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Total Synthesis of Tricyclic β-Lactams†

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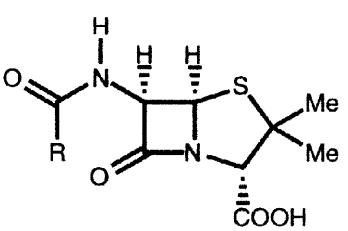
Abstract: The synthesis of tricyclic carbapenam and penems was achieved by highly stereoselective Lewis acid-catalyzed reactions of 4-substituted 1-trimethylsilyloxyfurans with a 4-acetoxy azetidinone chiron, and further elaboration of the resulting condensation products using intramolecular Michael cyclizations.

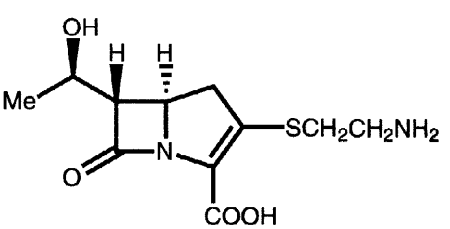
INTRODUCTION

Ever since the discovery of penicillin, the β-lactam group of antibiotics has occupied a prominent position in the arsenal of chemotherapeutic agents.[1] The continuing quest for new structural types with broad-spectrum activity, and their resistance to inactivation by β-lactamases has resulted in a plethora of semi-synthetic or totally synthetic products. Nature has also helped with the discovery of new structural types such thienamycin,[2] the first example of a carbapenem (Figure 1). This extremely potent antibiotic reported from the Merck Laboratories over twenty years ago, triggered intense interest in the field of β-lactam antibiotics. Two unique functional and structural features found in thienamycin compared to the traditional penicillins are the α-hydroxyethyl side-chain which replaces the traditional 6-acylamino group, and the presence of an unsaturated substituted pyrrolidine ring. This unusual substitution pattern has fostered intense efforts aimed at producing analogs that combine certain features from different classes of β-lactam antibiotics.

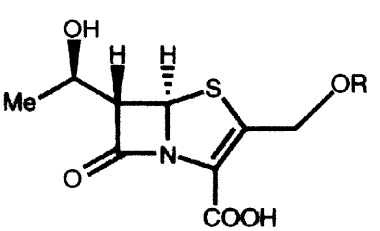
Figure 1



Penicillins



Thienamycin



Hybrid Penem, R=H, etc

† Dedicated to the memory of Sir Derek H. R. Barton, honoring his pioneering lifetime contributions to organic chemistry.

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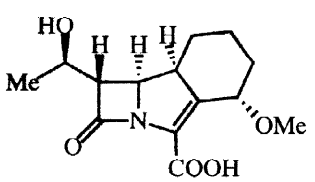
PII: S0040-4020(98)01152-1

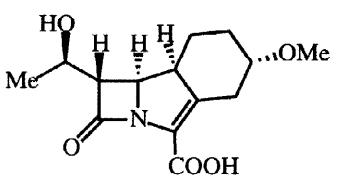
The idea of combining the reactivity determinants of penicillins and cephalosporins led to the synthesis of non-classical β-lactams called penems.[3] The discovery of thienamycin suggested grafting its peculiar 6-hydroxyethyl side-chain onto the penem sekeleton, leading to several potent hybrid penems (Figure 1).[4]

Recently, a new class of synthetic tricyclic β-lactam motifs were reported (Figure 2).[5,6] The most successful and clinically promising example is Glaxo's "trinem",[6] which is a tricyclic carbapenem that harbors a potential "leaving group" as a methoxy group. We have independently developed highly stereocontrolled total syntheses of the C-4 and C-5 trinems.[7,8] In our continuing studies in the design and synthesis of novel β-lactam structural types,[9] we reported syntheses of functionally and topologically novel tricyclic carbacephems (Figure 2).[10] In spite of their unique structures and topologies, these carbacephems with the exception of the 1-hydroxymethyl analog (Figure 2), were essentially inactive against a host of bacterial strains. We reasoned that this biological inactivity may be result of low "reactivity" of the β-lactam carbonyl group,[11] or due to subtle conformational effects. In this paper, we report the results of our further studies in this regard, which resulted in the synthesis of functionally and topologically novel tricyclic carbapenams and carbapenems (Figure 2). It was anticipated that these structures would possess certain elements of constraint, thereby increasing the reactivity of the β-lactam carbonyl group toward serine proteases.

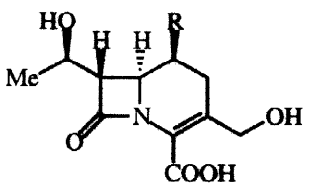
Figure 2



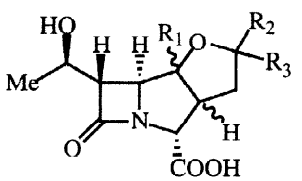
Glaxo's C-4 Trinem[6,7] (Sanfetrinem)



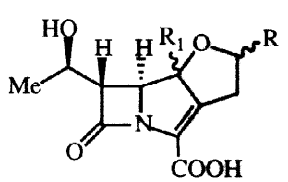
C-5 Trinem[8]



R= Me, CH_2OH, CH_2NHAc



Tricyclic carbapenams
R_1= Me or H; R_2 and R_3= usable functionalities



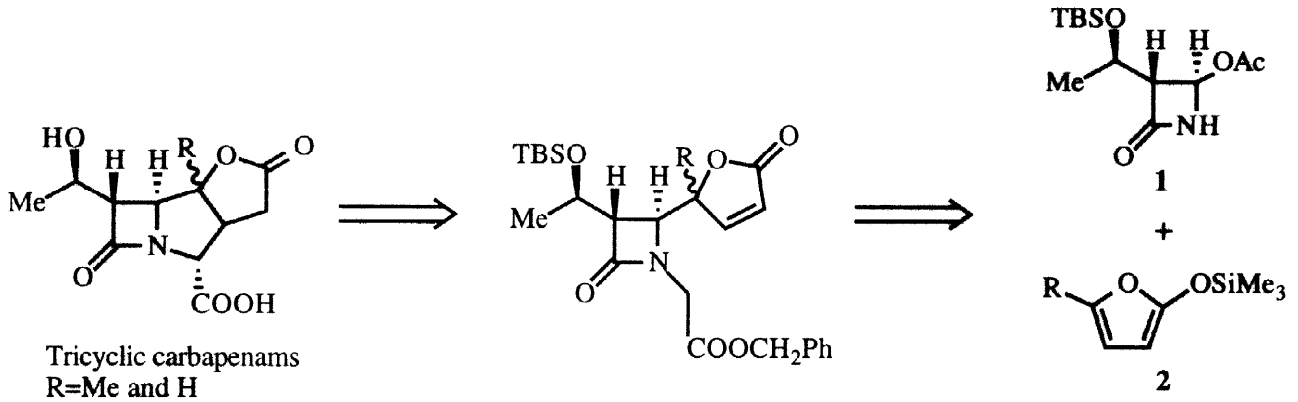
Tricyclic carbapenems
R_1= Me or H; R = OAc, OMe or H

Synthesis of Tricyclic Carbapenams.

Characteristic of these novel carbapenams (Figure 2) is the presence of a third ring in the form of a fused tetrahydrofuran unit and the lack of an enamine double bond. It was thought that the strain introduced in such tricyclic ring systems may compensate for the lack of the double bond as found in the traditional carbapenems.

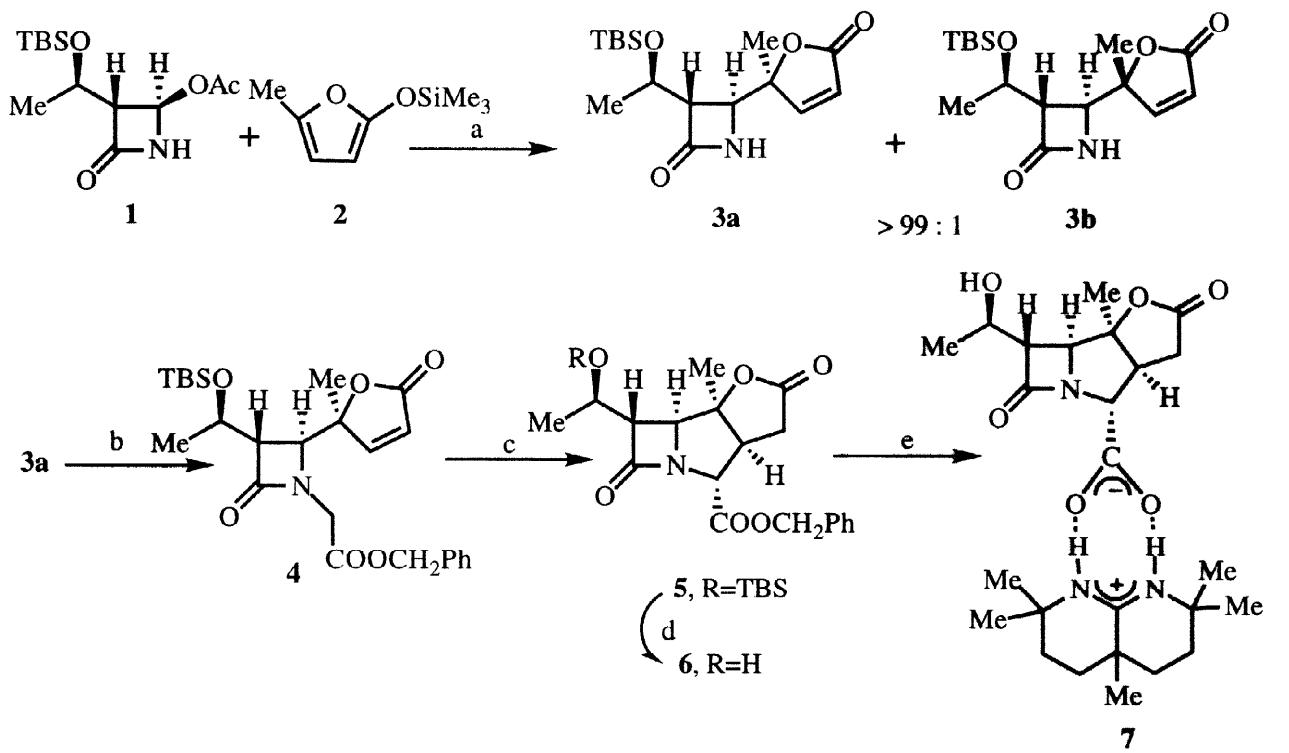
Our disconnective analysis and synthesis plan for these tricyclic carbapenams is shown in Figure 3, where commercially available 4-acetoxy azetidinone **1**[12] and trimethylsilyloxyfuran **2**,[13] are the starting materials. The plan called for an extension at C-4 of **1** with **2**, and construction of a carbapenam tricyclic system via a intramolecular Michael-type ring closure.

Figure 3



The general approach to these tricyclic derivatives is described in Schemes 1 and 2. Treatment of the 4-acetoxy azetidinone **1** with 2-trimethylsilyloxyfuran **2** in the presence of $BF_3.Et_2O$ gave a modest diastereomeric ratio (87:13) of **3a** and **3b** (Scheme 1). However, the zinc chloride catalyzed reaction was highly diastereoselective and afforded virtually one isomer **3a** in high yield. The structures of **3a** and **3b** were unambiguously established from nOe studies and ultimately from X-ray crystal structure analysis of an advanced intermediate. The next steps were concerned with the introduction of an acetic acid side-chain, and an intramolecular ring-closure reaction to give the tricyclic skeleton.

Scheme 1

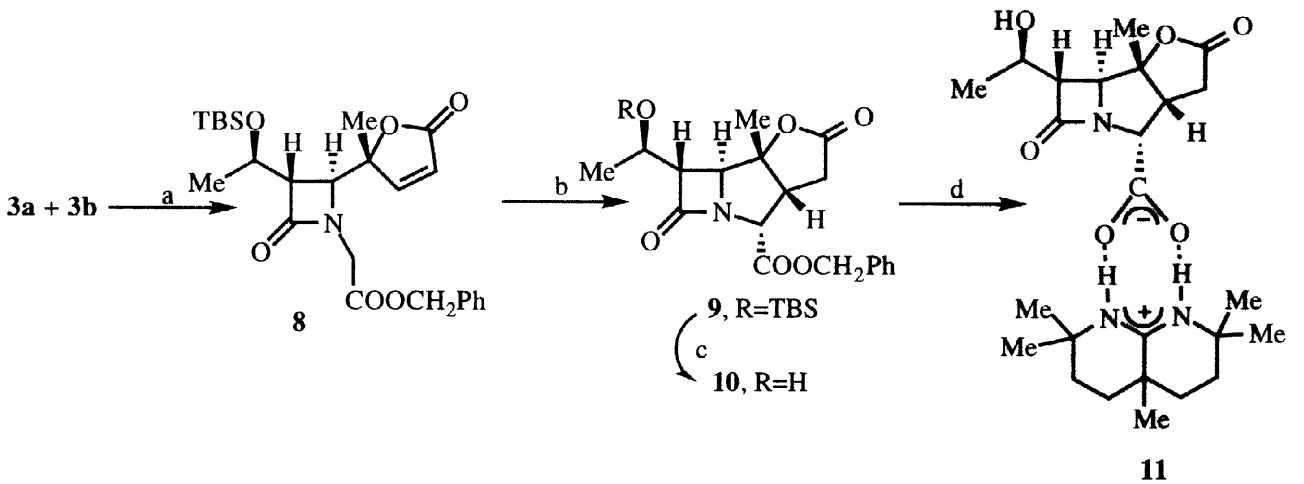


(a) $ZnCl_2$, CH_2Cl_2, r.t., slow addition of furan, 10h, 80-92%; (b) NaHMDS, THF, -78 °C, $BrCH_2COOCH_2Ph$, 30 m, 71%; (c) LiHMDS, THF, -78 °C to r.t., 12 h , 94%; (d) HF (48% aq, excess), MeCN, 0 °C to r.t., 1 h, 83%; (e) 10% Pd/C,THF, H_2, amidine, 71%.

The N-alkylation of **3a** with benzyl bromoacetate was done using NaHMDS as base to give **4** in good yield. Upon treatment with LiHMDS at -78 °C, intramolecular cyclization took place to give the tricyclic carbapenam **5** as a single isomer in high yield. The stereochemistry of **5** was assigned after extensive nOe studies of the corresponding methyl ester. The desilylation of **5** with HF-acetonitrile[14] afforded hydroxy compound **6**, which on hydrogenolysis in presence of the Eschenmoser amidine[15] led to the desired crystalline tricyclic carbapenam lactone **7** as the amidinium salt in excellent yield.

The successful construction of the tricyclic carbapenam motif **7**, prompted us to explore the synthesis of structural variants, such as the lactone **11** with an angular β-methyl group as found in the well known 1-β-methyl carbapenems[16] (Scheme 2).

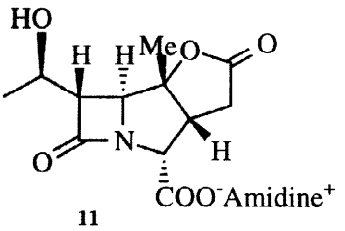
Scheme 2



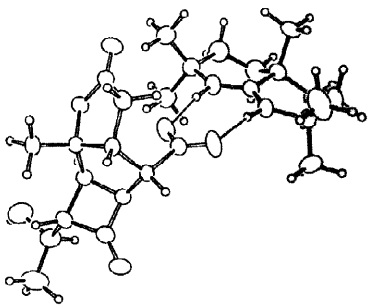
(a) LiHMDS, THF, -78°C, $BrCH_2COOCH_2Ph$, 30 m, 7% of **8**, 14% of **9** and 26% of **4** (the reaction was done with a mixture of **3a** and **3b**); (b) LiHMDS, THF, -78°C to r.t., 30 m, 76%; (c) TBAF, acetic acid, r.t., 40 h, 74%; (d) 10% Pd/C,THF, H_2, amidine, 95%.

As shown in Scheme 2, the crude diastereomeric mixture of **3a** and **3b** was N-alkylated with benzyl bromoacetate using LiHMDS to give **8**, which on intramolecular Michael cyclization gave tricyclic adduct **9** as a single isomer. The minor isomer **3b** could also be cyclized in the same way. Removal of the TBS group and hydrogenolysis of the resulting **10** led to the desired crystalline tricyclic carbapenam isolated as the amidinium salt **11**. Absolute stereochemistry was unambiguously established from an X-ray crystal structure (Figure 4).

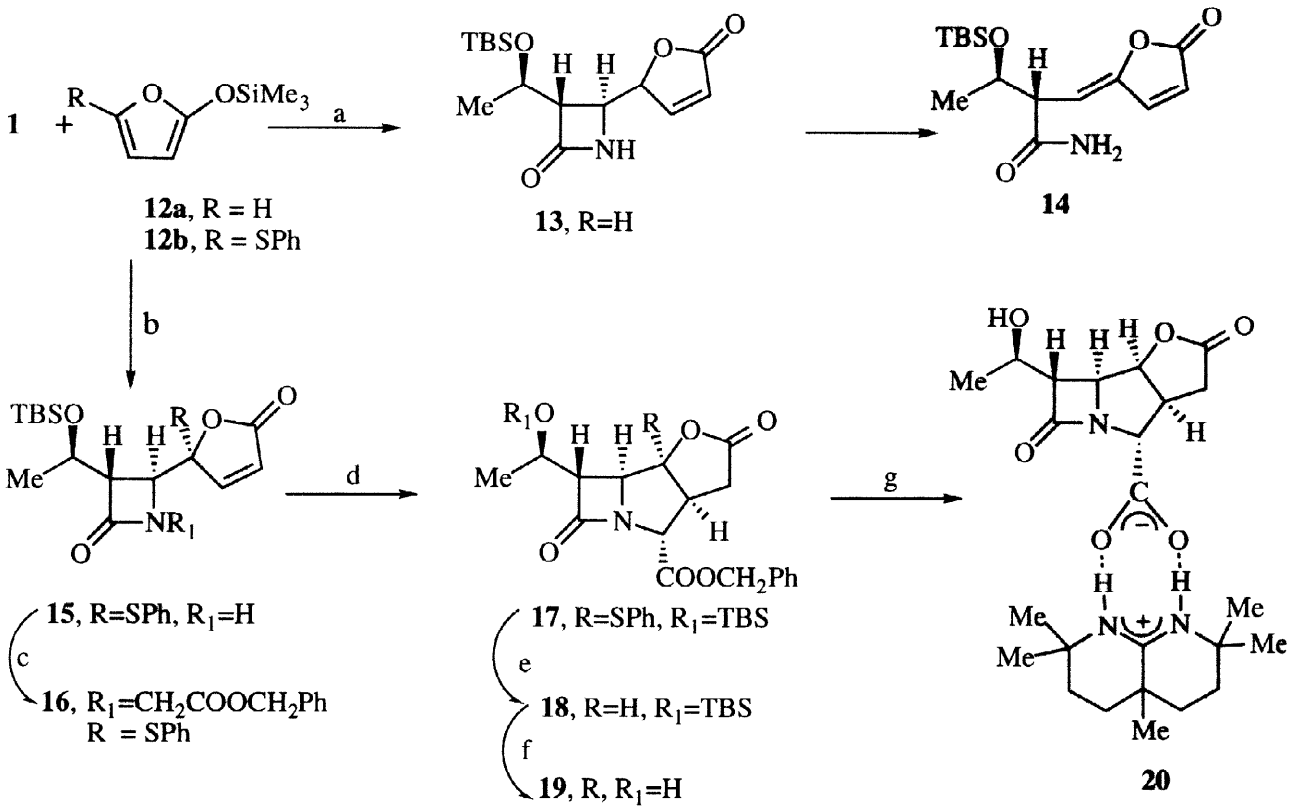
Figure 4



11



Scheme 3



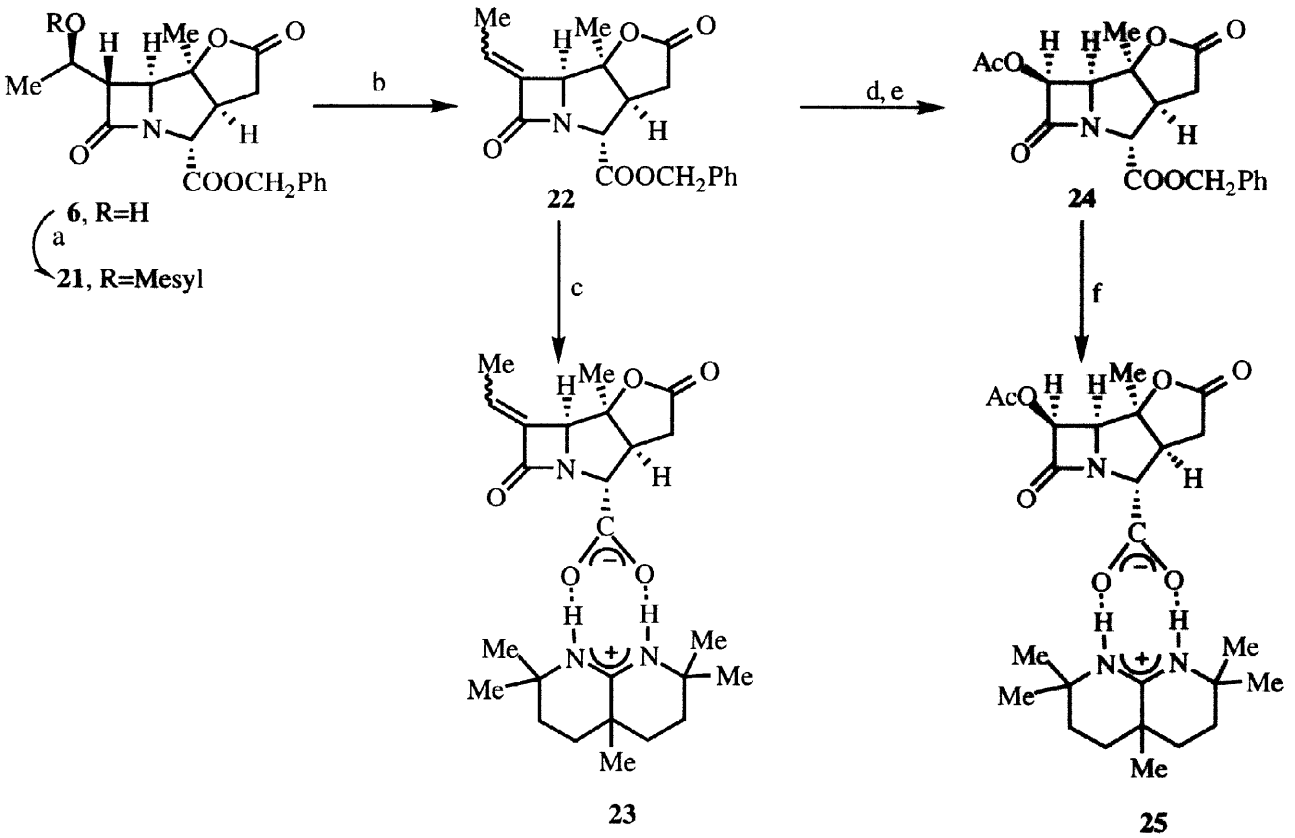
(a) $ZnCl_2$, CH_2Cl_2, r.t., slow addition of **12** (R=H) over 10 h, 80%; (b) $ZnCl_2$, CH_2Cl_2, r.t., addition **12b** (R=SPh), 20 h, 80%; (c) LiHMDS, $BrCH_2COOCH_2Ph$, THF, -78°C to r.t., 6 h, 63%; (d) LiHMDS, THF, -78°C, 30 m, 81%; (e) Bu_3SnH, AIBN , toluene, 90°C, 2 h, 71%; (f) TBAF, AcOH, THF, r.t., 48 h, 58%; (g) 10% Pd/C, THF, H_2, amidine, r.t., 20 m, 65%.

After having secured a method for the formation of the tricyclic ring systems with an angular 1α - or 1β - methyl group, we embarked upon the synthesis of a tricyclic analog without the methyl group (Scheme 3). Treatment of unsubstituted TMS-furan **12a** (R=H) with 4-acetoxy azetidinone **1** in the presence of $ZnCl_2$ led to the corresponding butenolide adduct **13** (R=H) as single isomer in excellent yield. Unfortunately, all efforts at N-alkylation of **13** with benzyl bromoacetate under a variety of conditions led to the opening of β-lactam ring to give **14**. Thus, we were compelled to adopt an indirect route to the intended target. Treatment of **1** with 4-

thiophenyl-1-trimethylsilyloxyfuran **12b**[17] in the presence of zinc chloride led to the corresponding butenolide adduct **15** in excellent yield. The N-alkylation of **15** with benzyl bromoacetate and intramolecular Michael cyclization of **16** gave tricyclic adduct **17**, as a single isomer. Reductive removal of the angular thiophenyl group with tributyl tin hydride gave **18** in excellent yield. Removal of the TBS group and hydrogenolysis led to the desired crystalline tricyclic carbapenam lactone analog **20**[18] in good yield.

In spite of their novel structures, the tricyclic carbapenams **7**, **11** and **20** were inactive against a host of bacterial strains. This may be due to inherent structural, stereochemical and functional problems related to the reactivity of the β-lactam carbonyl group in these structures. In an effort to enhance the reactivity of the β-lactam, we chose to prepare an exocyclic methylene derivative as shown in Scheme 4.

Scheme 4



(a) MsCl, Et_3N, CH_2Cl_2, r.t., 1 h, 77%; (b) DBU, benzene, r.t., 1.5 h, 90%; (c) 10% Pd/C, amidine, THF, r.t., 10 m, 78%; (d) O_3, CH_2Cl_2, -78°C, 15 m, then r.t., THF, 0°C, $NaBH_3CN$, 30 m, 66%; (e) pyridine, Ac_2O, CH_2Cl_2, r.t., 20 h, 85%; (f) 10% Pd/C, amidine, THF, r.t., 2 h, 76%.

Treatment of the compound **6**, with mesyl chloride in Et_3N gave mesylate **21**, which upon treatment with DBU gave the α,β-unsaturated product **22** in high yield with an *E,Z* ratio of 87:13. Hydrogenolysis of **22** in the presence of an amidine[15] led to the desired tricyclic carbapenam **23** in excellent yield. We also explored the synthesis of a structural variant as in the acetoxy tricyclic carbapenam **25**. Thus, ozonolysis of **22** and reductive workup afforded a hydroxy compound, which on treatment with Ac_2O in pyridine led to **24**. Hydrogenolysis of

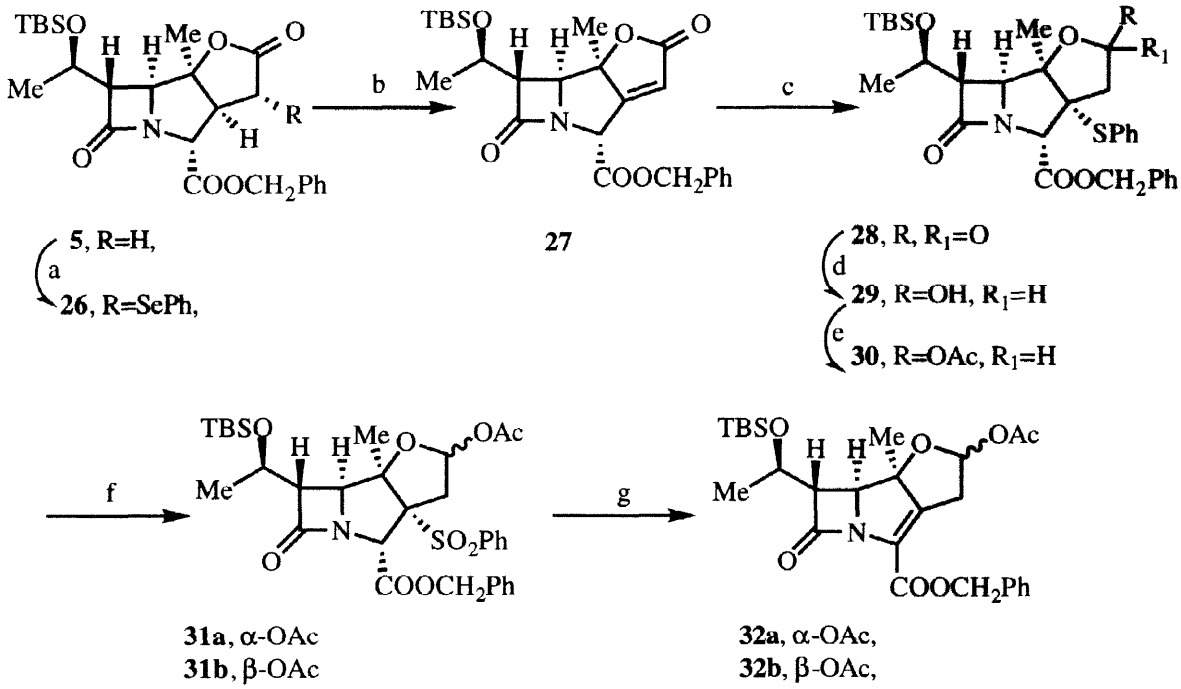
24 in the presence of the Eschenmoser amidine led to the desired tricyclic carbapenam **25** in excellent yield (Scheme 4).

The above tricyclic carbapenams were also tested in a preliminary fashion in the human leukocyte elastase assay[19] but no inhibition was observed.

Synthesis of Tricyclic Carbapenems

After the successful construction of tricyclic carbapenam motifs, we embarked upon the synthesis of tricyclic carbapenems, which are structurally and functionally close to the potent bicyclic carbapenems. Our plans to achieve the synthesis of such motifs was viewed with guarded optimism because of a real concern with their potential chemical instability.

Scheme 5



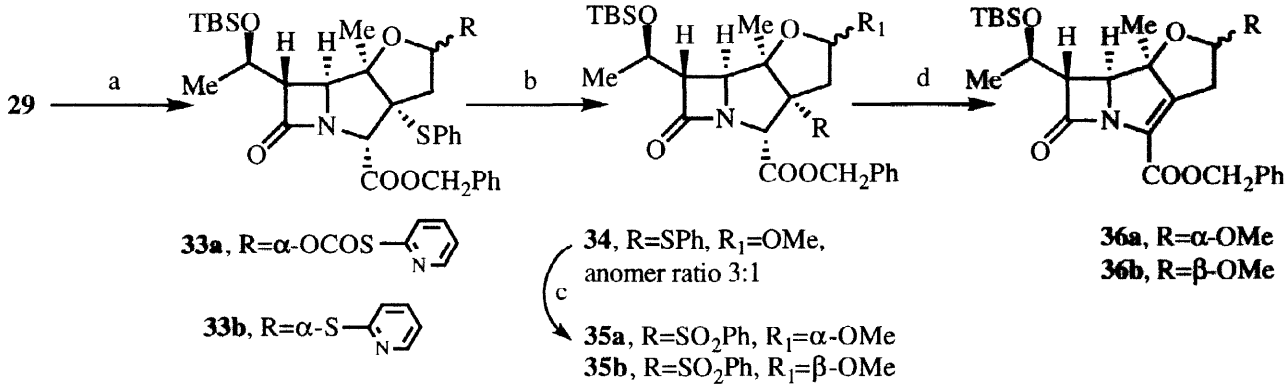
(a) NaHMDS, THF, PhSeBr, -78°C, 1 h, 78%; (b) m-CPBA, CH_2Cl_2, rt, 61%; (c) PhSH, benzene, diisopropyl ethyl amine, rt, 1 h, 83%; (d) DIBAL-H, THF, -78°C, 30 m, 66%; (e) Ac_2O, pyridine, CH_2Cl_2, rt, 10 h, 74%; (f) m-CPBA, CH_2Cl_2, rt, 2 h, 88%; (g) DBU, CCl_4, rt, 6 h, 70%.

As shown in the Scheme 5, we chose the protected tricyclic penam **5** as a representative example for the introduction of the enamine double bond. After considering a number of approaches we decided on a selenylation and oxidative elimination strategy to introduce the double bond.[20] Direct selenylation of **5** at the α-benzyloxy carbonyl position with phenylselenyl bromide under variety of conditions proved to be extremely difficult, resulting in recovery of starting material or decomposition. Interestingly, treatment of compound **5** with two equivalents of NaHMDS and subsequently with PhSeBr gave **26**, which upon oxidative elimination gave **27**. Unfortunately, all efforts to migrate the double bond in **27** resulted in decomposition. Thus, we were

once more compelled to adopt an indirect route to the intended target. Addition of thiophenol[21] to **27** under base-catalyzed conditions occurred smoothly to give **28**. Oxidation and base-catalyzed elimination of **28** resulted in partial decomposition and gave back the starting material **27**. Meanwhile reduction of **28** with DIBAL-H resulted in an inseparable mixture of lactols **29** in the ratio of 1.83:1, which on acetylation with Ac_2O afforded **30** as an inseparable anomeric mixture. Oxidation of **30** afforded sulfones **31a** (α-OAc) and **31b** (β-OAc), which could be separated by flash chromatography using silica gel. The stereochemistry of the major (α-OAc) **31a** and the minor (β-OAc) **31b** isomers was assigned based on nOe studies.

Elimination of sulfone **31a** was effectively accomplished in the presence of DBU to give unstable **32a**, which slowly decomposed slowly in few hours. Under the same conditions the β-OAc **31b** gave a mixture of products. The instability of compounds **32a** and **32b** could arise from easy elimination of the acetate function. This led us to explore the synthesis of tricyclic carbapenems **36** with an anomeric methoxy group as a more stable analog (Scheme 6).

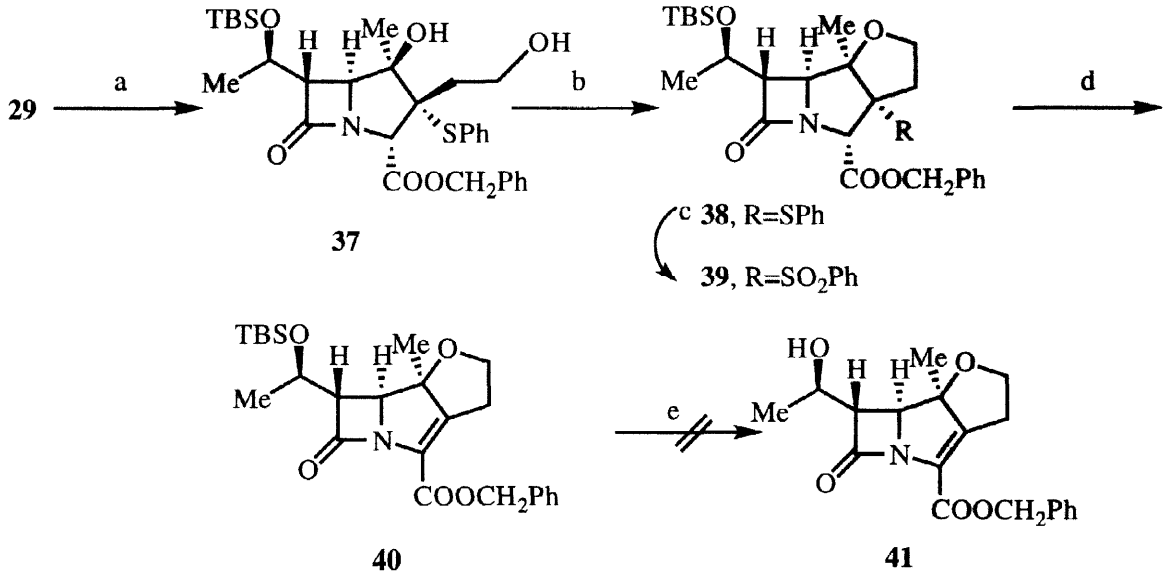
Scheme 6



(a) Bis-2,2-thiopyridyl carbonate, Et_3N, DMAP, CH_2Cl_2, rt, 22 h, **33a** (50%), **33b** (29%); (b) Ag(OTf) , MeOH, CH_2Cl_2, rt, 30 m, 81%; (c) m-CPBA , CH_2Cl_2, rt, 12 h, 77% (separable anomers); (d) major anomer, DBU, CCl_4, rt, 3 h, 79%; minor anomer decomposed under these conditions.

Unfortunately all attempts at direct O-methylation of the anomeric lactal **29** (Scheme 7) were unsuccessful. On the other hand, treatment of **29** with bis-2,2-thiopyridyl carbonate[22] in basic conditions afforded **33a** and **33b** which upon treatment with MeOH in the presence of silver triflate gave **34** as an inseparable anomeric mixture. Oxidation of **34** with mCPBA gave a mixture of sulfones **35a** (α-OMe) and **35b** (β-OMe), which were separated by flash column chromatography on silica gel. The α,β-stereochemistry was assigned based on NMR data of the corresponding acetates **31a** and **31b**. Elimination of the sulfone group in **35a** in the presence of DBU resulted in **36a**, which slowly decomposed in few hours. Under the same conditions the sulfone **35b** also gave a multi-product mixture.

Scheme 7



(a) $NaBH_4$, MeOH, rt, 30 m, 60-72%; (b) mesyl chloride, pyridine, CH_2Cl_2, rt, 3 h, 78%; (c) m-CPBA, CH_2Cl_2, rt, 7 h, 95%; (d) DBU, CCl_4, rt, 1 h, 74%; (e) PPTS, THF, water, rt, 30 m.

Finally, we attempted the synthesis of another structural variant of these tricyclic carbapenems having the tetrahydrofuran system **41** (Scheme 7). Reduction of lactol **29** with $NaBH_4$ resulted in diol **37**, which was easily cyclized to tetrahydrofuran motif **38**.[22] Oxidation to the sulfone **39** and elimination in the presence of DBU gave a stable tricyclic motif **40** with the desired enamine double bond. Unfortunately, all attempts as desilylation of **40** resulted in the gradual decomposition of the substrate, a problem which is not uncommon in carbapenem chemistry.[23]

In conclusion, we have designed and developed novel tricyclic β-lactams motifs through a versatile and stereocontrolled functionalization of the 4-acetoxy azetidinone **1**, with readily available furan derivatives. In spite of their unique structures, the carbapenams **7**, **11** and **20** were inactive against a host of selected bacterial strains. The introduction of enamine double bond in these structures resulted in unstable motifs such as **8**, **32**, **36** and **41**.[24]

Experimental section

^1H NMR spectra were recorded on a 300 MHz VARIAN and 300 MHz Bruker instruments using deuteriochloroform as solvent. Only data for ^{13}C resonances at 75 Mhz are included here. Infrared spectra were recorded with a Perkin-Elmer 781 infrared spectrometer. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. Column chromatography was done by the flash method.[25] Melting points were not corrected. CI and EI mass spectra were obtained on VG-1212 low resolution and Kratos-50 high resolution spectrometers. Usual workup of reaction mixtures consisted in drying organic layers with sodium sulfate, filtration and evaporation to dryness.

3*S*-[1*R*-(*tert*-Butyl-dimethylsilanyloxy)-ethyl]-4*S*-(2*S*-methyl-5-oxo-2,5-dihydro-furan-2-yl)-azetidin-2-one, 3a. To a solution of **1** (21.50 g, 75 mmol) in 300 mL of CH_2Cl_2 was added $ZnCl_2$ (1M

solution of Et_2O, 20 mL, 20 mmol) at the room temperature. Silyloxyfuran **2** (in 40 mL of CH_2Cl_2) was added using a syringe pump for 8 h. The reaction mixture was stirred for 20 h, the solvent was evaporated, and the crude reaction mixture was purified by column chromatography (EtOAc:hexanes, 1:1) to give pure **3a** (22.51 g, 92%); mp 82-83 °C; $[\alpha]_D^{25}$ -58.14 (c 8.390, $CHCl_3$). ^{13}C NMR (75 MHz, $CDCl_3$); δ 171.62, 168.12, 156.99, 122.00, 87.17 (tertiary carbon), 64.73, 60.73, 54.07, 25.48 (C_3H_9Si), 22.55, 20.13, 17.62 (C_3H_9-*C*-Si), -4.64 (CH_3Si), -5.11 (CH_3Si).

[3*S*-[1*R*-(*tert*-Butyl-dimethyl-silanyloxy)-ethyl]-2*S*-(2-methyl-5-oxo-2,5-dihydro-furan-2-yl)-4*S*-oxo-azetidin-1-yl]-acetic acid benzyl ester, 4. To a solution of **3a** (17.81 g, 54.8 mmol) in THF (300 mL) at -78 °C was added NaHMDS (1M solution in THF, 56 mL, 56 mmol). The reaction mixture was stirred for 10 min and benzyl bromoacetate (8.8 mL, 55 mmol) was added. After stirring for 6h, the mixture was quenched with satd. NH_4Cl and extracted with EtOAc (500 mL x 2). The combined organic layers were separated and washed with water and brine. Usual workup and purification by column chromatography (20% EtOAc in hexanes) gave pure **4** (18.35 g, 71%); $[\alpha]_D^{25}$ - 53.96 (c 1.40, $CHCl_3$); ^{13}C NMR (75 MHz, $CDCl_3$); δ 171.24, 167.70, 167.32, 157.97, 134.75 (tertiary carbon of phenyl), 128.54, 128.37, 121.94, 88.19 (tertiary carbon), 67.26 (CH_2), 66.11, 60.53, 60.43, 72.76 (CH_2), 25.65 (*C_3H_9*-C-Si), 22.73, 19.25, 17.71 (C_3H_9-*C*-Si), -4.60 (CH_3Si), -4.66 (CH_3Si); HRMS: Calcd. for $C_{25}H_{35}NO_6Si$ + H: 474.2312; found: 474.2341.

Synthesis of the tricyclic β-lactam 5. To a solution of **4** (18.01 g, 38 mmol) in THF (200 mL) was added LiHMDS (1M THF solution, 10 mL, 10 mmol) at -78 °C and the mixture was stirred at room temperature for 12 h. After quenching with satd. NH_4Cl (100 mL), extraction with EtOAc and usual workup, the crude product was purified by column chromatography (25% EtOAc in hexanes) to give 16.90 g (94%) of **5** as a syrup, $[\alpha]_D^{25}$ + 19.34 (c 1.83, $CHCl_3$). HRMS: Calcd. for $C_{25}H_{35}NO_6Si$ + H: 474.2312; found: 474.2317.

Synthesis of 6. To a solution of **5** (153 mg, 0.32 mmol) in THF (40 mL) was added pre-prepared TBAF (600 mg of TBAF and 90 μL of AcOH in 20 mL THF) solution in THF (45 mL). The reaction mixture was stirred at room temperature for 24 h, then an extra amount of TBAF (600 mg) in THF (25 mL) was added. The reaction mixture was stirred for 40 h, the solvent was evaporated under vacuum and the crude residue was dissolved in CH_2Cl_2 (50 mL) and washed with water and brine. The organic layer was dried, filtered, concentrated and purified by reverse phase chromatography (Lichroprep. RP-18, particle size: 40:60 nm eluent 50% MeOH in water) **6** (58 mg, 50%) mp 129-131 °C; $[\alpha]_D^{25}$ +76.90 (c 0.550, $CHCl_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.09, 172.68, 169.46, 134.70 (tertiary carbon of phenyl), 128.59, 128.16, 90.84 (tertiary carbon), 67.57, 64.70, 63.62, 62.84, 59.968, 54.49, 34.97 (CH_2), 21.91, 21.52; HRMS: Calcd. for $C_{19}H_{21}NO_6$ + H: 360.1447; found: 360.1444.

Synthesis of 7. A mixture of **6** (38 mg, 0.105 mmol), the amidine (21 mg, 0.10 mmol) and Pd/C (20 mg) in THF (3 mL) was stirred in an atmosphere of hydrogen for 30 min. The catalyst was filtered and the filtrate was concentrated to give amidinium salt **7** (50 mg). This was crystallized from CH_2Cl_2/hexanes to give **7** as colorless crystals (36 mg, 71%), mp 205 °C (dec.); $[\alpha]_D^{25}$ +62.50 (c 0.200, $CHCl_3$).

[3*S*-[1*R*-(*tert*-Butyl-dimethyl-silanyloxy)ethyl]-2*R*-(2-methyl-5-oxo-2,5-dihydro-furan-2-yl-4*S*-oxo-azetidin-1-yl]acetic acid benzyl ester, 8. To a solution of **3a** and **3b** (1.061 g., 3.26 mmol) (87:13 ratio) in THF (25 mL) at -78 °C was added freshly prepared LiHMDS solution (3.96 mmol in 5 mL of THF). The reaction mixture was stirred at -78 °C for 10 min. Benzyl bromoacetate (916 mg, 4 mmol) was added and the mixture was stirred at -78 °C for 1h, then at room temperature for 5h. The reaction mixture was quenched with satd. NH_4Cl (20 mL), processed as usual and the crude product was purified by column chromatography (30 % EtOAc in hexanes) to give **8** (113 mg, 7%), **4** (396 mg, 26%), and the tricyclic product **9** (145 mg, 14%) in an overall yield of 47%, as an oil.

For **8**; $[\alpha]_D^{25}$ +7.71 (c 0.70, $CHCl_3$); IR ($CHCl_3$): 3020, 2955, 2925, 1755 (broad), 1520, 1415, 1230, 1190, 1110, 925 cm^{-1}. ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.02, 167.48, 167.34, 156.32, 134.73 (tertiary carbon), 67.26 (CH_2), 66.39, 60.51, 60.19, 42.97 (CH_2), 25.66, 22.76, 21.65, 17.72 (C_3H_9-*C*-Si), -4.55 (CH_3Si), -4.62 (CH_3Si). MS(EI): 474 (M^++H), 430, 416, 396, 372, 338, 326, 282, 226, 200, 115, 91 (100%); HRMS: Calcd. for $C_{25}H_{35}NO_6Si$ + H: 474.2312; found: 474.2389.

Synthesis of 9 from 3b. To a solution of **3b** (78 mg, 0.17 mmol) in THF (1 mL) at -78 °C under argon was added freshly prepared LiHMDS (0.18 mmol in 0.5 mL THF) followed by benzyl bromoacetate. The reaction mixture was stirred for 30 min. at -78 °C then treated with LiHMDS (0.10 mmol in 0.5 mL THF). After 30 min at -78 °C and 30 min at room temperature, the reaction mixture was processed as usual and the crude product was purified by column chromatography (30 % EtOAc in hexanes) to give 59 mg of pure product **9** as an oil, (76%); $[\alpha]_D^{25}$ +17.42 (c 0.970, $CHCl_3$); IR ($CHCl_3$): 3020, 2960, 2920, 1770 (broad), 1520, 1440, 1220, 920 cm^{-1}; ^{13}C NMR (75 MHz, $CDCl_3$); δ 173.52, 167.96, 154.54, 134.38 (tertiary carbon of phenyl), 128.66, 128.62, 128.57, 90.79 (tertiary carbon), 67.64 (CH_2) 65.13, 63.46, 62.49, 60.31, 52.69, 31.32 (CH), 25.48 (C_3H_9-*C*-Si), 22.41, 22.35, 17.71 (C_3H_9-*C*-Si), -4.49 (CH_3Si), -5.17 (CH_3Si); MS[EI]; 474 (M^++1), 430, 416, 274, 159, 136, 115, 91 (100%), 75. HRMS: Calcd. for $C_{25}H_{35}NO_6Si$ + H: 474.2312; found: 474.2298.

Synthesis of 10. To a solution of **9** (55 mg, 0.12 mmol) in THF (30 mL) was added a solution of TBAF (600 mg) and AcOH (90μL) in THF (20 mL). An additional 200 mg of TBAF were added and stirring was continued for 20 h. The solvent was evaporated under vacuum, the crude product was dissolved in CH_2Cl_2 (50 mL) and washed several times with water. The organic layer was processed as usual and the crude product was purified by reverse phase column chromatography (50% water in MeOH as eluent) to give pure **10** (24 mg, 57%) and 8 mg of starting material; mp 137-138 °C; $[\alpha]_D^{25}$ +78.6 (c 0.30, $CHCl_3$); IR($CHCl_3$); 3400 (broad), 2960, 2920, 1770 (broad), 1300, 1270, 1180 cm^{-1}. ^{13}C NMR (75 MHz, $CDCl_3$); 173.37, 173.26, 168.07, 134.36 (tertiary carbon of phenyl) 128.75, 128.65, 90 (tertiary carbon), 67.72 (CH), 65.27, 63.65, 61.58, 59.92, 52.71, 31.39 (CH), 22.09, 21.62; MS(EI): 360 (M^++H), 326, 315, 300, 286, 274, 224 (100%), 180, 136, 126, 108, 97.

Synthesis of 11. To the hydroxy compound **10** (31 mg, 0.086 mmol) and the amidine reagent (18 mg, 0.86 mmol) was added Pd/C (10%, 20 mg) in THF and the suspension was stirred under a H_2 atmosphere for 1h. The reaction mixture was filtered, and the residue was washed with MeOH (3 x 10 mL). The combined extract was concentrated to give 39 mg of solid product (95 %) which was recrystallized using CH_2Cl_2/hexane; mp 193-195 °C (dec.); $[\alpha]_D^{25}$ +63.2 (c 0.310, $CHCl_3$); IR ($CHCl_3$): 3300, 2980, 1755, 1660, 1460, 1410, 1310, 1150 cm^{-1}. HRMS: Calcd. for $C_{25}H_{39}N_3O_6$ + H: 478.2917; found: 478.2946.

3*S*-[1*R*-(*tert*-Butyl-dimethyl-silanyloxy)-ethyl]-4*S*-(5-oxo-2,5-dihydro-furan-2*S*-yl)-azetidin-2-one, 13. To a solution of **1** (5.74 g, 20 mmol) in 150 mL of CH_2Cl_2 was added $ZnCl_2$ (1M solution of Et_2O, 4 mL, 4 mmol) at room temperature. The silyloxyfuran **12** (in 20 mL of CH_2Cl_2) was added using a syringe pump over 10 h. The reaction mixture was stirred for 10 h, then quenched with satd. NH_4Cl. The organic layer was processed as usual and the crude product was purified by column chromatography (50% EtOAc in hexanes) to give pure **13** essentially as a single isomer (5.268 g, 85%); mp 117-118 °C; $[\alpha]_D^{25}$ - 44.0 (c 1.0, $CHCl_3$) IR ($CHCl_3$); 3390, 2940, 2900, 2840, 1780, 1740, 1350, 1145 cm^{-1}; ^{13}C NMR ($CDCl_3$): δ 172.16 (-C=O), 16.42 (C=O), 152.50, 123.14, 83.73, 64.95, 60.84, 51.18, 25.51, 22.42, 17.67 (Si-*C*-C_4H_9), -4.55 (Si-CH_3), -5.08 (Si-CH_3); MS(EI): 296 (M-15, loss of Me), 254 (M-57, loss of t-Bu, 100%), 210, 182, 159, 130, 118, 75, 73; HRMS: Calcd. for $C_{25}H_{25}O_4SiN$-*t*-Bu: 254.08486; found; 254.08485.

3*S*-[1*R*-[*tert*-Butyl-dimethyl-silanyloxy)-ethyl-4*S*-(5-oxo-2*R*-phenylsulfanyl-2,5-dihydro-furan-2-yl)azetidin-2-one, 15. To a solution of **1** (3.157 g, 11 mmol) in 100 mL of CH_2Cl_2 was added 2-trimethylsilyloxyfuran (5.625 g, 21 mmol) and $ZnCl_2$ (11 mL of 1N ether solution) at room temperature. The

solution was stirred for 20 h and quenched with satd. NH_4Cl (50 mL). The organic layer was processed as usual and purified by column chromatography on silica gel (25% of EtOAc in hexanes), to give 3.67 g (80%) of **15**, mp 126-127 °C, $[\alpha]_D^{25}$ + 138.13 (c 0.97, $CHCl_3$); IR ($CHCl_3$): 3410, 2975, 2925, 2855, 1770 (broad), 1600, 1470, 1440, 1260, 1140, 1080, 975, 950, 900, 840, 830 cm^{-1}; ^{13}C NMR (75 MHz, $CDCl_3$), δ 169.89, 167.20, 153.68, 136.71, 130.23, 129.25, 126.49 (tertiary carbon of phenyl), 123.16, 96 (tertiary carbon, PhS-*C*-O-), 64.10, 61.67, 52.58, 25.61 (*C*$_4H_9$-C-Si), 22.60, 17.79 (Si-*C*-C_4H_9), -4.46 (Si-CH_3), -5.18 (Si-CH_3); HRMS: Calcd. for $C_{21}H_{29}NO_4SiS$-*t*-Bu: 362.0882; found: 362.0871.

[3*S*-[1*R*-(*tert*-Butyl-dimethyl-silanyloxy)-ethyl]-2-oxo-4*S*-(5-oxo-2*R*-phenylsulfanyl-2,5-dihydro-furan-2-yl)-azetidin-1-yl]-acetic acid benzyl ester, 16. To a solution of **15** (329 mg, 0.785 mmol) in 5 mL of THF at -78 °C under argon was added freshly prepared LiHMDS (2 mL of 0.9 mmol THF solution. After stirring at -78 °C for 30 min, benzyl bromoacetate (1 mmole) was added dropwise. The reaction mixture was stirred at -78 °C for 5 h then at room temperature for 1 h. Usual processing and purification by column chromatography (silica gel, 20% EtOAc in hexanes) gave 279 mg (63%) of **16**; $[\alpha]_D^{25}$ + 70 (c 0.910, $CHCl_3$); IR ($CHCl_3$): 2950, 2925, 2855, 1765 (broad), 1215, 1200, 1180, 830 cm^{-1}; ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.91, 168.15, 166.95, 154.73, 136.51, 134.81 (tertiary carbon of phenyl), 130.09, 129.17, 128.56, 128.52, 128.38, 126.35 (tertiary carbon of phenyl), 122.84, 96.95 (tertiary carbon, PhS-*C*-O), 67.31 (CH_2Ph), 65.02, 60.99, 58.85, 43.13 (N-*C*H_2-CO), 25.57 (C_4H_9-Si), 22.46, (CH_3), 17.66 (Si-*C*-C_4H_9), -4.56 (Si-CH_3), -4.99 (Si-CH_3); HRMS: Calcd. for $C_{26}H_{28}NO_6SiS$ (loss of *t*-Bu): 510.1414; found: 510.1421.

Synthesis of 17. To a solution of **16** (1.92 g, 3.40 mmol) in 50 mL of THF at -78 °C under an argon atmosphere was added freshly prepared LiHMDS (7.0 mmol, 10 mL THF solution). After stirring at -78 °C for 30 min, the reaction mixture was quenched with satd. NH_4Cl (50 mL) and the organic layer was processed as usual. The crude product was purified by column chromatography (silica gel, 20% EtOAc in hexanes) to give 1.551 g (81%) of product **17**; $[\alpha]_D^{25}$ + 21.60 (c 0.860, $CHCl_3$); IR ($CHCl_3$): 2955, 2920, 2850, 1795, 1775, 1740, 1290, 1260, 1170, 1068, 1005, 910, 840 cm^{-1}; ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.60, 172.19, 168.69, 135.88, 134.64 (tertiary carbon of phenyl), 130.10, 129.43, 128.43, 128.38, 128.17, 128.01 (tertiary carbon of phenyl), 98.25 (tertiary carbon, PhS-*C*-O), 67.42 (CH_2), 63.61, 63.48, 63.11, 61.05, 56.06, 35.42 (CH_2), 25.40 (Si-C-*C*$_4H_9$), 21.53, 17.65 (Si-*C*-C_3H_9), -4.73, -5.45. HRMS: Calcd. for $C_{30}H_{38}NO_6SiS$: 568.2189; found: 568.2170.

Synthesis of 18. To a solution of **17** (569 mg, 1 mmol) in 20 mL of toluene under argon was added Bu_3SnH (705 mg, 2.5 mmol) and a catalytic amount of AIBN. The reaction mixture was heated at 90 °C for 2 h then the solvent was removed in vacuo. The crude product was purified by silica gel column chromatography (20% EtOAc in hexanes) to give 327 mg (71%) of **18** as an oil; $[\alpha]_D^{25}$ +72.86 (c 0.420, $CHCl_3$); IR ($CHCl_3$): 3155, 3020, 2960, 2930, 2860, 1790, 1770, 1740, 1470, 1380, 1215, 1170, 1140, 1095 cm^{-1}. ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.84, 172.86, 169.19, 134.66 (tertiary carbon of phenyl), 128.40, 128.33, 128.06, 82.03, 67.28 (CH_2), 64.27, 63.08, 59.45, 57.93, 49.71, 34.70 (CH_2), 25.36 (Si-C-*C*$_3H_9$), 22.39, 17.62 (Si-*C*-C_3H_9), -4.63, -5.39; HRMS: Calcd. for CHNOSi-*t*-Bu: 402.1373; found: 402.1400.

Synthesis of 19. To a solution of **18** (60 mg, 0.13 mmol) in THF (20 mL) was added a solution of TBAF (300 mg) and acetic acid (90 μL) in THF (10 mL). The reaction mixture was stirred at room temperature for 24 h. An additional 300 mg of TBAF in THF (10 mL) were added and the mixture was stirred for 24 h. Concentration and purification by reverse phase column chromatography (50% MeOH in water as eluent) gave 26 mg (58%) of **19** as an oil; $[\alpha]_D^{25}$ + 109.20 (c 0.750, $CHCl_3$); IR($CHCl_3$): 3680, 3610, 3020, 2970, 1790, 1770, 1740, 1520, 1230, 1050, 930 cm^{-1}; ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.41, 172.56, 169.06, 134.40 (tertiary carbon of phenyl), 128.33, 127.89, 81.80, 67.32 (CH_2), 64.82, 63.07, 58.96, 58.79, 49.75, 34.60 (CH_2), 21.60; MS(EI) 346(M+H), 322, 291, 260, 208, 193, 179, 167, 149, 135, 123.

Synthesis of 20. To a solution of **19** (15 mg, 0.043 mmol) in 1 mL of THF was added the amidine reagent and Pd/C (10%, 2 mg) and the suspension was stirred under a H_2 atmosphere for 20 min. The reaction mixture was filtered and the residue was washed with MeOH several times. The filtrate was concentrated and recrystallized (CH_2Cl_2/hexanes) to give **20** (13 mg, 65%); mp 137-139 °C; $[\alpha]_D^{25}$ +48.29 (c 0.350, $CHCl_3$); IR($CHCl_3$): 3280 (broad), 2980, 2950, 2930, 1760 (broad), 1660, 1460, 1405, 1310, 1150 cm^{-1}.

Synthesis of 21. To a solution of **6** (2.25 g, 6.27 mmol) in 60 mL of CH_2Cl_2 was added Et_3N (2.0 mL, 15 mmol) and MsCl (700 μL, 9 mmol) at room temperature. The solution was stirred for 1h then concentrated. The residue was dissolved in EtOAc and washed with water and brine. The organic layer was processed as usual then purified by column chromatography on silica gel (50% hexanes in EtOAc) to give 21.15 g (77%) of **21** as an oil; $[\alpha]_D^{25}$ + 88.52 (c 1.35, $CHCl_3$); IR ($CHCl_3$): 2800, 1790, 1780, 1750, 1460, 1360, 1175, 910 cm^{-1}; HRMS: Calcd. for $C_2OH_{24}O_8NS$: 438.12100; found: 438.12225.

Synthesis of 22. To a solution of **21** (2.151 g, 6.31 mmol) in 20 mL of benzene was added DBU (1.01 g, 4.92 mmol) at room temperature. The solution was stirred for 1.5 h, then concentrated in vacuo and purified by column chromatography on silica gel (30% EtOAc in hexanes) to give 1.51 g of (90%) pure **22** (83:17 ratio of isomers; mp 75-77 °C; $[\alpha]_D^{25}$ +117.7 (c 0.7, $CHCl_3$); IR ($CHCl_3$): 2700, 1790, 1770, 1500, 1460, 1450, 1390, 1130, 970, 920 cm^{-1}; ^{13}C NMR (75 MHz, $CDCl_3$): 172.67, 69.31, 169.08, 136.65, 134.15, 128.68, 128.07, 127.77, 90.32 (tertiary carbon), 68.02, 67.02 (CH_2), 63.75, 54.2, 34.19 (CH_2), 23.21, 14.86; HRMS: Calcd. for $C_{19}H_{20}O_5N$: 342.12961; found: 342.13416.

Synthesis of 23. To a solution of **22** (50 mg, 0.147 mmol) in 2 mL of THF was added 10% Pd/C (5 mg) and the amidine reagent (31 mg, 0.148 mmol) at room temperature. The reaction mixture was stirred under a H_2 atmosphere for 10 min, then filtered through Celite and washed with THF several times. Concentration gave **23** as a white solid from hexanes (50 mg, 78%); mp 78-81 °C; $[\alpha]_D^{25}$ +75.57 (c 0.61, $CHCl_3$): 2960, 2940, 2880, 1770, 1670, 1570, 1460, 1160, 970 cm^{-1}; ^{13}C NMR (75 MHz): 176.04, 174.761, 167.19, 138.46, 126.75, 91.65, 68.35, 67.59, 55.67, 53.31, 35.42, 31.60, 31.41, 31.09, 30.90, 30.87, 30.73, 30.62, 29.84, 29.77, 24.95, 24.31, 22.48. 15.18, 13.96; MS (fab): 342 M+1, 314, 289, 274, 228, 206, 178, 154, 136, 122.

Synthesis of 24. Into a solution of **22** (100 mg, 0.29 mmol) in CH_2Cl_2 (5 mL) was bubbled O_3 for 15 min at -78 °C. The CH_2Cl_2 was slowly evaporated, 5 mL THF was added, and the reaction mixture was cooled to 0 °C. To the stirred solution was added $NaBH_3CN$ (32 mg, 0.32 mmol) and after 10 min the solution was concentrated and the residue was purified by column chromatography on silica gel (60% EtOAc in hexanes) to give 63 mg (66% yield) of the hydroxy compound as an oil. To this was added pyridine (100 μL, 1.2 mmol) and Ac_2O (50 μL, 0.52 mmol). The reaction mixture was stirred for 20 h and concentrated. The crude residue was purified by chromatography (40% EtOAc in hexanes) to give 60 mg (85%) of **24**; $[\alpha]_D^{25}$ +173.4 (c 0.05, $CHCl_3$); IR ($CHCl_3$): 2980, 1800, 1700, 1460, 1380, 1135, 1100, 930 cm^{-1}; ^{13}C NMR ($CDCl_3$, 75 MHz): 172.42, 170.35, 169.72, 168.43, 133.94, 128.17, 128.11, 127.78, 91.46, 74.78, 67.25, 64.51, 63.85, 55.25, 32.81, 21.58, 19.60; HRMS: Calcd. for $C_{19}H_{220}NO_7$: 374.12396; found: 374.12560.

Synthesis of 25. To a solution of **24** (35 mg, 0.094 mmol) in THF at room temperature was added Pd/C (5 mg) and the amidine reagent (20 mg, 0.096 mL). The reaction mixture was stirred under H_2 atmosphere for 2 h. After completion of the reaction, it was filtered through Celite, washed several times with THF and the combined THF solution was evaporated in vacuo to give 35 mg (76%) of **25**; mp 160-165 °C (dec.); $[\alpha]_D^{25}$ +111.5 (c 0.4, $CHCl_3$); IR($CHCl_3$): 2980, 1790, 1750, 1655, 1480, 1380, 1155 cm^{-1}; ^{13}C NMR (75 MHz, $CDCl_3$): 174.81, 174.03, 170.66, 169.95, 166.73, 92.04, 75.59, 67.19, 63.40, 56.01, 52.82, 33.85, 31.09, 30.55, 30.21, 29.32, 29.27, 23.80, 23.44, 19.67.

Synthesis of 26. To a solution of **5** (1.25 g, 2.64 mmol) in 20 mL of THF was added NaHMDS (1M THF solution, 5.5 mL, 5.5 mmol) at -78 °C. The reaction mixture was stirred at -78 °C for 30 min and PhSeBr was

added. The reaction mixture was stirred for 30 min at -78 °C, then it was quenched with satd. NH_4Cl. Usual workup and purification by column chromatography on silica gel (25% EtOAc in hexanes) gave 1.29 g (78%) of **26**.

Synthesis of 27. To a solution of **26** (1.49 g, 2.37 mmol) in 20 mL of CH_2Cl_2 was added m-CPBA (552 mg, 3.2 mmol). The reaction mixture was stirred for 1h and concentrated in vacuo. The crude product was purified by column chromatography on silica gel (20 % ethyl acetane hexanes) to give 683 mg (61%) of pure **27** as an oil; ^{13}C NMR (75 MHz, $CDCl_3$): δ 178.09, 171.58, 171.43, 165.86, 134.28 (tertiary carbon of phenyl), 128.82, 128.63, 128.53, 115.19, 88.63, 68.11 (CH_2), 64.24, 62.16, 58.36, 55.81, 25.52, 25.12, 22.03, 17.79, -4.39, -5.25.

Synthesis of 28. To a solution of **27** (366 mg, 0.78 mmol) in 10 mL of benzene was added PhSH (165 μL, 1.5 mmol), followed by Hunig's base (140 μL, 0.8 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 1h, then the mixture was loaded on silica gel column (eluent 10% EtOAc in hexanes) to give pure **28** as an oil (373 mg, 83%); $[\alpha]_D^{25}$ -1.73 (c 1.50, $CHCl_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.64, 170.92, 167.45, 135.96, 134.44 (tertiary carbon of ArH), 129.89, 129.54, 128.85, 128.81, 128.62, 128.55, 93.83, 69.23, 68.82, 67.71, 64.86, 62.31, 61.54, 40.86, 25.55, 22.50, 20.63, 17.77, -4.00, -4.5; MS (EI): M+1 582.0, 554.0, 523.9, 472.1, 416.1, 382.1, 291.8, 273.8, 251.9, 236.0, 228.1, 208.1, 199.1, 178.1, 159.1, 147.0, 117.0, 115.1, 91.1.

Synthesis of 29. To a solution of **28** (30 mg, 0.05 mmol) in 1 mL of THF was added DIBAL-H (75 μL of 1M CH_2Cl_2, 0.05 mmol) at -78 °C. The reaction mixture was stirred at room temperature for 30 min, then it was quenched with satd. NH_4Cl (100 μL) and stirred for 30 min. The crude reaction mixture was processed as usual then purified by column chromatography (30% EtOAc in hexanes) to give pure **29** as an inseparable mixture of anomers (20 mg, 66%); $[\alpha]_D^{25}$ +0.93 (c 4.75, $CHCl_3$); IR ($CHCl_3$): 3610, 2960, 2940, 2860, 1760 (broad), 1470, 1460, 1380, 1160, 1110 cm^{-1}; MS (EI): M+1, 584.0, 525.9, 448.0, 419.0, 408.0, 384.1, 366.1, 341.9, 321.8, 311.8, 293.8, 281.7, 251.9, 237.9, 208.1, 199.1, 180.1, 159.0, 136.0, 115.0, 91.1 (100%); HRMS: Calcd. for $C_{31}H_{42}NO_6OSiS$: 584.25021; found 584.25018.

Synthesis of 30. To a solution of **29** (25 mg, 0.043 mmol) in 0.5 mL of CH_2Cl_2 was added pyridine (158 mg, 2.0 mmol) followed by Ac_2O (102 mg, 1.0 mmol) at room temperature. The reaction mixture was stirred for 10 h, processed as usual then purified by column chromatography (30% EtOAc in hexanes) to give 20 mg (74%) of pure **30** as an inseparable mixture of anomers (2:1); $[\alpha]_D^{25}$ +6.78 (c 1.80, $CHCl_3$); IR ($CHCl_3$): 2960, 2940, 2860, 1760, 1465, 1380, 1110, 1010, 840 cm^{-1}; HRMS: Calcd. for $C_{33}H_{44}NO_7SiS$: 626.26078; found: 626.26080.

Synthesis of 31a and 31b. To a solution of **30** (155 mg, 0.24 mmol) in 4 mL of CH_2Cl_2 was added m-CPBA (224 mg of 60%, 1.3 mmol) at room temperature. The reaction mixture was stirred for 13 h, then processed as usual to give 140 mg (88%) of a crude product as a mixture of anomers that were separable by chromatography (30% EtOAc in hexanes); for the faster moving major isomer **31a**; $[\alpha]_D^{25}$ +11.30 (c 2.30, $CHCl_3$); IR ($CHCl_3$): 2980, 2940, 2865, 1760 (broad), 1330, 1320, 1150, 1010 cm^{-1}; ^{13}C NMR (75 MHz, $CDCl_3$): δ 176.09, 169.38, 167.44, 138.11, 134.65, 134.59, 129.99, 129.18, 128.49, 128.37, 95.77, 92.71, 87.33, 67.93, 66.04, 65.50, 63.25, 39.71, 25.62, 22.46, 20.97, 19.83, 17.73, -4.42, -4.93; HRMS: Calcd. for $C_{33}H_{44}NO_9SiS$: 658.25061; found: 658.25061; for the minor isomer **31b** (oil); $[\alpha]_D^{25}$ -5.56 (c 0.90, $CHCl_3$); IR ($CHCl_3$): 2980, 2940, 2860, 1760, 1450, 1330, 1150, 1010 cm^{-1}; ^{13}C NMR (75 MHz, $CDCl_3$): 175.18, 169.39, 167.57, 138.06, 134.74, 134.58, 129.83, 129.22, 128.47, 128.33, 95.96, 94.82, 86.20, 67.94, 65.17, 64.70, 63.14, 60.37, 39.96, 25.58, 22.50, 21.22, 20.79, 17.75, -4.45, -5.04; HRMS: Calcd. for $C_{33}H_{44}NO_9SiS$: 658.25061; found: 658.25061.

Synthesis of 32a. To a solution of **31a** (33 mg, 0.05 mmol) in 2 mL of CCl_4 was added DBU (9 mg, 0.06 mmol) at room temperature. The reaction mixture was stirred for 6 h then loaded on a silica gel column and eluted with 20% EtOAc in hexanes to give 18 mg (70%) of **32a**, which was unstable and decomposed upon standing.

Synthesis of 33a and 33b. To a solution of **29** (45 mg, 0.077 mmol) in 2 mL of CH_2Cl_2 was added 2,2'-dithiopyridyl carbonate (76 mg, 0.308 mmol), DMAP (catalytic) and Et_3N (44 μL, 0.32 mmol), at room temperature. The reaction mixture was stirred for 22 h then it was chromatographed on a silica gel column (25% EtOAc in hexanes as eluent) to give 28 mg (50%) of **33a** and 16 mg (29%) of compound **33b.**

Synthesis of 34. To a solution of **33a** (95 mg, 0.13 mmol) in 2 mL of CH_2Cl_2 was added dry MeOH (15 μL, 0.38 mmol) followed by AgOTf (70 mg, 0.27 mmol) at room temperature. The reaction mixture was stirred for 30 min and concentrated. The crude product was purified by column chromatography (20% EtOAc in hexanes) to give 64 mg (81%) of **34** as a 3:1 anomeric mixture. For pure major isomer: $[\alpha]_D^{25}$ -4.81 (c 0.52, $CHCl_3$); IR ($CHCl_3$): 2960, 2940, 2860, 1760, 1380, 1110, 1020 cm^{-1}; HRMS: Calcd. for $C_{32}H_{44}NO_6SiS$: 598.26680; found: 598.26587.

Synthesis of 35a and 35b. To a solution of **34** (42 mg, 0.70 mmol) in 2 mL of CH_2Cl_2 was added m-CPBA (33 mg, 0.192 mmol) at room temperature and the mixture was stirred for 10 h. Concentration and purification by column chromatography (25% of EtOAc in hexanes) gave 34 mg (77%) of a mixture, which was further purified to give 18 mg of major isomer **35a** and 16 mg of minor isomer **35b.** For **35a** (oil): $[\alpha]_D^{25}$ +2.42 (c 0.60, $CHCl_3$). IR ($CHCl_3$): 2960, 2940, 2860, 1760, 1450, 1320, 1150, 840 cm^{-1}; HRMS: Calcd. for $C_{32}H_{44}NO_8SiS$: 630.25740; found: 630.25568.

Synthesis of 36a. To a solution of **35a** (18 mg, 0.026 mmol) in 500 μL of CCl_4 was added DBU (10 μL, 0.066 mmol) at room temperature and the mixture was stirred for 3 h. Concentration and purification by column chromatography (20% EtOAc in hexanes) gave 11 mg (79%) of pure **36a**, which decomposed slowly upon standing.

Synthesis of 37. To a solution of **29** (89 mg, 0.153 mmol) in 3 mL of MeOH was added $NaBH_4$ at room temperature and the mixture was stirred for 30 min. Concentration and purification on silica gel column (50 % EtOAc in hexanes) gave 64 mg (72%) of pure **37** as an oil; $[\alpha]_D^{25}$ -10.26 (c 0.40, $CHCl_3$); IR ($CHCl_3$): 3360, 2960, 2940, 2860, 1760 cm^{-1}; HRMS: Calcd. for $C_{31}H_{44}NO_6SiS$: 586.26586; found: 586.26740.

Synthesis of 38. To a solution of **37** (as an oil) (61 mg, 0.104 mmol) in 2 mL of CH_2Cl_2 was added pyridine (123 μL, 1.5 mmol), followed by MsCl (24 μL, 0.3 mmol) at room temperature. After stirring for 3 h, the reaction mixture was concentrated and the residue was purified by column chromatography (20% EtOAc in hexanes) to give 46 mg (78%) of pure **38** as an oil; $[\alpha]_D^{25}$ +2.89 (c 1.90, $CHCl_3$); IR ($CHCl_3$): 2960, 2940, 2860, 1760, 1465, 1380, 1150, 1020 cm^{-1}; ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.48, 168.73, 135.75, 134.94, 130.52, 128.94, 128.64, 128.53, 128.42, 128.31, 91.80, 73.06, 68.66, 67.22, 65.52, 65.44, 62.89, 59.92, 37.47, 25.58, 22.64, 19.78, 17.75, -4.39, -5.02; HRMS: Cacld. for $C_{31}H_{42}NO_5SiS$: 568.25531; found: 568.25300.

Synthesis of 39. To a solution of **38** (25 mg, 0.044 mmol) in 2 mL of CH_2Cl_2 was added m-CPBA (17 mg, 0.1 mmol) at room temperature. The reaction mixture of stirred for 1.5 h and an additional 17 mg of m-CPBA was added. The reaction mixture was stirred for 6 h, then passed through a silica gel column (30% EtOAc in hexanes) to give 25 mg (95%) of pure **39** as an oil; $[\alpha]_D^{25}$ +12.06 (c 1.70, $CHCl_3$); IR ($CHCl_3$): 2960, 2940, 2860, 2900, 1760, 1465, 1450, 1320, 1150, 1080, 980, 910 cm^{-1}; ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.93, 167.56, 137.92, 134.37, 134.11, 129.59, 128.83, 128.21, 128.16, 128.06, 91.09, 87.29, 67.64,

65.16, 64.74, 64.56, 62.69, 58.92, 32.78, 25.30, 22.17, 18.79, 17.42, -4.69, -5.28; HRMS: Calcd. for $C_{31}H_{42}NO_7SiS$: 600.24512; found: 600.24280.

Synthesis of 40. To a solution of **39** (25 mg, 0.042 mmol) in 1 mL of CCl_4 was added DBU (10 μL) at room temperature and the reaction mixture was stirred for 1 h. The crude product was loaded on a silica gel column (35% EtOAc in hexanes) to give 14 mg (74%) of **40**.

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