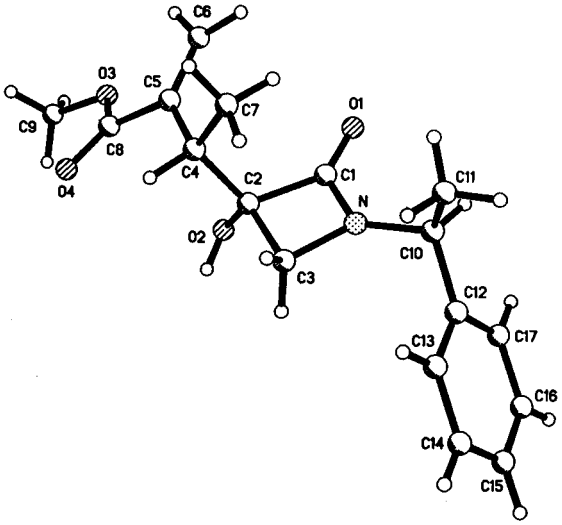


Figure 3. ORTEP diagram of **18a**.

on the strength of a crystallographic analysis (Figure 3). On this basis, assignment of the absolute configuration to the two newly introduced stereogenic centers could be made with confidence. The stereochemical assignment to **19a** is based on a detailed chemical shift comparison with **18a**, **25a**, and **26a**. For example, a characteristic feature of those diastereomers having the (*S*)-benzyl, 3(*R*),α(*S*)- or (*R*)-1-naphthyl,3(*S*),α(*R*)-configurations as in **18a** and **25a** is a relatively close spacing of the chemical shifts of the AB doublets due to the ring methylene protons at C4. In these two examples, the Δδ values are closely comparable at 0.25 and 0.28. For the (*S*)-benzyl,3-(*S*),α(*R*)- and (*R*)-1-naphthyl,3(*R*),α(*S*)-diastereomers **19a** and **26a**, the magnitude of Δδ is significantly larger (0.54 and 0.48, respectively). The result of a confirmatory crystallographic analysis of **26a** is provided in Figure 7. The third, very minor product is necessarily an "anti" isomer. No effort has been expended to allow a distinction to be made between **20a** and **21a**.

The indium-promoted coupling of **4b** to **17** resulted in the more equitable production of four diastereomers, although again with a predominance of the "syn" carbinols **18b** and **19b**. The high crystallinity of the individual isomers made possible a direct assessment of the absolute configurations of **19b**, **20b**, and **21b** by X-ray analysis (Figures 4−6). By the process of elimination, **18b** must

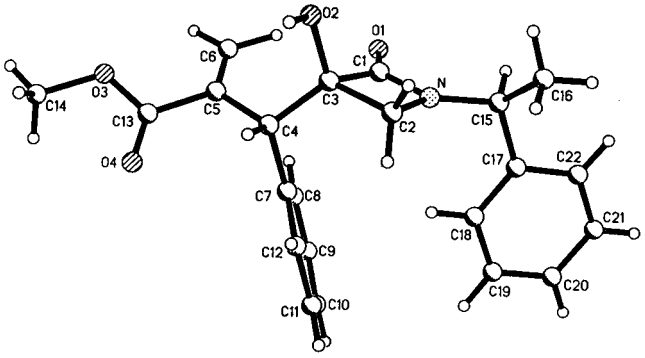


Figure 4. ORTEP diagram of **19b**.

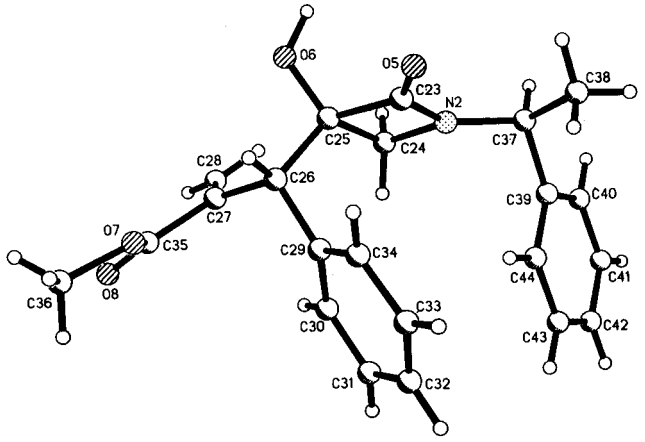


Figure 5. ORTEP diagram of **20b**.

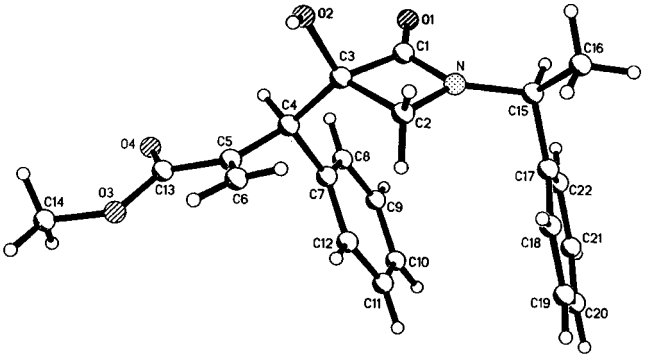


Figure 6. ORTEP diagram of **21b**.

be the "syn" isomer shown, a conclusion also in line with its Δδ (CH_2) value of 0.18. Another nontrivial property of **18b**−**21b** is their polarity. The order of their elution from silica, which is given in Scheme 3, appears to hold generality (see Scheme 5), although the database is rather limited. Our general experience in this study has been that "syn" isomers bind less tightly to the adsorbent than to their "anti" counterparts.

The experimental results realized with **17** and cinnamyl bromide under the standard conditions were to deliver a 63:37 mixture of **22** and **23** in 85% yield (Scheme 4). On the basis of the earlier studies involving **3**, anti diastereomers were anticipated to dominate heavily and this was indeed the case. Since neither **22** nor **23** is a nicely crystalline substance, correlation was made with the naphthyl homologues **29** and **30** with particular emphasis on the crystallographic data available for the latter (Figure 9). The similarity in ^{1}H NMR spectral

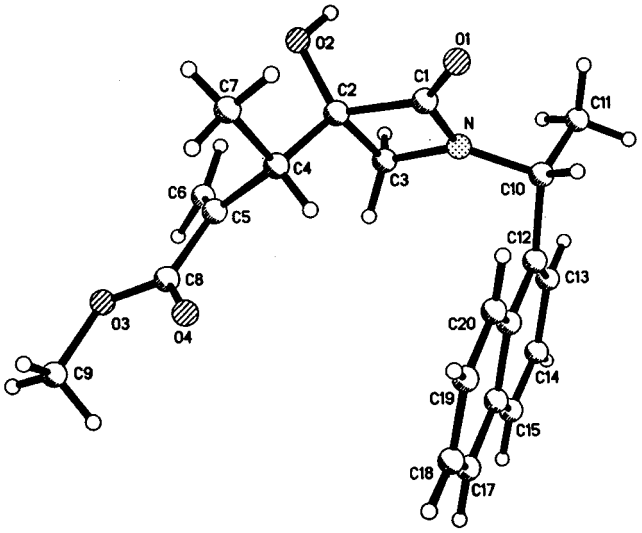
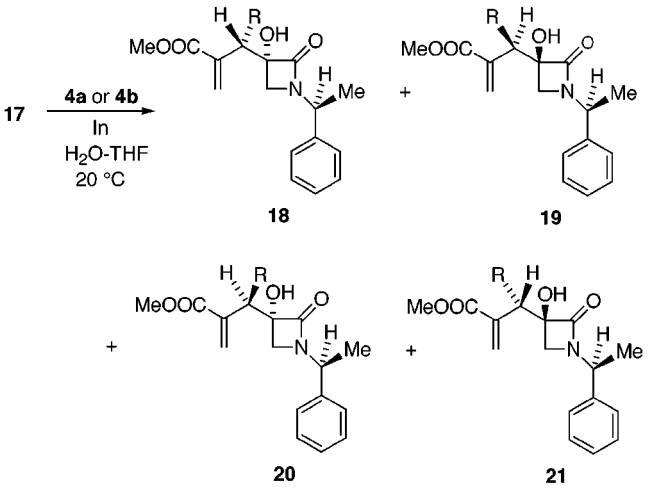


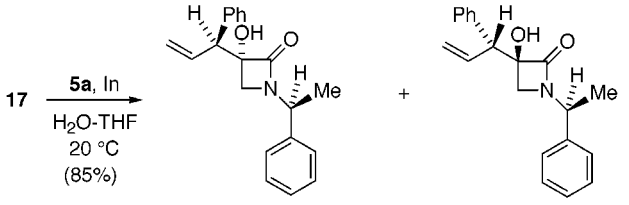
Figure 7. ORTEP diagram of **26a**.

Scheme 3



a: R = Me (75%); **18 : 19 : 20** or **21** (50 : 41 : 9).
b: R = Ph (76%); **18 : 19 : 20 : 21** (28 : 28 : 16 : 28).

Scheme 4



63 : 37

shifts is striking and reflects the heightened magnetic anisotropy provided by a naphthyl ring relative to the smaller benzyl substituent tethered to the nitrogen. Thus, the signals attributable to the C4 methylene protons (δ 3.33, 3.00; $\Delta\delta$ = 0.33) and central vinylic hydrogen (δ 6.19) in **22** are more widely separated and shifted to lower field, respectively, than they are in **23** (δ 3.22, 3.19; $\Delta\delta$ = 0.03, and δ 6.10). This trend is closely mirrored in **29** (δ 3.30, 2.71; $\Delta\delta$ = 0.59, and δ 6.20) and **30** (δ 3.22, 2.89; $\Delta\delta$ = 0.33, and δ 5.92), with anticipated

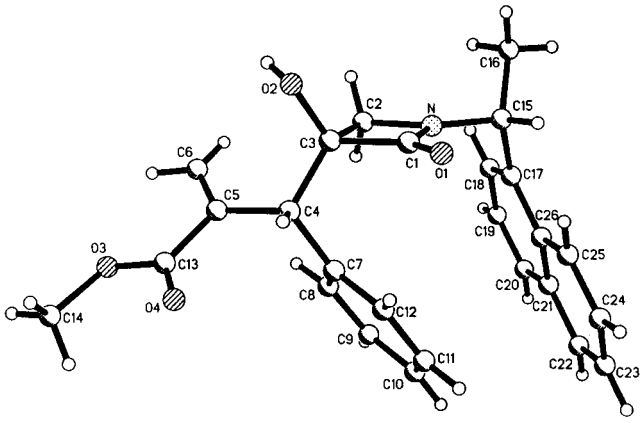
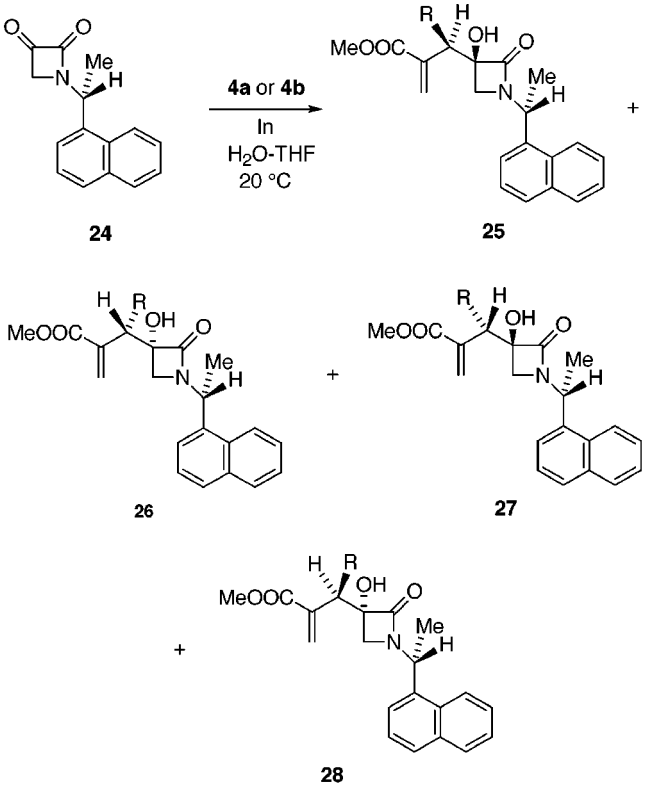


Figure 8. ORTEP diagram of **28b**.

Scheme 5



a: R = Me (72%); **25 : 26 : 27** or **28** (66 : 27 : 7).
b: R = Ph (68%); **25 : 26 : 27 : 28** (32 : 32 : 4 : 32).

enhancements in the shift differences brought on by the more extended aromatic moiety.

Confirmation of Long-Range Stereocontrol: The (*R*)-α-(1-Naphthyl)ethyl Case Study. The findings made concerning the single asymmetric reactions of the α-naphthyl homologue **24** with bromides **4a** and **4b** are summarized in Scheme 5. The configurational assignments, initially formulated on the strength of spectal comparisons, were corroborated by solid-state structural studies on **26a** (Figure 7) and **28b** (Figure 8). Comparison of the data in Scheme 5 versus those collected in Scheme 3 reveals that, when R is methyl, the production of syn diastereomers continues to be heavily favored. The replacement of methyl by phenyl again has a normalizing effect, although the syn isomers **25b** and **26b** do pre-

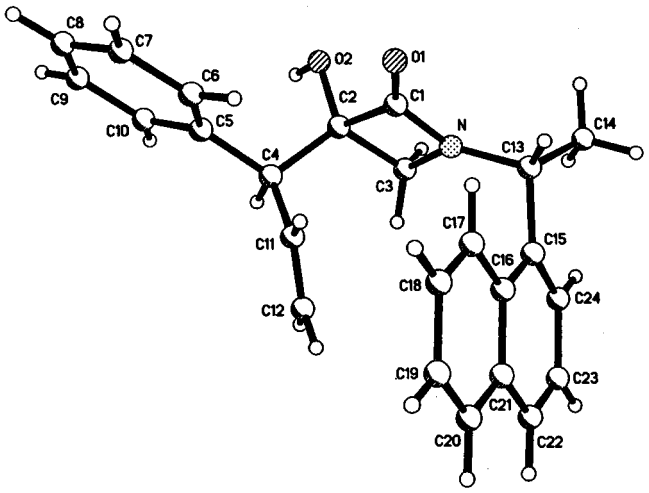
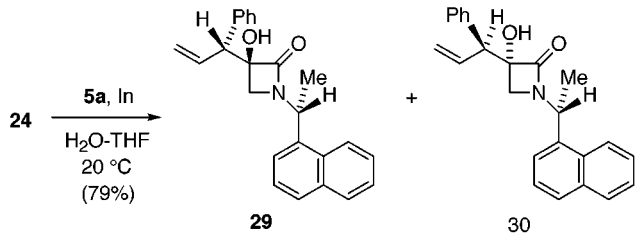


Figure 9. ORTEP diagram of **30**.

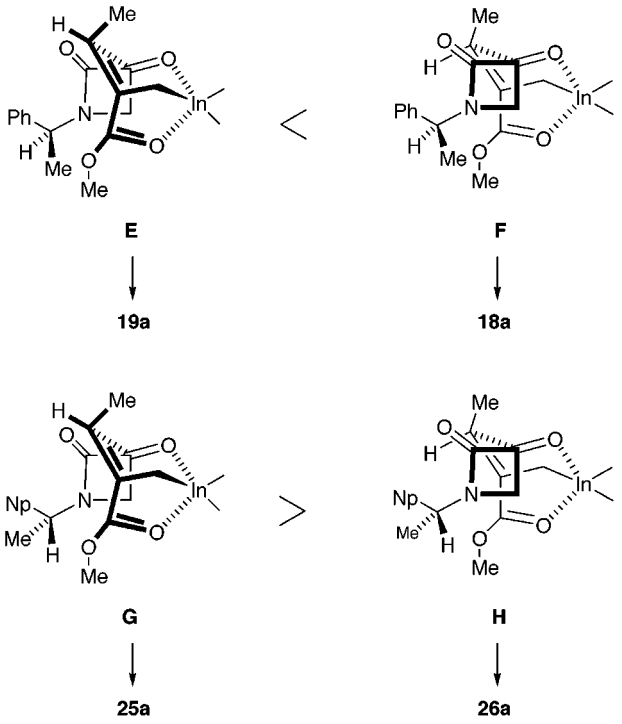
Scheme 6



dominate slightly. Of greatest interest is the fact that the change in the configuration at the carbon α to nitrogen from *S* to *R* leads to a reversal in the π-facial selectivity of the coupling process. Thus, for example, the absolute configurations of the carbinol and R substituted centers in **25a** (66%) are opposite to those resident in major product **18a**. Similarly, the minor syn diastereomer **26a** (17%) is antipodal to **19a** at the same two positions. These observations are directly attributable to the alteration of the sense of chirality adjacent to nitrogen. Clearly evident is the ability of the methyl group resident at this site to guide capture of the indium reagent from a specific π surface. A change in the absolute configuration of this exocyclic center linked directly to nitrogen is met with a kinetic preference for attack from the opposite plane adopted by the ketonic carbonyl.

These features are all the more revealing when (*E*)-cinnamyl bromide is involved (Scheme 6). For **24**, the major anti adduct is necessarily **29** (71%) since the minor constituent has been unequivocally identified by way of X-ray crystallography (Figure 9). The relevant comparisons are **29** with **22** and **30** with **23**. Since separation of the diastereomers in either set is readily accomplished chromatographically, this type of reaction appears to be well suited to enantiocontrolled organic synthesis. Amplification of the long-range effect demonstrated here likewise falls well within the range of feasibility.

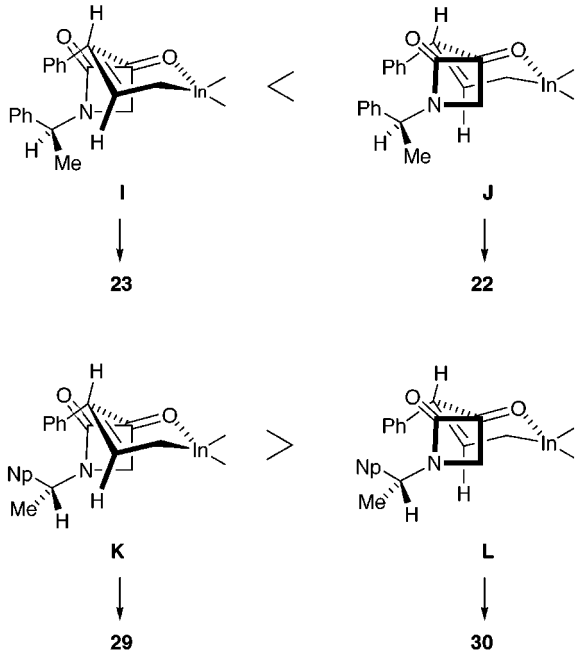
Possible transition states for the reactions of **17** and **24** with **4a** are depicted as **E**−**H**. The available evidence suggests that utilization of the trajectory involving *re* face attack as in **F** is marginally favored over the *si* alternative **E** for the (*S*)-α-methylbenzyl example. The influence of the (*R*)-α-(1-naphthyl)ethyl substituent is more pronounced in the reverse direction, with the involvement of **G** operating 2.5 times more often than the pathway involving **H**. The improved and reversed stereocontrol



exhibited by **24** relative to **17** conforms to expectations based on the increased steric bulk offered by the naphthyl substituent. More significantly, the observed stereochemical interdependence lends itself particularly well to mechanistic interpretation in terms of highly coordinated activated complexes, whose cyclic nature brings the allyl double bond and its substituents into relatively close spatial proximity.

Whereas **4a** projects only a relatively planar and perhaps chelated carbomethoxy group into the critical region for nonbonded steric interaction (see **A** and **E**), the (*E*)-cinnamyl reagent **5a** orients a phenyl substituent in the direction of the exocyclic stereogenic center bonded to nitrogen. Like **4a**, **5a** maintains the stereochemical integrity of its double bond during conversion to the indium reagent.[6,7] It is intriguing to note that the impact of a phenyl group in transition states **I**−**L** exerts greater stereocontrol than the carbomethoxy substituent in **E**−**H**. Thus, when azetidinedione **17** is involved, the selectivity of C−C bond formation on the *re* face as in **J** (leading to **22**) operates at the 63% level. In line with our other observations, recourse to **24** as the reaction partner enhances overall enantioselectivity (now 71% of **29**) while simultaneously redirecting nucleophilic attack preferably to the *si* face as in **K**. In our view, these long-range stereoselectivities should prove amenable to enhanced modulation with modification of the structural features of the chiral inducer in the electrophilic four-membered ring.

Conclusion. The present results provide the first unambiguous insight into the manner in which 2,3-azetidinediones and substituted allylindium reagents undergo coupling in an aqueous environment. The crossover in facial selectivity of nucleophilic attack that accompanies a change in the absolute configuration at



the extracyclic carbon α to nitrogen provides experimental evidence for adoption of cyclic transition states. These chairlike arrangements introduce a structural scenario where nonbonded interactions between the two reacting components can control π-facial stereoselectivity to a significant degree. The absolute configuration resident in the carbon center directly linked to nitrogen is notably serviceable as a means of defining the manner in which the two new stereogenic centers in the products are established. The two N-substituents examined presently are benzylic in nature and in principle subject to reductive cleavage.[23] Removal of the chiral auxiliaries in this fashion would provide a direct means for transforming simple azetidinediones patterned after **3** into enantiomerically pure, highly functionalized β-lactam derivatives.

Experimental Section[24]

General Procedure for Additions Involving 3. To a vigorously stirred solution of **3**[16,17] (100 mg, 0.57 mmol) and the allylic bromide (1.14 mmol) in 2 mL of 1:1 THF/water was added indium powder (130 mg, 1.13 mmol). After 5 h, the products were extracted into ether (2 × 20 mL) and the combined organic phases were washed with brine, dried, and concentrated. The residue was purified by flash chromatography on silica gel, and the relative amounts of the diastereomers were determined by weighing.

A. Reaction with 4a: 10:90 mixture of **7a** and **8a** in 61% yield. For **8a**: IR ($CHCl_3$, cm^{-1}) 3368, 1748, 1408; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40−7.20 (m, 5 H), 6.26 (s, 1 H), 5.90 (s, 1 H), 4.41 (d, J = 15 Hz, 1 H), 4.33 (d, J = 15 Hz, 1 H), 3.72 (s, 3 H), 3.17 (q, J = 7.2 Hz, 1 H), 3.16 (d, J = 5.6 Hz, 1 H), 3.08 (d, J = 5.6 Hz, 1 H), 1.30 (d, J = 7.2 Hz, 3 H) (OH signal not observed); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 169.9, 168.4, 140.9, 135.0, 128.8 (2 C), 128.1 (2 C), 128.0, 127.8, 86.4, 53.6, 52.3, 45.6, 39.6, 14.9; MS m/z (M^+) calcd 289.1314, obsd 289.1347.

Anal. Calcd for $C_{16}H_{19}NO_4$: C, 66.42; H, 6.62. Found: C, 66.04; H, 6.62.

For **8a**: ^1H NMR (300 MHz, $CDCl_3$) δ 7.40−7.15 (m, 5 H), 6.32 (s, 1 H), 5.71 (s,1 H), 4.75 (d, J = 14.9 Hz, 1 H), 4.29 (br s, 1 H), 4.28 (d, J = 14.9 Hz, 1 H), 3.79 (s, 3 H), 3.21 (d, J = 5.9 Hz, 1 H), 3.19 (q, J = 7.2 Hz, 1 H), 3.09 (d, J = 5.9 Hz, 1 H), 1.17 (d, J = 7.2 Hz, 3 H).

B. Reaction with 4b: 81:19 mixture of **7b** and **8b** in 75% yield. For **7b**: colorless crystals, mp 137−139 °C; IR ($CHCl_3$, cm^{-1}) 3340(br), 1749, 1260; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40−7.20 (m, 8 H), 6.79 (m, 2 H), 6.52 (s, 1 H), 5.85 (s, 1 H), 4.60 (br s, 1 H), 4.55 (s, 1 H), 4.40 (d, J = 15 Hz, 1 H), 4.09 (d, J = 15 Hz, 1 H), 3.68 (s, 3 H), 3.38 (d, J = 5.8 Hz, 1 H), 3.26 (d, J = 5.8 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 169.7, 167.6, 138.1, 137.3, 134.4, 129.0 (2 C), 128.0 (3 C), 127.8 (2 C), 127.5 (2 C), 127.4 (2 C), 86.3, 52.6, 52.2, 50.5, 45.4; MS m/z (M^+) calcd 351.1471, obsd 351.1470.

Anal. Calcd for $C_{21}H_{21}NO_4$: C, 71.78; H, 6.02. Found: C, 71.82; H, 6.06.

For the X-ray crystallographic analysis, see Figure 1.

For **8b**: colorless crystals, mp 152−153 °C; IR (CH_2Cl_2, cm^{-1}) 3344, 1738, 1298; ^1H NMR (300 MHz, $CDCl_3$) δ 7.39−7.19 (m, 8 H), 6.82−6.79 (m, 2 H), 6.74 (s, 1 H), 6.57 (s, 1 H), 4.46 (s, 1 H), 4.37 (d, J = 15.3 Hz, 1 H), 4.11 (d, J = 15.3 Hz, 1 H), 3.66 (s, 3 H), 3.41 (br s, 1 H), 3.19 (d, J = 5.7 Hz, 1 H), 3.17 (d, J = 5.7 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 168.6, 167.0, 138.6, 136.1, 134.2, 129.7 (2 C), 128.6 (2 C), 128.5 (2 C), 128.1, 127.7 (2 C), 127.6, 127.5, 86.7, 52.2, 52.1, 51.5, 45.4.

C. Reaction with 5a: 91:9 mixture of **9a** and **10a** in 73% yield. For **9a**: colorless crystals, mp 95−97 °C; IR ($CHCl_3$, cm^{-1}) 3556 (br), 1748, 1410, 1219; ^1H NMR (300 MHz, $CDCl_3$) δ 7.45−6.90 (m, 10 H), 6.17 (ddd, J = 18.0, 10.3, 8.3 Hz, 1 H), 5.20 (m, 2 H), 4.43 (d, J = 15.1 Hz, 1 H), 4.17 (d, J = 15.1 Hz, 1 H), 3.82 (d, J = 8.3 Hz, 1 H), 3.30 (d, J = 5.6 Hz, 1 H), 3.27 (s, 1 H), 3.16 (d, J = 5.6 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 169.5, 137.9, 135.3, 134.6, 129.2, 128.9, 128.8 (2 C), 128.7 (2 C), 128.5 (2 C), 127.6, 127.4, 119.3, 86.4, 54.3, 51.5, 45.5; MS m/z (M^+) calcd 293.1416, obsd 293.1386.

Anal. Calcd for $C_{19}H_{19}NO_2$: C, 77.79; H, 6.53. Found: C, 77.84; H, 6.58.

For the X-ray crystallographic analysis, see Figure 2.

For **10a**: ^1H NMR (300 MHz, $CDCl_3$) δ 7.45−6.90 (m, 10 H), 6.25 (m, 1 H), 5.25 (m, 2 H), 4.42 (d, J = 15 Hz, 1 H), 4.16 (d, J = 15 Hz, 1 H), 3.70 (d, J = 8.0 Hz, 1 H), 3.23 (d, J = 5.6 Hz, 1 H), 3.15 (d, J = 5.6 Hz, 1 H) (OH not observed).

D. Reaction with 5b: 88:12 mixture of **9b** and **10b** in 81% yield. For **9b**: colorless gum; IR ($CHCl_3$, cm^{-1}) 3329 (br), 1748, 1437, 1219; ^1H NMR (300 MHz, $CDCl_3$) δ 7.33−7.15 (m, 5 H), 5.96 (ddd, J = 19.1, 10.4, 8.8 Hz, 1 H), 5.28 (m, 2 H), 4.71 (s, 1 H), 4.42 (d, J = 15 Hz, 1 H), 4.35 (d, J = 15 Hz, 1 H), 3.71 (s, 3 H), 3.50 (d, J = 8.8 Hz, 1 H), 3.34 (d, J = 5.7 Hz, 1 H), 3.19 (d, J = 5.7 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 171.8, 167.9, 134.7, 129.9, 128.8 (2 C), 128.2 (2 C), 127.8, 121.1, 84.3, 53.4, 52.9, 52.5, 45.7; MS m/z (M^+) calcd 275.1157, obsd 275.1163.

E. Reaction with 6a: 75:25 mixture of **11a** and **12a** in 80% yield. For **11a**: white solid, mp 89−93 °C; IR ($CHCl_3$, cm^{-1}) 3295 (br), 1748, 1406, 1256; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40−7.20 (m, 5 H), 5.08 (s, 1 H), 5.06 (s, 1 H), 4.60 (s, 1 H), 4.45 (d, J = 15 Hz, 1 H), 4.33 (d, J = 15 Hz, 1 H), 3.82 (d, J = 7.6 Hz, 1 H), 3.25 (d, J = 5.5 Hz, 1 H), 3.19 (d, J = 5.5 Hz, 1 H), 2.59 (s, 2 H), 2.00−1.00 (series of m, 11 H), 0.89 (s, 9 H), 0.07 (s, 3 H), 0.04 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 170.6, 144.4, 135.2, 128.8 (2 C), 128.1 (2 C), 127.7, 116.3, 83.7, 81.6, 54.4, 45.5, 40.9, 36.9, 29.7, 28.9, 26.5, 26.2, 26.1, 25.9 (3 C), 18.2, −4.3, −4.8; MS m/z (M^+) calcd 443.2856, obsd 443.2853.

Anal. Calcd for $C_{26}H_{41}NO_3Si$: C, 70.38; H, 9.31. Found: C, 70.35; H, 9.38.

For **12a**: ^1H NMR (300 MHz, $CDCl_3$) δ 7.40−7.20 (m, 5 H), 5.02 (s, 1 H), 5.00 (s, 1 H), 4.51 (d, J = 15 Hz, 1 H), 4.31 (d, J = 15 Hz, 1 H), 3.71 (d, J = 9.1 Hz, 1 H), 3.23 (m, 2 H), 2.79 (d, J = 14.8 Hz, 1 H), 2.40 (d, J = 14.8 Hz, 1 H), 2.00−1.00 (series of m, 11 H), 0.88 (s, 9 H), 0.11 (s, 3 H), 0.02 (s, 3 H) (OH not observed); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 170.5, 144.7, 135.3, 129−127 (5 C), 119.5, 83.9, 82.5, 54.1, 45.6, 40.6, 37.6, 30.0−26.0 (5 C), 25.8 (3 C), 18.2, −3.9, −4.6.

(23) (a) Williams, R. M.; Lee, B. H.; Miller, M. M.; Anderson, O. P. *J. Am. Chem. Soc.* **1989**, *111*, 1073. (b) Shibasaki, M.; Ishida, Y.; Iwasaki, G.; Iimori, T. *J. Org. Chem.* **1987**, *52*, 3488. (c) Yamada, T.; Suzuki, H.; Mukaiyama, T. *Chem. Lett.* **1987**, 293. (d) Annis, G. D.; Hebblethwaite, E. M.; Hodgson, S. T.; Hollishead, D. M.; Ley, S. V. *J. Chem. Soc., Perkin Trans. 1* **1983**, 2851.

(24) For generic experimental details, consult ref 5b.

F. Reaction with 6b: 55:45 mixture of **11b** and **12b** in 79% yield. This mixture is a colorless solid, mp 103−110 °C. For **11b**: IR ($CHCl_3$, cm^{-1}) 3343 (br), 1736, 1450, 1219; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40−7.20 (m, 5 H), 5.06 (s, 1 H), 4.99 (s, 1 H), 4.43 (d, J = 15 Hz, 1 H), 4.32 (d, J = 15 Hz, 1 H), 3.71 (d, J = 8.1 Hz, 1 H), 3.26 (d, J = 5.6 Hz, 1 H), 3.21 (d, J = 5.6 Hz, 1 H), 2.73 (d, J = 14.4 Hz, 1 H), 2.47 (d, J = 14.4 Hz, 1 H), 2.10−0.75 (series of m, 1 H) (OH's not observed); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 171.6, 144.3, 134.9, 128.9 (2 C), 128.1 (2 C), 127.9, 119.2, 83.3, 81.1, 54.6, 45.7, 40.5, 37.1, 29.4, 29.3, 26.3, 25.8, 25.7; MS m/z ($M^+ + H$) calcd 330.1992, obsd 330.2072.

Anal. Calcd for $C_{20}H_{27}NO_3$: C, 72.92; H, 8.26. Found: C, 72.63; H, 8.34.

For **12b**: ^1H NMR (300 MHz, $CDCl_3$) δ 7.40−7.20 (m, 5 H), 5.06 (s, 1 H), 5.01 (s, 1 H), 4.40 (m, 2 H), 3.81 (d, J = 9.5 Hz, 1 H), 3.30 (d, J = 5.4 Hz, 1 H), 3.16 (d, J = 5.4 Hz, 1 H), 2.70−2.30 (m, 2 H), 2.00−0.75 (series of m, 11 H) (OH's not observed); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 170.0, 144.4, 134.9, 128.9 (2 C), 128.1 (2 C), 127.9, 119.1, 83.3, 80.9, 55.8, 45.6, 40.4, 39.6, 29.6, 29.4, 29.1, 26.4, 25.9.

Methyl (2*RS*,3*RS*)-3-Hydroxy-2-[[[(α*S*)-α1-methylbenzyl]amino]methyl]butyrate (14). A solution of **13** (15.0 g, 0.114 mmol) and (*S*)-α-methylbenzylamine (13.8 g, 0.114 mmol) in dry methanol (200 mL) was stirred under N_2 for 48 h. Following the evaporation of solvent, purification was accomplished by chromatography on silica gel (elution with 20% ethyl acetate in hexanes) to provide 20.7 g (91%) of **14** as a clear oil: IR (CH_2Cl_2, cm^{-1}) 3310, 1731, 1245; ^1H NMR (300 MHz, $CDCl_3$) δ 7.37−7.22 (m, 5 H), 4.27−4.12 (m, 1 H), 3.70 and 3.67 (2s, total 3 H), 3.71−3.57 (m, 3 H), 3.01−2.77 (m, 2 H), 2.47−2.33 (m, 1 H), 1.39−1.32 (overlapping d, total 3 H), 1.21 (d, J = 6.3 Hz, 2 H), 1.06 (d, J = 6.3 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 173.5, 144.0, 128.7, 128.6, 127.4, 127.3, 126.8, 126.4, 70.1, 70.0, 58.9, 58.5, 51.8, 51.7, 51.1, 50.9, 47.0, 46.5, 24.1, 23.9, 21.8, 21.7 (other signals are overlapping); MS m/z (M^+) calcd 251.1521, obsd 251.1545; $[\alpha]^{22}_D$ −38.9 (*c* 0.036, C_2H_5OH).

(3*RS*)-3-[(1*RS*)-1-Hydroxyethyl]-1-[(α*S*)-α-methylbenzyl]-2-azetidinone (15). A nitrogen-blanketed stirred slurry of magnesium turnings (16.03 g, 0.655 mmol) in dry THF (400 mL) was brought to reflux and treated dropwise with *tert*-butyl chloride (80 mL, 0.72 mol). Once reaction commenced, the heating mantle was removed and the addition rate was adjusted to maintain reflux. When the addition was complete, heating was resumed for an additional 60 min prior to the dropwise introduction of a solution of **14** (40 g, 0.17 mmol) in dry THF (100 mL) during 3 h. The reaction mixture was cooled and carefully quenched with a saturated NH_4Cl solution. The organic phase was washed with a $NaHCO_3$ solution, dried, filtered, and evaporated. The residue was purified by chromatography on silica gel (elution with 5% methanol in CH_2Cl_2) to provide 24.9 g (67%) of **15** as a pale yellow oil: IR ($CHCl_3$, cm^{-1}) 3427, 1731, 1247, 1046; ^1H NMR (300 MHz, $CDCl_3$) δ 7.38−7.12 (m, 5 H), 4.98−4.75 (m, 1 H), 4.23−3.80 (m, 1 H), 3.28−2.90 (m, 3 H), 2.57−2.08 (br s, 1 H), 1.67−1.48 (m, 3 H), 1.34−1.10 (m 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 167.8, 140.5, 128.7, 127.6 (2 C), 126.7, 126.6, 66.6, 65.2, 65.1, 55.7, 51.3, 51.2, 39.3, 39.1, 21.3, 21.0, 18.6 (other signals overlap); MS m/z (M^+) calcd 219.1259, obsd 219.1267; $[\alpha]^{22}_D$ −60.0 (*c* 0.085, C_2H_5OH).

3-Ethylidene-1-[(α*S*)-α-methylbenzyl]-2-azetidinone (16). A solution of **15** (3.41 g, 15.6 mmol) in CH_2Cl_2 (125 mL) containing triethylamine (1.8 mL, 18 mmol) was cooled to 0 °C in an ice bath, treated dropwise with methanesulfonyl chloride (1.39 mL, 18 mmol), and stirred cold for 1 h. The reaction mixture was washed with a saturated $NaHCO_3$ solution (200 mL) and brine prior to drying and solvent evaporation. The residue was immediately taken up in dry benzene (200 mL) to which DBU (2.69 mL, 18 mmol) was added. This solution was heated at reflux overnight and processed in the predescribed manner. Purification by chromatography on silica gel (elution with 40% ethyl acetate in hexanes) furnished **16** (2.75 g, 87%) as a colorless oily mixture of isomers: IR ($CHCl_3$, cm^{-1}) 1680, 1320, 1300, 1180, 1100; MS m/z (M^+) calcd 201.1154, obsd 201.1166; $[\alpha]^{22}_D$ −17.8 (*c* 0.045, C_2H_5OH).

For the *Z* isomer: ^1H NMR (300 MHz, $CDCl_3$) δ 7.43−7.20 (m, 5 H), 5.58 (d, J = 7.1 Hz, 1 H), 5.01 (q, J = 7.0 Hz, 1 H), 3.68 (d, J = 5.7 Hz, 1 H), 3.42 (d, J = 5.7 Hz, 1 H), 2.02 (d, J = 7.1 Hz, 3 H), 1.62 (d, J = 7.0 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 163.4, 140.6, 137.5, 128.7 (2 C), 127.5, 126.7 (2 C), 121.1, 51.2, 44.5, 18.5, 14.1.

For the *E* isomer: ^1H NMR (300 MHz, $CDCl_3$) δ 7.45−7.15 (m, 5 H), 6.12 (q, J = 7.2 Hz, 1 H), 5.02 (q, J = 6.9 Hz, 1 H), 3.60 (d, J = 5.7 Hz, 1 H), 3.43 (d, J = 5.7 Hz, 1 H), 1.70 (d, J = 7.2 Hz, 3 H), 1.61 (d, J = 6.9 Hz, 3 H).

1-[(α*S*)-α-Methylbenzyl]-2,3-azetidinedione (17). A methanolic (200 mL) solution of **16** (5.3 g, 26 mmol) was diluted with water (150 mL) and treated sequentially with sodium periodate (14.6 g, 68.2 mmol) and osmium tetraoxide (20 mg). The reaction mixture was stirred for 24 h, Celite (12 g) was introduced, and stirring was maintained for 1 h prior to filtration and concentration to $^1/_3$ volume. The chiefly aqueous solution was extracted with ethyl acetate (3 × 100 mL), and the pooled organic phases were dried and concentrated. Chromatography of the residue on silica gel (elution with 50% ethyl acetate in hexanes) gave **17** (3.17 g, 64%) as a pale yellow oil: IR ($CHCl_3$, cm^{-1}) 1820, 1747; ^1H NMR (300 MHz, $CDCl_3$) δ 7.43−7.26 (m, 5 H), 5.29 (q, J = 7.0 Hz, 1 H), 3.84 (d, J = 9.9 Hz, 1 H), 3.64 (d, J = 9.9 Hz, 1 H), 1.73 (d, J = 7.0 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 192.7, 162.8, 138.4, 129.1 (2 C), 128.4, 126.8 (2 C), 57.3, 52.8, 17.8; MS m/z (M^+) calcd 189.0790, obsd 189.0774; $[\alpha]^{22}_D$ −15.5 (*c* 0.11, C_2H_5OH).

Anal. Calcd for $C_{11}H_{11}NO_2 \cdot {}^1/_2H_2O$: C, 66.65; H, 6.10. Found: C, 66.68; H, 6.09.

General Procedure for Additions Involving 17. The bromide (0.39 mmol) was placed with indium powder (45 mg, 0.35 mmol) in 5 mL of water. This mixture was stirred at 0 °C for 1 h in advance of the introduction of a solution of **17** (50 mg, 0.26 mmol) in 5 mL of THF, allowed to warm to room temperature, and agitated vigorously overnight. After being washed with saturated $NaHCO_3$ solution and brine, the aqueous layers were back-extracted with CH_2Cl_2, and the combined organic phases were dried and evaporated. The product mixtures were separated into their components by chromatography on silica (elution with 50% ethyl acetate in hexanes).

A. Reaction with 4a: 50:41:9 mixture of **18a**, **19a**, and **20a** (or **21a**) in 75% yield. For **18a**: colorless crystals, mp 105−107 °C; IR (CH_2Cl_2, cm^{-1}) 3410, 1731, 1454, 1274, 1154; ^1H NMR (300 MHz, $CDCl_3$) δ 7.38−7.24 (m, 5 H), 6.23 (s, 1 H), 5.28 (s, 1 H), 4.91 (q, J = 7.0 Hz, 1 H), 4.21 (br s, 1 H), 3.75 (s, 3 H), 3.20 (d, J = 5.0 Hz, 1 H), 3.17 (q, J = 7.0 Hz, 1 H), 2.95 (d, J = 5.6 Hz, 1 H), 1.59 (d, J = 7.0 Hz, 3 H), 1.33 (d, J = 7.1 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 169.0, 168.6, 140.8, 140.1, 128.7 (2 C), 128.1, 127.7, 126.7 (2 C), 85.0, 52.4, 51.5, 50.7, 40.0, 18.2, 14.7; MS m/z (M^+) calcd 287.1521, obsd 287.1555; $[\alpha]^{22}_D$ −13.2 (*c* 0.95, C_2H_5OH).

Anal. Calcd for $C_{17}H_{21}NO_4$: C, 67.31; H, 6.98. Found: C, 67.04; H, 6.91.

For the X-ray crystallographic analysis, see Figure 3.

For **19a**: colorless crystals, mp 125−128 °C; IR (CH_2Cl_2, cm^{-1}) 3380, 1730, 1454, 1402, 1275; ^1H NMR (300 MHz, $CDCl_3$) δ 7.37−7.23 (m, 5 H), 6.30 (s, 1 H), 5.95 (s, 1 H), 4.90 (q, J = 7.0 Hz, 1 H), 4.54 (br s, 1 H), 3.75 (s, 3 H), 3.24 (d, J = 5.6 Hz, 1 H), 3.23−3.20 (m, 1 H), 2.96 (d, J = 5.6 Hz, 1 H), 1.55 (d, J = 7.0 Hz, 3 H), 1.32 (d, J = 7.1 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 169.1, 168.4, 140.9, 139.8, 129.8, 128.6 (2 C), 127.8, 127.6, 126.7 (2 C), 52.3, 51.5, 51.2, 39.6, 18.3, 14.8; MS m/z (M^+) calcd 287.1521, obsd 287.1551; $[\alpha]^{22}_D$ −5.0 (*c* 0.34, C_2H_5OH).

Anal. Calcd for $C_{17}H_{21}NO_3$: C, 67.31; H, 6.98. Found: C, 67.19; H, 6.97.

For **20a** (or **21a**): ^1H NMR (300 MHz, $CDCl_3$) δ characteristic peaks at 6.33 (s, 1 H), 5.73 (s, 1 H), 4.91 (q, J = 7.0 Hz, 1 H), 3.79 (s, 1 H), 3.27 (d, J = 5.8 Hz, 1 H), 3.20 (d, J = 5.8 Hz, 1 H), 1.55 (d, J = 7.0 Hz, 3 H).

B. Reaction with 4b: 28:28:16:28 mixture of **18b**, **19b**, **20b**, and **21b** in 76% yield. For **18b**: colorless oil; IR (CH_2-

Cl_2, cm^{-1}) 3400, 1730, 1330, 1260, 1150; ^1H NMR (300 MHz, $CDCl_3$) δ 7.83−7.23 (m, 8 H), 7.04−7.01 (m, 2 H), 6.82 (s, 1 H), 5.58 (s, 1 H), 4.73 (q, J = 7.0 Hz, 1 H), 4.47 (s, 1 H), 3.86 (s, 1 H), 3.66 (s, 3 H), 3.19 (d, J = 5.6 Hz, 1 H), 3.01 (d, J = 5.6 Hz, 1 H), 1.17 (d, J = 7.0 Hz, 3 H) (OH not observed); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 167.9, 167.1, 139.5, 138.5, 136.3, 128.7 (2 C), 128.5 (2 C), 127.7 (2 C), 127.6 (2 C), 85.4, 53.7, 52.2, 51.9, 51.3, 50.0, 41.7, 24.0, 17.8; MS m/z (M^+) calcd 365.1627, obsd 365.1603; $[\alpha]^{22}_D$ +12.0 (c 0.25, C_2H_5OH).

For **19b**: colorless crystals, mp 135−138 °C; IR (CH_2Cl_2, cm^{-1}) 3330, 1730, 1400, 1260; ^1H NMR (300 MHz, $CDCl_3$) δ 7.41−7.18 (m, 8 H), 6.83−6.79 (m, 2 H), 6.76 (s, 1 H), 6.55 (s, 1 H), 4.78 (q, J = 7.0 Hz, 1 H), 4.42 (s, 1 H), 3.65 (s, 3 H), 3.45 (br s, 1 H), 3.23 (d, J = 5.6 Hz, 1 H), 3.10 (d J = 5.6 Hz, 1 H), 1.50 (d, J = 7.0 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 168.0, 167.0, 139.4, 138.6, 129.7 (2 C), 129.6 (2 C), 128.5 (2 C), 128.3, 128.2, 127.6, 127.3, 126.3 (2 C), 85.6, 52.1, 51.7, 50.6, 50.0, 18.2; MS m/z (M^+) calcd 365.1627, obsd 365.1629; $[\alpha]^{22}_D$ +60.8 (c 0.12, C_2H_5OH).

For the X-ray crystallographic analysis, see Figure 4.

For **20b**: colorless crystals, mp 125−127 °C; IR (CH_2Cl_2, cm^{-1}) 3350, 1740, 1270; ^1H NMR (300 MHz, $CDCl_3$) δ 7.42−7.16 (m, 8 H), 7.05−7.02 (m, 2 H), 6.54 (s, 1 H), 5.83 (s, 1 H), 4.68 (q, J = 7.0 Hz, 1 H), 4.56 (s, 1 H), 4.21 (s, 1 H), 3.68 (s, 3 H), 3.40 (d, J = 5.8 Hz, 1 H), 3.10 (d, J = 5.8 Hz, 1 H), 1.14 (d, J = 7.0 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 169.0, 167.6, 139.5, 138.1, 137.3, 129.1 (2 C), 128.8, 128.7 (2 C), 128.6 (2 C), 128.5, 127.6, 127.4, 126.7 (2 C), 84.7, 52.2, 51.6, 50.6, 18.0; MS m/z (M^+) calcd 365.1627, obsd 365.1610; $[\alpha]^{22}_D$ −140.1 (c 0.23, C_2H_5OH).

For the X-ray crystallographic analysis, see Figure 5.

For **21b**: colorless crystals, mp 140−142 °C; IR (CH_2Cl_2, cm^{-1}) 3380, 1730, 1400, 1250, 1140; ^1H NMR (300 MHz, $CDCl_3$) δ 7.37−7.19 (m, 8 H), 6.82−6.79 (m, 2 H), 6.51 (s, 1 H), 5.84 (s, 1 H), 4.77 (q, J = 7.0 Hz, 1 H), 4.61 (s, 1 H), 4.58 (s, 1 H), 3.67 (s, 3 H), 3.33 (d, J = 5.8 Hz, 1 H), 3.29 (d, J = 5.8 Hz, 1 H), 1.49 (d, J = 7.0 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 169.3, 167.6, 139.3, 138.1, 137.3, 129.1 (2 C), 128.6 (2 C), 127.3 (2 C), 126.4 (2 C), 85.1, 52.2, 50.5, 50.4, 50.3, 18.0; MS m/z (M^+) calcd 365.1627, obsd 365.1638; $[\alpha]^{22}_D$ +89.4 (c 0.216, C_2H_5OH).

Anal. Calcd for $C_{22}H_{23}NO_4$: C, 72.31; H, 6.34. Found: C, 72.12; H, 6.39.

For the X-ray crystallographic analysis, see Figure 6.

C. Reaction with 5a: 63:27 mixture of **22** and **23** in 85% yield. For **22**: colorless oil; IR ($CHCl_3$, cm^{-1}) 3380, 1730, 1216; ^1H NMR (300 MHz, $CDCl_3$) δ 7.50−7.25 (m, 10 H), 6.19 (ddd, J = 10.7, 8.4, 1.9 Hz, 1 H), 5.32 (s, 1 H), 5.28 (s, 1 H), 4.78 (q, J = 7.1 Hz, 1 H), 3.81 (d, J = 8.2 Hz, 1 H), 3.33 (d, J = 5.6 Hz, 1 H), 3.00 (d, J = 5.6 Hz, 1 H), 1.31 (d, J = 7.0 Hz, 3 H) (OH not observed); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 168.5, 137.9, 136.7, 135.4, 131.2, 129.2, 128.72, 128.69, 128.6, 127.7, 127.4, 126.7, 126.5, 119.3, 84.8, 63.7, 54.5, 51.4, 49.5, 18.1; MS m/z (M^+ + H) calcd 308.1573, obsd 308.1653; $[\alpha]^{22}_D$ −45.2 (c 0.20, C_2H_5OH).

For **23**: colorless crystals, mp 128−129 °C; IR (CH_2Cl_2, cm^{-1}) 3358, 1730; ^1H NMR (300 MHz, $CDCl_3$) δ 7.42−7.01 (series of m, 10 H), 6.16−6.03 (m, 1 H), 5.19 (d, J = 8.0 Hz, 1 H), 5.30 (s, 1 H), (s, 1 H), 4.84 (q, J = 7.0 Hz, 1 H), 3.74 (d, J = 7.7 Hz, 1 H), 3.22 (d, J = 5.5 Hz, 1 H), 3.19 (d, J = 5.5 Hz, 1 H), 2.75 (s, 1 H), 1.52 (d, J = 7.0 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 168.6, 139.7, 137.9, 135.3, 129.2, 128.7 (2 C), 128.6 (2 C), 128.5, 127.5, 127.4, 126.6, 119.2, 85.0, 54.5, 50.6, 49.4, 30.9, 18.1; MS m/z (M^+) calcd 307.1572, obsd 307.1535; $[\alpha]^{22}_D$ −44.4 (c 0.25, C_2H_5OH).

1-[(1*R*)-1-(Naphthyl)ethyl]-2,3-azetidinedione (24). Stirring of **13** (12.03 g, 92.5 mmol) with (*R*)-α-(1-naphthyl)-ethylamine (15.85 g, 92.15 mmol) in dry methanol (200 mL) under N_2 for 2 h with workup as above (elution with 50% ethyl acetate in hexanes) gave 25.6 g (92%) of the 1,4-adduct as a mixture of diastereomers: IR (CH_2Cl_2, cm^{-1}) 3250, 1730, 1100; ^1H NMR (300 MHz, $CDCl_3$) δ 8.13 (t, J = 8.3 Hz, 1 H), 7.86 (d, J = 7.4 Hz, 1 H), 7.75 (d, J = 7.4 Hz, 1 H), 7.60−7.25 (m, 4 H), 4.63 (overlapping q, J = 6.6 Hz, 1 H), 4.25 (overlapping q, J = 6.3 Hz, 1 H), 3.70 and 3.67 (2s, total 3 H), 3.78−3.61 (m, 2 H), 3.07−2.90 (m, 2 H), 2.51−2.39 (m, 1 H), 1.51 (overlapping t, J = 6.5 Hz, 3 H), 1.24 and 1.13 (2d, J = 6.3 Hz, total 2 H) (OH not observed); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 173.8, 173.7, 140.0, 139.7, 134.0, 131.2, 129.1, 127.6, 127.5 (2 C), 126.0, 125.7 (2 C), 125.6, 125.5 (2 C), 122.9, 122.6, 122.3, 69.9, 69.8, 53.9, 53.6, 51.8 (2 C), 51.4, 51.2, 47.1, 46.8, 23.6, 23.4, 21.8, 21.7; MS m/z (M^+) calcd 301.1678, obsd 301.1672; $[\alpha]^{22}_D$ +22.0 (c 0.156, C_2H_5OH).

Submission of a 10 g (74 mmol) sample of the above ester to the action of 92 mmol of *tert*-butylmagnesium chloride according to the above procedure (elution with 75% ethyl acetate in hexanes) delivered 7.45 g (74%) of the β-lactam as a diastereomeric mixture: colorless crystals, mp 102−104 °C; IR ($CHCl_3$, cm^{-1}) 3413, 1732, 1450, 1396, 1265; ^1H NMR (300 MHz, $CDCl_3$) δ 8.18−8.13 (m, 1 H), 7.89−7.80 (m, 2 H), 7.60−7.43 (m, 4 H), 5.73 (q, J = 6.9 Hz, 1 H), 4.20−3.93 (m, 1 H), 3.22−2.99 (m, 2 H), 2.73−2.67 (m, 1 H), 2.00 (br s, 1 H), 1.76−1.68 (m, 3 H), 1.29−1.23 (m, 1.5 H), 1.14 (d, J = 6.3 Hz, 1 H), 1.07 (d, J = 6.3 Hz, 0.5 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 167.6, 133.8, 131.0, 129.0, 128.9, 128.8, 128.63, 128.60, 126.7, 126.6, 125.9, 125.51, 125.46, 125.0, 123.5, 123.0, 65.3, 64.9, 55.6, 55.5, 46.9, 46.8, 39.1, 38.6, 21.2, 21.1, 17.91, 17.88 (other signals overlapped); MS m/z (M^+) calcd 269.1416, obsd 269.1431; $[\alpha]^{22}_D$ +10.5 (c 0.134, C_2H_5OH).

Anal. Calcd for $C_{17}H_{19}NO_2$: C, 75.81; H, 7.11. Found: C, 75.88; H, 7.08.

Dehydration of the preceding material (3.82 g, 14.20 mmol) with methanesulfonyl chloride (1.62 mL, 21.3 mmol), triethylamine (2.11 mL, 21.3 mmol), and DBU (3.18 mL, 21.3 mmol) in the manner detailed earlier afforded 3.0 g (84%) of the ethylidene derivative as an *E*:*Z* mixture. Olefinic cleavage in the above intermediate was accomplished with sodium periodate (14.8 g, 68.9 mmol) and osmium tetraoxide (25 mg) in methanol (150 mL) and water (100 mL) to give 4.93 g (74%) of **24** as a colorless oil: IR ($CHCl_3$, cm^{-1}) 1820, 1780, 1350, 1100; ^1H NMR (300 MHz, $CDCl_3$) δ 8.15 (d, J = 8.4 Hz, 1 H), 7.89 (t, J = 7.7 Hz, 1 H), 7.60−7.20 (m, 4 H), 6.15 (q, J = 6.9 Hz, 1 H), 3.75 (d, J = 9.9 Hz, 1 H), 3.25 (d, J = 9.9 Hz, 1 H), 1.95 (d, J = 6.9 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 192.5, 162.6, 133.9, 133.0, 130.9, 129.5, 129.1, 127.4, 126.3, 125.1, 123.9, 123.4, 56.9, 48.0, 17.3; MS m/z (M^+) calcd 239.0946, obsd 239.0958; $[\alpha]^{22}_D$ +19.7 (c 0.152, C_2H_5OH).

Anal. Calcd for $C_{15}H_{13}NO_2 \cdot {}^1/_3H_2O$: C, 73.45; H, 5.62. Found: C, 73.87; H, 5.64.

General Procedure for Additions Involving 24. A suspension of the bromide (0.31 mmol) and indium powder (40 mg, 0.34 mmol) in water (5 mL) was stirred vigorously for 1 h, treated with a solution of **24** (50 mg, 0.21 mmol) in THF (5 mL), and continuously agitated for 12 h prior to dilution with ethyl acetate and the usual workup.

A. Reaction with **4a**: 66:27:7 mixture of **25a**, **26a**, and **27a** (or **28a**) in 72% yield. For **25a**: colorless oil; IR (neat, cm^{-1}) 3380, 1728, 1274; ^1H NMR (300 MHz, $CDCl_3$) δ 8.18−7.25 (m, 7 H), 6.29 (s, 1 H), 5.92 (s, 1 H), 5.72 (q, J = 6.9 Hz, 1 H), 3.95 (s, 1 H), 3.74 (s, 3 H), 3.19 (d, J = 5.6 Hz, 1 H), 2.64 (d, J = 5.6 Hz, 1 H), 1.74 (d, J = 6.9 Hz, 3 H), 1.34 (d, J = 7.1 Hz, 3 H) (OH not observed); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 168.6, 140.9, 134.7, 133.8, 131.0, 128.8, 128.0, 126.9, 125.9, 124.9, 123.6, 122.9, 100.2, 98.7, 84.9, 52.4, 51.4, 46.9, 39.7, 17.9, 14.9; MS m/z (M^+) calcd 353.1627, obsd 353.1650; $[\alpha]^{22}_D$ +40.6 (c 0.17, C_2H_5OH).

For **26a**: colorless crystals, mp 109−110 °C; IR ($CHCl_3$, cm^{-1}) 3379, 1728, 1273; ^1H NMR (300 MHz, $CDCl_3$) δ 8.15 (d, J = 8.4 Hz, 1 H), 7.90−7.80 (m, 1 H), 7.61−7.45 (m, 5 H), 6.04 (s, 1 H), 5.79 (q, J = 6.9 Hz, 1 H), 5.38 (s, 1 H), 4.53 (br s, 1 H), 3.65 (s, 3 H), 3.06 (d, J = 5.5 Hz, 1 H), 2.75 (q, J = 7.2 Hz, 1 H), 2.58 (d, J = 5.5 Hz, 1 H), 1.75 (d, J = 6.9 Hz, 3 H), 1.15 (d, J = 7.2 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 168.7, 168.5, 140.8, 134.7, 133.9, 131.0, 128.9, 128.7, 128.3, 126.7, 125.9, 125.1, 123.7, 123.1, 85.0, 52.4, 50.9, 46.2, 41.1, 17.5, 14.5; MS m/z (M^+) calcd 353.1627, obsd 353.1650; $[\alpha]^{22}_D$ −180.8 (c 0.12, C_2H_5OH).

Anal. Calcd for $C_{21}H_{23}NO_4$: C, 71.37 H, 6.56. Found: C, 71.36; H, 6.65.

For the X-ray crystallographic analysis, see Figure 7.

For **27a** (or **28a**): colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.21−7.42 (series of m, 7 H), 6.31 (s, 1 H), 5.73 (q, J = 8.0 Hz, 1 H), 5.72 (s, 1 H), 3.77 (s, 3 H), 3.25 (d, J = 5.9 Hz, 1 H), 2.65 (d, J = 5.9 Hz, 1 H), 3.24−3.13 (m, 1 H), 1.74 (d, J = 8.0 Hz, 3 H), 1.20 (d, J = 7.2 Hz, 3 H) (OH not observed).

B. Reaction with 4b: 32:32:8:32 mixture of **25b**, **26b**, **27b**, and **28b** in 68% yield. For **25b**: colorless oil; IR (CH_2Cl_2, cm^{-1}) 3500, 1760, 1250; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.13−6.82 (series of m, 12 H), 6.60 (d, J = 7.2 Hz, 1 H), 6.34 (s, 1 H), 5.84 (s, 1 H), 5.60−5.56 (m, 2 H), 3.25 (s, 3 H), 3.21 (d, J = 6.3 Hz, 1 H), 2.35 (d, J = 6.3 Hz, 1 H), 1.64 (d, J = 7.2 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 167.6, 167.0, 138.5, 138.2, 136.2, 134.3, 133.8, 129.8 (2 C), 128.7, 128.5 (2 C), 128.3, 127.8, 126.9, 126.0, 125.0, 123.5, 122.8, 85.2, 57.9, 52.2, 51.9, 49.6, 46.5, 17.0; MS m/z (M^+) calcd 415.1865, obsd 416.1850; $[\alpha]^{22}_D$ −25.8 (c 0.66, C_2H_5OH).

For **26b**: colorless oil; IR (CH_2Cl_2, cm^{-1}) 3400, 1730, 1260, 1160; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.15−7.14 (series of m, 12 H), 6.82 (s, 1 H), 6.59 (s, 1 H), 5.68 (q, J = 6.9 Hz, 1 H), 4.45 (m, 1 H), 3.65 (s, 3 H), 3.17 (d, J = 5.6 Hz, 1 H), 2.89 (br s, 1 H), 2.68 (d, J = 5.6 Hz, 1 H, 1.27 (d, J = 6.9 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 167.6, 167.0, 138.5, 137.2, 134.3, 133.8, 129.8 (2 C), 129.6, 128.8, 128.7, 128.6, 128.5 (2 C), 128.2, 127.8, 126.9, 126.0, 125.0, 123.5, 122.8, 85.2, 51.9, 49.5, 46.5, 17.0; MS m/z (M^+ + H) calcd 416.1862, obsd 418.1866; $[\alpha]^{22}_D$ −42.9 (c 0.089, C_2H_5OH).

For **27b**: colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.25−7.00 (series of m, 12 H), 6.50 (d, J = 7.0 Hz, 2 H), 6.43 (s, 1 H), 5.78 (s, 1 H), 5.60 (q, J = 7.0 Hz, 1 H), 4.52 (s, 1 H), 4.25 (s, 1 H), 3.70 (s, 3 H), 3.37 (d, J = 5.8 Hz, 1 H), 2.76 (d, J = 5.8 Hz, 1 H), 1.70 (d, J = 7.2 Hz, 3 H); MS m/z (M^+ + H) calcd 416.1862, obsd 416.1848.

For **28b**: colorless crystals, mp 157−160 °C; IR (CH_2Cl_2, cm^{-1}) 3300, 1730, 1320; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05−7.03 (series of m, 12 H), 6.33 (s, 1 H), 5.77 (s, 1 H), 5.67 (q, J = 6.9 Hz, 1 H), 4.27 (s, 1 H), 4.14 (s, 1 H), 3.64 (s, 3 H), 3.33 (d, J = 5.7 Hz, 1 H), 2.94 (d, J = 5.7 Hz, 1 H), 1.70 (d, J = 6.9 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 168.6, 168.0, 138.2, 137.3, 134.6, 133.9, 130.8, 129.5, 128.8, 128.7, 128.6, 128.4, 127.1, 126.7, 125.8, 125.0, 123.3, 122.9, 84.7, 76.6, 72.3, 52.3, 51.2, 51.1, 46.4, 17.7; MS m/z (M^+ + H) calcd 416.1861, obsd 416.1840; $[\alpha]^{22}_D$ −51.4 (c 0.422, C_2H_5OH).

Anal. Calcd for $C_{26}H_{25}NO_4$: C, 75.16; H, 6.07. Found: C, 74.51; H, 6.10.

For the X-ray crystallographic analysis, see Figure 8.

Reaction with 5a: 71:29 mixture of **29** and **30** in 79% yield. For **29**: colorless oil; IR ($CHCl_3$, cm^{-1}) 3364, 1727; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.12 (d, J = 8.2 Hz, 1 H), 7.85−7.76 (m, 2 H), 7.57−7.26 (series of m, 9 H), 6.25−6.16 (m, 1 H), 5.60 (q, J = 7.0 Hz, 1 H), 5.27 (m, 3 H), 3.82 (d, J = 8.2 Hz, 1 H), 3.30 (d, J = 5.6 Hz, 1 H), 2.71 (d, J = 5.6 Hz, 1 H), 1.42 (d, J = 7.0 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 168.5, 138.1, 135.5, 134.6, 133.8, 130.9, 129.3, 128.8, 128.7, 127.4, 126.8, 125.9, 124.9, 123.5, 122.9, 119.1, 76.6, 54.4, 49.4, 46.9, 17.6; MS m/z molecular ion too fleeting for mass measurement; $[\alpha]^{22}_D$ +5.5 (c 0.42, C_2H_5OH).

Anal. Calcd for $C_{23}H_{23}NO_2$: C, 79.97; H, 6.71. Found: C, 79.80; H, 6.69.

For **30**: colorless crystals, mp 144 °C; IR ($CHCl_3$, cm^{-1}) 3411, 1726; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.12 (d, J = 8.4 Hz, 1 H), 7.88−7.78 (m, 2 H), 7.59−7.07 (series of m, 9 H), 5.98−5.86 (m, 1 H), 5.72 (q, J = 6.9 Hz, 1 H), 4.94−4.88 (m, 1 H), 4.88−4.73 (m, 1 H), 3.52 (d, J = 5.5 Hz, 1 H), 3.22 (d, J = 5.5 Hz, 1 H), 3.08 (s, 1 H), 2.89 (d, J = 5.5 Hz, 1 H), 1.72 (d, J = 6.9 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 168.4, 137.9, 135.6, 134.7, 133.9, 129.0 (2 C), 128.8 (2 C), 128.6, 128.5, 127.2, 126.6, 125.9, 124.9, 123.4, 123.2, 118.6, 84.7, 54.9, 49.4, 46.3, 17.6; MS m/z (M^+) molecular ion too fleeting for mass measurement; $[\alpha]^{22}_D$ −10.4 (c 0.29, C_2H_5OH).

For the X-ray crystallographic analysis, see Figure 9.

Acknowledgment. We thank the U.S. Environmental Protection Agency for financial support (Grant R82-4725-010) and Dr. Kurt Loening for assistance with nomenclature.

Supporting Information Available: Tables giving the crystal data and structure refinement information, bond lengths and bond angles, atomic and hydrogen coordinates, and isotropic and anisotropic displacement coordinates for **7b**, **9a**, **18a**, **19b**, **20b**, **21b**, **26a**, **28b**, and **30** (58 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO980372E