Stereoselective Synthesis of a Key Intermediate of Sanfetrinem by Means of a Chelated Tin(IV) Enolate

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Received November 8, 1996[⊗]

(2*S*)-2-Methoxycyclohexanone [(2*S*)-**6**], reacts with the 4-acetoxyazetidinone **3a** in the presence of $SnCl_4$ and a tertiary amine base (such as *N*,*N*-diisopropylethylamine) to give the ketoazetidinone **5** (a key intermediate in the synthesis of the broad-spectrum antibiotic sanfetrinem **2a**) with high yield and diastereoselectivity. Low-temperature NMR studies of the reaction indicated the formation of a 1:1 chelate complex **11** between $SnCl_4$ and (2*S*)-**6** which, on addition of the base is transformed into the highly reactive chelated tin enolate **12**. The formation of compound **11** has been confirmed by single-crystal X-ray analysis. The high diastereoselectivity observed is believed to derive from an open transition state where the chelated $SnCl_4$ amplifies the stereochemical influence of the methoxy group. This reaction offers considerable advantages over all existing syntheses of the ketoazetidinone **5** and is currently under evaluation for inclusion in the industrial synthesis of sanfetrinem.

Introduction

In recent years our interest on the synthesis of new antibacterial agents has been concentrated on a new class of antibiotics, the trinems (**1**), first disclosed in our laboratories,[1] which demonstrated extremely interesting biological properties both *in vitro* and *in vivo*. Sanfetrinem (GV104326, **2a**)[2] (Figure 1) and its metabolically labile ester **2b** have been selected for development studies and are currently in phase II clinical trials.

Due to the complexity of the structure, bearing five stereogenic centers, and the large amounts of final drug material required to support development studies, a high-yielding, short, practical, and robust route to **2a** and **2b** was required. Although the existing route[1c] proved to be robust and provided us with multikilogram quantities of the desired trinems to support early development studies, it suffered from two major drawbacks: (a) low overall chemical yields (8−9%); (b) high number of stages (11 steps, 15 chemical transformations).

We have already reported our results in the direct synthesis of two key intermediates **4**[3,4] and **5**[5,6] from commercially available acetoxyazetidinone **3a** (Scheme 1). In both approaches significant advances have been made both in terms of yields and in the reduction of number of stages. Although a convergent and stereoselective synthesis of ketoazetidinone **5** could be conveniently established, the procedure was still rather complicated by the fact that in order to ensure high yield and good diastereoselectivity, a protection−deprotection step of the azetidinone nitrogen was also required.[5] Moreover, enantiomerically pure silyl enol ether derivative of (2*S*)-**6**, required for this coupling, could be obtained with high regioselectivity only under strictly controlled conditions, employing the expensive trimethylsilyl trifluoromethanesulfonate.

An alternative linear route to **5** has also recently been published[7] but was not considered amenable to an industrial synthesis of sanfetrinem.

A less complicated procedure for the synthesis of **5** from **3a** was highly desirable, and we decided to turn our

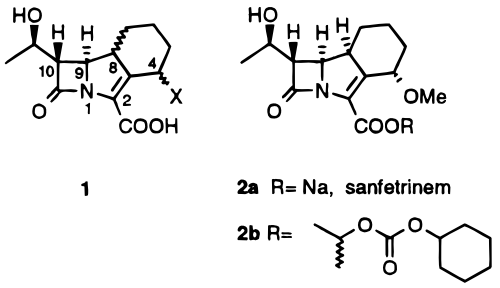
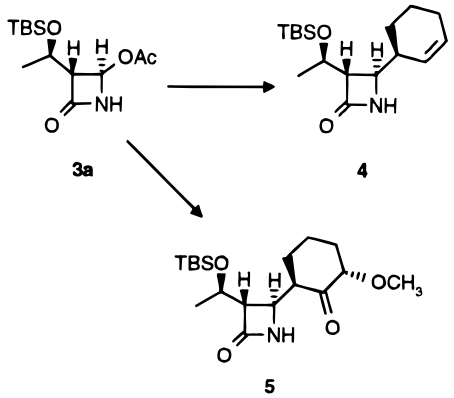


Figure 1.

Scheme 1



TBS= *tert*-butyldimethylsilyl

[⊗] Abstract published in *Advance ACS Abstracts,* February 1, 1997.

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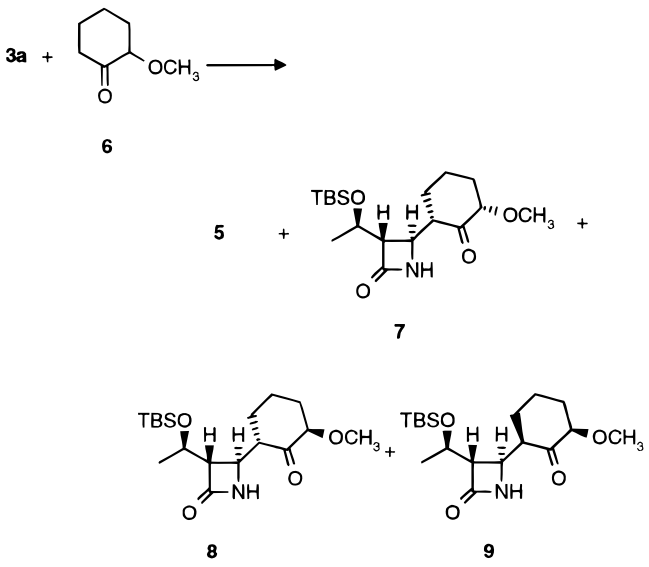
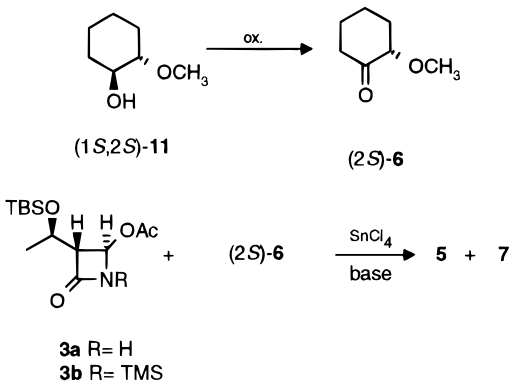
Scheme 2



Scheme 3



attention to the direct coupling between 2-methoxycyclohexanone (**6**) and acetoxyazetidinone **3a**.

Tin Enolate Chemistry

It is well known that titanium(IV) chloride can promote base-mediated enolization of ketones.[8] Treatment of titanium enolates thus formed with an aldehyde leads to the formation of aldol condensation products. This protocol has been applied by Cozzi and co-workers in the stereoselective synthesis of β-lactams from chelated thiopyridyl ester enolates and imines.[9]

A 1:1 complex between 2-methoxycyclohexanone and $TiCl_4$ has been the subject of NMR studies by Reetz and co-workers.[10] We reasoned that an enolate formed from this chelate complex could give preferentially the required diastereomer with good diastereoselectivity in the condensation reaction with **3a**.

We decided to initiate our studies on the direct coupling between the titanium enolate of 2-methoxycyclohexanone (**6**) and 4-acetoxyazetidinone **3a** (Scheme 2). Thus, treatment of 2 equiv of a 1:1 mixture of **6** and $TiCl_4$ with triethylamine in anhydrous dichloromethane at −78 °C followed by addition of 1 equiv of **3a** at −78 °C did not give any detectable reaction product. Increasing reaction temperature and variation of reactant ratios did not result in any improvement and, at temperatures above −10 °C extensive decomposition of **3a** was observed. This was in line with previous observations made during our studies in the Lewis acid-mediated coupling of silyl enol ethers with **3a** and its *N*-trimethylsilyl derivative **3b**.[5] The use of $TiCl_4$ always led to poor results and extensive decomposition of the 4-acetoxyazetidinone.

Table 1. Influence of the Reaction Temperature and Effect of Different Lewis Acids[a]

entry	Lewis acid (equiv)	base (equiv)	*T* (°C)	**5** yield[b] (%)	ratio **5**:**7**[c]
1	$SnCl_4$ (3)	Et_3N (2.2)	−78 to 0	35	13:1
2	$SnCl_4$ (3)	Et_3N (2.2)	−20 to 0	39	16:1
3	$SnCl_4$ (3.4)	Et_3N (2.6)	−20 to 0	50	10:1
4	$SnBr_4$ (3.4)	Et_3N (2.6)	−20 to 0	38	10:1
5	$TiCl_4$ (3.4)	Et_3N (2.6)	−20 to 0	0	
6	$SnCl_4$ (3.4)	Et_3N (2.6)	0 to 10	60	8.3:1
7[d]	$SnCl_4$ (3.4)	Et_3N (2.6)	0 to 10	44	30:1

[a] Reaction in anhydrous CH_2Cl_2; 1 g of **3** and 2 equiv of (2*S*)-**6** were used; (2*S*)-**6** was purified by flash chromatography prior to use. [b] Solution yield determined by HPLC (Hypersil ODS2, 250 mm × 4 mm × 5 μm, buffer $(NH_4)H_2PO_4$ 50 mM/CH_3CN 45/55, flow rate 1.0 mL/min, UV at 205 nm, **5** as external standard). [c] Ratios determined by NMR. [d] Compound **3b** was employed.

On the basis of these results we decided to replace $TiCl_4$ with another Lewis acid that could efficiently activate **3a** under the reaction conditions. Tin(IV) chloride was considered a possible candidate because it had already demonstrated its efficacy in the one-pot formation of **5**.[5]

The availability of sufficient amounts of enantiomerically pure (2*S*)-**6**[5,11] led us to initiate our studies with this reactant in order to reduce the complexity of the reaction mixture by reducing the number of the possible isomers. Initial experiments were made under standard protocol conditions (generation of the enolate at −78 °C followed by addition of either **3a** or a preformed mixture of **3a** and a Lewis acid), but we were able to detect only traces of coupling products **5** and **7** (HPLC and NMR analysis of the crude reaction mixtures). However, variation of the reaction conditions led us to find a simpler and more satisfactory protocol: addition of triethylamine to a mixture of **3a**, (2*S*)-**6**, and $SnCl_4$, respectively at −78 °C and then raising the temperature to 0 °C resulted in the formation of a mixture of products in which the presence of compounds **5** and **7** could be measured (HPLC and NMR). The results of these initial experiments are reported in Table 1. We were pleased to observe that the ratio of the two isomers originated by the same enantiomer (2*S*)-**6** (**5** and **7**) was high and in favor of the desired ketoazetidinone **5**. Increasing the reaction temperatures resulted in a significant increase in solution yield although a reduction in stereoselectivity was observed. Under these new conditions $TiCl_4$ again failed to give the desired reaction products while $SnBr_4$ gave similar results to $SnCl_4$. The use of *N*-silylated derivative **3b** gave a reduction in yields and, as expected, an improvement in terms of stereoselectivity (compare entries 6 and 7). Due to the more complicated conditions that have to be employed when working with **3a** we decided to carry out all subsequent studies on **3b**. A

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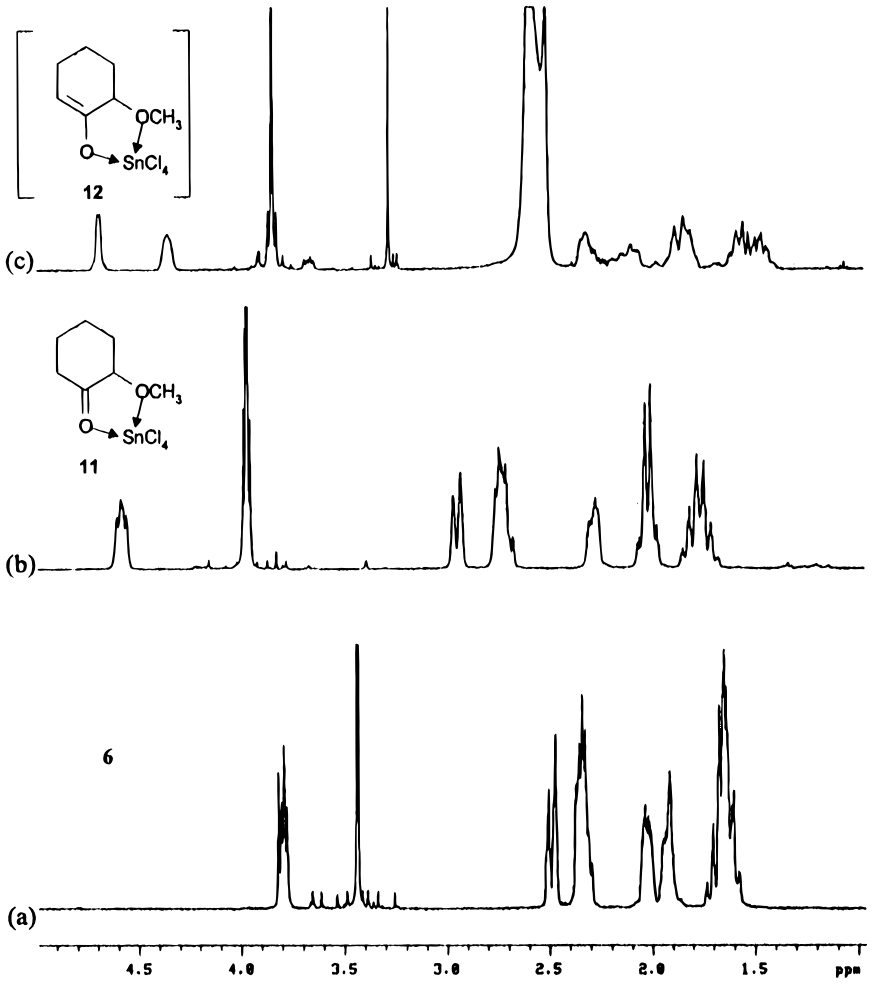

Figure 2. ^{1}H-NMR at −40 °C: (a) **6**; (b) **6** + 1 equiv of $SnCl_4$; (c) 6 + 1 equiv of $SnCl_4$ + 1 equiv of lutidine.

Table 2. Influence of Bases and Solvents[a]

entry	solvent	base (equiv)	*T* (°C)	**5** (yield)[b]	ratio **5**:**7**[c]
1	PhCl	Et_3N (2.6)	-20 to 0	49%	22:1
2	PhF	Et_3N (2.6)	-20 to 0	54%	11:1
3	$PhCH_3$	Et_3N (2.6)	-20 to 0	5%	nd
4	CH_2Cl_2	*i*-Pr_2EtN (2.6)	-5 to 0	65%	15:1
5	CH_2Cl_2	*i*-Bu_3N (2.6)	- 5 to 0	77%	11:1
6	CH_2Cl_2	2,6-lutidine (2.6)	-5 to 0	60%	25:1
7[d]	CH_2Cl_2	*i*-Bu_3N (2.6)	-10 to 0	70%	18:1

[a] One gram of **3,** 2 equiv of (2*S*)-**6** and 3.4 equiv of $SnCl_4$ were used; (2*S*)-**6** was purified by flash chromatography prior to use. [b] Solution yield determined by HPLC (**5** as external standard). [c] Ratios determined by NMR. [d] A total of 1.2 eq of (2*S*)-**6** were used.

number of experiments with racemic **6** were also carried out; mixtures of diastereomers **5** and **7**−**9** were always observed. Ketoazetidinones **5** and **8** (originated by the two enantiomers of **6**) were the major isomers and their ratio by NMR of the crude reaction mixture was always close to 1:1, indicating no difference in reactivity between the two enantiomers.

Encouraged by these promising initial observations, studies on the reaction conditions were immediately undertaken. The influence of the base, reagent proportions, temperature, and solvents were analyzed and some representative results are reported in Table 2. Among the amines studied, triethylamine, *N*,*N*-diisopropylethylamine, triisobutylamine and 2,6-lutidine were found to be effective and high solution yields were measured. Dichloromethane and chlorobenzene, with reaction temperatures of 0−5 °C gave consistently the best results while it was found that reduction of the equivalents of (2*S*)-**6** did not result in a dramatic decrease in yield and gave a substantial reduction in side products of the reaction (Table 2, entry 7).

NMR Studies

In order to gain an insight into the reaction mechanism, variable-temperature NMR studies were undertaken.

A first set of experiments on 2-methoxycyclohexanone (**6**) were carried out at various temperatures between −40 and 23 °C in CD_2Cl_2.[12] The addition of measured amounts of $SnCl_4$ to a solution of **6** in CD_2Cl_2 resulted in a dramatic change of the ^{1}H-,^{13}C-, and ^{119}Sn-NMR spectra. In particular, after the addition of 1 molar equiv of tin(IV) chloride, the complete transformation of **6** into a new species was observed (Figures 2−4). In the proton spectrum, at −40 °C, all the proton signals were shifted downfield to varying degrees; in particular, the hydrogens at C-2, C-6, and those of the methoxy group showed the most significant changes in chemical shift: the proton at C-2 moves from 3.80 to 4.58 ppm with a change also in the coupling constant values, suggesting modification of the ring conformation, similarly, the chemical shift of

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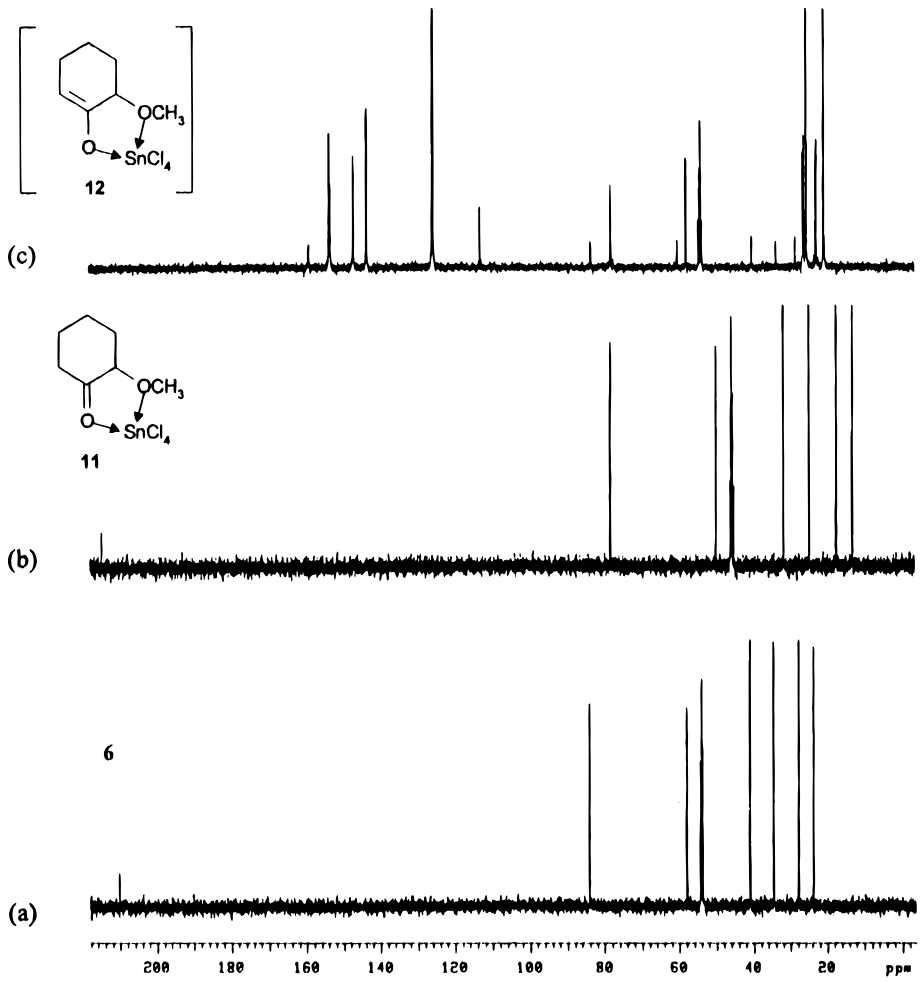

Figure 3. ^{13}C-NMR at −40 °C: (a) **6**; (b) **6** + 1 equiv of $SnCl_4$; (c) **6** + 1 equiv of $SnCl_4$ + 1 equiv of lutidine.

the methoxy group moves from 3.44 to 3.97 ppm. In the ^{13}C-NMR, carbons C-1 and C-2 and the methoxy group again showed the most significant change in chemical shifts (Figure 3): C-2 moves from 86.0 to 89.0 ppm, the carbonyl carbon undergoes a notable shift downfield from 212.1 to 240.3 ppm, and the methoxy carbon moves from 59.7 to 57.5 ppm. In the ^{119}Sn spectrum, a single signal at −542 ppm was observed, suggesting the formation of a hexacoordinate tin species.[13,14] On the basis of this evidence the formation of a 1:1 chelate complex (**11**, Figure 2) between **6** and $SnCl_4$ was proposed. This complex was found to be stable in CD_2Cl_2 at room temperature for at least one week.

Further support to our proposed structure (**11**) came from the literature. We have already mentioned that a 1:1 chelate complex between **6** and $TiCl_4$ has been reported;[9] moreover formation of stable 1:1 chelate complex between $SnCl_4$ and α-alkoxyaldehydes[15] and ketones[11] have been published.

In separate experiments 0.5 and 2 equiv respectively of $SnCl_4$ were added to **6** . In the first case a mixture of starting material **6** and complex **11** was measured while in the second case an excess of tin(IV) chloride did not result in detectable changes to the NMR spectra.

In a third series of experiments a 1:1 solution of **6** and $SnCl_4$ in CD_2Cl_2 was cooled to −40 °C and treated with 1 equiv of 2,6-lutidine. This base was selected both because it proved to work efficiently in the $SnCl_4$-promoted reaction between **3a** and **6** and for its low interference in the analysis of NMR spectra.

On recording the ^{1}H-,^{13}C-, and ^{119}Sn-NMR spectra at −40 °C showed the formation of a new species (Figures 2−4). Protons at C-2 and of the methoxy group were found to undergo a moderate shift upfield compared to **11**: the proton at C-2 moves from 4.58 to 4.35 ppm, protons of the methoxy group move from 3.97 to 3.85 ppm while disappearance of signals belonging to hydrogens at C-6 and appearance of a new signal at 4.69 ppm indicated the formation of enolate **12**. ^{13}C- and ^{119}Sn-NMR spectra were also in agreement with the proposed structure with C-6 giving a signal at 112.9 ppm. The ^{119}Sn-NMR spectrum showed a single peak at −546 ppm, again indicating the presence of a hexacoordinate tin atom. Intermediate **12** was stable at low temperatures (−40 °C) but degradation was found to occur rapidly at 0 °C.

A similar series of experiments were also run on 4-acetoxyazetidinone **3a**. The ^{1}H- and ^{13}C-NMR spectra of **3a** were first recorded at −40, 0, and 23 °C. Addition of measured amounts of $SnCl_4$ led to a significant change in the ^{1}H- and ^{13}C-NMR spectra (as shown in Figures 5 and 6). In particular, after addition of 0.5 molar equiv of $SnCl_4$ the disappearance of signals corresponding to

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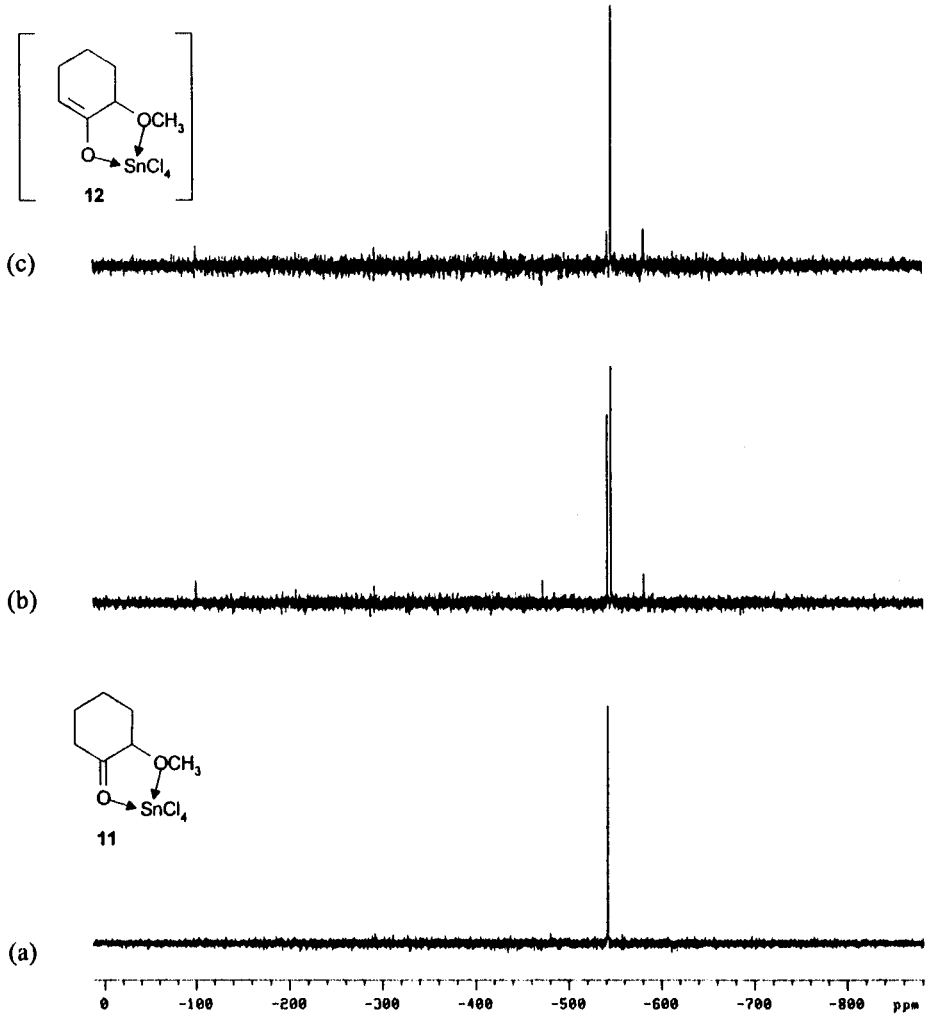

Figure 4. ^{119}Sn-NMR at −40 °C: (a) **6** + 1 equiv of $SnCl_4$; (b) **6** + 1 equiv of $SnCl_4$ + 0.5 equiv of lutidine; (c) **6** + 1 equiv of $SnCl_4$ + 1 equiv of lutidine.

3a and the formation of a new species was observed. Further addition of $SnCl_4$ did not modify the NMR spectra. The ^{119}Sn-NMR spectra, recorded at −60 °C (Figure 7), showed a sharp peak at −645 ppm. On the basis of these initial observations one only could hypothesize, in agreement with previous observation by Denmark on NMR studies on benzaldehyde−$SnCl_4$ complexes,[12] the formation of a 2:1 complex between **3a** and $SnCl_4$. However a clear idea of the structure of the complex could not be inferred. Analysis of the ^{13}C-NMR spectra with heteronuclear correlation experiments permitted the precise assignment of C=O signals, leading us to establish that **3a** is complexed with $SnCl_4$ via the lactam carbonyl oxygen atom (**13**, Figure 5). This experiment allowed us to assign the signal at 168.7 ppm to the lactam carbon which, upon addition of $SnCl_4$, undergoes a dramatic shift from 168.4 to 177.6 ppm. This complex is rather unstable at temperatures above 0 °C but nevertheless satisfactory NMR spectra could also be recorded for a short time at room temperature.

In a final experiment 2 equiv of enolate **12** (generated from (2*S*)-**6** as described above in CD_2Cl_2 at −70 °C) were added to the preformed complex **13** at −40 °C. A proton NMR at −40 °C was recorded and showed an unreacted mixture of the two components. The reaction mixture was then warmed rapidly to 0 °C: NMR analysis showed the disappearance of **12** and the formation of a complex mixture of new products. HPLC analysis of the crude NMR reaction mixture, after quenching with bicarbonate and Rochelle's salt, showed the formation of the desired product **5** together with a small amount of its isomer **7** and starting materials **3a** and (2*S*)-**6**.

Isolation and Structure Elucidation of the Tin(IV) Chloride Chelate Complex 11

During our studies on this reaction we noticed that addition of $SnCl_4$ to a mixture of **3a** and **6** resulted in the formation of a white precipitate that upon addition of base, redissolved, giving a homogeneous solution.

Addition of $SnCl_4$ to a solution of (2*S*)-**6** in chlorobenzene resulted in a precipitation of an off-white solid that could be isolated by filtration under inert atmosphere and could be stored in a closed vessel at room temperature for several weeks. NMR spectra recorded for this compound were identical to those assigned to compound **11**. Crystals of this compound were obtained by recrystallization from chlorobenzene under an inert atmosphere and X-ray analysis confirmed the proposed structure **11** (Figure 8). This isolated complex was successfully used in the synthesis of **5**, giving similar results in terms of both yield and stereoselectivty to those obtained by employing **3a** and (2*S*)-**6**, under similar reaction conditions. In Table 3 a direct comparison between experiments with (2*S*)-**6** and **11** is made.

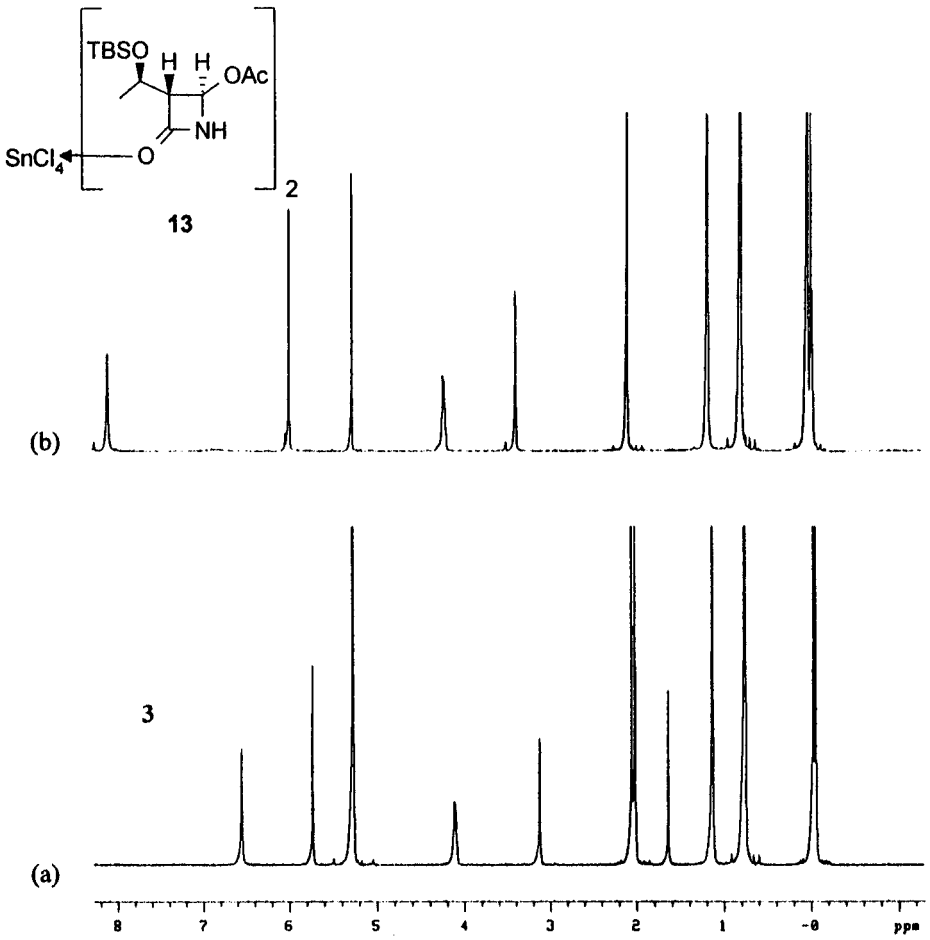

Figure 5. ^{1}H-NMR at −40 °C: (a) **3**; (b) **3** + 0.5 equiv of $SnCl_4$.

Table 3. Use of Chelate Complex 10

entry	method	solvent	base (equiv)	*T* (°C)	**5** yield[b]	ratio **5**:**7**[c]
1	A	CH_2Cl_2	*i*-Bu_3N (2.6)	-10 to 0	70%	18:1
2	A	PhCl	*i*-Bu_3N (2.6)	-10 to 0	64%	17:1
3	B	PhCl	*i*-Bu_3N (2.6)	-20 to 0	79%	23:1
4	B	CH_2Cl_2	*i*-Bu_3N (2.6)	-20 to 0	66%	15:1

[a] Method A. Addition of base to a precooled mixture containing 1 g of **3a**, 1.2 equiv of (2*S*)-**6**, and 3.4 equiv of $SnCl_4$. Method B. Addition of base to a precooled mixture containing 1 g of **3a**, 1.2 equiv of **10** and 2.2 equiv of $SnCl_4$. (2*S*)-**6** was purified by flash chromatography prior to use [b] Solution yield determined by HPLC (**5** as external standard). [c] Ratios determined by NMR.

The Reaction Mechanism

On the basis of NMR experiments an hypothesis on the reaction mechanism could be drawn. We believe that enolate **12** is the actual reacting species responsible for the nucleophilic attack on azetinone **A** (Figure 9), generated from **3a** under the influence of a Lewis acid.[16] Although NMR studies have demonstrated that **3a** is coordinated to $SnCl_4$ via its lactam oxygen, the existence, under the reaction conditions, of other different transient species that could promote the elimination of the acetoxy moiety thus generating **A** cannot be ruled out. The C−C bond formation occurs via an open transition state (intermediates **I**−**IV**); the stereoselectivity observed is caused by a double diastereoselective effect with the silyloxy side chain at C-3 of azetinone **A** being responsible for the facial selectivity on the azetidinone ring and the bulky chelated tin tetrachloride amplifying the steric effect of the methoxy group on **6** and preferentially orientating the elecrophile to attack **12** from the less hindered opposite face.

It is worth noting that under our best reaction conditions, the presence of regiosomers **14** and **15** (Figure 10)[1d], could not be detected (NMR and HPLC) in the crude reaction mixture, thus demonstrating that the regioselective enolization of **6**, as observed during low-temperature NMR experiments, does occur even at 0 °C. Moreover, the absence of diastereomers **8** and **9** in the crude reaction mixture, when enantiomerically pure (2*S*)-**6** was used, indicates that reaction conditions are mild enough to prevent racemization at the stereogenic center of **6**.

Preliminary Optimization Studies

Further optimization studies led us to conclude that a reduction in the ratio (2*S*)-**6**:**3a** from 2:1 to 1.2:1 did not dramatically affect yields but reduced the amounts of byproducts leading to a simpler purification procedure. On the other hand all the initial attempts to reduce the amounts of $SnCl_4$ and tertiary amines were not successful and, in our hands, the best results were obtained when 3.4 equiv of $SnCl_4$ and 2.6 equiv of base per equivalent of **3a** were employed. *N*,*N*-Diisopropylethylamine and triisobutylamine were the bases of choice and dichloromethane and chlorobenzene gave comparable results. When the reaction was carried out on a 5-g scale, solution yields were consistently close to 70% with isolated yield

(16) (a) Endo, M. *Can. J. Chem.* **1987**, *65*, 2140. (b) Martel A.; Daris, J. P.; Bachand, C.; Corbeil, J.; Menard, M. *Can. J. Chem.* **1988**, *66*, 1537.

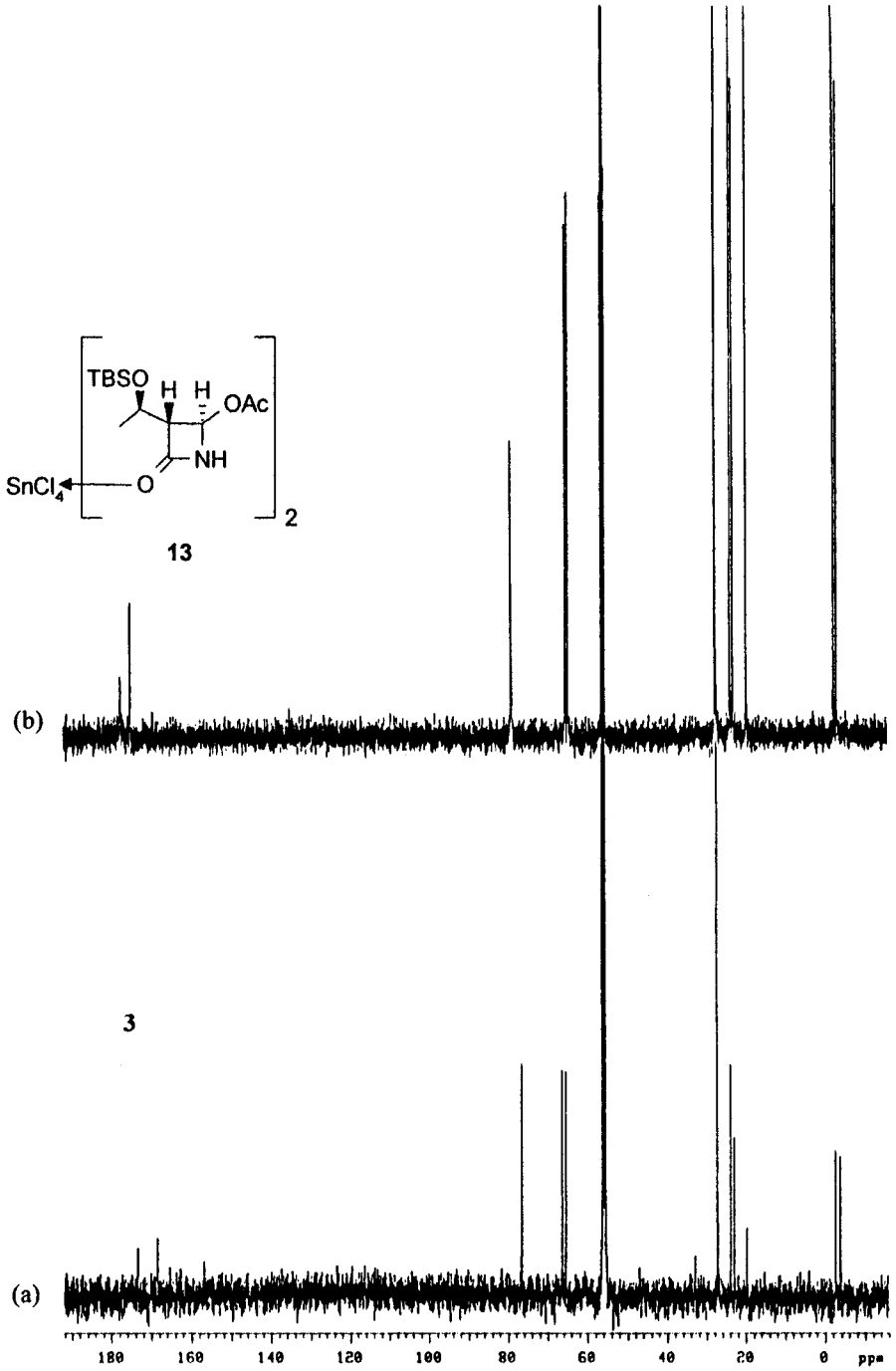

Figure 6. ^{13}C-NMR at −40 °C: (a) **3**; (b) **3** + 0.5 equiv of $SnCl_4$.

after crystallization between 60% and 66% (see Experimental Section).

Conclusions

We have demonstrated that a simple stereoselective synthesis of **5** in up to 66% isolated yield (74% solution yield) could be obtained from (2*S*)-**6** and **3a** under mild conditions by simple addition of a tertiary amine to a mixture of the two starting materials and $SnCl_4$ in dichloromethane or chlorobenzene. A high diastereoselectivity was observed even without using protecting groups at the azetidinone nitrogen. The yields obtained are higher compared to the previously reported method,[5] and a much simpler and economic procedure was established. This method appears to be a significant improvement toward the synthesis of GV104326. Studies aimed at a further optimization of the reaction conditions are currently ongoing and will be reported in due course.

Experimental Section

All reactions were performed in oven-dried glassware under a positive pressure of nitrogen. (1*S*,2*S*)-2-Methoxycyclohexanol was synthesized according to the reported procedure.[10] Solvents were distilled under a nitrogen atmosphere, P_2O_5 (CH_2Cl_2). Triethylamine, *N*,*N*-diisopropylethylamine, 2,6-lutidine, and triisobutylamine were distilled from CaH_2. Analytical thin-layer chromatography (TLC) was performed on E. Merck silica gel 60 F_{254} plates (0.25 mm). Compounds were visualized by dipping in a phosphomolybdic acid solution followed by heating. Flash chromatography was performed on E. Merck silica gel (230−400 mesh). Melting points are uncorrected and were determined with a capillary melting

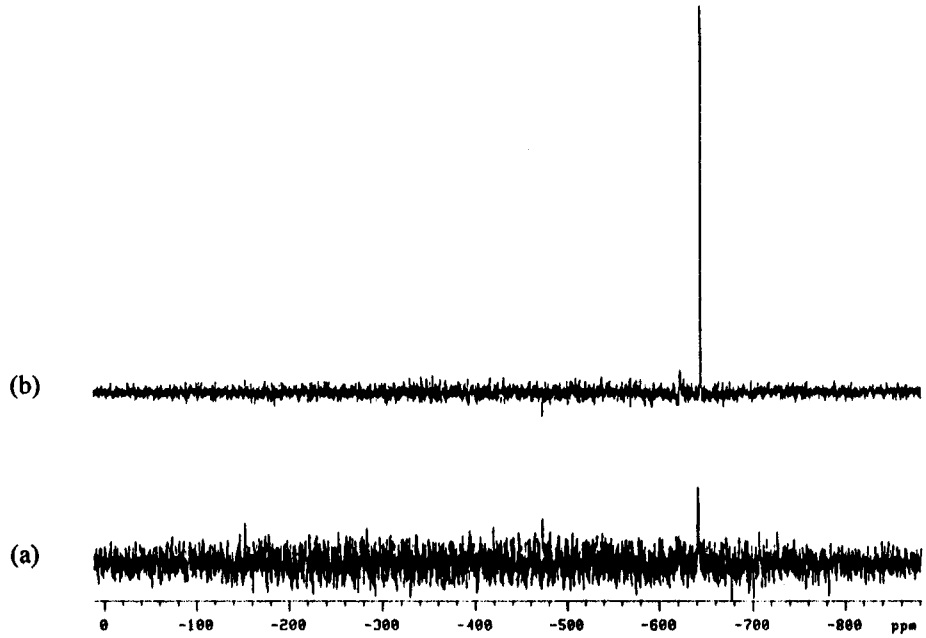

Figure 7. ^{119}S-NMR at −40 °C: (a) **3** + 0.5 equiv of $SnCl_4$; (b) **3** + 1 equiv of $SnCl_4$.

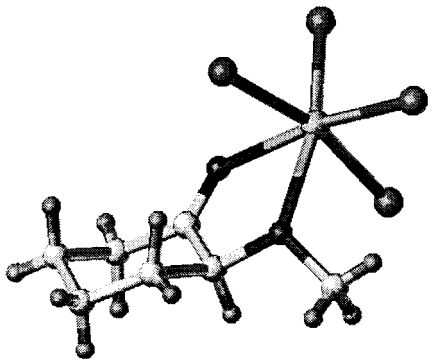

Figure 8.

point apparatus. IR spectra were recorded in $CDCl_3$ solution unless otherwise stated and are reported in wavenumbers (cm^{-1}). ^{1}H-NMR spectra were recorded at 400 or 500 MHz, ^{13}C-NMR were recorded at 100.57 or at 75.43 MHz: all the spectra were collected in $CDCl_3$ or CD_2Cl_2 at 25 °C. In the ^{1}H-NMR spectra, chemical shifts are reported in ppm with respect to residual $CHCl_3$ at 7.26 or to residual CH_2Cl_2 at 5.32 downfield from the TMS line while, in the carbon NMR spectra, the center line (δ 77.0 or 53.4) ^{13}C resonance of $CDCl_3$ or CD_2Cl_2 was used as internal reference. NMR assignments are assisted by NOE and 2D techniques. Low-temperature NMR studies were run at 400 MHz (^{1}H-NMR), 100.6 MHz (^{13}C-NMR), and 112 MHz (^{119}Sn-NMR) using CD_2Cl_2 as solvent (in the latter case tetramethyltin was used as external standard); the samples were placed in the probe at the appropriate temperature and allowed to equilibrate for a few minutes prior to acquisition of a spectrum. HPLC analyses were performed on a HPLC Hypersil ODS2 column (250 × 4 mm) × 5 μm, using a buffer of $(NH_4)H_2PO_4$ 50 mM/CH_3CN 45/55 and flow rate of 1.0 mL/min, while monitoring at UV at 205 nm. A pure sample of **5** was used as external standard. Chiral GC were performed on a Chiraldex G-TA (γ-cyclodextrin, trifluoroacetyl), using FID as a detector. Mass spectra were recorded in FAB^+ mode. All optical rotations [α] values were obtained in $CHCl_3$ or CH_2Cl_2 solutions at the sodium D line at 22 °C.

(2*S*)-2-Methoxycyclohexanone ((2*S*)-6). Concentrated sulfuric acid (6.1 mL) was added to a stirred solution of chromium trioxide (7 g, 70 mmol) in water (50 mL) at 0 °C. An aliquot of the resulting solution (30 mL) was added dropwise in 15 min to a solution of (1*S*,2*S*)-2-methoxycyclohexanol (1.95 g, 15 mmol) in dichloromethane (15 mL) at 0 °C under vigorous stirring. The reaction mixture was stirred for 1 h at 0 °C and then quenched by addition of isopropyl acohol (2.5 mL). The mixture was extracted with dichloromethane (3 × 50 mL), the combined extracts were washed with a saturated solution of $NaHCO_3$ (30 mL) and then with brine (50 mL) and dried over magnesium sulfate. The resulting mixture was filtered over a pad of celite and evaporated under reduced pressure at room temperature to give a pale yellow liquid (1.1g, w/w assay 98%, yield 56%). This material could be used without any further purification. Purification by flash chromatography gave a pure sample of the title compound as a colorless oil: $[\alpha]^{22}_D = -112.4°$ (c = 2.08, CH_2Cl_2); ee >99%

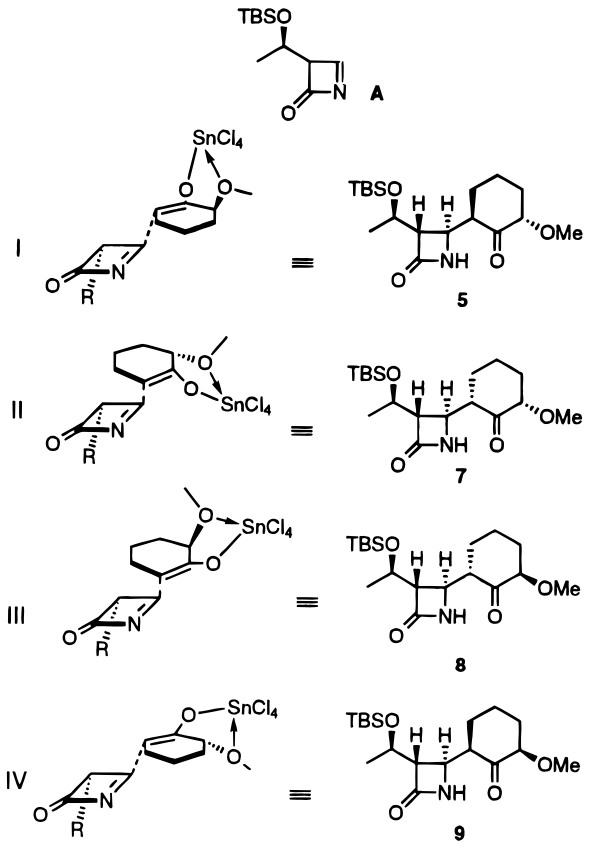

Figure 9. Schematization of the proposed transition states.

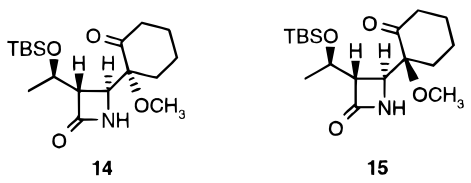

Figure 10.

(GC); ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 3.74 (m, 1H), 3.41 (s, 3H), 2.58−2.46 (m, 1H), 2.34−2.19 (m, 2H), 2.01−1.88 (m, 2H), 1.80−1.58 (m, 3H).

Method A. (3*S*,4*R*)-3-[(*R*)-1-[(*tert*-Butyldimethylsilyl)-oxy]ethyl]-4- [(*R*)-6′-((*S*)-2′-methoxy)-1′-oxocyclohexyl]-azetidin-2-one (5). To a stirred solution (2.65 g, 21 mmol) of (2*S*)-**6** in anhydrous dichloromethane (23 mL) at −20 °C was added $SnCl_4$ (6.95 mL, 59.16 mmol) dropwise. To the resulting suspension was added a solution of **3a** (5 g, 17.4 mmol) in dichloromethane (10 mL), and the resulting mixture was warmed to 0 °C. A solution of *N*,*N*-diisopropylethylamine (7.9 mL, 45.2 mmol) in dichloromethane (10 mL) was added over 20 min, maintaining the temperature between 0 and 5 °C. The reaction mixture was stirred for a further 40 min and then poured onto a 1:1 v/v mixture of saturated sodium hydrogen carbonate and saturated Rochelle's salt (300 mL). Ethyl acetate (150 mL) was added and the mixture was stirred for 1.5 h. The organic layer was separated, washed with brine, dried over magnesium sulfate, filtered, and evaporated under reduced pressure to give an off-white solid that was crystallized from *n*-hexane (160 mL) to give the title compound (3.8 g, w/w assay by HPLC: 97.5%; corrected yield 60%, mp 116−117.5 °C). Evaporation of the mother liquors gave an oily residue (2.45 g; w/w assay by HPLC 21.5%; yield 8.5%). NMR analysis of the crude reaction mixture revealed the following: molar ratio **5**:**7**, 15:1; ratio **5**:**3a**, 21:1; ratio **5**:**6**, 40:1. $[\alpha]^{20}_D$ = 29.6° (c = 0.98, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 5.76 (bs, 1H), 4.18 (m, J = 5.7, 6.0 Hz 1H), 4.00 (dd, J = 2.66, 3.8 Hz, 1H), 3.57 (t, J = 3.3 Hz, 1H), 3.28 (s, 3H), 3.10 (m, 1H), 2.88 (dd, J = 2.6, 5.7 Hz, 1H), 2.24 (m, 1H), 2.11 (m, 1H), 2.01 (m, 1H), 1.69 (m, 1H), 1.66 (m, 1H), 1.56 (m, 1H), 1.25 (d, J = 6.0 Hz, 3H), 0.88 (s, 9H), 0.09 (s, 3H), 0.007 (s, 3H); ^{13}C-NMR ($CDCl_3$, 100.6 MHz) δ 213.30, 168.57, 84.09, 66.11, 60.88, 57.01, 49.46, 48.53, 33.75, 28.26, 25.72, 22.52, 19.07, 17.89, −4.23, −5.07; IR (nujol mull) ν_{max} 3202, 1759, 1718 cm^{-1}; MS (FAB/NBA) m/z 356 $[MH]^+$, 340, 324, 298, 181 (100), 156. Anal. Calcd for $C_{18}H_{33}NO_4Si$: C, 60.79; H, 9.37; N, 3.94. Found: C, 60.73; H, 9.34; N, 4.06.

(3*S*,4*R*)-3-[(*R*)-1-[(*tert*-Butyldimethylsilyl)oxy]ethyl]-4-[(*R*)-6′-[(*S*)-2′-methoxy]-1′-oxocyclohexyl]azetidin-2-one (5). Tin(IV) chloride (6.95 mL, 59.1 mmol) was added dropwise to an efficiently stirred solution of (2*S*)-**6** (2.65 g, 20.3 mmol) in anhydrous chlorobenzene (75 mL) under nitrogen, maintaining the temperature below −20 °C. A solution of **3a** (5 g, 17.4 mmol) in anhydrous chlorobenzene (25 mL) was added dropwise over 15 min to the reaction mixture, keeping the temperature below −20 °C. The mixture was warmed to 0 °C and *N*,*N*-diisopropylethylamine (7.88 mL, 45.2 mmol) dissolved in anhydrous chlorobenzene (25 mL) was added dropwise over 20 min, maintaining the reaction temperature between 0 and 5 °C. The resulting yellow solution was stirred at 0−5 °C for 1 h and then poured onto a chilled (0−5 °C) mixture of a saturated solution of $NaHCO_3$ (150 mL) and a saturated solution of of Rochelle's salt (150 mL). The mixture was stirred for 1 h, and the organic phase was separated. The aqueous layer was extracted with ethyl acetate (150 mL). The organic extracts were washed in turn with a 10% aqueous solution of citric acid (150 mL), a saturated solution of $NaHCO_3$ (150 mL), and brine (150 mL). The organic solution was dried over magnesium sulfate and concentrated under reduced pressure to give the crude reaction mixture as an off-white solid (5.59 g, w/w assay by HPLC 68.53%; corrected yield 73.8%).

Crystallization from *n*-hexane (160 mL) gave 4.1 g of the title compound (w/w assay by HPLC 98.5%; corrected yield 66.7%). Evaporation of the mother liquors gave 2.15 g of a semisolid residue (w/w assay by HPLC 19.85%; corrected yield 6.9%).

NMR analysis of the crude reaction mixture revealed the following: molar ratio **5**:**7** = 20:1; ratio **5**:**3a** = 23:1; ratio **5**:**6** >100:1.

(2*S*)-2-Methoxycyclohexanone Tin(IV) Chloride 1:1 Chelate Complex (10). To a stirred solution of (2*S*)-**6** (2.0 g, 15.6 mmol) in dry chlorobenzene (15 mL) cooled at −5 °C was added $SnCl_4$ (4.4 g, 16.9 mmol) dropwise, at such a rate to maintain the temperature below 0 °C. The resulting suspension was stirred for further 15 min prior to filtering at the pump under an inert atmosphere. The filter cake was washed with *n*-hexane (30 mL) and dried *in vacuo* to give compound **10** as a white-pale pink solid (5.9 g, 97%): mp 162−163 °C dec; $[\alpha]^{20}_D$ = −15.1° (c = 0.935, CD_2Cl_2); ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 4.12 (m, 1H), 3.74 (s, 3H), 2.78 (m, 1H), 2.50 (m, 2H), 2.16 (m, 1H), 2.1−1.7 (m, 4H); ^{1}H-NMR (CD_2Cl_2, 500 MHz) δ 4.61 (m, 1H), 4.06 (s, 3H), 3.04 (m, 1H), 2.84 (m, 1H), 2.78 (m, 1H), 2.38 (m, 1H), 2.2−2.08 (m, 2H), 1.88 (m, 2H); ^{13}C-NMR (CD_2Cl_2, 75.4 MHz) δ 220.0, 83.28, 59, 31, 40.05, 33.11, 27.86, 22.90; IR (nujol mull) ν_{max} 1649 cm^{-1}.

Method B. (3*S*,4*R*)-3-[(*R*)-1-[(*tert*-Butyldimethylsilyl)-oxy]ethyl]-4- [(*R*)-6′-((*S*)-2′-methoxy)-1′-oxocyclohexyl]-azetidin-2-one (5). To a mixture of 4-acetoxyazetidinone **3a** (1.0 g, 3.47 mmol) and compound **10** (1.6 g, 4.11 mmol) was added anhydrous dichloromethane (25 mL). The resulting suspension was cooled to −20 °C with stirring, and $SnCl_4$ (1.98 g, 7.63 mmol) was added over 2 min. The reaction mixture was warmed to 0 °C, and a solution of triisobutylamine (2.2 mL, 9.02 mmol) in anhydrous dichloromethane (5 mL) was added via cannula over 20 min. The resulting solution was stirred for a further 40 min at 0 °C before pouring into a vigorously stirred mixture of saturated Rochelle's salt solution (75 mL), saturated sodium hydrogen carbonate solution (75 mL), and ethyl acetate (200 mL). After the solution was stirred for 20 min, the phases were separated and the organic layer washed in turn with a 3% citric acid solution (100 mL), saturated sodium hydrogen carbonate solution (50 mL), and brine (50 mL). The organic phase was dried over magnesium sulfate, filtered, and concentrated *in vacuo* to give the crude title compound as an off-white semicrystalline gum (1.8 g, w/w assay by HPLC 45.7%; corrected yield 66%). A 1.7 g sample of this material was recrystallized from *n*-hexane to give compound **5** (0.51 g. 45%).

Acknowledgment. We thank Dr. Clive Meerholz for helpful suggestions, Sean Lynn for providing the X-ray data, and Alberto Zanoni for HPLC analysis.

Supporting Information Available: Characterization data for compounds **7**, **13**, and **14** (6 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.

JO962095M