JOC*Article*

Synthesis of *N*-Methyl-*N*-{(1*S*)-1-[(3*R*)-pyrrolidin-3-yl]ethyl}amine†

Thomas J. Fleck,‡ William W. McWhorter, Jr.,*,§ Richard N. DeKam,‡ and Bruce A. Pearlman⊥

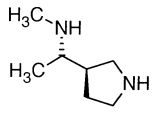
Early Process Research and Development, Medicinal Chemistry Research, and Chemical Research and Development, Pfizer, Inc., Kalamazoo, Michigan 49001

will.mcwhorter@worldnet.att.net

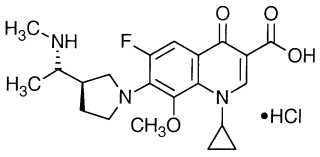
Received July 3, 2003

N-Methyl-*N*-{(1*S*)-1-[(3*R*)-pyrrolidin-3-yl]ethyl}amine (**1**)[1] is a key intermediate in the preparation of premafloxacin (**2**), which was under development as an antibiotic for use against pathogens of veterinary importance. This paper describes the development of a practical, efficient, and stereoselective process for the preparation of **1** from isobutyl (3*S*)-3-{methyl[(1*S*)-1-phenylethyl]-amino}butanoate (**5c**). The key steps in the synthetic sequence are an asymmetric Michael addition, which yields **5c**, and a stereoselective alkylation, which yields (3*S*,4*S*)-3-allyl-1,4-dimethylazetidin-2-one (**17**).

N-Methyl-*N*-{(1*S*)-1-[(3*R*)-pyrrolidin-3-yl]ethyl}amine (**1**)[1] is a key intermediate in the preparation of premafloxacin (**2**), which was under development as an antibiotic for use against pathogens of veterinary importance. Since the three stereoisomers of premafloxacin are much less active than premafloxacin itself, the development of a practical, efficient, stereoselective synthesis of the intermediate diamine **1** was of crucial importance.



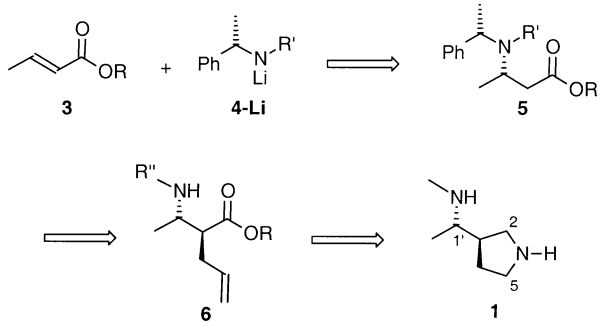
1



2

In this paper, we will describe the evolution of a method for the preparation of *N*-methyl-*N*-{(1*S*)-1-[(3*R*)-pyrrolidin-3-yl]ethyl}amine (**1**) into a highly efficient and stereoselective process. Our initial plan for the synthesis of **1** is shown in Scheme 1. We realized that the stereochemistry at the center that becomes C.1′ of **1** could be fixed in an absolute sense by means of an asymmetric Michael reaction.[2] The chiral lithium amide **4-Li** (R′ = Bn)[2b] has been shown to add to crotonate esters **3** to yield optically active *β*-aminobutyrates **5** with very high degrees of diastereoselectivity.[2] The chiral template, (*S*)-(*N*-benzyl)[*N*-(1-phenyl)ethyl]amine, can easily be prepared from the readily available (*S*)-(−)-α-methylbenzylamine. The chiral center at C.3 of **1** is then set relative to the previously prepared asymmetric center by using the chelation-controlled alkylation of *β*-aminobutanoates developed by Seebach and co-workers.[3] The use of allyl bromide as the alkylating agent should lead to **6**. We envisioned that the double bond of the allyl group could be cleaved oxidatively and the resulting aldehyde or alcohol could in turn be converted to an amine. A variety of methods for this transformation are available. This amine should readily cyclize to a *γ*-lactam, reduction of which results in the formation of **1**.

SCHEME 1



We prepared (*S*)-*β*-aminobutanoates using the asymmetric Michael addition as shown in Scheme 2. Davies and Ichihara[2b] reacted *tert*-butyl crotonate with the lithium amide prepared from (*S*)-(*N*-benzyl)[*N*-(1-phenyl)-ethyl]amine[4] at −78 °C in THF to obtain a diastereomerically pure product in high yield. We found that this reaction also occurred with complete diastereoselectivity at −40 °C. We investigated the addition of the same

* Address correspondence to this author. Phone: (269) 385-3003.

† This paper is dedicated to the memory of our colleague and friend, Tom Fleck, who passed away March 4, 2003.

‡ Early Process Research and Development.

§ Medicinal Chemistry Research.

⊥ Chemical Research and Development.

(1) Plummer, J. S.; Emery, L. A.; Stier, M. A.; Suto, M. A. *Tetrahedron Lett*. **1993**, *34*, 7529−7532.

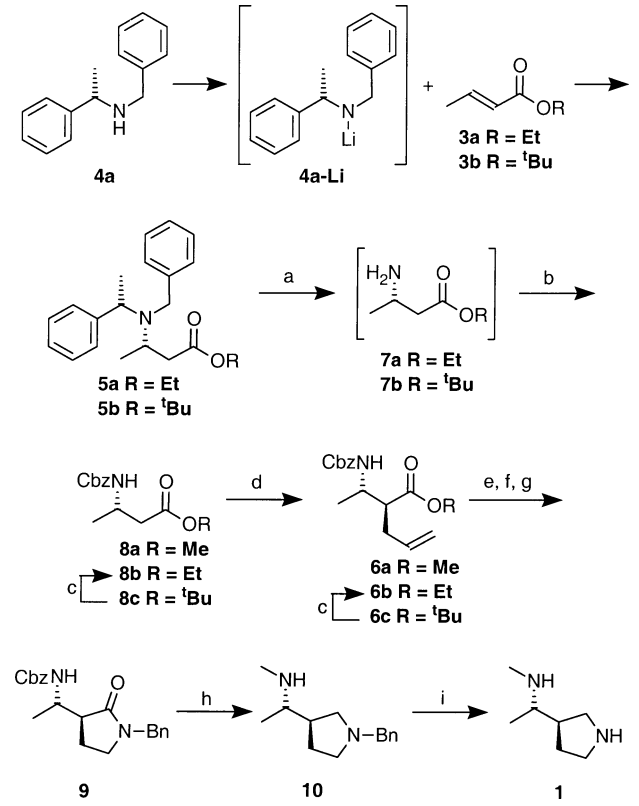
(2) (a) Hawkins, J. M.; Fu, G. C. *J. Org. Chem*. **1986**, *51*, 2820−2822. (b) Davies, S. G.; Ichihara, O. *Tetrahedron*: *Asymmetry* **1991**, *2*, 183−186. (c) Hawkins, J. M.; Lewis, T. A. *J. Org. Chem*. **1992**, *57*, 2114−2121. (d) Costello, J. F.; Davies, S. G.; Ichihara, O. *Tetrehedron*: *Asymmetry* **1994**, *5*, 1999−2008.

(3) (a) Seebach, D.; Estermann, H. *Tetrahedron Lett*. **1987**, *28*, 3103−3106. (b) Estermann, H.; Seebach D. *Helv. Chim. Acta* **1988**, *71*, 1824−1839.

(4) Davis, F. A.; McCauley, J. P., Jr.; Chattopadhyay, S.; Harakal, M. E.; Towson, J. C.; Watson, W. H.; Tavanaiepour, I. *J. Am. Chem. Soc*. **1987**, *109*, 3370−3377.

10.1021/jo0349633 CCC: $25.00
Published on Web 11/19/2003

SCHEME 2[a]



[a] Reagents and conditions: (a) $Pd(OH)_2/C$, 30 psi H_2, MeOH; (b) BnOCOCl, 1 M aq $KHCO_3$, EtOAc, MeOH (89% for a and b for the preparation of **8a**); (c) *p*-TsOH, EtOH; (d) LDA, allyl bromide, THF, −75 °C (77% when R = Me); (e) O_3, MeOH, −78 °C; (f) Me_2S; (g) $BnNH_2$, HOAc, $NaCNBH_3$, THF, MeOH (59% for e, f, and g when R = Me); (h) LAH, THF, reflux (85%); (i) $Pd(OH)_2/C$, 30 psi H_2, MeOH.

chiral lithium amide to ethyl crotonate because the *tert*-butyl ester did not participate in a subsequent reaction (vide infra). When ethyl crotonate was reacted with the chiral lithium amide in THF at −78 °C, the Michael adduct was obtained in 68% yield with a diastereoselectivity of 34:1.[5] Unlike the reactions with *tert*-butyl crotonate, a minor byproduct, a diastereomeric mixture of *β*-aminoamides,[6] resulted from attack of excess chiral lithium amide on the ethyl ester group of either the Michael adduct or the crotonate ester.

We synthesized the target pyrrolidine **1** from the di-*N*-benzyl-*β*-aminobutanoate products (**5a** and **5b**) of the Michael reaction as shown in Scheme 2. Hydrogenolytic cleavage of the two benzyl groups of the ethyl or *tert*-butyl *β*-aminobutanoate (**5a** or **5b**) at 30 psi of hydrogen in the presence of Pearlman's catalyst[7] cleanly yielded ethyl or *tert*-butyl (*S*)-*β*-aminobutanoate (**7a** or **7b**). The crude methanol solution of the *β*-aminobutanoate (**7a** or **7b)** was treated with benzyl chloroformate in a two-phase mixture of 1 M $KHCO_3$ and ethyl acetate to yield the benzyl carbamate (Cbz) derivative of the methyl or *tert*-butyl (*S*)-*β*-aminobutanoate (**8a** or **8c**) in high overall yield.[8] Ester exchange from an ethyl to a methyl ester takes place under these reaction conditions, but transesterification was not observed with the *tert*-butyl ester. Although distillation of the ethyl or *tert*-butyl (*S*)-*β*-aminobutyrate (**7a** or **7b**) can be carried out, this is not necessary prior to reprotection as the Cbz derivative.

Alkylation of the methyl or *tert*-butyl *β*-aminobutanoate **8a** or **8c** with allyl bromide according to the conditions of Seebach and Estermann yielded the corresponding α-allyl ester.[3] The diastereoselectivity was >91%.[9] Estermann and Seebach report a diastereoselectivity of 97% for the alkylation with allyl bromide of the very closely related methyl *β*-[(*N*-benzoyl)amino]butyrate.

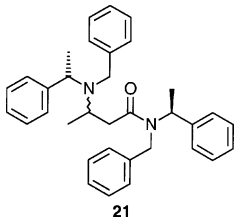
The methyl α-allyl-*β*-aminobutanoate **6a** was subjected to ozonolysis followed by reductive workup with dimethyl sulfide and the resulting mixture of cleavage products was reductively aminated with benzylamine and subsequently cyclized to pyrrolidinone **9**. Sodium cyanoborohydride was superior to sodium borohydride and sodium triacetoxyborohydride for this reductive amination. The methyl and ethyl α-allyl-*β*-aminobutanoates can be used in this ozonolysis/reductive amination reaction sequence; however, the *γ*-lactam cyclization product could not be detected when the corresponding *tert*-butyl ester was employed in this reaction sequence.

Pyrrolidinone **9** was reduced with lithium aluminum hydride in refluxing THF to yield pyrrolidine **10**. Hydrogenolysis of the benzyl group with Pearlman's catalyst under 30 psi of hydrogen yielded the target pyrrolidine **1** as a clear, volatile oil. The overall yield of benzyl pyrrolidine **10** from ethyl crotonate was 23% for seven steps.

To streamline the synthetic sequence, we sought to eliminate the need for the steps in which protecting groups are exchanged and to directly introduce the *N*-methyl group of **1** from the initial stages of the synthetic sequence. As shown in Table 1 and Scheme 3, we examined the addition of lithium amides derived from the sterically less demanding (*S*)-(*N*-methyl)[*N*-(1-phenyl)ethyl]amine[10,11] **4b** to a series of crotonate esters. This amine also showed a very high degree of diastereoselectivity (18:1) in the asymmetric Michael addition at

(5) The ratio was judged by peak heights in the NMR of the signals for the methylene protons α to the carbonyl of the ethyl ester in the two diastereomers.

(6) The following mass spectral data were obtained for the byproduct **21**: 491 ($M^+ + H$, rel intensity 52%); 399 (22); 385 (48); 281 (19); 238 (45); 210 (16); 105 (86); 91 (100). Integration of the signals for the methylene protons α to the carbonyl of the amide in the 300-MHz ^1H NMR indicated a 3.5:1 ratio of diastereomers.



(7) Furukawa, M.; Okawara, T.; Noguchi, Y.; Terawaki, Y. *Chem. Pharm. Bull. Jpn.* **1979**, *27*, 2223−2226.

(8) Schmidlin, T.; Burckhardt, P. E.; Waespe-Sarcevic, N.; Tamm, C. *Helv. Chim. Acta* **1983**, *66*, 450−465.

(9) The ratio was judged by peak heights in the NMR of the signals for the C-2′ methyl group in methyl (2*S*)-2-((1*S*)-1-{[(benzyloxy)carbonyl]amino}ethyl)pent-4-enoate and its diastereomer.

(10) (*S*)-(*N*-Methyl)[*N*-(1-phenyl)ethyl]amine (**4b**) was prepared from *N*-formyl-*N*-(*S*)-methylbenzylamine (**4c**), which was in turn prepared from (*S*)-methylbenzylamine.

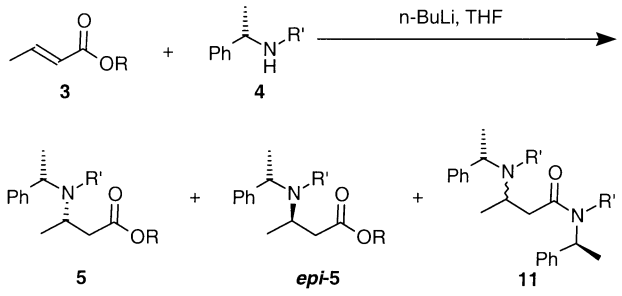
(11) After our initial disclosure of the use of this reagent in asymmetric Michael additions [WO 9426708 1994], Davies' group disclosed its use: Davies, S. G.; Smyth, GD. *Tetrahedron*: *Asymmetry* **1996**, *7*, 1001−1004.

TABLE 1. Asymmetric Michael Additions

R	R′	reaction temp, °C	yield of **5**, *epi*-**5**, %	diastereoselectivity[a]	yield of byproduct **11**, %
t-Bu	Bn	−78	95, −	one isomer detected	0
Et	Bn	−78	68, 2	34:1	minor product
Me	Me	−70	73, 4	18:1	23
Et	Me	−70	84, 5	17:1	11
i-Bu	Me	−70 (0.2 M)	88, 5	18:1	7
i-Bu	Me	−70 (0.6 M)	83, 5	17:1	12
i-Bu	Me	−40	78, 7	11:1	15
neo-Pen[b]	Me	−70	49, 12	4:1	39

[a] Ratio determined by comparing the peak heights of corresponding signals in the ^{1}H NMR spectra of the crude reaction products. [b] Inverse addition.

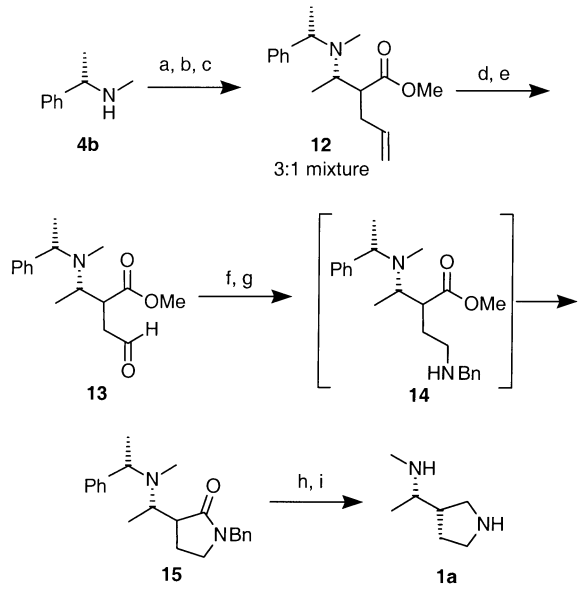
SCHEME 3



−70 °C. The degree of diastereoselectivity was maintained independent of the steric bulk of the ester alkyl group. The increasing bulk of the ester alkyl group did, however, minimize the formation of the amide byproducts. The level of amide byproduct is 7%, 11%, and 23% for isobutyl crotonate, ethyl crotonate, and methyl crotonate, respectively. These studies revealed that the reaction of isobutyl crotonate with the sterically less demanding lithium amide maximized the diastereoselectivity of the β-aminobutanoate formation and, at the same time, minimized the formation of byproduct amide **11**.[12] The diastereomer and byproduct amide could be completely removed by recrystallization to yield pure **5c** (**5**, where R = *i*-Bu and R′ = Me).

In an attempt to further streamline the synthesis of **1**, we examined the direct alkylation of the anion, which results from the addition of the lithium amide to the crotonate ester. In this way, we hoped to introduce the correct stereochemistry of the two chiral centers of **1** in one step. The anion, which resulted from addition of the chiral lithium amide of **4b** to methyl crotonate, was directly treated with allyl bromide in a one-pot procedure. This resulted in an inseparable mixture of products **12** in a 3:1 ratio in 75−80% yield. This mixture of isomers **12** was subjected to ozonolytic cleavage of the double bond to yield a diastereomeric mixture of aldehydes **13** after reductive workup with dimethyl sulfide. The mixture of isomers **13** was treated with benzylamine and the intermediate imine was directly reduced with sodium borohydride to yield **14**, which cyclized in situ to an isomeric mixture of lactams **15**. The diastereomers **15** could be chromatographically separated. The pyrrolidine that resulted from the major diastereomer was not **1**, but

SCHEME 4[a]



[a] Reagents and conditions: (a) *n*-BuLi (1 equiv), THF, −78 °C; (b) methyl crotonate, −78 °C; (c) allyl bromide (2 equiv), 0 °C (75−80% for a, b, and c); (d) O_3, MeOH; (e) Me_2S; (f) $BnNH_2$, THF, MeOH; (g) AcOH, $NaBH_4$; (h) LAH, THF; (i) $Pd(OH)_2$/C, H_2, EtOH.

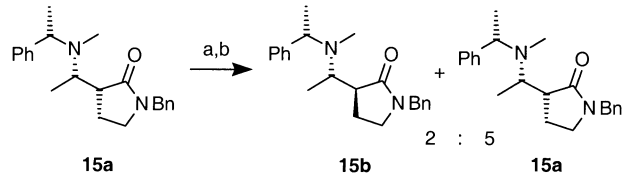
its diastereomer **1a**. Thus, the major isomer of the mixture of **12**, obtained from the tandem Michael addition−alkylation sequence, apparently had the syn stereochemistry. Davies and co-workers have demonstrated that there is a general, but modest tendency for the anti stereochemistry to predominate over the syn stereochemistry in closely related tandem Michael addition−alkylation reactions.[13] Epimerization at the center α to the methyl ester during the conversion of **12** to **1a** could explain this discrepancy; however, we did not observe epimerization at this center during the similar conversion of **6** to **1** (Scheme 2). A modest preference for the syn product in one case relative to a slight preference for the anti product in the other represents a very modest shift in the relative free energies of the respective transition states.

We attempted to convert the pyrrolidinone **15a**, which has the incorrect stereochemistry at C.3, to its epimer

(12) Although better diastereoselectivity is obtained in the Michael reaction when *tert*-butyl crotonate is used as opposed to isobutyl crotonate, the high cost and relative unavailability of *tert*-butyl crotonate precluded its development as a reagent for the Michael addition for large-scale synthesis.

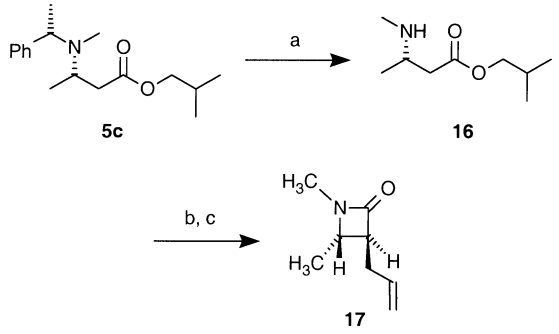
(13) (a) Davies, S. G.; Walters, I. A. S. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1129−1139. (b) Bunnage, M. E.; Davies, S. G.; Goodwin, C. J.; Walters, I. A. S. *Tetrahedron: Asymmetry* **1994**, *5*, 35−36. (c) Chippindale, A. M.; Davies, S. G.; Iwamoto, K.; Parkin, R. M.; Smethurst, C. A. P.; Smith, A. D.; Rodriguez-Solla, H. *Tetrahedron* **2003**, *59*, 3253−3265.

SCHEME 5[a]



[a] Reagents and conditions: (a) KO*t*-Bu, THF; (b) saturated NH_4Cl.

SCHEME 6[a]

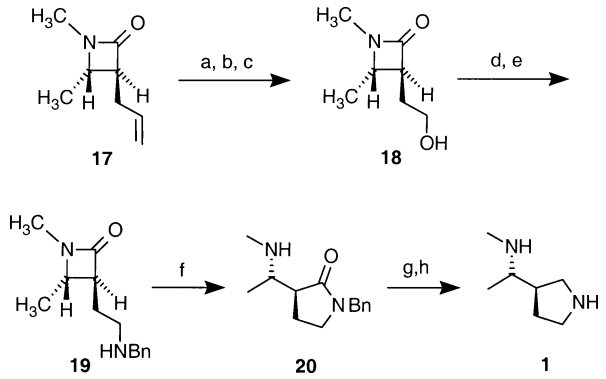


[a] Reagents and conditions: (a) $Pd(OH)_2$, H_2, EtOH; (b) LDA (2.2 equiv), THF, −40 °C; (c) allyl bromide (1.9 equiv).

with the correct configuration by equilibration with KO*t*-Bu in THF followed by quenching with saturated ammonium chloride. Unfortunately, the mixture from this attempted epimerization contained a 5:2 ratio of pyrrolidinones in which the diastereomer **15a**, with the incorrect stereochemistry at C.3, predominated. The poor diastereoselectivities observed during this reaction sequence caused us to abandon this route.

We next attempted to improve the diastereoselectivity of the allylation step through a variation of the chelation-controlled alkylation of *β*-aminobutanoates developed by Seebach and co-workers.[3] Hydrogenolysis of **5c**, as shown in Scheme 6, yielded isobutyl (*S*)-3-(*N*-methyl)aminobutyrate (**16**). Deprotonation of **16** can potentially lead to a lithium-chelated dianion intermediate that can be stereoselectively alkylated. When amine **16** was treated with 2 equiv of LDA and allyl bromide (1.9 equiv) was added to the resulting anion, we observed the formation of a single *β*-lactam **17**. A search of the literature showed several cases in which deprotonation of *β*-alkylamino esters yielded *β*-lactams.[14] Alkylation of the lithium-chelated dianion can occur with subsequent closure to a *β*-lactam, or the initially formed lithium amide can cyclize to the *β*-lactam, which is subsequently deprotonated and alkylated. The alkylation of the lithium-chelated dianion, as judged by our experience with the alkylation of **8a** and **8c**, is not likely to be completely stereoselective, but once the *β*-lactam has been formed, the diastereomer could be epimerized to **17** under the basic reaction conditions. With all of these possible reaction pathways, formation of the desired diastereomer would be the expected outcome. The stereocontrolled alkylation of *β*-lactams is well precedented by numerous examples in the literature;[15] however, this is the first direct formation and alkylation of a *β*-lactam in one pot.

SCHEME 7[a]



[a] Reagents and conditions: (a) O_3, H_2O, 0 °C; (b) $NaBH_4$; (c) CH_2Cl_2 extraction (70−85% for a, b, and c); (d) MsCl, Et_3N, THF; (e) $BnNH_2$, 50−60 °C (75−90% for e and d); (f) toluene, reflux, 3 h (90−95%); (g) LAH, THF, reflux; (h) $Pd(OH)_2$, H_2, MeOH (75−90% for g and h).

The *β*-lactam **17** was converted to the amino *β*-lactam **19** by a two-step procedure. Ozonolytic cleavage of the double bond followed by reduction of the resulting methoxyhydroperoxide with dimethyl sulfide produced an aldehyde. This unstable aldehyde was not isolated, but was converted to the amino *β*-lactam by a reductive amination. A higher yielding method for the preparation of this amino *β*-lactam involves reductive workup of the ozonolysis product with $NaBH_4$ to yield alcohol **18**. The initial ozonolyses were done in CH_2Cl_2 or in CH_2Cl_2:MeOH solutions; however, large-scale (>1 kg) reactions required a safer system in which to run these O_2-rich reactions. The *β*-lactam **17** is soluble in water and since water has been used successfully as an ozonolysis solvent, we tried the ozonolysis in water. The reaction worked cleanly to give an aldehyde, which was reduced in situ with $NaBH_4$, as shown in Scheme 7. Alcohol **18** was activated as the mesylate, which was displaced with benzylamine at 50−60 °C to yield a mixture of amino *β*-lactam **19** and pyrrolidinone **20**.

Complete conversion of amino *β*-lactam **19** to pyrrolidinone **20** was accomplished in toluene at 80−90 °C in 90−95% yield. No epimerization occurred under these conditions. When this reaction was carried out under basic conditions with LDA at −50 °C in THF, epimerization occurred at the α-carbon. The transamidation could, however, be carried out under acidic conditions (AcOH, MeOH, 60 °C, 4 h) without epimerization.

Reduction of *γ*-lactam **20** with LAH in refluxing THF occurred without epimerization to give the *N*-benzylpyrrolidine in 90% yield. Hydrogenolysis of the *N*-benzylpyrrolidine to diamine **1** occurred in 65−70% yield. Problems with CO_2 absorption onto the diamine probably caused the lower yield for this hydrogenolysis.

Conclusion

We have produced a synthesis of *N*-methyl-*N*-{(1*S*)-1-[(3*R*)-pyrrolidin-3-yl]ethyl}amine (**1**) in nine steps from isobutyl crotonate in 38% overall yield. This synthesis uses an asymmetric Michael reaction of a chiral lithium amide, derived from (*S*)-(*N*-methyl)[*N*-(1-phenyl)ethyl]-

(14) Gennari, C.; Venturini, I.; Gislon, G.; Schimperna, G. *Tetrahedron Lett.* **1987**, *28*, 227−230.

(15) Durst, T.; LeBelle, M. J. *Can. J. Chem.* **1972**, *50*, 3196−3201.

amine, to establish the stereochemistry at C.1′ of **1**. The stereochemistry at C.3 is set by using the stereochemistry at C.1′ to control the outcome of the stereoselective alkylation, which yields the key β-lactam intermediate **17**. We have also presented our first synthesis of **1**, which relied on the stereoselective alkylation of a β-aminobutanoate to establish the stereochemistry at C.3.

Experimental Section

***N*-Formyl-*N*-(*S*)-methylbenzylamine (4c).** (*S*)-Methylbenzylamine (107 g, 0.88 mol) and ethyl formate (180 g, 2.4 mol) were heated to reflux (51 °C) for 18 h. THF (110 mL) was added, and the solution was distilled to dryness. In the ^{1}H and ^{13}C NMR, the compound exists as a 90:10 mixture of rotamers about the C−N bond of the acyl group. Only data for the major isomer are listed. IR (liq) 3277 (b), 3031, 2976, 1996 (w), 1952 (w), 1661 (s), 1534, 1495, 1451, 1384, 1378, 1239, 762, 699 (s), 608, cm^{-1}; ^{1}H NMR (400 MHz, d_6-DMSO) δ 1.36 (3H, d, J = 7.0 Hz), 5.00 (1H, quintet, J = 7.5 Hz), 7.20−7.26 (3H, m), 7.30−7.35 (2H, m), 8.04 (1H, s), 8.53 (1H, d, J = 7.1 Hz); ^{13}C NMR (125 MHz) δ 23.3, 47.4, 126.8, 127.6, 129.1, 145.0, 160.9; MS (FAB) *m*/*z* (rel intensity) 150 (MH^+, 99), 303 (4), 300 (10), 299 (47), 253 (5), 151 (11), 150 (99), 148 (5), 106 (9), 105 (68), 46 (10); HRMS (FAB) calcd for $C_9H_{11}NO + H_1$ 150.0919, found 150.0924. Anal. Calcd for $C_9H_{11}NO$: C, 72.46; H, 7.43; N, 9.39. Found: C, 72.01; H, 7.46; N, 9.38.

Methyl (*S*)-Methylbenzylamine (4b). To THF (400 mL) was added a slurry of 10 wt % of $LiAlH_4$ (340 g, 0.90 mol), and the slurry was cooled to −20 °C. To the diluted $LiAlH_4$ slurry was added a solution of *N*-formyl-*N*-(*S*)-methylbenzylamine (121 g, 0.81 mol) dissolved in THF (220 mL) over 30 min. The solution was then heated to 63 °C for 8 h and then cooled to 8 °C. NaOH (50%, 750 g) was added over 2 h as the reaction mixture was cooled, using a CH_3CN/dry ice bath. Citric acid (50%, 880 g) was added to a pH of 10 followed by H_2O (500 mL). The product was extracted with EtOAc (2 × 800 mL). The combined EtOAc layers were washed with 2% Na_2CO_3 (400 mL), and the Na_2CO_3 solution was back extracted with EtOAc (600 mL). The combined EtOAc extracts were distilled and azeotroped with THF (750 mL) followed by toluene (400 mL) to remove water to give 90 g of methyl (*S*)-methylbenzylamine (83% yield from (*S*)-methylbenzylamine). IR (liq) 3025, 2970, 2932, 2869 (b), 2845, 2789, 2332 (w), 1996 (w), 1948 (w), 1493, 1476, 1450, 1137, 761 (s), 701 (s), cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.25 (3H, d, J = 6.6 Hz), 1.44 (1H, br s), 2.21 (3H, s), 3.54 (1H, q, J = 6.6 Hz), 7.10−7.26 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.2 (q), 34.8 (q), 60.5 (d), 126.8 (d), 127.1 (d), 128.7 (d), 145.6 (s); HRMS (FAB) calcd for $C_9H_{13}N + H_1$ 136.1126, found 136.1110. Anal. Calcd for $C_9H_{13}N$: C, 79.95; H, 9.69; N, 10.36. Found: C, 79.70; H, 9.46; N, 10.56.

Isobutyl (3*S*)-3-{Methyl[(1*S*)-1-phenylethyl]amino}-butanoate (5c). To a THF (2.6 L) solution of methyl (*S*)-methylbenzylamine (155 g, 1.15 mol) at −30 °C was added 24 wt % of *n*-BuLi (319 g, 1.19 mol) over 50 min. The solution was stirred for 30 min and cooled to −75 °C. A solution of isobutyl crotonate (155 g, 1.09 mol) in THF (680 mL) was added over 4 h and the solution was stirred an additional 30 min. The reaction was quenched at −70 °C over 1 h with a 14 wt % aqueous solution of NH_4Cl (245 g) to a pH of 2.4. The solution was warmed to 20 °C and diluted with H_2O (225 mL). The aqueous layer was separated and washed with EtOAc (1.4 L). The organic extracts were combined and the solution was distilled to a volume of 300 mL. The resulting slurry was filtered and washed with EtOAc (300 mL). The filtrate was distilled to a volume of 350 mL and MeOH (600 mL) was added. The solution was cooled to −5 °C and 37% HCl (116 g, 1.14 mol) was added over 25 min. MTBE (3 L) was added and the mixture was cooled to −20 °C and stirred for 2 h. The resulting solids were filtered and rinsed with MTBE (220 mL). The solids were dissolved with CH_2Cl_2 (1.6 L). H_2O (400 mL) was added, and the pH was adjusted to 12 with 50% NaOH (75 mL). The layers were separated, and the aqueous layer was extracted again with CH_2Cl_2 (900 mL). The CH_2Cl_2 extractions were combined and distilled to give 0.142 g (80%) of isobutyl (3*S*)-3-{methyl[(1*S*)-1-phenylethyl]amino}butanoate. IR (liq) 2967 (s), 2939, 2312 (w), 1995 (w), 1948 (w), 1735 (s), 1453, 1369, 1302, 1293 (s), 1211, 1193 (s), 1079, 1009, 701 (s), cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.83 (6H, d, J = 6.6 Hz), 0.90 (3H, d, J = 6.6 Hz), 1.24 (3H, d, J = 6.6 Hz), 1.81 (1H, 9 line m, J = 6.6 Hz), 2.00 (3H, s), 2.18 (1H, dd, J = 13.8, 7.5 Hz), 2.47 (1H, dd, J = 13.8, 6.9 Hz), 3.49 (2H, m), 3.73 (1H, dd, J = 17.1, 6.6 Hz), 3.81 (1H, dd, J = 17.1, 6.6 Hz), 7.09−7.27 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.9 (q), 19.6 (q), 22.1 (q), 28.1 (d), 32.5 (t), 39.4 (t), 51.6 (d), 62.5 (d), 70.9 (d), 127.1 (d), 127.6 (d), 128.6 (d), 146.6 (s), 173.2 (s); HRMS (FAB) calcd for $C_{17}H_{27}NO_2 + H_1$ 278.2120, found 278.2120. Anal. Calcd for $C_{17}H_{27}NO_2$: C, 73.61; H, 9.81; N, 5.05. Found: C, 73.56; H, 9.73; N, 5.21.

Isobutyl (3*S*)-3-(Methylamino)butanoate (16). To a hydrogenation vessel containing 5% Pd/C (50 g, 30 wt %) was added isobutyl (3*S*)-3-{methyl[(1*S*)-1-phenylethyl]amino}-butanoate (160 g, 0.61 mol) and 1.8 L of 2-propanol. Hydrogenation at 40 psig at 50 °C was carried out for 11.5 h until hydrogen uptake ceased. The slurry was filtered and rinsed with 2-propanol (100 mL). Azeotropic vacuum distillation with heptane (600 mL) gave 88 g (83%) of isobutyl (3*S*)-3-(methylamino)butanoate. IR (liq) 2965 (s), 2895, 2876, 1996 (w), 1733 (s), 1472, 1380, 1370, 1304, 1294, 1249, 1196, 1170, 1158 (s), 1006, cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.93 (6H, d, J = 6 Hz), 1.51 (3H, d, J = 6 Hz), 1.94 (1H, septet, J = 6.5 Hz), 2.70 (3H, s), 2.77 (1H, dd, J = 18, 9 Hz), 3.11 (1H, dd, J = 18, 6 Hz), 3.57 (1H, m), 3.92 (2H, m), 8.3−9.1 (1H, br s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.6 (q), 19.1 (q), 27.6 (d), 30.3 (q), 37.5 (t), 52.2 (d), 71.4 (t), 169.8 (s); MS (EI) *m*/*z* (rel intensity) 173 (M^+, 1), 158 (5), 102 (7), 59 (3), 58 (99), 57 (9), 56 (8), 43 (4), 42 (7), 41 (10), 39 (5); HRMS (EI) calcd for $C_9H_{19}NO_2$ 173.1416, found 173.1419. Anal. Calcd for $C_9H_{19}NO_2$: C, 62.39; H, 11.05; N, 8.08. Found: C, 62.35; H, 11.24; N, 8.03. $[\alpha]^{25}_D$ −1 (*c* 0.75).

(3*S*,4*S*)-3-Allyl-1,4-dimethylazetidin-2-one (17). To a freshly prepared LDA solution (122 g of diisopropylamine, 1230 mL of THF, and 514 g of 15% *n*-BuLi) at −75 °C was added a solution of isobutyl (3*S*)-3-(methylamino)butanoate (89 g, 0.51 mol) in THF (500 mL) over 2 h. The solution was stirred for 1 h and a solution of allyl bromide (125 g, 1.04 mol) in THF (450 mL) was added at −78 °C over 2 h. The reaction was quenched into a 0 °C aqueous NH_4Cl solution (181 g in 600 mL of H_2O). The pH was adjusted to 5 with 37% HCl (190 g). The organic layer was separated, and the aqueous layer was extracted with EtOAc (600 mL). The combined organic extracts were distilled and purified by plug chromatography, using 50:50 EtOAc: heptane, to give 60 g (83%) of (3*S*,4*S*)-3-allyl-1,4-dimethylazetidin-2-one. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.29 (3H, d, J = 6 Hz), 2.33 (1H, m), 2.52 (1H, m), 2.75 (3H, s), 2.76 (1H, br s), 3.29 (1H, dq, J = 6, 2 Hz), 5.05 (1H, dt, J = 10, 3 Hz), 5.08 (1H, dt, J = 15.5, 3 Hz), 5.81 (1H, dddd, J = 15, 11, 7, 7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.2 (q), 25.8 (q), 32.2 (t), 54.7 (d), 56.4 (d), 116.6 (t), 134.6 (d), 169.1 (s).

(3*S*,4*S*)-3-(2-Hydroxyethyl)-1,4-dimethylazetidin-2-one (18). A solution of (3*S*,4*S*)-3-allyl-1,4-dimethylazetidin-2-one (71 g, 0.36 mol) in H_2O (180 mL) was cooled to 0 °C. Ozonolysis was continued until the reaction was complete by GC. $NaBH_4$ (16 g, 0.42 mol) was added in 1−2 g shots. NaCl (100 g) was added and the product was extracted with CH_2Cl_2 (9 × 600 mL). The combined organic extracts were distilled and purified by plug chromatography, using 50:50 EtOAc: heptane, to give 35.6 g (49%) of (3*S*,4*S*)-3-(2-hydroxyethyl)-1,4-dimethylazetidin-2-one. IR (liq) 3415 (b), 2962, 2929, 2879 (b), 2465 (w), 2155 (w), 1996 (w), 1731 (s), 1428, 1398, 1381, 1363, 1347, 1052, 1001, cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.31 (3H, d, J = 6.0 Hz), 1.88 (2H, dt, J = 6.0, 3.0 Hz), 2.73 (1H, t, J = 7.6 Hz), 2.75 (3H, s), 3.33 (1H, dq, J = 6.0, 3.0 Hz),

3.71 (2H, t, J = 5.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) 17.4 (q), 26.4 (q), 31.6 (d), 55.6 (t), 56.0 (t), 61.3 (d), 170.6 (s); HRMS (FAB) calcd for $C_7H_{13}NO_2 + H_1$ 144.1024, found 144.1014.

(3*S*)-1-Benzyl-3-[(1*S*)-1-(methylamino)ethyl]pyrrolidin-2-one (20). To a solution of (3*S*,4*S*)-3-(2-hydroxyethyl)-1,4-dimethylazetidin-2-one (35 g, 0.24 mol) in CH_2Cl_2 (640 mL) at 0 °C was added Et_3N (62 g, 0.61 mol) followed by a solution of MsCl (30 g, 0.26 mol) in CH_2Cl_2 (45 mL) over 30 min. The reaction was quenched with a dilute aqueous HCl solution (76 g of 37% HCl and 300 mL of H_2O). The aqueous phase was separated and extracted with CH_2Cl_2 (400 mL). The combined CH_2Cl_2 extracts were again washed with a dilute aqueous HCl solution (38 g of 37% HCl and 300 mL of H_2O). The aqueous phase was back extracted with CH_2Cl_2 (400 mL). The combined CH_2Cl_2 extracts were vacuum distilled. THF (400 mL) was added and the resulting solution was again vacuum distilled. THF (1.0 L) and benzylamine (65 g, 0.61 mol) were added, and the solution was heated to 60 °C for 64 h. The reaction mixture was cooled to 0 °C, filtered, and distilled to a volume of 200 mL. A pure sample was obtained by chromatography. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.98 (3H, d, J = 6.5 Hz), 1.71 (1H, m), 1.97 (1H, m), 2.37 (3H, s), 2.54 (1H, q, J = 8.5 Hz), 2.85 (1H, quintet, J = 6.5 Hz), 2.99 (1H, br s), 3.08−3.11 (2H, m), 4.32 (1H, d, J = 14.7 Hz), 4.40 (1H, d, J = 14.7 Hz), 7.13−7.25 (5H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.2 (q), 20.7 (t), 33.5 (q), 44.7 (t), 45.3 (d), 46.5 (t), 56.3 (d), 127.4 (d), 127.9 (d), 128.5 (d), 135.3 (s), 175.5 (s).

***N*-{(1*S*)-1-[(3*R*)-1-Benzylpyrrolidin-3-yl]ethyl}-*N*-methylamine (10).** The crude (3*S*)-1-benzyl-3-[(1*S*)-1-(methylamino)ethyl]pyrrolidin-2-one was dissolved in THF (100 mL) and added over 2 h to a 70 °C slurry of 10 wt % of $LiAlH_4$ (140 g, 0.36 mol) in THF (600 mL). After the solution was stirred for 64 h, the product slurry was cooled to 10 °C and quenched with 50% NaOH (75 g). Citric acid (50%, 65 g) was added to a pH of 11. The reaction was diluted with H_2O (500 mL) and the phases were separated. The aqueous phase was extracted with THF (400 mL). The combined THF extracts were vacuum distilled. Toluene (400 mL) was added and the resulting solution was vacuum distilled. H_2O (500 mL), NaCl (50 g), and EtOAc (150 mL) were added, and the EtOAc layer was separated. The aqueous layer was extracted with THF (1 × 200 mL, 1 × 400 mL). The organic extracts were combined and vacuum distilled. Toluene (400 mL) was added and the resulting solution was vacuum distilled to give crude *N*-{(1*S*)-1-[(3*R*)-1-benzylpyrrolidin-3-yl]ethyl}-*N*-methylamine. A pure sample was obtained by chromatography. IR 2962, 2787, 1453, 1375, 1151, 738, 698 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.02 (3H, d, J = 6.3 Hz), 1.51 (1H, m), 1.88 (1H, m), 2.14 (1H, m), 2.25 (1H, dd, J = 8.8, 7.6 Hz), 2.37 (3H, s), 2.35−2.47 (2H, m), 2.66 (1H, br q, J = 7.7 Hz), 2.76 (1H, dd, J = 8.5, 8.1 Hz), 3.39 (1H, br s), 3.58 (1H, d, J = 12.9 Hz), 3.60 (1H, d, J = 12.9 Hz), 7.15−7.32 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.5 (q), 27.6 (t), 34.8 (q), 43.7 (d), 54.1 (t), 57.7 (t), 58.9 (d), 60.7 (t), 77.0 ($CDCl_3$), 126.8 (s), 128.1 (s), 128.7 (s), 139.1 (s); MS (EI, 70 eV) *m*/*z* (rel intensity) 218 (M^+, 3), 203 (2), 187 (48), 172 (36), 91 (100), 58 (59); $[\alpha]_D$ +2° (*c* 1.02, MeOH).

***N*-Methyl-*N*-{(1*S*)-1-[(3*R*)-pyrrolidin-3-yl]ethyl}amine (1).** To a hydrogenation vessel was added 20 wt % of $Pd(OH)_2$ (2 g, 8 wt %), crude *N*-{(1*S*)-1-[(3*R*)-1-benzylpyrrolidin-3-yl]-ethyl}-*N*-methylamine, and MeOH (400 mL). Hydrogenation at 20 °C was performed for 64 h with the addition of three more aliquots of 2, 8, and 8 g of $Pd(OH)_2$ until the reaction was complete. The slurry was filtered, rinsed with MeOH (50 mL), and distilled to an oil. The oil was distilled at very high vacuum to give 13.9 g (44% overall yield from (3*S*,4*S*)-3-(2-hydroxyethyl)-1,4-dimethylazetidin-2-one). IR (liq) 3290 (s, b), 2965 (s), 2871 (s), 2793 (s), 1996 (w), 1546, 1477, 1446 (s), 1418 (s), 1372, 1329, 1157, 889, 814, 721, cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.06 (3H, d, J = 6.3 Hz), 1.39 (1H, dddd, J = 12.3, 8.1, 8.1, 8.1 Hz), 1.60 (2H, br s), 1.86 (1H, m), 2.00 (1H, 6 line m, J = 8.1 Hz), 2.40 (3H, br s), 2.42 (1H, m), 2.61 (1H, dd, J = 10.8, 7.8 Hz), 2.87−2.96 (2H, m), 3.11 (1H, dd, J = 10.8, 7.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.8 (q), 29.4 (t), 33.7 (q), 45.9 (d), 46.8 (t), 50.5 (t), 58.5 (d); MS (EI) *m*/*z* (rel intensity) 128 (M^+, 1), 98 (8), 97 (46), 84 (10), 82 (33), 71 (9), 70 (9), 69 (7), 68 (9), 58 (99), 56 (8); HRMS (FAB) calcd for $C_7H_{16}N_2 + H_1$ 129.1392, found 129.1395.

Acknowledgment. We are grateful to the Analytical Chemistry Department of Pfizer for acquiring the IR, UV, HRMS, and combustion analysis data. We thank Dr. Jed F. Fisher for assistance with the preparation of this manuscript.

Supporting Information Available: ^{1}H NMR spectra of **5a**, **5b**, **8a**, **8c**, **6a**, **6b**, **6c**, **9**, **10**, **10a**, and **1b**; ^{1}H−^{1}H COSY, HMQC, and HMBC NMR spectra of **1b**; general information of the experimental section and experimental procedures for **5a**, **5b**, **8a**, **7b**, **8c**, **8b**, **6a**, **6c**, **6b**, **9**, **10**, **10a**, and **1b**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0349633