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Diastereoselective Conjugate Reduction and Enolate Trapping with Glyoxylate Imines. A Concise Approach to β-Lactams that Involves a Ternary Combination of Components

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The development of efficient approaches to the stereocontrolled synthesis of β-lactams continues to be of crucial importance within the context of the most widely employed class of antimicrobial agents, the β-lactam antibiotics.[1] The most commonly used strategy to access to these systems lies, Figure 1, in the prior construction of a monocyclic β-lactam such as **2** followed by chemical manipulations at N-1 and C-4 positions of the azetidinone nucleus and ring closure at a later stage in the synthesis.[2] Besides this significance, 3-alkyl-4-alkoxycarbonylazetidin-2-ones **2** are also excellent candidates for the development of synthetic inhibitors of elastase enzymes.[3] Three representative examples, Figure 2, of the latter are the L-652117 **3**,[4] compound **4**,[5] and L-680,833 **5**.[6] Therefore, it is not surprising that a vast number of methods are now available for the stereoselective synthesis of monocyclic β-lactams.[7] With few exceptions, the majority of these methods involve a combination of two reactants that provide the required β-lactam framework in a single

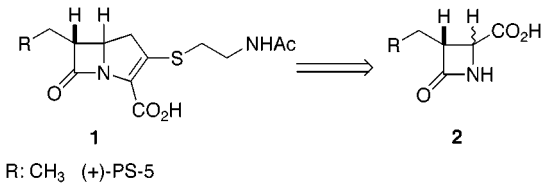

Figure 1.

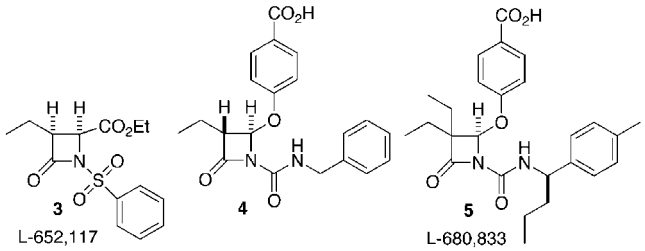

Figure 2.

synthetic step. Special attention has been put on the use of the metal ester enolate-imine condensation because of the easy availability of the starting materials and the high levels of asymmetric induction often attained through the use of either chiral carboxylic acid esters or chiral imines.[8] We report here a conceptually different, but in practice equivalent, strategy to access to β-lactams that is based on a ternary combination of components. Namely, the conjugate addition of hydride reagents to enoates or related systems and subsequent condensation of the resulting enolate with an imine.

Prior to the present investigation, very few studies concerning the coupling reaction of three reactants to furnish β-lactams have been described. All of these cases have dealt with the addition of nitrogen nucleophiles to enoates followed by enolate trapping with an electrophile.[9] The resulting intermediate β-amino acid and/or ester, upon cyclization at a separate step, led to the corresponding β-lactam product. Contemporary to these studies, we have also reported on the addition of the higher order Fleming's cyanosilylcuprate reagent to methyl crotonate followed by condensation with glyoxylate imines.[10] In these instances, the resulting β-amino ester intermediate cyclized spontaneously to give the desired β-lactam product in a single pot operation albeit in its recemic form. As an extension of this work and in

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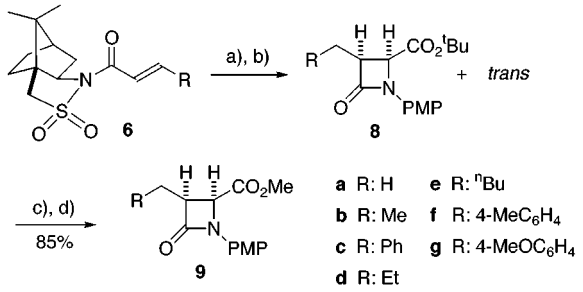
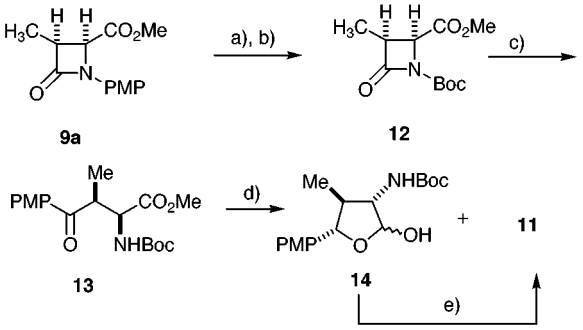
Scheme 1[a]



[a] Reagents and conditions: (a) M-Selectride (2.2 equiv). $CuBr \cdot SMe_2$ (1.1 equiv), SMe_2 (17 equiv), THF, −78 °C, 1 h; (b) PMP-N=CH-CO_2-*t*-Bu **7**, −78 °C to rt, 16 h; (c) F_3CCO_2H (40 equiv), CH_2Cl_2, rt, 4 h; 73−91%; (d) CH_2N_2, Et_2O, 0 °C. PMP: 4-$MeOC_6H_4$.

Scheme 2[a]



[a] Reagents and conditions: (a) CAN, MeCN; (b) $(Boc)_2O$; (c) 4-$MeOC_6H_4MgBr$, THF, −40 °C; (d) L-Selectride, THF, −78 °C; (e) nicotinic acid CrO_3 (NDC), pyridine, toluene. PMP: 4-$MeOC_6H_4$.

view of the existing precedents on asymmetric conjugate reductions,[11] we thought that this approach would also be valuable for the synthesis of nonracemic *β*-lactams both as intermediates of *β*-lactam antibiotics and elastase inhibitors.

For the study, we elected to use *N*-enoylsultams **6a**−**g** which have proven to be good acceptors in conjugate reductions.[12] Initially, the approach (Scheme 1) was examined under established conditions[13] by the addition of either L-Selectride or K-Selectride to each *N*-enoylsultam **6a**−**g** in THF at −78 °C. After 1 h at the same temperature, the glyoxylate imine **7** was added. Unfortunately, only the *N*-acylsultams from the reduction of **6a**−**g** were obtained in each case tested along with traces of the expected *β*-lactam products. Increasing the temperature of the enolate trapping step from −78 °C to room-temperature did not improve the results. Under the above conditions, N-Selectride also proved to be effective for the conjugate reduction but not for the carbon−carbon bond-forming step. Variations on the reaction solvent

Table 1. Conjugate Reduction of 6a−g Followed by Enolate Trapping with Imine 7[a]

entry	R	M	product	yield (%)[b]	cis:trans[c]	ee (%)[d]
1	H	Li	**8a**	52	73:27	75 (97)[e]
2	H	K	**8a**	40	88:12	≥99
3	H	Na	**8a**	55	98:2	≥99
4	Me	Li	**8b**	72	72:28	97
5	Me	K	**8b**	50	98:2	≥99
6	Me	Na	**8b**	70	98:2	≥99
7	Ph	Li	**8c**	54	72:28	82
8	Ph	K	**8c**	35	98:2	≥99
9	Ph	Na	**8c**	40	85:15	≥99
10	Et	Na	**8d**	60	95:5	98
11	*n*-Bu	Na	**8e**	60	99:1	98
12	4-MeC_6H_4	Na	**8f**	55	≥99:5[f]	98
13	4-$MeOC_6H_4$	Na	**8g**	50	≥99:5[f]	96

[a] Reactions carried out in THF on 1 mmol scale, see Experimental Section, using the following molar ratio of reagents: *N*-enoylsultam (0.25 M)/M-Selectride (1.0 M)/$CuBr \cdot SMe_2$/SMe_2 1:2.2:1.1:17. The reduction step was performed at −78 °C for 30 min and the trapping with the imine **7** (0.5 M in THF) from −78 °C to 25 °C for 16 h. For entries **12** and **13**, the reduction step was performed at −50 °C for 2.5 h. [b] Yields of the pure isolated cis isomers. [c] The cis:trans ratio measured by GC-MS analysis (major isomers gave longer retention times than minor ones). The cis:trans ratio was also confirmed by ^{1}H NMR. [d] Values related to major cis-(3*S*,4*S*) isomers after derivatization to the *cis*-3-alkyl-4-(methoxycarbonyl)-*β*-lactams **9**. The ee values were determined by chiral stationary phase HPLC analysis (column: Chiralpak-AS 250 × 4.6 mm; eluant: *i*-PrOH/hexane; flow 50/50 to 70/30 mL/min). [e] Value in parentheses indicates ee after a single crystallization from cyclohexane. [f] Determined by ^{1}H NMR.

(THF−HMPA, toluene, or diethyl ether) and/or temperature conditions for enolate trapping all met with failure.[14] The finding was that copper halide complexes ($CuX \cdot SMe_2$) in a molar ratio 1:2 (complex:M-Selectride) along with dimethyl sulfide as cosolvent efficiently promoted both the conjugate reduction and the enolate trapping, resulting in a clean formation of *β*-lactams **8a**−**g**. In every case, after the addition of the imine **7**, the latter step of the reaction was carried out by leaving off the cooling of the mixture from −78 °C to room temperature during 16 h. Noticeably, when the whole process was performed entirely at −78 °C overnight, no *β*-lactam product was formed. Likewise, trapping of the enolate at 0 °C did not lead to the formation of the expected *β*-lactam. As the results in Table 1 show, L-Selectride, under the established conditions, afforded *β*-lactams **8a**−**c** (entries 1, 4, and 7) in reasonable yields, but the cis:trans selectivity was poor. K-Selectride (entries 2, 5, and 8) provided better stereochemical control and enantiomeric purity for the corresponding cis-(3*S*,4*S*) isomers. However, in these cases, the yields were only moderate. The best results were achieved by the use of N-Selectride as the reducing agent. On the other hand, although the choice of the halide in the copper additive was unimportant ($CuCl \cdot SMe_2$ and $CuI \cdot SMe_2$ gave similar results to $CuBr \cdot SMe_2$), the nature of the ligand used appeared to be critical as shown by the fact that dicoordinated $CuX \cdot$TMEDA complex[15] gave only 20% yield of **8b** from **6b** and N-Selectride. Increasing the SMe_2:CuX molar ratio from an equimolar amount to an excess (typically, 15 equiv of SMe_2 per mol of CuX), raised the yield of isolated **8a** from 20 to 55% (entry 3). In a similar way, **8b** and **8c** were

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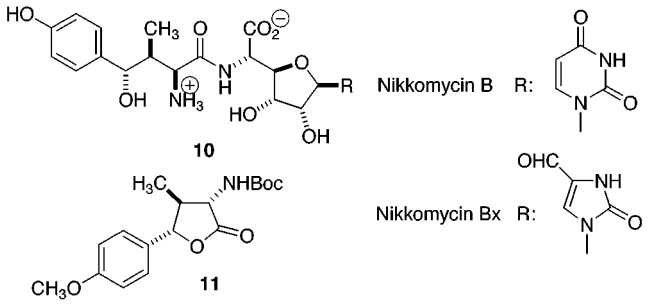

Figure 3.

produced in substantially lower yields when the process was carried out in the absence of the SMe_2 cosolvent. In general, the method affords β-lactams either from 2-alkyl-1-enoyl- or 2-aryl-1-enoylsultams **6** in moderate to good yields and with remarkable diastereo- and enantioselectivity. *N*-Cinnamoylsultams **6f**,**g** bearing electron-donating substituents required temperatures of −50 °C to give a complete conjugate reduction with N-selectride (entries 12 and 13). In particular, the enolate resulting from **6g** (entry 13) gave the β-lactam **8g** only if the trapping step was carried out by warming the reaction mixture from −78 to 25 °C during a period not exceeding for 3 h. As a final remark, a change of the CuBr·SMe_2:M-Selectride molar ratio from 1:2 to 1:1 rendered the reaction sluggish, affording traces of the expected β-lactams toghether with undefined byproducts.

For each compound **8a**−**e**, the cis relative disposition of the vicinal methine protons at C-3 and C-4 positions was easily established on the basis of the ^{1}H NMR coupling constants ($J_{3,4} \approx 5.9$ Hz), and the enantiomeric purity was determined by comparative chiral stationary phase HPLC analysis of 4-methoxycarbonylazetidinones **9a**−**e**, derivatized from **8a**−**e**, and their equivalent racemic β-lactams.[16] Obviously, by simply changing the *N*-enoylsultams employed in this strategy to their enantiomers, the corresponding enantiomers of both **8** and **9** would be equally available. The enantiomer of **9b** would be the precursor of either the antibiotic (+)-PS-5[17] or the elastase inhibitors **3**−**5**, while the β-lactams **9c** and **9g** constitute valuable precursors of inhibitors of prostate specific antigen.[18] Besides this significance, ring opening of these β-lactam products by oxygen and nitrogen nucleophiles is expected to give β-alkyl aspartic acid derivatives.[19] Product **9a**, on the other hand, can be transformed into the amino lactone **11**, Figure 3, the cyclized form of the *N*-terminal amino acid residue found in the antibiotic family of nikkomycins (**10**).[20] For example, *N*-dearylation of **9a** according to the Kronenthal procedure[21] and subsequent Boc introduction afforded **12** in 60% yield over the two steps. Ring opening of **12** with the corresponding Grignard reagent led to the β-amino ketone **13**. As expected by our previous work on racemic nikkomycin,[22] the L-Selectride reduction of **13** provided aminolactone **11** along with **14**. The latter, after chromatographic separation, was transformed into **11** in 76% overall yield. A comparative chiral HPLC analysis of **11** with the equivalent racemic compound, Figure 4, showed its enantiomeric purity, and the comparison of the optical rotation of **11** with the reported values confirmed its absolute configuration. The configuration of the β-lactam products was established by analogy and by assuming a uniform mechanism for the present three-component coupling reaction.[23]

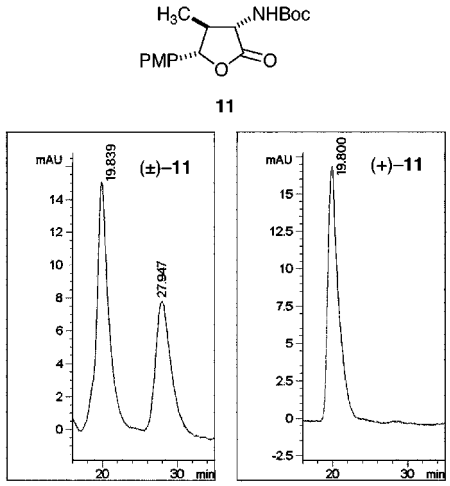

Figure 4. Enantiomeric excess determination by chiral stationary phase HPLC analysis for the aminolactone **11** by comparison with the racemic mixture (±)-**11**: column Chiralpak-AS 250 x 4.6 mm; eluant *i*-PrOH/hexanes 50/50. The enantiomeric purity of the β-lactams **9a**−**g** was determined in the same way by comparison with the corresponding racemic compounds (see ref 16).

In summary, the examples described here demonstrate that N-Selectride in combination with CuX_2·SMe_2 halides efficiently promote both conjugate reduction and enolate trapping with glyoxylate imines leading to important β-lactam intermediates with remarkable enantioselectivity.

Experimental Section

Melting points were determined with capillary apparatus and are uncorrected. ^{1}H NMR (300 MHz) spectra and ^{13}C NMR

(16) 4-*tert*-Butoxycarbonyl-β-lactams **8a**−**c** showed very deficient chromatographic peak resolution in comparison with β-lactams **9a**−**c**, which were prepared in their racemic form by the ketene−imine [2 + 2] cycloaddition reaction of the corresponding alkanoyl chlorides with the imine derived from *p*-anisidine and methyl glyoxylate, according to our previously reported procedure: Palomo, C.; Ontoria, J. M.; Odriozola, J. M.; Aizpurua, J. M.; Ganboa, I., *J. Chem. Soc., Chem. Commun*. **1990**, 248.

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(23) Another paper will deal with conjugate additions of carbon nucleophiles and enolate trapping with glyoxylate imines, see: Palomo, C.; Aizpurua, J. M.; Gracenea, J. J.; Garcia-Granda, S.; Pertierra, P. *Eur. J. Org. Chem*. **1998**, *2201*, 1.

spectra (75 MHz) were recorded at room temperature for $CDCl_3$ solutions, unless otherwise stated. All chemical shifts are reported as δ values (ppm) relative to, respectively, residual $CHCl_3$ δ_H (7.26 ppm) and $CDCl_3$ δ_C (77.0 ppm) as internal standards. Mass spectra were obtained with a mass spectrometer (70 eV), equipped with ion-trap, and using GC-MS coupling (column of fused silica, 15 m, 0.25 mm, 0.25 μm phase SPB-5). Optical rotations were measured at 25 ± 0.2 °C in methylene chloride unless otherwise stated. HPLC analyses were performed on a preparative column (25 cm, 3.0 cm, 7 μm phase Lichrosorb-Si60) with flow rates of 10 mL/min and using a UV detector (254 nm). Flash chromatography was performed on silica gel (230−400 mesh) using mixtures of ethyl acetate and hexane as eluants. Tetrahydrofuran was distilled over sodium and benzophenone (indicator). Methylene chloride was shaken with concentrated sulfuric acid, dried over potassium carbonate, and distilled. Commercially available compounds were used without further purification. The *N*-enoylsultams **6a**[24] and **6b**−**g**[25] were prepared by literature procedures. Nicotinic acid CrO_3 complex (NDC) was prepared as described.[26]

General Procedure for the Three-Component Synthesis of β-Lactams 8a−g. M-Selectride, 1 M in THF, (2.2 mL, 2.2 mmol) was dropped over a solution of $CuBr{\cdot}SMe_2$ (0.23 g, 1.1 mmol) and SMe_2 (1.4 mL) in THF kept under nitrogen at −78 °C, and the mixture was stirred for 30 min at the same temperature. A solution of *N*-enoylsultam **6** (1 mmol) in THF (4 mL) was added dropwise, and the mixture was stirred for 1 h at the same temperature. A solution of the imine **7** (0.47 g, 2 mmol) in THF (4 mL) was then added, and the mixture was allowed to reach room temperature during 16 h. After this time, the reaction mixture was diluted in CH_2Cl_2 (30 mL), washed with saturated NH_4Cl (3 × 30 mL), and dried over $MgSO_4$. Evaporation of the solvents yielded a crude containing cis and trans isomers from which the cis isomer was purified by column chromatography (230−400 mesh silica gel; eluant EtOAc/hexane 1/14). Analytical samples were obtained by crystallization from cyclohexane.

(3*S*,4*S*)-4-*tert*-Butoxycarbonyl-3-methyl-1-(4-methoxyphenyl)azetidin-2-one (8a). The general procedure was followed using N-Selectride, 1 M in THF, (2.2 mL, 2.2 mmol) and (1*S*)-*N*-(acryloyl)-2,10-camphorsultam (0.27 g, 1 mmol): yield: 0.16 g (55%); mp 94−95 °C (cyclohexane); $[\alpha]_D^{25} = -132.3$ (c = 1.0, CH_2Cl_2); IR (KBr, υ cm^{-1}) 1734 (C=O); MS (*m*/*z*, rel intensity) 291 (10.3), 235 (40.7), 163 (100.0), 134 (66.2); ^{1}H NMR ($CDCl_3$, δ ppm) 7.24 (d, 2H, J = 9.0 Hz), 6.85 (d, 2H, J = 9.0 Hz), 4.46 (d, 1H, J = 6.2 Hz), 3.78 (s, 3H), 3.63 (dq, 1H, J = 7.5, 6.2 Hz), 1.46 (s, 9H), 1.32 (d, 3H, J = 7.3 Hz); ^{13}C NMR ($CDCl_3$, δ ppm) 167.9, 166.3, 156.2, 131.2, 117.9, 114.3, 83.0, 56.2, 55.4, 47.6, 28.1. Anal. Calcd for $C_{16}H_{21}NO_4$ (291.35): C, 65.96; H, 7.26; N, 4.81. Found: C, 65.50; H, 6.43; N, 4.71.

(3*S*,4*S*)-4-*tert*-Butoxycarbonyl-3-ethyl-1-(4-methoxyphenyl)azetidin-2-one (8b). The general procedure was followed using N-Selectride, 1 M in THF, (2.2 mL, 2.2 mmol) and (1*S*)-*N*-crotyl-2,10-camphorsultam (0.28 g, 1 mmol): yield 2.1 g (70%); mp 74−76 °C (cyclohexane); $[\alpha]_D^{25} = -113.5$ (c = 1.0, CH_2Cl_2); IR (KBr, υ cm^{-1}) 1730, 1734 (C=O); MS (*m*/*z*, rel intensity) 222 (0.5), 149 (29.3), 134 (70.6), 57 (100.0); ^{1}H NMR ($CDCl_3$, δ ppm) 7.24 (d, 2H, J = 9.0 Hz), 6.86 (d, 2H, J = 9.0 Hz), 4.47 (d, 1H, J = 6 Hz), 3.78 (s, 3H), 3.46 (dt, 1H, J = 6.0, 8.0 Hz), 1.87−1.68 (m, 2H), 1.46 (s, 9H), 1.12 (t, 3H, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$, δ ppm) 168.0, 165.9, 156.1, 131.1, 117.8, 114.2, 82.8, 55.9, 55.4, 54.4, 27.9, 18.8, 12.1. Anal. Calcd. for $C_{17}H_{23}NO_4$ (305.37): C, 66.86; H, 7.59; N, 4.59. Found: C, 66.67; H, 8.18; N, 5.05.

(3*S*,4*S*)-3-Benzyl-4-*tert*-butoxycarbonyl-1-(4-methoxyphenyl)azetidin-2-one (8c). The general procedure was followed using N-Selectride, 1 M in THF, (2.2 mL, 2.2 mmol) and (1*S*)-*N*-cinamoyl-2,10-camphorsultam (0.35 g, 1 mmol): yield 0.15 g (40%); $[\alpha]_D^{25} = -72.0$ (c = 1.0, CH_2Cl_2); IR (KBr, υ cm^{-1}) 1751, 1728 (C=O); MS (*m*/*z*, rel intensity) 367 (2.0), 149 (16.8), 134 (100.0); ^{1}H NMR ($CDCl_3$, δ ppm) 7.36−7.19 (m, 7H, J = 9.0 Hz), 6.86 (d, 2H, J = 9.0 Hz), 4.55 (d, 1H, J = 6.0 Hz), 3.89 (dt, 1H, J = 8.2, 6.0 Hz), 3.78 (s, 3H), 3.24 (dd, 1H, J = 15.5, 7.4 Hz), 3.03 (dd, 1H, J = 15.5, 8.4 Hz), 1.46 (s, 9H); ^{13}C NMR ($CDCl_3$, δ ppm) 167.8, 165.1, 156.2, 137.8, 131.1, 128.7, 128.5, 126.6, 117.8, 114.3, 83.2, 56.2, 55.4, 52.9, 30.7, 27.8. Anal. Calcd. for $C_{22}H_{25}NO_4$ (367. 44): C, 71.91; H, 6.86; N, 3.81. Found: C, 71.60; H, 6.63; N, 3.73.

(3*S*,4*S*)-4-*tert*-Butoxycarbonyl-1-(4-methoxyphenyl)-3-*n*-propylazetidin-2-one (8d). The general procedure was followed using N-Selectride, 1 M in THF, (2.2 mL, 2.2 mmol) and (1*S*) *N*-(*E*)-pentenoyl-2,l0-camphorsultam (0.30 g, 1 mmol): yield 0.18 g (60%); mp 52−54 °C (EtOAc/hexane); $[\alpha]_D^{25} = -122.1$ (c = 0.7, CH_2Cl_2); IR (KBr, υ cm^{-1}) 1751 (C=O); MS(*m*/*z*, rel intensity) 134 (21.9), 162 (67.1), 263 (100.0), 319 (18.4); ^{1}H NMR ($CDCl_3$, δ ppm) 7.24 (d, 2H, J = 9.0 Hz), 6.85 (d, 2H, J = 9.0 Hz), 4.45 (d, 1H, J = 6.0 Hz), 3.78 (s, 3H), 3.51 (dt, 1H, J = 6.0, 7.4 Hz), l.90−1.42 (m, 4H), 1.46 (s, 9H), 1.32−1.28 (m, 4H), 0.89 (t, 3H, J = 6.4 Hz); ^{13}C NMR ($CDCl_3$, δ ppm) 168.0, 166.0, 156.1, 131.2, 117.8, 114.2, 82.9, 56.0, 55.5, 52.8, 28.0. 27.5, 20.8, 13.9. Anal. Calcd for $C_{18}H_{25}NO_4$ (319.40): C, 67.69; H, 7.89; N, 4.39. Found: C, 67.67; H, 8.02; N, 4.62.

(3*S*,4*S*)-4-*tert*-Butoxycarbonyl-1-(4-methoxyphenyl)-3-*n*-pentylazetidin-2-one (8e). The general procedure was followed using N-Selectride, 1 M in THF, (2.2 mL, 2.2 mmol) and (1*S*)-*N*-(*E*)-heptenoyl-2,10-camphorsultam (0.32 g, 1 mmol): yield 0.21 g (60%); mp 52−54 °C (EtOAc/hexane); $[\alpha]_D^{25} = -76.1$ (c = 0.7, CH_2Cl_2); IR (KBr, υ cm^{-1}) 1749, 1725 (C=O); MS(*m*/*z*, rel intensity) 347 (16.1), 291 (100.0), 219 (48.0); ^{1}H NMR ($CDCl_3$, δ ppm) 7.23 (d, 2H, J = 9.l Hz), 6.85 (d, 2H, J = 9.l Hz), 4.45 (d, 1H, J = 6.0 Hz), 3.78 (s, 3H), 3.52 (dt, 1H, J = 7.8, 6.0 Hz), 1.87−1.68 (m, 4H), 1.46 (s, 9H), 0.92 (t, 3H, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$, δ ppm) 168.0, 166.0, 156.1, 131.1, 117.8, 114.2, 82.9, 56.1, 55.4, 53.0, 31.7. 28.0, 27.2, 25.5, 22.4, 14.0. Anal. Calcd for $C_{20}H_{29}NO_4$ (347.45): C, 69.14; H, 8.41; N, 4.03. Found: C, 69.35; H, 8.35; N, 3.98.

(3*S*,4*S*)-4-*tert*-Butoxycarbonyl-1-(4-methoxyphenyl)-3-[(4-methylphenyl)methyl]azetidin-2-one (8f). The general procedure was followed using N-Selectride, 1 M in THF, (2.2 mL, 2.2 mmol) and (1*S*)-*N*-(*p*-methylcinamoyl)-2,10-canphorsultam (0.36 g, 1 mmol); yield 0.21 g (55%); $[\alpha]_D^{25} = -64.0$ (c = 1.0, CH_2Cl_2); IR (KBr, υ cm^{-1}) 1751, 1734 (C=O); ^{1}H NMR ($CDCl_3$, δ ppm) 7.25 (d, 2H, J = 9.0 Hz), 7.17 (d, 2H, J = 6.3 Hz), 7.12 (d, 2H, J = 6.3 Hz), 6.86 (d, 2H, J = 9.0 Hz), 4.53 (d, 1H, J = 6.0 Hz), 3.85 (dt, 1H, J = 7.9, 6.0 Hz), 3.78 (s, 3H), 3.18 (dd, 1H, J = 15.0, 7.3 Hz), 2.98 (dd, 1H, J = 15.0, 8.2 Hz), 2.32 (s, 3H), 1.38 (s, 9H); ^{13}C NMR ($CDCl_3$, δ ppm) 167.9, 165.2, 156.2, 136.1, 134.7, 131.1, 129.2, 128.4, 117.8, 114.3, 83.2, 56.3, 55.5, 53.2, 30.4, 27.9, 21.0. Anal. Calcd for $C_{23}H_{27}NO_4$ (381.46): C, 72.42; H, 7.13; N, 3.67. Found: C, 72.32; H, 7.15; N, 3.71.

(3*S*,4*S*)-4-*tert*-Butoxycarbonyl-1-(4-methoxyphenyl)-3-[(4-methoxyphenyl)methyl]azetidin-2-one (8g). The general procedure was followed using N-Selectride, 1 M in THF, (2.2 mL, 2.2 mmol) and (1*S*)-*N*-(4-methoxycinamoyl)-2,10-camphorsultam (0.38 g, 1 mmol): yield 0.2 g (50%); mp 110−112 °C (cyclohexane); $[\alpha]_D^{25} = -80.2$ (c = 1.0, CH_2Cl_2); IR (KBr, υ cm^{-1}) 1756, 1735 (C=O). ^{1}H NMR ($CDCl_3$, δ ppm) 7.26 (m, 2H, J = 9.0 Hz), 7.22 (m, 2H, J = 9.0 Hz), 6.87 (d, 4H, J = 9.0 Hz), 4.54 (d, 1H, J = 6.0 Hz), 3.84 (dt, 1H, J = 7.9, 6.0 Hz), 3.80 (s, 3H), 3.78 (s, 3H), 3.16 (dd, 1H, J = 15.2, 7.8 Hz), 2.96 (dd, 1H, J = 15.2, 7.9 Hz), 1.40 (s, 9H); ^{13}C NMR ($CDCl_3$, δ ppm) 167.9, 165.2, 158.2, 156.2, 129.8, 129.5, 117.7, 114.3, 114.0, 113.8, 83.1, 56.2, 55.4, 53.3, 30.0, 27.9. Anal. Calcd for $C_{23}H_{27}NO_5$ (397.46): C, 69.50; H, 6.85; N, 3.52. Found: C, 69.42; H, 6.77; N, 3.63.

Typical Procedure for the Synthesis of β-Lactams 9a−g. A solution of β-lactam (1.0 mmol) in CH_2Cl_2 (15 mL) was treated with trifluoroacetic acid (2.97 mL, 40 mmol) at room temperature for 4 h. The organic layer was washed with water (4 × 15 mL) and dried over $MgSO_4$, and the solvents were evaporated. To the resulting crude material was added Et_2O (5 mL), and the resulting mixture was treated with a solution of 0.6−0.7 M CH_2N_2 in Et_2O (8.0 mL, 5.0 mmol). The Et_2O was evaporated, and the resulting crude material was purified by column chromatography (230−400 mesh silica gel; eluant EtOAc/hexane 1:14).

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(3*S*,4*S*)-3-Methyl-4-(methoxycarbonyl)-1-(4-methoxyphenyl)azetidin-2-one (9a). The general procedure was followed using **6a** (0.29 g, 1 mmol): yield 0.21 g (85%); mp 80−82 °C (cyclohexane); $[\alpha]_D^{25} = -175.6$ (c = 1.0, CH_2Cl_2); IR (KBr, υ cm^{-1}) 1746 (C=O); MS(*m*/*z*, rel intensity) 249 (11.5), 149 (27.9), 134 (100.0); ^{1}H NMR ($CDCl_3$, δ ppm) 7.25 (d, 2H, J = 9.1 Hz), 6.89 (d, 2H, J = 9.1 Hz), 4.61 (d, 1H, J = 6.1 Hz), 3.80 (s, 3H), 3.78 (s, 3H), 3.67 (dq, 1H, J = 6.1, 7.6 Hz), 1.28 (d, 3H, J = 7.6 Hz); ^{13}C NMR ($CDCl_3$, δ ppm) 167.8, 165.1, 156.2, 137.8, 131.1, 128.7, 128.5, 126.6, 117.8, 114.3, 83.2, 56.2, 55.4, 52.9, 30.7, 27.8. Anal. Calcd for $C_{13}H_{15}NO_4$ (249.27): C, 62.64; H, 6.07; N, 5.62. Found: C, 63.01; H, 6.32; N 5.75.

(3*S*,4*S*)-3-Ethyl-4-(methoxycarbonyl)-1-(4-methoxyphenyl)azetidin-2-one (9b). The general procedure was followed using **6b** (0.37 g, 1 mmol): yield 0.19 g (73%); mp 102−104 °C (cyclohexane); $[\alpha]_D^{25} = -136.3$ (c = 1.0, CH_2Cl_2); IR (KBr, υ cm^{-1}) 1732 (C=O); MS(*m*/*z*, rel intensity) 263 (16.3), 149 (44.6), 134 (100.0); ^{1}H NMR ($CDCl_3$, δ ppm) 1.11 (d, 3H, J = 6.8 Hz), 1.56−1.98 (m, 2H), 3.54 (dt, 1H, J = 6.0, 8.0 Hz), 3.81 (s, 3H), 3.83 (s, 3H), 4.63 (d, 1H, J = 6.0 Hz), 6.89 (d, 2H, J = 9.0 Hz), 7.26 (d, 2H, J = 9.0 Hz); ^{13}C NMR ($CDCl_3$, δ ppm) 169.5, 165.6, 156.2, 131.0, 117.8, 114.4, 55.5, 55.3, 54.7, 52.4, 19.0. Anal. Calcd for $C_{14}H_{17}NO_4$ (263.29): C, 63.87; H, 6.51; N, 5.32. Found: C, 63.50; H, 6.60; N, 5.23.

(3*S*,4*S*)-3-Benzyl-4-(methoxycarbonyl)-1-(4-methoxyphenyl)azetidin-2-one (9c). The general procedure was followed using **6c** (0.30 g, 1 mmol): yield 0.29 g (90%); mp 112−114 °C (cyclohexane); $[\alpha]_D^{25} = -63.3$ (c = 1.0, CH_2Cl_2); IR (KBr, υ cm^{-1}) 1736, 1727 (C=O); MS(*m*/*z*, rel intensity) 325 (22.7), 149 (59.3), 134 (100.0); ^{1}H NMR ($CDCl_3$, δ ppm) 2.96 (dd, 1H, J = 9.3, 15.0 Hz), 3.25 (dd, 1H, J = 6.8, 15.0 Hz), 3.65 (s, 3H), 3.78 (s, 3H), 3.96 (dt, 1H, J = 6.6, 9.2 Hz), 4.60 (d, 1H, J = 6.0 Hz), 6.86 (d, 2H, J = 9.0 Hz), 7.22−7.34 (m, 7H); ^{13}C NMR ($CDCl_3$, δ ppm) 169.1, 164.7, 156.2, 137.2, 130.7, 128.7, 128.4, 126.5, 117.6, 114.2, 55.2, 54.9, 53.4, 52.2, 30.8. Anal. Calcd for $C_{19}H_{19}NO_4$ (325.36): C, 70.14; H, 5.89; N, 4.31. Found: C, 69.80; H, 6.01; N, 4.33.

(3*S*,4*S*)-4-(Methoxycarbonyl)-1-(4-methoxyphenyl)-3-*n*-propylazetidin-2-one (9d). The general procedure was followed using **8d** (0.35 g, 1 mmol): yield 0.22 g (80%); mp 84−86 °C (cyclohexane); $[\alpha]_D^{25} = -148.7$ (c = 1.0, CH_2Cl_2); IR (KBr, υ cm^{-1}) 1748 (C=O), 1734 (C=O); ^{1}H NMR ($CDCl_3$, δ ppm) 0.96 (t, 3H, J = 6.8 Hz), 1.42−1.80 (m, 4H), 3.58 (dt, 1H, J = 6.0, 7.4 Hz), 3.79 (s, 3H), 3.80 (s, 3H, OMe), 4.60 (d, 1H, J = 6.0 Hz), 6.86 (d, 2H, J = 9.0 Hz), 7.24 (d, 2H, J = 9.0 Hz); ^{13}C NMR ($CDCl_3$, δ ppm) 13.9, 20.6, 27.5, 52.4, 53.0, 53.4, 55.4, 55.5, 114.4, 117.8, 131.0, 156.2, 165.8, 169.6; MS (*m*/*z*, % intensity) 277 (8.4), 149 (34.8), 134 (l00.0). Anal. Calcd for $C_{15}H_{19}NO_4$ (277.33): C, 64.97; H, 6.91; N, 5.05. Found: C, 65.07; H, 6.60; N, 5.13.

(3*S*,4*S*)-4-(Methoxycarbonyl)-1-(4-methoxyphenyl)-3-*n*-pentylazetidin-2-one (9e). The general procedure was followed using **8e** (0.37 g, 1 mmol): yield 0.21 g (73%); mp 50−52 °C (cyclohexane); $[\alpha]_D^{25} = -110.9$ (c = 1.0, CH_2Cl_2); IR (KBr, υ cm^{-1}) 1738 (C=O), 1728 (C=O); ^{1}H NMR ($CDCl_3$, δ ppm) 0.88 (t, 3H, J = 6.4 Hz), 1.24−1.77 (m, 8H), 3.55 (dd, 1H, J = 6.0, 7.9 Hz), 3.76 (s, 3H), 3.78 (s, 3H), 4.58 (d, 1H, J = 6.0 Hz), 6.84 (d, 2H, J = 9.0 Hz), 7.21 (d, 2H, J = 9.0 Hz); ^{13}C NMR ($CDCl_3$, δ ppm) 13.9, 22.3, 25.4, 26.9, 31.6, 52.3, 53.1, 55.3, 55.4, 114.3, 117.7, 130.9, 156.2, 165.7, 169.5; MS (*m*/*z*, % intensity) 305 (7.2), 149 (39.1), 134 (l00.0). Anal. Calcd for $C_{17}H_{23}NO_4$ (305.37): C, 66.86; H, 7.59; N, 4.59. Found: C, 65.07; H, 6.60; N, 5.13.

(3*S*,4*S*)-3-[(4-Methylphenyl)methyl]-4-(methoxycarbonyl)-1-(4-methoxyphenyl)azetidin-2-one (9f). The general procedure was followed using **8f** (0.38 g, 1 mmol): yield 0.23 g (88%); mp 94−96 °C (cyclohexane); $[\alpha]_D^{25} = -53.4$ (c = 1.0, CH_2Cl_2); IR (KBr, υ cm^{-1}) 1736, 1727 (C=O); MS (*m*/*z*, % intensity) 339 (87.8), 311 (40.5), 252 (100.0), 134 (35.2); ^{1}H NMR ($CDCl_3$, δ ppm) 2.32 (s, 3H), 2.90 (dd, 1H, J = 9.3, 15.0 Hz), 3.19 (dd, 1H, J = 6.9, 15.0 Hz), 3.66 (s, 3H), 3.77 (s, 3H), 3.92 (dt,1H,J = 6.0, 9.2 Hz), 4.59 (d, 1H, J = 6.0 Hz), 6.85 (d, 2H, J = 9.0 Hz), 7.11 (s_b, 5H), 7.23 (d, 2H, J = 9.0 Hz); ^{13}C NMR ($CDCl_3$, δ ppm) 169.3, 165.0, 156.4, 136.3, 134.3, 130.8, 129.2, 128.4, 117.8, 114.4, 55.5, 55.2, 53.9, 52.4, 30.6, 21.0. Anal. Calcd for $C_{20}H_{21}NO_4$ (339.15): C, 70.78; H, 6.24; N, 4.13. Found: C, 70.75; H, 6.11; N, 4.23.

(3*S*,4*S*)-3-[(4-Methoxyphenyl)methyl]-4-(methoxycarbonyl)-1-(4-methoxyphenyl)azetidin-2-one (9g). The general procedure was followed using **8g** (0.40 g, 1 mmol): yield 0.32 g (91%); mp 172−174 °C (cyclohexane); $[\alpha]_D^{25} = -41.2$ (c = 1.0, CH_2Cl_2); IR (KBr, υ cm^{-1}) 1736, 1727 (C=O); MS(*m*/*z*, % int.) 355 (73.1), 327 (29.9), 268 (100.0), 193 (7.82), 134 (27.6); ^{1}H NMR ($CDCl_3$, δ ppm) 7.19 (d, 2H, J = 9.0 Hz), 7.15 (d, 2H, J = 9.0 Hz), 6.85 (d, 2H, J = 9.0 Hz), 6.84 (d, 2H, J = 9.0 Hz), 4.58 (d, 1H, J = 5.9 Hz), 3.84 (dt,1H,J = 5.9, 7.1 Hz), 3.78 (s, 3H), 3.77 (s, 3H), 3.67 (s, 3H), 3.16 (dd, 1H, J = 7.1, 15.0 Hz), 2.88 (dd, 1H, J = 9.0, 15.0 Hz); ^{13}C NMR ($CDCl_3$, δ ppm) 169.3, 165.0, 158.3, 156.4, 130.8, 129.5, 128.8, 117.8, 114.4, 113.9, 55.4, 55.2, 53.9, 52.4, 30.2. Anal. Calcd for $C_{20}H_{21}NO_5$ (355.14): C, 67.59; H, 5.96; N, 3.94. Found: C, 69.80; H, 6.01; N, 4.33.

(3*S*,4*S*)-1-(*tert*-Butoxycarbonyl)-3-methyl-4-(methoxycarbonyl)azetidin-2-one (12). A solution of $(NH_4)_2Ce(NO_3)_6$ (16.4 g, 30 mmol) in water (120 mL) was added dropwise to a solution of the β-lactam **9a** (2,49 g, 10 mmol) in acetonitrile (125 mL) at −10 °C. The mixture was stirred at this temperature for 30 min. Water (400 mL) was then added, and this mixture was treated again with EtOAc (3 × 150 mL) and washed with a saturated solution of $NaHCO_3$ (350 mL). The aqueous layer of $NaHCO_3$ was extracted again with EtOAc (60 mL), and the combined organic layers were washed with $NaHSO_3$ (40%) (4 × 300 mL) and saturated solutions of $NaHCO_3$ (70 mL) and NaCl (70 mL). The organic layer was dried over $MgSO_4$, and the solvents were removed in vacuo. The crude β-lactam was dissolved in acetonitrile (10 mL) and di-*tert*-butyl dicarbonate (1.4 mL, 10 mmol) and DMAP (0.12 g, 1.0 mmol) were added, and the reaction was stirred for 16 h. The organic layer was diluted in CH_2Cl_2 (25 mL) and washed with HCl (25 mL) and $NaHCO_3$ (10 mL), and the solvents were evaporated. The resulting crude was purified by column chromatography (230−400 mesh silica gel; eluant EtOAc/hexane 1:10): yield 1.46 g (60%); colorless oil; $[\alpha]_D^{25} = -95.3$ (c = 1.0, CH_2Cl_2); IR (KBr, υ cm^{-1}) 1808, 1743, 1723 (C=O); MS(*m*/*z*, rel intensity) 187 (10.8), 142 (57.5), 100 (77.0), 57 (100.0); ^{1}H NMR ($CDCl_3$, δ ppm) 4.50 (d, 1H, J = 6.8 Hz), 3.80 (s, 3H), 3.54 (m, 1H), 1.50 (s, 9H), 1.20 (d, 3H, J = 7.6 Hz); ^{13}C NMR ($CDCl_3$, δ ppm) 168.3, 165.9, 54.7, 52.3, 47.3, 27.8, 9.0.

(2*S*,3*S*)-Methyl 2-(*tert*-Butoxycarbonylamino)-4-(4-methoxyphenyl)-3-methyl-4-oxobutanoate (13). Over a solution of **12** (0.24 g, 1.0 mmol) in THF (3 mL) a solution of 4-methoxyphenylmagnesium bromide 1 M in THF (1.3 mL, 1.3 mmol) was added at −78 °C. The reaction mixture was stirred at −40 °C for 1 h, and the reaction was quenched at this temperature with a saturated solution of NH_4Cl. The organic layer was stracted with CH_2Cl_2 (10 mL) and dried over $MgSO_4$, and the solvents were evaporated. The crude was purified by column chromatography (230−400 mesh silica gel; eluant EtOAc/hexane 1:5): yield 0.26 g (75%); colorless oil; $[\alpha]_D^{25} = +15.7$ (c = 0.75, CH_2Cl_2); IR (KBr, υ cm^{-1}) 3335 (NH), 1735, 1708 (C=O); MS (*m*/*z*, rel intensity) 295 (2.7), 136 (9.2), 135 (100.0); ^{1}H NMR ($CDCl_3$, δ ppm) 7.96 (d, 2H, J = 9.0 Hz), 6.95 (d, 2H, J = 9.0 Hz), 5.31 (d, 1H, J = 8.1 Hz), 4.59 (dd, 1H, J = 5.9, 8.3 Hz), 4.07 (m, 1H), 3.87 (s, 3H), 3.74 (s, 3H), 1.42 (s, 9H), 1.28 (d, 3H, J = 7.3 Hz); ^{13}C NMR ($CDCl_3$, δ ppm) 199.3, 171.7, 163.6, 155.2, 130.6, 113.8, 79.9, 55.6, 55.4, 52.3, 42.7, 28.1, 13.8.

(2*S*,3*S*,4*R*)-2-(*tert*-Butoxycarbonylamino)-3-methyl-4-(4-methoxyphenyl)butyrolactone (11). To solution of **13** (0.35 g, 1.0 mmol) in THF (6 mL) at −78 °C a solution of L-Selectride, 1 M in THF, was added, and the reaction mixture was stirred for 1 h at the same temperature. The reaction was then quenched with a saturated solution of NH_4Cl (6 mL), extracted with Et_2O (15 mL), and filtered through Celite to give an organic solution which was dried over $MgSO_4$ and evaporated in vacuo to afford a 63:37 mixture of **11** and **14** as a colorless oil. Separation by column chromatography (230−400 mesh silica gel; eluant EtOAc/hexane 1:10 and then 1:5) gave compounds **11** and **14.** A solution of **14** (89 mg, 0.28 mmol) in toluene (0.5 mL) was added to a suspension of NDC (320 mg, 0.70 mmol) and pyridine (0.45 mL, 5.57 mmol) in the same solvent (1 mL), and the mixture was stirred at room temperature for 4 h. Afterward, the suspension was filtered through a pad of silica gel, and the organic solution was washed with 6 N HCl (1 mL) and $NaHCO_3$ (1 mL), dried over $MgSO_4$, and evaporated to give **11** as a viscous oil. Yield from **14**: 074 mg (83%). Overall yield of **11**: 0.23 g (73%). $[\alpha]_D^{25} = +20.1$ (c = 0.8, $CDCl_3$); lit[18b] $[\alpha]_D^{25} = +20.1$ (c =

0.82, $CDCl_3$); lit[18g] $[\alpha]_D^{25} = +20.6$ ($c = 1.17$, $CDCl_3$). IR (KBr, υ cm^{-1}): 1781, 1707 (C═O). MS (*m*/*z*, rel intensity): 321 (1.1), 176 (36.4), 160 (100.0), 135 (48.1). ^1H NMR ($CDCl_3$, δ ppm): 7.28 (d, 2H), 6.92 (d, 2H), 5.10 (d, 1H, $J = 7.6$ Hz), 4.83 (d, 1H, $J = 10.3$ Hz), 4.26 (dd, 1H, $J = 11.5$, 7.6 Hz), 3.82 (s, 3H), 2.34 (m, 1H), 1.47 (s, 9H), 1.17 (d, 3H, $J = 6.4$ Hz). ^{13}C NMR ($CDCl_3$, δ ppm): 174.2, 160.2, 155.5, 136.0, 128.1, 114.1, 84.7, 80.5, 57.9, 55.3, 46.8, 28.2, 13.6.

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