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Toward the Development of a General Chiral Auxiliary. 9. Highly Diastereoselective Alkylations and Acylations to Form Tertiary and Quaternary Centers

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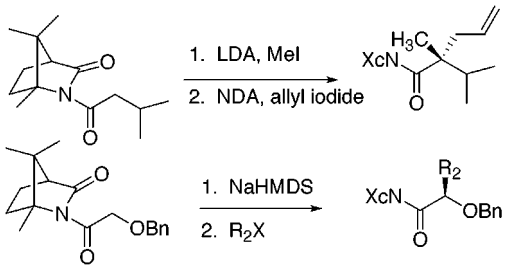
ABSTRACT



Enolates of a new camphor-derived lactam auxiliary are shown to monoalkylate with very high diastereoselectivity. A second alkylation occurs with reactive alkylating agents to afford quaternary centers also with high diastereoselectivity. In accord with a proposed model for diastereoselection, lithium and sodium enolates provide products with an opposite sense of asymmetric induction.

Chiral auxiliary based alkylation methodologies have centered on forming tertiary centers with enolates of sterically constrained amides or imides,[1] esters,[2] and *N*-acylsultams.[3] Some examples exist of the successful formation of chiral quaternary carbon centers. However, highly substituted enolates, particularly those derived from acyclic imide and *N*-acylsultams, are generally too unstable to allow creation of quaternary carbon centers, readily undergoing elimination to ketenes.[4] Recent advances have also been made in catalytic asymmetric alkylation, particularly as applied to α-amino acid synthesis.[5]

The class of camphor lactam auxiliaries **1**−**3** (Figure 1) developed in our laboratories have shown considerable utility in asymmetric Diels−Alder and aldol reactions, particularly

(1) (a) Evans, D. A.; Ennis, M. D., Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737−1739. (b) Kawanami, Y.; Ito, Y.; Kitagawa, T.; Taniguchi, Y.; Katsuki, T.; Yamaguchi, M. *Tetrahedron Lett.* **1984**, *25*, 857−860. (c) Jeong, K. S.; Parris, K.; Ballester, P.; Rebek, J., Jr. *Angew. Chem.* **1990**, *102*, 550−551. (d) Yan, T. H.; Chu, V. V.; Lin, T. C.; Wu, C. H.; Liu, L. H. *Tetrahedron Lett.* **1991**, *32*, 4959−4962. (e) Rueck, K. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 433−435. (f) Crimmins, M. T.; Emmitte, K. A.; Katz, J. D. *Org. Lett.* **2000**, *2*, 2165−2167.

(2) (a) Schmierer, R.; Grotemeier, G.; Helmchen, G.; Selim, A. *Angew. Chem.* **1981**, *93*, 209−211. (b) Helmchen, G.; Wierzchowski, R. *Angew. Chem.* **1984**, *96*, 59−60. (c) Duhamel, P.; Eddine, J.; Valnot, J. Y. *Tetrahedron Lett.* **1984**, *25*, 2355−2358. (d) Alvarez-Ibarra, C.; Csakye, A. G.; Maroto, R.; Quiroga, M. L. *J. Org. Chem.* **1995**, *60*, 7934−7940.

(3) (a) Oppolzer, W.; Moretti, R.; Thomi, S. *Tetrahedron Lett.* **1989**, *30*, 5603−5606. (a) Martin, N.; Martinez-Grau, A.; Seoane, C.; Marco, J. L. *Tetrahedron Lett.* **1993**, *34*, 5627−5630. (b) Lin, J.; Chan, W. H.; Lee, A. W. M.; Wong, W. Y. *Tetrahedron* **1999**, *55*, 13983−13998.

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(5) Corey, E. J.; Xu, F.; Noe, M. C. *J. Am. Chem. Soc.* **1997**, *119*, 12414−12415. (b) Imai, M.; Hagihara, A.; Kawasaki, H.; Manabe, K.; Koga, K. *Tetrahedron* **1999**, *56*, 179−185. (c) Matsuo, J.-i.; Odashima, K.; Kobayashi, S. *Org. Lett.* **1999**, *1*, 345−347. (d) Ooi, T.; Takeuchi, M.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc.* **2000**, *122*, 5228−5229.

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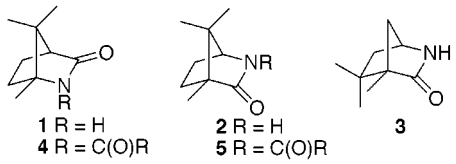


Figure 1. The camphor-derived chiral auxiliaries.

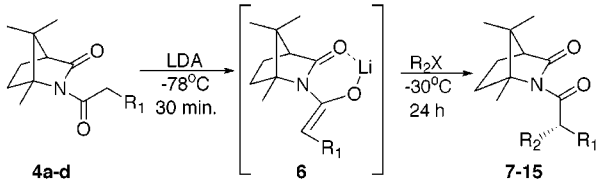
for the creation of quaternary carbon centers.[6] Key to extending the scope of these auxiliaries to include construction of tertiary and quaternary centers by alkylation and acylation will be the stability of imide enolates derived from **1** and **2**, relative to those derived from *N*-acyloxazolidinones and sultams.[1,3]

The lithium salts of **1** and **2** (*n*-BuLi/THF) are readily acylated with a variety of acid chlorides and mixed pivaloyl anhydrides to afford the imides **4** and **5**.[6] Subsequent deprotonation of imides **4** with LDA affords exclusively the *Z* enolates **6** as demonstrated by the NOE exhibited by the TBS *N*,*O*-keteneacetals derived by trapping with *tert*-butyldimethylsilyl (TBS) chloride.[7] Treatment of **6** with a variety of alkyl halides, including methyl, allylic, and benzylic bromides and iodides cleanly affords 50−92% yields of monoalkylation products having diastereomeric ratios >49:1 (Table 1). The sense of asymmetric induction found for the resulting monoalkylation products **7**−**15** is consistent with approach of the electrophile to the face of the enolate **6** opposite to the bulky *gem*-dimethyl bridge, resulting from a combination of steric factors and restricted rotation about the $C-N_{aux}$ bond in **6** owing to chelation.

The more reactive benzoyl and propionyl chlorides afforded selectivities of 20−50:1. Success with benzoyl chloride is especially noteworthy given the ease of epimerization in this case (Table 1). The nearly enantiomerically pure α-substituted acyl groups could be cleaved from the auxiliary by hydrolysis or alcoholysis (LiOOH, LiOBn),[1,6] reductively (LAH, $LiBH_4$),[1,3,6] or by conversion to the Weinreb amide ($EtAlClN(OCH_3)CH_3$) or thio ester (LiSEt). The latter are particularly versatile undergoing direct conversion to esters and amides and by reduction with DIBAl-H to aldehydes.

Despite some prior successes,[4] recent literature reports document continuing difficulties in achieving high diastereoselectivities and yields in the creation of quaternary carbon centers.[10] Since imides derived from **2** have been shown to

Table 1. Alkylations and Acylations To Give Tertiary Centers



4 R_1	R_2X	dr[a]	yield (%)	product
a CH_3	$CH_2{=}CHCH_2Br$	49:1	90	**7**
a CH_3	$PhCH_2Br$	99:1	89[b]	**8**
a CH_3	$PMBOCH_2CH{=}CHCH_2I$	99:1	70	**9**
a CH_3	tBuCH=CHCH=$CHCH_2I$	99:1	85	**10**
b C_2H_5	CH_3I	99:1	50	**11**
c iC_3H_7	CH_3I	49:1	92[c]	**12**
d allyl	CH_3I	49:1	73[c]	**13**
a CH_3	PhCOCl	20:1	82	**14**
b C_2H_5	C_2H_5COCl	50:1	68[d,e]	**15**

[a] Diastereomeric ratio was determined by ^1H NMR. [b] Configuration was proven by cleaving the auxiliary with LAH and comparing the optical rotation to the known alcohol.[1a] [c] Absolute configuration was verified by cleaving the auxiliary to the carboxylic acid with LiOH and comparing the optical rotation to known compounds.[8] [d] Also, 28% of O-acylation product was observed. [e] Absolute configuration was determined by reducing the ketone with $ZnBH_4$, cleaving the auxiliary with LAH, and comparing the optical rotation to a known diol.[9]

permit facile, highly diastereoselective monoalkylation and acylation, we went on to investigate the more challenging second alkylation to afford quaternary carbon centers.

Our initial attempts to effect introduction of the second alkyl group employed the lithium enolate generated by treatment of **12** with LDA as before. The resulting lithium enolate afforded products **16** and **17** in low chemical yield with poor diastereoselectivity. We first ascertained whether the problem lay in inefficient or nonselective enolate formation. The enolate generated with LDA was readily trapped with TBS chloride in quantitative yield. Analysis of the resulting *N*,*O*-keteneacetal by NOE showed that enolate formation was highly Z-selective.[7] Thus problems with enolate formation are not the origin of the low reactivity and selectivity.

To rule out unusually stable enolate aggregates, we utilized lithium salts and HMPA to disrupt aggregation. However, little improvement in the diastereoselectivity was observed. The major product was determined to be (*S*)-**17**, which supports the model invoking chelation coupled with steric factors to control the diastereoselectivity.

Use of more ionic sodium enolates was expected to enhance reactivity.[1f,11] Generation of the enolate **12** and **15**

(6) (a) Boeckman, R. K., Jr.; Liu, Y. *J. Org. Chem.* **1996**, *61*, 7984−7985. (b) Boeckman, R. K., Jr.; Wrobleski, S. T. *J. Org. Chem.* **1996**, *61*, 7238−7239. (c) Boeckman, R. K., Jr.; Connell, B. T. *J. Am. Chem. Soc.* **1995**, *117*, 12368−12369. (d) Boeckman, R. K., Jr.; Johnson, A. T.; Musselman, R. A. *Tetrahedron Lett.* **1994**, *35*, 8521−8524. (e) Boeckman, R. K., Jr.; Nelson, S. G.; Gaul, M. D. *J. Am. Chem. Soc.* **1992**, *114*, 2258−2260.

(7) A 12−20% NOE enhancement of the *cis* methyl, methylene, or methine protons was observed (difference 1D NOE) upon irradiation of the methyl groups of the TBS group of the *O*,*N*-silylketeneacetal.

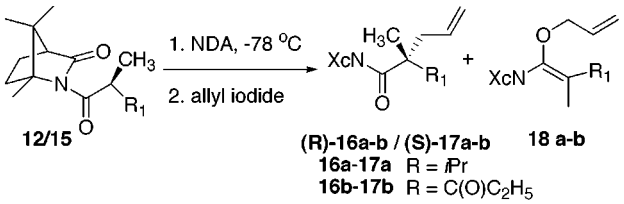
(8) (a) Lardicci, L.; Menicagli, R.; Caporusso, A. M.; Giacomelli, G. *Chem. Ind. (London)* **1973**, 184−185. (b) Evans, D. A.; Takacs, J. M. *Tetrahedron Lett.* **1980**, *21*, 4233−4236.

(9) Oppolzer, W.; Blagg, J.; Rodriguez, I.; Walther, E. *J. Am. Chem. Soc.* **1990**, *112*, 2767−2772.

(10) (a) Hanamoto, T.; Katsuki, T.; Yamaguchi, M. *Tetrahedron Lett.* **1986**, *27*, 2463−2464. (b) Roth, G. P.; Leonard, S. F.; Tong, L. *J. Org. Chem.* **1996**, *61*, 5710−5711. (c) Schwarz, J. B.; Meyers, A. I. *J. Org. Chem.* **1998**, *63*, 1619−1629. (d) Dalko, P. I.; Brun, V.; Langlois, Y. *Tetrahedron Lett.* **1998**, *39*, 8979−8982. (e) Van der Werf, M. J.; De Bont, J. A. M.; Swarts, H. J. *Tetrahedron: Asymmetry* **1999**, *10*, 4225−4230. (f) Hosokawa, S.; Sekiguchi, K.; Enemoto, M.; Kobayashi, S. *Tetrahedron Lett.* **2000**, *41*, 6429−6433.

using sodium diisopropylamide (NDA),[12] shown to be >49:1 Z by NOE as above,[7] led to high diastereomeric ratios and modest to excellent yields and conversions upon reaction with allyl iodide (Table 2). Reaction temperatures of −30

Table 2. Alkylations Creating a Quaternary Center



R_1	temp[a] (°C)	yield (conv) **16** + **17** (%)	**16a**,**b**:**17a**,**b**[b,c]	**18** (%)
12 ^{i}Pr	0	36 (65)	13.7:1	0
12 ^{i}Pr	−30	60 (76)	20.5:1	10
15 C(O)Et	−40	67 (100)	99:1	0

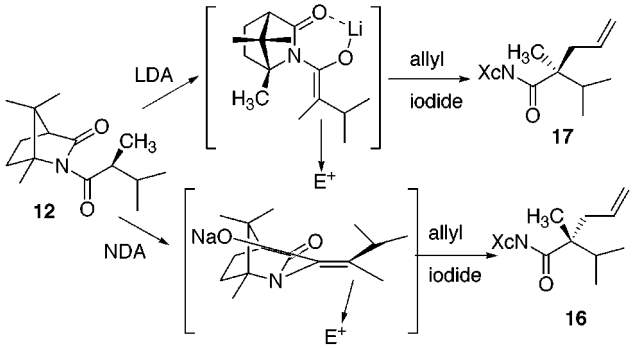
[a] General reaction conditions: a solution of **12** in dry THF was added to 2 equiv of NDA in THF at −45 °C, followed by addition of neat allyl iodide (10 equiv) after 40 min, warming to −30 or 0 °C, and stirring for 4 h. [b] The diastereomeric ratio was quantified by GLC. [c] Derivatization was employed to determine the absolute configuration as detailed in the Supporting Information.

to −40 °C were optimal for enhancing reactivity and inhibiting enolate decomposition. Less polar mixtures of THF and toluene gave improved diastereoselectivity (as high as 49:1) but did not afford yields or conversions as high as THF alone.

The major products **16** were determined to have the *R* configuration, established by chemical correlation or X-ray analysis, opposite to that obtained with the lithium enolate. The stereochemical outcome is best rationalized by assuming that the sodium enolate orients itself perpendicular to the endocyclic lactam π system to avoid unfavorable electronic interactions as do amide and N-acylsultam enolates.[13] The enolate conformation where the C−O bond bisects the C_4−C_7 lactam bond is much preferred on the basis of molecular mechanics calculations (MacroModel, ver. 6, 1998).[14] The electrophile then approaches the least hindered enolate face.

Alkylation of chiral enolates bearing an α-heteroatom have been extensively studied.[1f,15] Chiral imide enolates experience problems possibly arising from competitive chelation of the counterion by the heteroatom rather than the imide carbonyl. Loss of control about the enolate N_{aux}−C bond occurs, which is required for high levels of diastereoselectivity. Indirect methods have been used to introduce the heteroatom in the

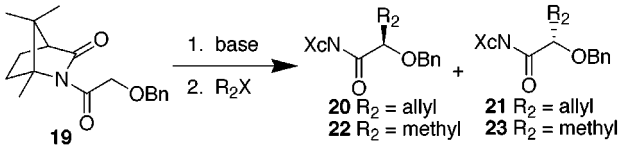
Scheme 1. Stereochemistry of Alkylation of **12**



case of nitrogen.[11,16] Compounding the difficulties is the increased tendency of electron-rich enolates to decompose to ketene and auxiliary.

To determine if **1** and **2** offered any advantage, **1** was acylated with benzyloxyacetyl chloride to afford **19**. Deprotonation of **19** using both sodium and lithium hexamethyldisilazane as bases and then treatment with allyl or methyl iodide afforded the expected monoalkylation products in good yields (Table 3).[17] Unfortunately, only modest diastereoselectivites (1.4−3.6:1) were observed favoring the *R* isomers **20**/**22** at the optimal temperature (−40 °C).

Table 3. Alkylation of Glycolate **19**



base[a]	R_2X	yield (%)	dr[b]	**1**[c] (%)
LiHMDS	CH_2=$CHCH_2I$	74	2.2:1	21
LiHMDS	CH_3I	66	2.5:1	20
NaHMDS	CH_2=$CHCH_2I$	67	3.6:1	32
NaHMDS	CH_3I	62	1.4:1	10

[a] General reaction conditions: a solution of **19** in dry THF was added to a 0.5 M solution of base (1.5 equiv) at −78 °C, followed by immediate addition of neat R_2X, warming to −40 °C, and stirring for 24 h. [b] The absolute configuration was determined by cleaving the auxiliary to the Weinreb amide, reducing with DIBAl-H and, comparing the optical rotation to the known aldehydes.[18] [c] The remainder of the mass is recovered starting material.

(11) Evans, D. A.; Wu, L. D.; Wiener, J. J. M.; Johnson, J. S.; Ripin, D. H. B.; Tedrow, J. S. *J. Org. Chem.* **1999**, *64*, 6411−6417.

(12) Lochmann, L.; Trekoval, J. *J. Organomet. Chem.* **1979**, *179*, 123−132.

(13) (a) Pugh, J. K.; Streitwieser, A. *J. Org. Chem.* **2001**, *66*, 1334−1338. (b) Oppolzer, W.; Poli, G.; Starkemann, C.; Bernardinelli, G. *Tetrahedron Lett.* **1988**, *29*, 3559−3562.

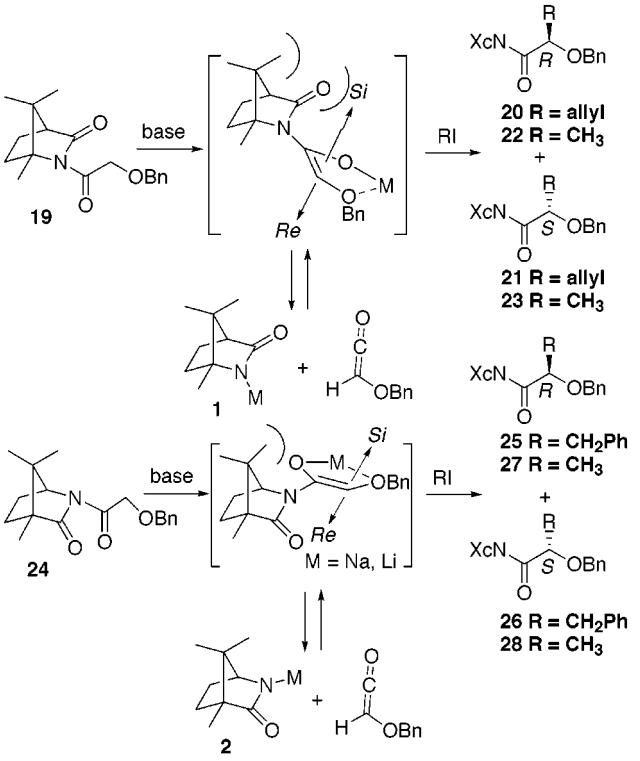
(14) Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440−467.

(15) (a) Frater, G.; Mueller, U.; Guenther, W. *Tetrahedron Lett.* **1981**, *22*, 4221−4224. (b) Kelly, T. R.; Arvanitis, A. *Tetrahedron Lett.* **1984**, *25*, 39−42. (c) Helmchen, G.; Wierzchowski, R. *Angew. Chem.* **1984**, *96*, 59−60. (d) Enomoto, M.; Ito, Y.; Katsuki, T.; Yamaguchi, M. *Tetrahedron Lett.* **1985**, *26*, 1343−1344. (e) Pearson, W. H.; Cheng, M. C. *J. Org. Chem.* **1986**, *51*, 3746−3748. (f) Ludwig, J. W.; Newcomb, M.; Bergbreiter, D. E. *Tetrahedron Lett.* **1986**, *27*, 2731−2734. (g) Cardillo, G.; Orena, M.; Romero, M.; Sandri, S. *Tetrahedron* **1989**, *45*, 1501−1508. (h) Burke, S. D.; Quinn, K. J.; Chen, V. J. *J. Org. Chem.* **1998**, *63*, 8626−8627. (i) Chappell, M. D.; Stachel, S. J.; Lee, C. B.; Danishefsky, S. J. *Org. Lett.* **2000**, *2*, 1633−1636. (j) Jung, J. E.; Ho, H.; Kim, H.-D. *Tetrahedron Lett.* **2000**, *41*, 1793−1796.

(16) (a) Evans, D. A.; Britton, T. C.; Ellman, J. A.; Dorow, R. L. *J. Am. Chem. Soc.* **1990**, *112*, 4011−30. (b) Evans, D. A.; Britton, T. C.; Dellaria, J. F., Jr. *Tetrahedron* **1988**, *44*, 5525−40.

To our surprise, the *R* diastereomer was major independent of both base and electrophile, consistent with reaction via a conformer comparable to that shown in Scheme 2. No

Scheme 2. Stereochemistry of Alkylation of **19** and **24**



dependence on counterion supports the idea that the lower diastereoselectivity results from loss of control over the C−N_{aux} bond in the enolate.

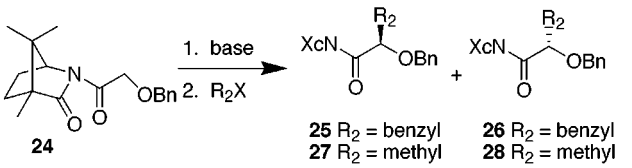
To determine whether the bridgehead methyl is critical to the observed stereochemistry, we examined enolates derived from **24**. As shown in Table 4, alkylation of Li and Na enolates derived from **24**,[17] itself obtained by acylation of **2**, provided alkylation products **25**−**27** in excellent yield. The diastereoselectivity was improved (4.4−6.4:1) somewhat. During our studies Crimmins reported even higher selectivity for cases limited to allylic iodides.[1f]

Surprisingly, *the major diasteromers (R)-25/(R)-27 obtained using **24** were not only independent of counterion but were identical to the major products obtained from **19***, inconsistent with our stereochemical model and unprecedented for imides derived from **1** and **2** (Scheme 2).

Other factors were thus influencing the stereochemical outcome. The role of ketene formation was investigated,

(17) >98% Z selectivity in enolate formation was verified by NOE.[7]

Table 4. Alkylation of Glycolate **24**



base[a]	R_2X	yield (%)	dr[b]	**2**[c] (%)
LiHMDS	$C_6H_5CH_2Br$	95	3.5:1	0
LiHMDS	CH_3I	74	3.8:1	11
NaHMDS	$C_6H_5CH_2Br$	99	4.4:1	0
NaHMDS	CH_3I	86	6.4:1	7

[a] General reaction conditions: a solution of **24** in dry THF was added to an 0.5 M solution of of the base (1.5 equiv) at −78 °C, followed by immediate addition of neat R_2X, warming to −40 °C, and stirring for 24 h. [b] The diastereomeric ratio was determined by ^{1}H NMR. [c] The remainder of the mass is recovered starting material.

since varying amounts of **1** and **2** (and occasionally N-alkylated analogues) were obtained during alkylations of **19** and **24** (Tables 3 and 4). Treatment of **24** with NaHMDS and CH_3I, followed by quenching and aliquot analysis at 1 min intervals, revealed that almost all of **24** was consumed within 5 min, affording 75% of **27** and **28** (4.7:1) and 25% lactam **2**. Over 24 h, the amount of lactam decreased to 7% and the diastereomeric ratio steadily increased (see Table 4). When the enolate from **19** was examined, consumption of **19** was slower. Initially, the *S* diastereomer predominated (after 5 min conversion to 20% of **22** and **23** (2.3:1) and 32% of **1**), but after 24 h, the diastereomeric ratio **22**/**23** had degraded to 0.95−1.4:1. Thus, reversible conversion of the enolates from both **19** and **24** to the corresponding ketenes and the lactam anions from **1** and **2** appears to be dramatically impacting stereochemical outcome.[19]

Further studies of the role of ketene formation in determining diastereoselectivity are ongoing to enhance stereocontrol in alkylation of α-heteroatom enolates.

Acknowledgment. We are grateful to NIGMS of the National Institutes of Health for the award of a research grant (GM-30345) in support of these studies.

Supporting Information Available: Characterization data for **4b**−**d**, **7**−**16**, **19**−**20**, **22**, **24**−**28** and experimental procedures for correlation of **16**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) Control experiments using the lactam anion of **1** and a mixture of **22**/**23** (9:1) showed no formation of crossover products or change in the diastereomeric ratio of **22**/**23**.