Catalytic, Asymmetric Synthesis of the Carbacephem Framework

Peter R. Guzzo and Marvin J. Miller*

Department of Chemistry and Biochemistry, University of Notre Dame, Notre Dame, Indiana 46556

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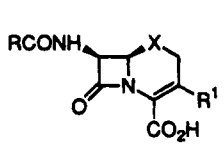
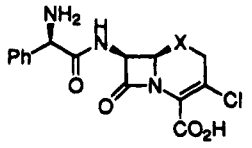
A catalytic, asymmetric synthesis of the carbacephem β-lactam framework is reported. The initial asymmetric center was established by catalytic hydrogenation of β-keto ester **12** with (*S*)-Ru-BINAP. The β-lactam ring was prepared using the hydroxamate approach (**14** → **15**). The nitrogen substituent at C7 was introduced by the nucleophile transfer reaction (**15** → **17**), and the six-membered ring of the carbacephem was prepared by a directed Dieckmann condensation (**24** → **25**).

Introduction

After 50 years, β-lactam antibiotics are still among the most beneficial compounds for the treatment of often otherwise fatal infections. However, the developed resistance by bacteria to β-lactam antibiotics has motivated the scientific community to seek solutions to this daunting problem. In an ongoing search for new and better antibiotics, the carbacephem β-lactam nucleus **1**, a carbon analog of the most widely used cephalosporin class of antibiotics **2**, was first introduced in 1974.[1] In 1992, Lorabid (**3**), the first in the new class of carbacephem antibiotics, received FDA approval for marketing. Interestingly, Lorabid (**3**) possesses a spectrum of biological activity similar to Ceclor (**4**), the largest selling oral antibiotic, but is substantially superior in chemical stability.[2] Thus, there is considerable potential for designing new and more reactive carbacephems with potent antibacterial activity that have no parallel cephalosporin derivative.[3]

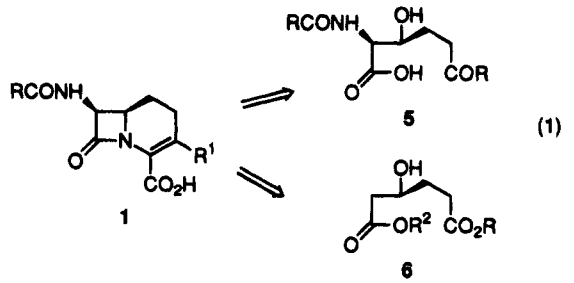


1 carbacephem X = CH_2
2 cephalosporin X = S



3 Lorabid X = CH_2
4 Ceclor X = S

The carbacephem nucleus has been the target of much synthetic effort, although the development of practical syntheses for pharmaceutical application is still of considerable interest.[4] A previous publication from our laboratory described a short, diastereoselective synthesis of the carbacephem framework from a key β-hydroxy-α-amino acid derivative **5** (equiv 1).[5] In addition, a new



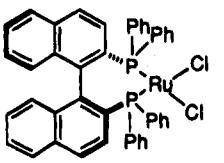
(1)

1 **5** **6**

method for the synthesis of a carbacephem precursor was developed from key intermediate β-hydroxy ester **6**.[6] Described herein is the first catalytic, asymmetric synthesis of this important ring system from a simple β-hydroxy acid derivative **6**.

Results and Discussion

Optically active β-lactams can be prepared from chiral β-hydroxy acid derivatives utilizing the hydroxamate approach developed in our laboratories.[7] In the realm of burgeoning asymmetric reactions, the BINAP chiral catalysts (e.g., **7**) are now well established for catalyzing



S-Ru-BINAP
7

several synthetic transformations with high enantioselectivity.[8] The high enantioselectivity and the remarkable substrate to catalyst ratios observed with Ru-BINAP in the asymmetric hydrogenation of β-keto esters was particularly encouraging for developing an efficient route to the carbacephems and β-lactam derivatives in general.[9] The Ru-BINAP-catalyzed asymmetric reduction has been

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(1) Guthikonda, R. N.; Cama, L. D.; Christensen, B. G. *J. Am. Chem. Soc.* **1974**, *96*, 7584.

(2) (a) Matsukuma, I.; Yoshiiye, S.; Mochida, K.; Hashimoto, Y.; Sato, K.; Okachi, R.; Hirata, T. *Chem. Pharm. Bull.* **1989**, *37*, 1239. (b) Blaszczak, L. C.; Brown, R. F.; Cook, G. K.; Hornback, W. J.; Hoying, R. C.; Indelicato, J. M.; Jordan, C. L.; Katner, A. S.; Kinnick, M. D.; McDonald, J. H., III; Morin, J. M., Jr.; Munroe, J. E.; Pasini, C. E. *J. Med. Chem.* **1990**, *33*, 1656. (c) Howard, A. J.; Dunkin, K. T. *J. Antimicrob. Chemother.* **1988**, *22*, 445. (d) Mochida, K.; Ogasa, T.; Shimada, J.; Hirata, T.; Sato, K.; Okachi, R. *J. Antibiot.* **1989**, *42*, 283. (e) Sato, K.; Okachi, R.; Matsukuma, I.; Mochida, K.; Hirata, T. *J. Antibiot.* **1989**, *42*, 1844. (f) Pasini, C. E.; Indelicato, J. M. *Pharm. Res.* **1992**, *9*, 250.

(3) Cooper, R. D. G. In *The Chemistry of Beta-Lactams*; Page, M. I., Ed.; Chapman & Hall: London, 1992; p 272–305.

(4) (a) Deeter, J. B.; Hall, D. A.; Jordan, C. L.; Justice, R. M.; Kinnick, M. D.; Morin, J. M., Jr.; Paschal, J. W.; Ternansky, R. J. *Tetrahedron Lett.* **1993**, *34*, 3051. (b) Frazier, J. W.; Staszak, M. A.; Weigel, L. O. *Tetrahedron Lett.* **1992**, *33*, 857. (c) For a review of synthetic methods see ref 3.

(5) Lotz, B. T.; Miller, M. J. *J. Org. Chem.* **1993**, *58*, 618.

(6) Teng, M.; Gasparski, C. M.; Williams, M. A.; Miller, M. J. *BioMed. Chem. Lett.* **1993**, *3*, 2431.

(7) Miller, M. J. *Acc. Chem. Res.* **1986**, *19*, 49.

(8) (a) Noyori, R.; Takaya, H. *Acc. Chem. Res.* **1990**, *23*, 345. (b) Noyori, R. *Science* **1990**, *248*, 1194.

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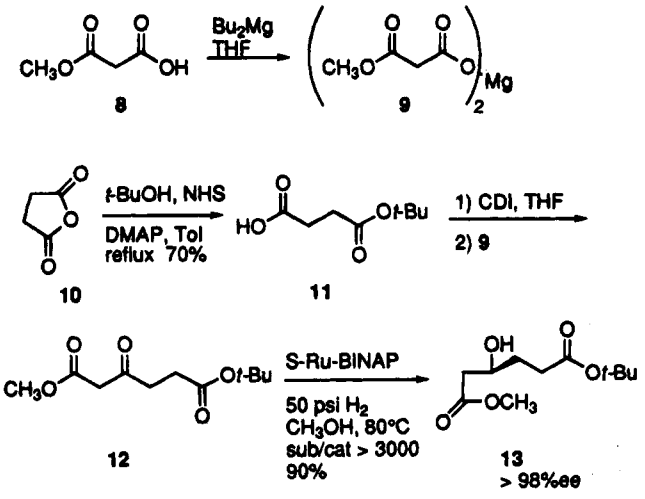
Scheme 1



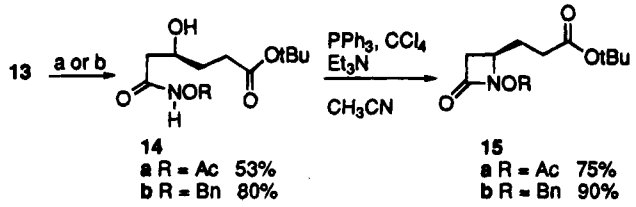
used to make the α-hydroxyethyl side chain of a key intermediate for the synthesis of thienamycin and other biologically active β-lactams.[9d-f]

The differentiated β-keto diester **12**, which contains six of the eight carbons of the carbacephem framework, was prepared to test the Ru-BINAP methodology (Scheme 1). Refluxing succinic anhydride **10**, *t*-BuOH, and catalytic amounts of DMAP and *N*-hydroxysuccinimide in toluene provided mono *tert*-butyl ester **11**. The magnesium salt **9** from acid **8**[10] was prepared as an acetate anion equivalent. Activation of acid **11** with carbonyldiimidazole and addition of magnesium salt **9**, according to literature precedent, gave β-keto ester **12**.[11]

The (*S*)-Ru-BINAP catalyst was prepared from commercially available (*S*)-BINAP and $(RuCl_2$·cyclooctadiene$)_n$ according to precedent.[12] The crude catalyst smoothly reduced β-keto ester **12** to afford β-hydroxy ester **13** under the routinely accessible conditions of 50 psi of hydrogen and 80 °C. Enantiomeric excesses were generally 98% or better, and substrate to catalyst ratios greater than 3000 could be obtained without any observable loss of enantioselectivity. The enantioselectivity of the reduction could be accurately measured by integration of the *tert*-butyl ester resonance in the ^{1}H NMR spectrum in the presence of the chiral shift reagent Eu(hfc)$_3$.[13] The (*S*) absolute configuration shown for β-hydroxy ester **12** is based upon considerable precedent.[8a,12] Interestingly, if temperatures greater than 100 °C were used a loss of enantioselectivity was observed.

β-Hydroxy ester **13** was transformed into crystalline hydroxamates **14a,b** by two different procedures. Hydroxaminolysis of **13** followed by acetylation provided hydroxamate **14a** after an aqueous extractive workup.[14] Alternatively, hydroxamate **14b** was prepared in higher yield by treatment with *O*-benzylhydroxylamine·HCl in the presence of a stoichiometric amount of Me_3Al catalyst without coincident elimination of the β-hydroxyl group.[15] Several other procedures for preparing hydroxamate **14b** directly from methyl ester **13** and *O*-benzylhydroxylamine were unsuccessful. Both hydroxamates **14a,b** were cyclized to the corresponding β-lactams **15a,b** using triphenylphosphine and carbon tetrachloride in the presence of triethylamine.[14,16] The lower yield of β-lactam **15a** probably reflects the lability of the acetate group upon column chromatography.

Scheme 2



conditions a: 1) NH_2OH·HCl, 2eq. KOH, CH_3OH 2) Ac_2O
conditions b: HCl·H_2NOBn, $(CH_3)_3Al$, CH_2Cl_2

Having set the absolute stereochemistry at C4 of the β-lactam, a nitrogen substituent was still needed at the C3 position. A mild and general reaction was recently discovered in this laboratory for the introduction of nucleophiles to the α-position of β-lactams utilizing the additional reactive NO functionality.[17] Both β-lactams **15a,b** were transformed to azido β-lactam **17** utilizing the "nucleophile transfer reaction". A one-pot reaction was developed for transforming β-lactam **15a** to azido β-lactam **17**. The acetate of **15a** was easily removed by base hydrolysis, and the intermediate *N*-hydroxy-β-lactam was immediately carried on due to known rearrangements of this type of compound.[18] Reaction with 1 equiv of tosylazide[19] and 2 equiv of triethylamine provided for moderate yields (30%) of azido β-lactam **17**. The addition of 0.5 equiv of $TMSN_3$ to the same reaction increased the yield of the reaction to 58% for the overall transformation of **15a** to **17** accomplishing acetate removal, diastereoselective azide introduction, and N—O bond reduction in one pot.

The overall conversion from **15b** to **17** could also be carried out stepwise. The benzyl group of **15b** was removed by hydrogenolysis, and the intermediate *N*-hydroxy-β-lactam was converted to tosylate derivative **16** which could be isolated after chromatography and characterized. The azide substituent was introduced by

(9) (a) Noyori, R.; Ohkuma, T.; Kitamura, M.; Takaya, H.; Sayo, N.; Kumobayashi, H.; Akutagawa, S. *J. Am. Chem. Soc.* **1987**, *109*, 5856. (b) Kitamura, M.; Tokunaga, M.; Ohkuma, T.; Noyori, R. *Org. Synth.* **1992**, *71*, 1. (c) A recent report from a Merck process group demonstrated substrate/catalyst ratios of up to 10 000 in a standard Parr Shaker at 40 °C/30 psi with the presence of trace amounts of strong acid. King, S. A.; Thompson, A. S.; King, A. O.; Verhoeven, T. R. *J. Org. Chem.* **1992**, *57*, 6689. (d) Kitamura, M.; Tokunaga, M.; Noyori, R. *J. Am. Chem. Soc.* **1993**, *115*, 144. (e) Noyori, R.; Ikeda, T.; Ohkuma, T.; Widhalm, M.; Kitamura, M.; Takaya, H.; Akutagawa, S.; Sayo, N.; Saito, T.; Taketomi, T.; Kumobayashi, H. *J. Am. Chem. Soc.* **1989**, *111*, 9134. (f) Murahashi, S.; Naota, T.; Kuwabara, T.; Saito, T.; Kumobayashi, H.; Akutagawa, S. *J. Am. Chem. Soc.* **1990**, *112*, 7820.

(10) Hutchinson, C. R.; Nakane, M.; Gollman, H.; Knutson, P. L. *Organic Syntheses;* Wiley: New York, 1990; Collect. Vol. VII, p 323.

(11) (a) Brooks, D. W.; de Lee, N. C.; Peevey, R. *Tetrahedron Lett.* **1984**, *25*, 4623. (b) Brooks, D. W.; Lu, L. D.; Masamune, S. *Angew. Chem., Int. Ed. Engl.* **1979**, 72.

(12) Taber, D. F.; Silverberg, L. J. *Tetrahedron Lett.* **1991**, *32*, 4227.

(13) Fraser, R. R. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1983; p 173.

(14) Miller, M. J.; Biswas, A.; Krook, M. A. *Tetrahedron* **1983**, *39*, 2571.

(15) (a) Basha, A.; Lipton, M.; Weinreb, S. M. *Tetrahedron Lett.* **1977**, 4171. (b) Lipton, M. F.; Basha, A.; Weinreb, S. M. *Organic Syntheses;* Wiley: New York, 1988; Collect. Vol. VI, p 492. (c) Levin, J. I.; Turos, E.; Weinreb, S. M. *Synth. Commun.* **1982**, *12*, 989.

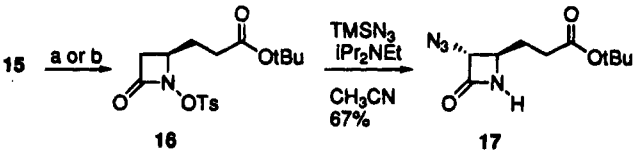
(16) For a review of the Mitsunobu reaction see: Hughes, D. L. *Org. React.* **1992**, *42*, 335.

(17) (a) Gasparski, C. M.; Teng, M.; Miller, M. J. *J. Am. Chem. Soc.* **1992**, *114*, 2741. (b) Teng, M.; Miller, M. J. *J. Am. Chem. Soc.* **1993**, *115*, 548.

(18) (a) Hirose, T.; Chiba, K.; Mishio, S.; Nakano, J.; Uno, H. *Heterocycles* **1982**, *19*, 1019. (b) Baldwin, J. E.; Adlington, R. M.; Birch, D. J. *Tetrahedron Lett.* **1985**, *26*, 5931. (c) Baldwin, J. E.; Adlington, R. M.; Birch, D. J. *J. Chem. Soc., Chem. Commun.* **1985**, 256. (d) Zercher, C. K.; Miller, M. J. *Tetrahedron Lett.* **1989**, *30*, 7009.

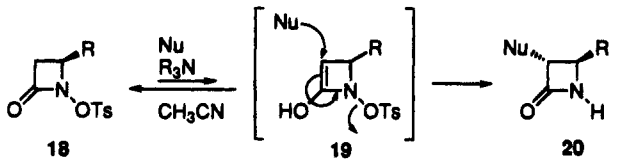
(19) Regitz, M.; Hocker, J.; Liedhegener, A. *Organic Syntheses;* Wiley: New York, 1973; Collect. Vol. V, p 179.

Scheme 3



[a] Conditions: (a) one-pot reaction to **17** from **15a**, (1) Na_2CO_3, CH_3OH; HCl, (2) TsN_3, Et_3N, $TMSN_3$, CH_3CN, 58%; (b) (1) Pd/C, H_2, CH_3OH; (2) TsCl, Et_3N, CH_2Cl_2 96%.

Scheme 4

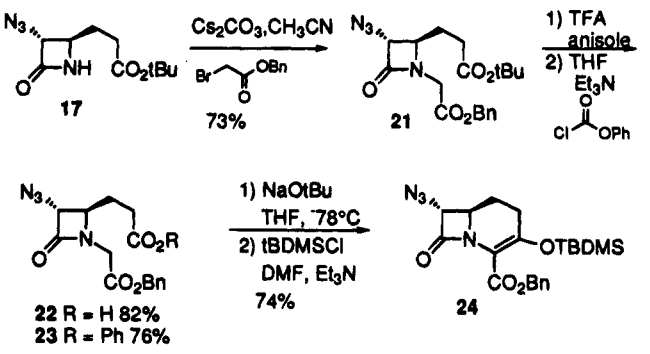


treatment of activated β-lactam **16** with $(iPr)_2NEt$ and $TMSN_3$ in CH_3CN to provide **17** in 67% yield following chromatographic purification.

Although other mechanisms have not been rigorously excluded, the mechanism for addition of nucleophiles to the α-position of *N*-(tosyloxy)-β-lactams is believed to proceed through an S_N2' addition of appropriate nucleophiles to enol **19** providing β-lactams **20** with predominantly *trans* stereochemistry. Due to the generality of the Ru-BINAP methodology and the nucleophile transfer reaction, the methodology described here offers tremendous potential for the synthesis of a variety of β-lactams **20** with near-exclusive control of absolute stereochemistry and type of substituents at both the C3 and C4 stereocenters. Although there are several strategies for asymmetric synthesis of β-lactams, this synthesis represents a flexible catalytic, asymmetric synthesis.[20] Also, considering the structural variety of nontraditional β-lactams having inhibitory activity against serine protease, human leukocyte elastase,[21] and cysteine proteases,[22] this synthesis offers much potential for preparation of a large variety of β-lactams for determining structure–activity relationships in these new areas of rapid development.

To complete the synthesis of the carbacephem framework, several methods were contemplated. The six-membered ring of the bicyclic carbacephem nucleus has been formed by a rhodium-catalyzed insertion reaction of α-diazo-β-keto esters in our laboratory and others.[23] The directed Dieckmann cyclization also is efficient for forming the six-membered ring of carbacephems.[24] To demonstrate the flexibility of our methodology, appropriate precursors for the Dieckmann condensation were made (Scheme 5). Azido β-lactam **17** was alkylated with benzyl bromoacetate using cesium carbonate[25] as base to furnish **21** with all the carbons needed for the carbacephem framework. The *tert*-butyl ester was selectively removed with trifluoroacetic acid to give acid **22**, which

Scheme 5



was purified by aqueous extraction. The phenyl ester **23** was obtained by treating acid **22** with phenyl chloroformate and triethylamine. Treatment of diester **23** with NaO-*t*-Bu at −78 °C for 5 min gave a bicyclic β-lactam which was generally not isolated. Instead, the crude mixture was treated with *tert*-butyldimethylsilyl chloride and Et_3N in DMF to provide the protected carbacephem framework **24** in good yield.

For biological activity with carbacephems, *cis* stereochemistry is required for the substituents on C6–C7 of the β-lactam ring.[26] There are several procedures for epimerizing the C7 stereocenter of the β-lactam based upon quench of a kinetic enolate,[27] thermodynamic epimerization with weak base,[26] or hydride reduction of chloral imines at C7.[28] To avoid the need for a stereochemical correction, methods for stereoselective introduction of a nitrogen substituent with an *intramolecular* nucleophile transfer reaction are being investigated and will be reported in the future.

In conclusion, a catalytic, asymmetric synthesis of the carbacephem framework was developed. Through the use of the Ru-BINAP-catalyzed asymmetric hydrogenation and the nucleophile transfer reaction methodology, there is great potential for the synthesis of β-lactam derivatives in general with near-exclusive control of stereochemistry and types of substituents at C3 and C4 of the β-lactam ring.

Experimental Section

General Methods. Descriptions of instruments, general procedures, and chromatographic procedures have been published previously.[29]

Butanedioic Acid, Mono-1,1-dimethylethyl Ester (11).[30] Succinic anhydride (60 g, 0.6 mol) was suspended in 350 mL of toluene under an argon atmosphere. *N*-Hydroxysuccinimide (0.3 equiv, 20 g, 0.18 mol), 4-(dimethylamino)pyridine (0.1 equiv, 0.06 mol, 7 g), dry *tert*-butyl alcohol (3 equiv, 170 mL), and Et_3N (0.3 equiv, 0.18 mol, 25 mL) were added to the solution. Dissolution occurred upon refluxing for 1 day. After cooling, ethyl acetate (150 mL) was added, and the organic layer was washed three times with 10% citric acid and once with brine, dried over $MgSO_4$, filtered, and evaporated to give 74.3 g (71%) of brown solid. Recrystallization with ether gave white crystals of **11** [mp = 49–51°C, (lit.[30] mp = 50–51.5 °C)].

(20) For a review of β-lactam chemistry see: *The Organic Chemistry of β-lactams*; Georg, G. I., Ed.; VCH Publishers, Inc.: New York, 1993.
(21) Georg, G. I., Ed. *BioMed. Chem. Lett.* **1993**, *3*, symposia in Print no. 8, 2259–2298 and references cited therein.
(22) Skiles, J. W.; McNeil, D. *Tetrahedron Lett.* **1990**, *31*, 7277.
(23) (a) Teng, M.; Gasparski, C. M.; Williams, M. A.; Miller, M. J. *BioMed. Chem. Lett.* **1993**, *3*, 2431. (b) Salzmann, T. N.; Ratcliffe, R. W.; Christensen, B. G. *Tetrahedron Lett.* **1980**, *21*, 1193. (c) Evans, D. A.; Sjogren, E. B. *Tetrahedron Lett.* **1985**, *26*, 3787.
(24) Jackson, B. G.; Gardner, J. P.; Heath, P. C. *Tetrahedron Lett.* **1990**, *31*, 6317.
(25) (a) Gala, D.; Steinman, M.; Jaret, R. S. *J. Org. Chem.* **1986**, *51*, 4488. (b) Girijavallabhan, V. M.; Ganguly, A. K.; Pinto, P.; Versace, R. *J. Chem. Soc., Chem. Commun.* **1983**, 908.
(26) Bodurow, C. C.; Levy, J. N.; Wiitala, K. W. *Tetrahedron Lett.* **1992**, *33*, 4283.
(27) (a) Firestone, R. A.; Maciejewicz, N. S.; Ratcliffe, R. W.; Christensen, B. G. *J. Org. Chem.* **1974**, *39*, 437. (b) Dunlap, N. K.; Dezube, M.; Keith, D. D.; Weigele, M. *Tetrahedron Lett.* **1992**, *33*, 6103.
(28) Aoki, T.; Haga, N.; Sendo, Y.; Konoike, T.; Yoshioka, M.; Nagata, W. *Tetrahedron Lett.* **1985**, *26*, 339.
(29) Teng, M.; Miller, M. J. *J. Am. Chem. Soc.* **1993**, *115*, 548.
(30) Petragnani, N.; Yonashiro, M. *Synthesis* **1980**, 710.

Hexanedioic Acid, 3-Oxo-1-methyl-6-(1,1-dimethylethyl) Ester (12).[31] Monomethyl malonate (**8**, 1.1 equiv, 7.522 g, 63.7 mmol) was dissolved in THF (100 mL) and cooled to −78 °C. A 0.5 M solution of dibutylmagnesium in heptane (0.55 equiv, 31.8 mmol, 63.7 mL, Aldrich) was added slowly. The solution was stirred at −78 °C for 10 min and then allowed to warm to room temperature for 1 h. The solvent was removed to give **9** as a white hygroscopic solid.

Succinate **11** (10.08 g, 57.9 mmol) was dissolved in THF (100 mL) and cooled to 0 °C. Vigorous bubbling was observed upon addition of 1,1'-carbonyldiimidazole (1.1 equiv, 10.327 g, 63.7 mmol). The solution was warmed to room temperature for 1 h and then transferred to solid **9** via cannula. After 2 days, the solution was evaporated to half volume, and 150 mL of EtOAc was added. The resulting organic solution was washed with three 75-mL portions of 10% citric acid, two 75-mL portions of saturated $NaHCO_3$, and 50 mL of brine, dried over $MgSO_4$, filtered, and evaporated. Chromatographic purification of the residue with 30% EtOAc in hexanes gave 10.89 g (82%) of **12** as an oil: ^1H NMR ($CDCl_3$) δ 3.74 (s, 3H), 3.51 (s, 2H), 2.81 (t, 2H, 6.3 Hz), 2.53 (t, 2H, J = 6.3 Hz), 1.44 (S, 9H); ^{13}C ($CDCl_3$) δ 200.62, 171.46, 167.35, 80.78, 52.14, 49.07, 37.69, 29.39, 28.13; IR (neat, cm^{-1}) 3440 (br), 2960−2850, 1740 + 1715 (as a shoulder); HRMS calcd for $C_7H_9O_4$ (M −73, C_4H_9O) 157.0501, found 157.0521.

Hexanedioic Acid, 3-Hydroxy-1-methyl-6-(1,1-dimethylethyl) Ester (13). β-Keto diester **12** (1.703 g, 7.40 mmol) was dissolved in methanol (25 mL) and cooled to −30 °C under an argon atmosphere. Bubbling was observed upon addition of $NaBH_4$ (84 mg, 0.3 equiv, 2.22 mmol). The mixture was warmed to 10 °C and after 15 min quenched with 25 mL of cold brine. The solution was extracted with three 25-mL portions of ether. The organic layer was dried over $MgSO_4$, filtered, and evaporated. The residue was purified chromatographically with 30% ethyl acetate in hexanes to give 1.326 g (77%) of alcohol **13** as an oil: ^1H NMR ($CDCl_3$) δ 4.04 (m, 1H), 3.71 (s, 3H), 3.2 (s br, 1H), 2.38−2.50 (m, 4H), 1.72−1.8 (m, 2H), 1.45 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 173.08, 173.05, 80.48, 67.40, 51.75, 41.27, 31.72, 31.51, 28.11; IR (neat) cm^{-1} 3460 (s br), 2900−2980 (s), 1725 (vs); HRMS calcd for $C_7H_{11}O_5$ (M −56, C_4H_8) 176.068 47, found 176.0681.

Preparation of (*S*)-Ruthenium(II) Chlorobis(diphenylphosphino)binaphthyl. The Ru-BINAP catalyst is air sensitive; all procedures were carried out under an argon atmosphere. The reaction vessel was a thick-walled round-bottom flask equipped with a pressure resistant stopcock. Use of a Firestone valve allowed manipulations without air contamination. The reaction vessel was charged with BINAP (100 mg, 0.161 mmol, Aldrich), $RuCl_2$−cyclooctadiene (39 mg, 0.139 mmol, Fluka), triethylamine (0.275 mL), and toluene (4 mL). The mixture was deoxygenated by repeatedly (4×) drawing a vacuum and venting to argon through a Firestone valve. The vessel was sealed and heated with an oil bath to 130 °C for 2.5 h. After 45 min, the solution became dark red. After the solution was cooled to room temperature, the solvent was removed *in vacuo* for 1.5 h to give a bright orange solid. The solid was dissolved in 10 mL of THF to give an orange liquid with some undissolved precipitate. The catalyst was generally used on the same day that it was prepared; however, it was usually active for 1 week, and color was indicative of activity. Orange to red color represented an active catalyst while dark green to brown catalysts generally led to lower enantioselectivities and catalyst turnover.

Hexanedioic Acid, 3-Hydroxy-1-methyl-6-(1,1-dimethylethyl) Ester ((*S*)-13). β-Keto ester **12** (9.8 g, 42.6 mmol) was dissolved in deoxygenated methanol (25 mL) and placed in a Parr Shaker bottle under argon. The catalyst in 1.0 mL of THF (0.0139 mmol) was added to the solution by syringe. The Parr Shaker bottle was quickly attached to the Parr Shaker equipped with a *Teflon stopper*. The bottle was evacuated and filled with 20 psi of hydrogen three times and finally filled to 50 psi, wrapped in a heating mantle, and heated (80 °C outside temperature, 65 °C internal solution temperature). After 20 h, the bottle was removed and the solvent was evaporated to give a brown liquid. The residue was purified chromatographically with 30% EtOAc in hexanes on silica gel to give 8.89 g (90%) of an oil. A 10-mg portion of **13** and 16 mg of tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]europium(III) derivative ($Eu(hfc)_3$, Aldrich) were dissolved in $CDCl_3$ and filtered through a cotton plug into an NMR tube. Analysis by ^1H NMR revealed only one enantiomer (>98% ee) by integration of the *tert*-butyl ester region. $[\alpha]_D$ = −3.9° (CH_3OH, c = 1).

Hexanoic Acid, 4-Hydroxy-6-oxo-6-[(1-oxoethoxy)amino]-(1,1-dimethylethyl) Ester ((*S*)-(14a). Hydroxylamine hydrochloride (3.73 g, 53.66 mmol) was dissolved in methanol (60 mL) with gentle steam heating, and KOH (6.0 g, 107 mmol) was suspended in methanol (60 mL) with steam heating. After being cooled to room temperature, the KOH solution was added to the NH_2OH·HCl solution to give an immediate white precipitate of KCl. This solution was added to methyl ester **13** (8.30 g, 35.78 mmol) with ice cooling. After 24 h, acetic anhydride (4.5 mL, 48.3 mmol) was added followed by 0.25-mL portions until the mixture was 1% aqueous $FeCl_3$ negative (no red color). The solution was quickly added to a separatory funnel containing 100 mL of 5% Na_2CO_3 and 250 mL of ethyl acetate. The organic layer was washed with two 75-mL portions of 5% Na_2CO_3. The combined aqueous extracts were acidified with 6 M HCl to pH 5−6 and extracted with four 150-mL portions of CH_2Cl_2. The organic extracts were dried over $MgSO_4$, filtered, and evaporated to give a white crystalline material **14a** (5.22 g, 53%). Recrystallization from ether gave an analytical sample (mp = 72−74 °C): ^1H NMR ($CDCl_3$) δ 4.07 (m, 1H), 2.47−2.39 (m, 4H), 2.23 (s, 3H), 1.81 (q, 2H, J = 6.6 Hz), 1.45 (s, 9H); ^{13}C ($CDCl_3$) δ 173.73, 169.61, 168.88, 81.05, 67.89, 40.76, 31.92, 31.57, 28.05, 18.27; $[\alpha]_D$ = +12.8° (CH_2Cl_2, c = 1); IR cm^{-1} 3650 br, 3200 br, 1790−1780, 1730−1675; HRMS calcd for $C_8H_{13}NO_6$ (M − 56, C_4H_8) 219.074 29, found 219.0741. Anal. Calcd for $C_{12}H_{21}NO_6$: C, 52.35; H, 7.69; N, 5.09. Found: C, 52.09; H, 7.72; N, 5.06.

Hexanoic Acid, 4-Hydroxy-6-oxo-6-[(phenylmethoxy)amino]-1,1-dimethylethyl Ester ((*S*)-14b). To a suspension of HCl·H_2NOBn (2.8 g, 17.5 mmol, Aldrich) in CH_2Cl_2 (40 mL) with ice bath cooling was added Me_3Al (8.8 mL, 17.5 mmol, 2 *M solution in hexanes, Aldrich) over 10 min. The solution* was warmed to room temperature for 1 h and then recooled with an ice bath. Methyl ester **12** (2.32 g, 10 mmol) in 10 mL of CH_2Cl_2 was added dropwise. The cloudy solution was stirred overnight to give a clear solution. The solution was cooled in an ice bath, and 50 mL of 10% citric acid solution was added slowly and stirred for 1 h. The mixture was extracted with *three 50-mL portions of* CH_2Cl_2. *The organic layer* was extracted with two 50-mL portions of 10% citric acid, once with 50 mL of $NaHCO_3$, and once with 40 mL of brine, dried over $NaSO_4$, filtered, and evaporated to give 2.65 g (82%) of **14b** as a white solid. An analytical sample was obtained by recrystallization from ether/hexanes (mp = 72−74 °C): R_f = 0.18 (1:1 EtOAc:hexanes); ^1H NMR ($CDCl_3$) δ 9.45 (br s, 1H), 7.35 (s, 5H), 4.87 (s, 2H), 3.94 (m, 1H), 3.45 (br s, 1H), 2.1−2.5 (m, 4H), 1.6−1.75 (m, 2H), 1.43 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 173.24, 169.54, 135.06, 128.98, 128.41, 128.26, 80.39, 77.91, 67.53, 39.99, 31.62, 31.52, 27.85; IR cm^{-1} in $CHCl_3$ 3330 br, 2880−3040, 1735, 1650, 1365, 1150, 740; $[\alpha]_D$ = +13.3° ($CHCl_3$, c = 1); HRMS IBCI calcd MH^+ for $C_{17}H_{25}NO_5$ 324.1811, found 324.1820. Anal. Calcd for $C_{17}H_{25}NO_5$ C, 63.14; H, 7.79; N, 4.33. Found: C, 63.01; H, 7.74; N, 4.37.

2-Azetidinepropanoic Acid, 1-(1-Oxoethoxy)-4-oxo-(1,1-dimethylethyl) Ester ((*R*)-15a). To hydroxamate **14a** (2.188 g, 7.95 mmol) dissolved in CH_3CN (55 mL) and CCl_4 (2 mL) was added triethylamine (1.2 mL, 8.74 mmol) and triphenylphosphine (2.30 g, 8.74 mmol). The reaction was stirred overnight and evaporated to give a solid. The residue was purified chromatographically with 30% EtOAc in hexanes to give 1.545 g of **15a** (76%) as a clear oil: ^1H NMR ($CDCl_3$) δ 4.11 (ddd, 1H, J = 2.7 Hz, 6 Hz, 12.3 Hz), 3.04 (dd, 1H, J = 13.8 Hz, 5.7 Hz), 2.56 (dd , 1H, J = 13.8 Hz, 2.7 Hz), 2.39 (t,

(31) Brooks, D. W.; de Lee, N. C.; Peevey, R. *Tetrahedron Lett.* **1984**, *25*, 4623.

2H, J = 7.5 Hz), 2.18 (s, 3H), 2.08–1.95 (m, 2H), 1.45 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 171.53, 167.88, 164.18, 80.89, 58.20, 38.00, 31.41, 28.03, 27.90, 17.98; IR cm^{-1} (neat oil) 1810–1770, 1720; HRMS calcd for $C_8H_{11}NO_5$ (M − 56, C_4H_8) 201.063 72, found 201.0635; isobutane CI for $C_{12}H_{19}NO_5$ MH$^+$ of 258; $[\alpha]_D$ = −18.8° (CH_2Cl_2, c = 1).

2-Azetidinepropanoic Acid, 4-Oxo-1-(phenylmethoxy)-(1,1-dimethylethyl) Ester ((*R*)-15b). Prepared by the same procedure as for **15a**: R_f = 0.50 (50% EtOAc in hexanes); ^{1}H NMR ($CDCl_3$) δ 7.4 (m, 5H), 4.98 (d, 1H, J = 11.1 Hz), 4.930 (d, 1H, J = 11.1 Hz), 3.57 (m, 1H), 2.719 (dd, 1H, J = 5.1, 13.5 Hz), 2.311 (dd, 1H, J = 2.4, 13.5 Hz), 2.19–2.25 (m, 2H), 1.85–1.95 (m, 1H), 1.65–1.80 (m, 1H), 1.44 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 171.60, 163.85, 135.06, 129.21, 128.92, 128.54, 80.66, 78.03, 56.87, 37.49, 31.29, 27.96, 27.63; IR cm^{-1} neat oil 1770 s, 1725s, 1415 s, 1200s; $[\alpha]_D$ = +14.6° ($CHCl_3$, c = 1); HRMS IBCI MH$^+$ calcd for $C_{17}H_{23}NO_4$ 306.1703, found 306.1691.

2-Azetidinepropanoic Acid, 1-[[(4-Methylphenyl)sulfonyl]oxy]-4-oxo-2-(1,1-dimethylethyl) Ester ((*R*)-16). To β-lactam **15b** (890 mg, 2.92 mmol) dissolved in MeOH (6 mL) was added 10% Pd/C (200 mg). The solution was then placed under a H_2 atmosphere with a balloon for 1.5 h until judged complete by TLC (product R_f = 0.17, PMA visualization, 50% EtOAc in hexanes). The catalyst was filtered off through a Celite pad and rinsed thoroughly with EtOAc. The filtrate was evaporated, redissolved in CH_2Cl_2 (5 mL), and tosyl chloride (557 mg, 2.92 mmol) followed by Et_3N (407 μL, 2.92 mmol) were added. After 30 min, the solvent was evaporated. The residue was redissolved in a minimal amount of $CHCl_3$ and purified chromatographically with 40% EtOAc in hexanes to give 1.03 g (96%) of **16** as a clear oil which crystallized in the freezer (mp 60–61.5 °C): ^{1}H NMR ($CDCl_3$) δ 7.87 (d, 2H, J = 8.4 Hz), 7.38 (d, 2H, J = 8.4 Hz), 4.04 (m, 1H), 2.86 (dd, 1H, J = 6.0, 14.4 Hz), 2.46 (s, 3H) overlapped with (dd, 1H), 2.25–2.33 (m, 2H), 2.1–2.2 (m, 1H), 1.8–1.95 (m, 1H), 1.45 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 171.41, 164.94, 146.37, 130.42, 129.91, 129.03, 80.75, 58.97, 37.82, 30.97, 27.91, 27.13, 21.70; IR cm^{-1} neat oil 1800, 1725, 1595; $[\alpha]_D$ = 81.0° ($CHCl_3$, c = 1); HRMS (FAB) MH$^+$ calcd for $C_{17}H_{23}NO_6S$ 370.1324, found 370.1330.

2-Azetidinepropanoic Acid, 3-Azido-4-oxo-(1,1-dimethylethyl) Ester (*trans*-(2*R*,3*R*)-17). To β-lactam acetate **15a** (334 mg, 1.298 mmol) dissolved in 10 mL of methanol and 5 mL of water was added Na_2CO_3 (343 mg, 3.25 mmol, 2.5 equiv) followed by another 2 mL of water to promote dissolution of the salt. After 20 min, only N-hydroxy-β-lactam was apparent by TLC (R_f = 0.16, 1:1 EtOAc:hexanes). The reaction mixture was acidified to pH 5 with 3 M HCl and extracted with four 15-mL portions of CH_2Cl_2. The organic layer was dried over $MgSO_4$, filtered, and evaporated. The residue was immediately dissolved in 9 mL of dry CH_3CN with ice bath cooling. To this solution was added tosyl azide (427 mg, 1.389 mmol, 1.07 equiv), triethylamine (452 μL, 3.245 mmol, 2.5 equiv), and trimethylsilyl azide (77 μL, 0.584 mmol, 0.45 equiv). The reaction was stirred and warmed to room temperature overnight. The solution turned red. The solvent was evaporated, and the residue was dissolved in 15 mL of EtOAc and washed once with 10% citric acid solution and three times with 10% $NaHCO_3$ solution. The organic layer was dried over $MgSO_4$, filtered, and evaporated. The residue was chromatographed with 25% EtOAc in hexanes to give, after evaporation, 172 mg (58% overall) of **17** as colorless crystals which were recrystallized from CH_2Cl_2/hexanes (mp = 61–63 °C): ^{1}H NMR ($CDCl_3$) δ 6.6 (br s, 1H), 4.26 (t, 1H, J = 1.65 Hz), 3.56 (dt, 1H, J = 2.1 Hz, 6.6 Hz), 2.34 (t, 2H, J = 7.2 Hz), 1.90–2.02 (m, 2H), 1.46 (s, 9H); ^{13}C ($CDCl_3$) δ 171.68, 164.26, 81.28, 69.55, 56.38, 31.84, 28.53, 28.06; IR cm^{-1} 3280 br, 2110 vs, 1770, 1720; $[\alpha]^{24}$ = +94.4° (CH_2Cl_2, c = 1.35); CIMS m/e MH$^+$ = 241. Anal. Calcd for $C_{10}H_{16}N_4O_3$: C, 49.99; H, 6.71; N, 23.32. Found: C, 50.37; H, 6.74; N, 23.29.

Preparation of 17 from 16. To β-lactam **16** (2.21 g, 5.99 mmol) dissolved in CH_3CN (75 mL) was added iPr_2NEt (2.8 mL, 16.75 mmol, 2.75 equiv) and $TMSN_3$ (1.6 mL, 11.98 mmol, 2 equiv, Aldrich). After 2 h, the solution turned from clear to red. After 2 days, the solvent was evaporated and the residue was purified chromatographically with 40% EtOAc in hexanes to give 960 mg (67%) of **17** as a white solid.

2-Azetidinepropanoic Acid, 1-[2-(Phenylmethoxy)-2-oxoethyl]-4-oxo-3-azido-(1,1-dimethylethyl) Ester (*trans*-(2*R*)-21). To azido β-lactam **17** (1.0 g, 4.149 mmol) dissolved in dry CH_3CN (65 mL) under an argon atmosphere was added cesium carbonate (1.43 g, 4.387 mmol, 1.07 equiv) and benzyl-2-bromoacetate (985 μL, 6.22 mmol, 1.5 equiv). After 4 h, TLC analysis with 50% EtOAc in hexanes showed the bromoacetate starting material at R_f = 0.54 (UV visualization) and product at R_f = 0.40 (UV, PMA blue). The precipitate was filtered and the solvent removed *in vacuo*. The residue was purified chromatographically with 30% EtOAc in hexanes to give 1.18 g (73%) of **21** as an oil: ^{1}H NMR ($CDCl_3$) δ 7.37 (s, 5H), 5.18 (s, 2H), 4.29 (d, 1H, J = 1.8 Hz), 4.22 (d, 1H, J = 18 Hz), 3.84 (d, 1H, J = 18 Hz), 3.74 (ddd, 1H, 2.1, 4, 9 Hz), 2.31 (t, 2H, J = 7.5 Hz), 2.0–2.1 (m, 1H), 1.77–1.90 (m, 1H), 1.45 (s, 9H); ^{13}C ($CDCl_3$) δ 171.34, 167.39, 164.10, 134.79, 128.72, 128.59, 81.29, 69.01, 67.59, 60.39, 41.74, 31.08 , 28.04, 25.82; IR cm^{-1} neat oil 2105 s, 1770 s, 1745 s, 1720 s; $[\alpha]_D$ = 78.9° ($CHCl_3$, c = 0.9); HRMS calcd for $C_{19}H_{24}N_4O_5$ (M$^+$ − 28, N_2) 360.16852, found 360.1676.

2-Azetidinepropanoic Acid, 1-[2-(Phenylmethoxy)-2-oxoethyl]-4-oxo-3-azide (*trans*-(2*R*)-22). To *tert*-butyl ester **21** (152 mg, 0.392 mmol) was added anisole (43 μL, 0.392 mmol) and trifluoroacetic acid (1.5 mL). After 15 min the solution was evaporated. The residue was dissolved in 10 mL of EtOAc and extracted with four 4-mL portions of saturated $NaHCO_3$. The aqueous layer was acidified to pH 2 with 3 M HCl and extracted with four 10-mL portions of CH_2Cl_2. The organic layer was dried over $MgSO_4$, filtered, and evaporated to give 106 mg (82%) of **22** as an oil: ^{1}H NMR ($CDCl_3$) δ 9.5 (br s, 1H), 7.35 (s, 5H), 5.17 (s, 2H), 4.32 (d, 1H, J = 1.8 Hz), 4.19 (d, 1H, J = 18 Hz), 3.87 (d, 1H, J = 18 Hz), 3.73 (ddd, 1H, J = 2.1, 4.2, 9 Hz), 2.43 (t, 2H, J = 7.2 Hz), 2.10–2.15 (m, 1H), 1.80–1.93 (m, 1H); ^{13}C ($CDCl_3$) δ 176.91, 167.31, 164.40, 134.61, 128.58, 128.41, 68.72, 67.52, 60.36, 41.75, 29.58, 25.37; IR cm^{-1} neat oil 3500–3000 br, 2110, 1770–1700; $[\alpha]_D$ = 109.8° ($CHCl_3$, c = 0.9); HRMS calcd for $C_{15}H_{16}N_2O_5$ (M$^+$ − 28, N_2) 304.10592, found 304.1061; FAB MH$^+$ 333.

2-Azetidinepropanoic Acid, 1-[2-(Phenylmethoxy)-2-oxoethyl]-4-oxo-3-azidophenyl Ester (*trans*-(2*R*)-23). To a solution of β-lactam **22** (115 mg, 0.346 mmol) in THF (1.5 mL) with ice bath cooling was added Et_3N (53 μL, 0.381 mmol), phenyl chloroformate (48 μL, 0.381 mmol), and after 5 min phenol (33 mg, 0.346 mmol). After 3 h, 15 mL of EtOAc was added and the solution washed with two 5-mL portions of 0.5 M HCl, three 5-mL portions of 5% Na_2CO_3, and once with 5 mL of brine. The organic layer was dried over $MgSO_4$, filtered, and evaporated. The residue was purified chromatographically with 40% EtOAc in hexanes to give 107 mg (76%) of **23** as an oil; R_f = 0.4 (50% EtOAc in hexanes); ^{1}H NMR ($CDCl_3$) δ 7.31–7.41 (m, 7H), 7.24 (t, 1H, J = 7.5 Hz), 7.07 (d, 2H, J = 8.7 Hz), 5.16 (s, 2H), 4.34 (d, 1H, J = 2.1 Hz), 4.21 (d, 1H, J = 18 Hz), 3.86 (d, 1H, J = 18 Hz), 3.80 (ddd, 1H, J = 2.1, 4.2, 8.7 Hz), 2.64 (t, 2H, J = 7.5 Hz), 2.18–2.31 (m, 1H), 1.92–2.19 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 170.62, 167.31, 163.92, 150.26, 134.67, 129.44, 128.61, 128.45, 126.01, 121.27, 68.84, 67.49, 60.15, 41.73, 29.94, 25.60; IR cm^{-1} neat oil 2115, 1775–1740, 1200; $[\alpha]_D$ = +72.0° ($CHCl_3$, c = 1); HRMS (FAB) calcd for $C_{21}H_{20}N_4O_5$ (MH$^+$) 409.1512, found 409.1509.

1-Azabicyclo[4.2.0]oct-2-ene-2-carboxylic Acid, 3-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-8-oxo-7-azidophenylmethyl Ester (*trans*-(6*R*)-24). To β-lactam **23** (59 mg, 0.1446 mmol) dissolved in THF (1.5 mL) at −78 °C was added *t*-Bu ONa (55 mg, 0.578 mmol, 4 equiv). The resultant yellow solution was quenched with 1 mL of 0.5 M HCl and 1 mL of brine. To this solution was added 30 mL of ethyl acetate, and the organic layer was washed with 10 mL of saturated $NaHCO_3$ and 10 mL of brine, dried over $MgSO_4$, filtered, and evaporated. The residue was dissolved in 1 mL of DMF, and Et_3N (45 μL, 0.317 mmol) and *tert*-butyldimethylsilyl chloride (48 mg, 0.317 mmol) were added. A precipitate was visible after 5 min. After 30 min, 30 mL of EtOAc was added. The

organic layer was washed with three 10-mL portions of saturated $NaHCO_3$, and 10 mL of brine, dried over $MgSO_4$, filtered, and evaporated. The residue was purified chromatographically with 30% EtOAc in hexanes to give 46 mg (74%) of an oil after evaporation: $R_f = 0.50$ (50% EtOAc in hexanes, UV, PMA); ^1H NMR ($CDCl_3$) δ 7.25–7.33 (m, 5H), 5.34 (d, 1H, J = 12.3 Hz), 5.18 (d, 1H, J = 12.3 Hz), 4.19 (d, 1H, J = 1.5 Hz), 3.52 (ddd, 1H, J = 1.5, 3.6, 11.1 Hz), 2.24–2.45 (m, 3H), 1.68–1.83 (m, 1H), 0.90 (s, 9H), 0.16 (s, 3H), 0.14 (s, 3H); ^{13}C NMR (75 MHz) δ 160.76, 160.15, 152.18, 135.66, 128.50, 128.33, 128.04, 112.37, 68.89, 66.67, 54.11, 29.33, 25.48, 25.25, 18.24, −3.81, −3.84; IR cm^{-1} neat oil 2115, 1770, 1725, 1350; $[\alpha]_D$ = +96.9 (CH_2Cl_2, c = 0.9); HRMS (FAB) calcd for $C_{21}H_{28}N_4O_4Si$ (MH^+) 429.1958, found 429.1960.

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Supplementary Material Available: ^1H and ^{13}C NMR spectra of **12, 13, 15a/b, 16, 17, 21-24** and ^1H NMR chiral shift studies of **13** with $Eu(hfc)_3$ (21 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.