A Highly Stereoselective and Practical Total Synthesis of the Tricyclic β-Lactam Antibiotic GV104326 (4-Methoxytrinem)

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Abstract: A novel and practical total synthesis of a tricyclic β-lactam antibiotic, GV104326 (4-methoxytrinem or Sanfetrinem) has been achieved in nine steps and about 33% overall yield from a commercially available acetoxyazetidinone chiron. A key step in the highly diastereoselective synthesis is a protonation of a zinc enolate complex which circumvents the use of enantiomerically pure (*S*)-2-methoxycyclohexanone. A mechanistic rationale is presented and experimentally verified.

Due to the growing number of bacterial strains acquiring resistance to the current arsenal of chemotherapeutic drugs, the search for novel mechanism-based antibacterial agents continues to be a major area of research on many fronts. The effort in molecules containing the β-lactam motif alone has produced a plethora of novel chemical entities many of which are presently marketed as antibiotic agents.[1]

The report of the discovery of thienamycin by scientists at the Merck Laboratories in 1976[2] opened a new frontier in β-lactam research. Since then, great advances have been made in the chemistry and biology of the carbapenem class of β-lactam antibiotics. The superior stability of 1-substituted carbapenems toward dehydropeptidases[3] and the recent reports of interesting analogs having polar substituents at C-1[4] are just two examples of chemical modifications that have generated broad spectrum antibacterial activity.

Recently, the scientists at Glaxo have discovered a new family of synthetic β-lactam derivatives which bear the name "trinems" (previously referred to as tribactams)[5] (Figure 1). The incorporation of a cyclohexane ring onto the carbapenem nucleus provides sites for chemical functionalization, as exemplified by substituents at C-4 (Figure 1). The most promising candidate in this class, sodium (4*S*,8*S*,9*R*,10*S*)-4-methoxy-10-[(1*R*)-1-hydroxyethyl]-11-oxo-1-azatricyclo [7.2.0.0^{3,8}]undec-2-ene-2-carboxylate (**2**, X = OMe, R = Na, GV104326), has shown

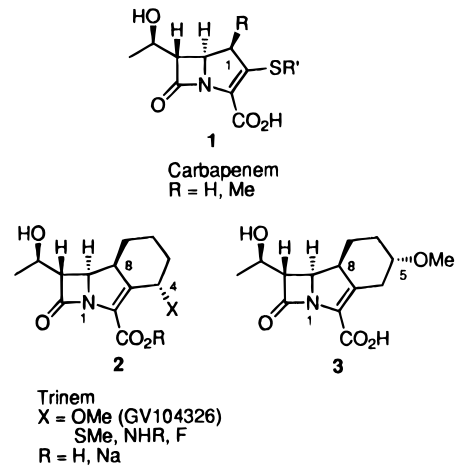

Figure 1.

excellent activity against a wide range of bacteria including β-lactamase producing strains and is presently undergoing clinical evaluation.[6]

The "trinem" **2** and its analogs present a number of synthetic challenges not the least of which is the development of an industrially viable route that is amenable to large scale production. Continuing our interest in the synthesis of structurally novel and diverse β-lactam-containing molecules,[7] we have explored methodology directed toward the synthesis of the trinems. Paramount in the synthesis of these molecules is the control of the configurations at C-4 and C-8 at strategic points in the elaboration of the tricyclic nucleus. The published syntheses of the 4-methoxy trinem (GV104326)[5a,e] proceed through intermediate **4** (Figure 2), which undergoes cyclization

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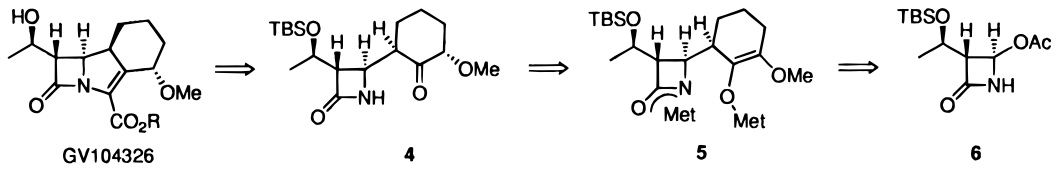

Figure 2.

to the tricyclic structure by a trialkyl phosphite-mediated reaction.[5f] This intermediate is produced by elaboration of the corresponding cyclohexene derivative. Several improvements have been made in the original synthesis,[8] which involves the use of enantiomerically pure (*S*)-2-methoxycyclohexanone. The quest for a convergent total synthesis avoiding the use of a chiral nonracemic cyclohexanone derivative is a much sought after objective.

Results and Discussion

We wish to report a practical and highly convergent total synthesis of the 4-methoxytrinem (GV104326), utilizing a strategy in which the stereochemical control in a key step is derived entirely from the inherent chirality of the commercially available azetidinone **6**.[9] Our disconnective analysis of the target structure is shown in Figure 2, and as in the previous syntheses, it hinges on the preparation of **4** in enantiomerically pure form. In our recently reported synthesis of the 5-methoxytrinem,[10] we showed that the coupling of 3-methoxy-6-((allyloxy)carbonyl)-2-cyclohexen-1-one with the azetidinone **6**,[11] followed by protection of the lactam and subsequent de(allyloxy)carbonylation[12] provided a highly stereocontrolled access to an intermediate in which the desired β-configuration at the cyclohexanone substitution site was secured.

Our strategy for the synthesis of **2** also relied on a similar coupling protocol. In addition, we also wished to avoid the use of enantiomerically pure cyclohexanone derivatives. We hoped that given the chiral nonracemic nature of the intended substrate **4**, we would be able to adjust the configuration at the methoxy center through an enolate such as **5**. We reasoned that with the appropriate choice of the metal cation (chelating or nonchelating) we could fix the conformation of the enolate leading to stereodifferention in the protonation step, resulting in a preponderance of the desired (2*S*) enantiomer **4** over the alternative (2*R*) isomer (cyclohexanone numbering, Figure 2).

Our synthesis started with the commercially available 2-methoxycyclohexanone (Scheme 1), which was (allyloxy)carbonylated using diallyl carbonate and sodium hydride in the presence of a catalytic amount of potassium hydride to produce the desired racemic β-ketoester **7**.[13] Reaction of the sodium salt of **7** with the commercially available acetoxyazetidinone **6** at −20 °C gave a mixture of the four possible diastereomers shown in expression **8**, which were N-protected as the *tert*-butyldimethylsilyl (TBS) derivative **9**. The stereochemistry at C-8 could now be secured by using a modified procedure of the de(allyloxy)carbonylation reaction.[12] Thus, treatment of the four diastereomers of **9** with 10 equiv of formic acid in the presence of a catalytic amount of palladium acetate provided a mixture of the N-TBS-protected compounds **10**, **11**, and **12** (ca. 4:4:1). At this point, it was possible to separate **10** from **11** and **12** for characterization. Selective N-deprotection of **10** provided **4**, while using the same conditions, **11** and **12** could be selectively deprotected to provide a mixture of **13** and **14** which could be separated. Routinely on larger scales, the first four steps were conducted with only one chromatographic separation at the end of a sequence to remove **14**, leaving a mixture of **4** and **13** (ca. 1:1 at C-4).

At this point we were faced with the task of finding the proper conditions for the conversion of the (2*R*) isomer **13** in the mixture of methoxy epimers to the desired (2*S*)-methoxy ketone intermediate **4**. Treatment of the β-methoxy derivative **13** with lithium diisopropylamide (LDA, 3 equiv, −78 °C, 30 min) followed by quenching the reaction with D_2O gave >95% incorporation of deuterium, showing that the formation of the dianion was possible. However, the products consisted of a 1:1.5 mixture of α- and β-methoxy derivatives **4** and **13**, respectively (Table 1, entry 1). The literature contains some reports of stereoselective protonations of enolates involving a variety of other proton sources.[14] Thus, methyl (*S*)-lactate (Table 1, entry 2), diethyl malonate (Table 1, entry 3), and pyrrolidinone (Table 1, entry 5) were tried as proton sources, but no stereochemical preference was seen in the mixture of epimers.

Given these results, we decided to study the protonation of the dianion as expressed in **5** in the presence of a bidentate chelating metal. We reasoned that, in addition to a favorable geometry, the metal would provide a coordination site onto which a suitable reagent could anchor itself for a more selective

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Scheme 1

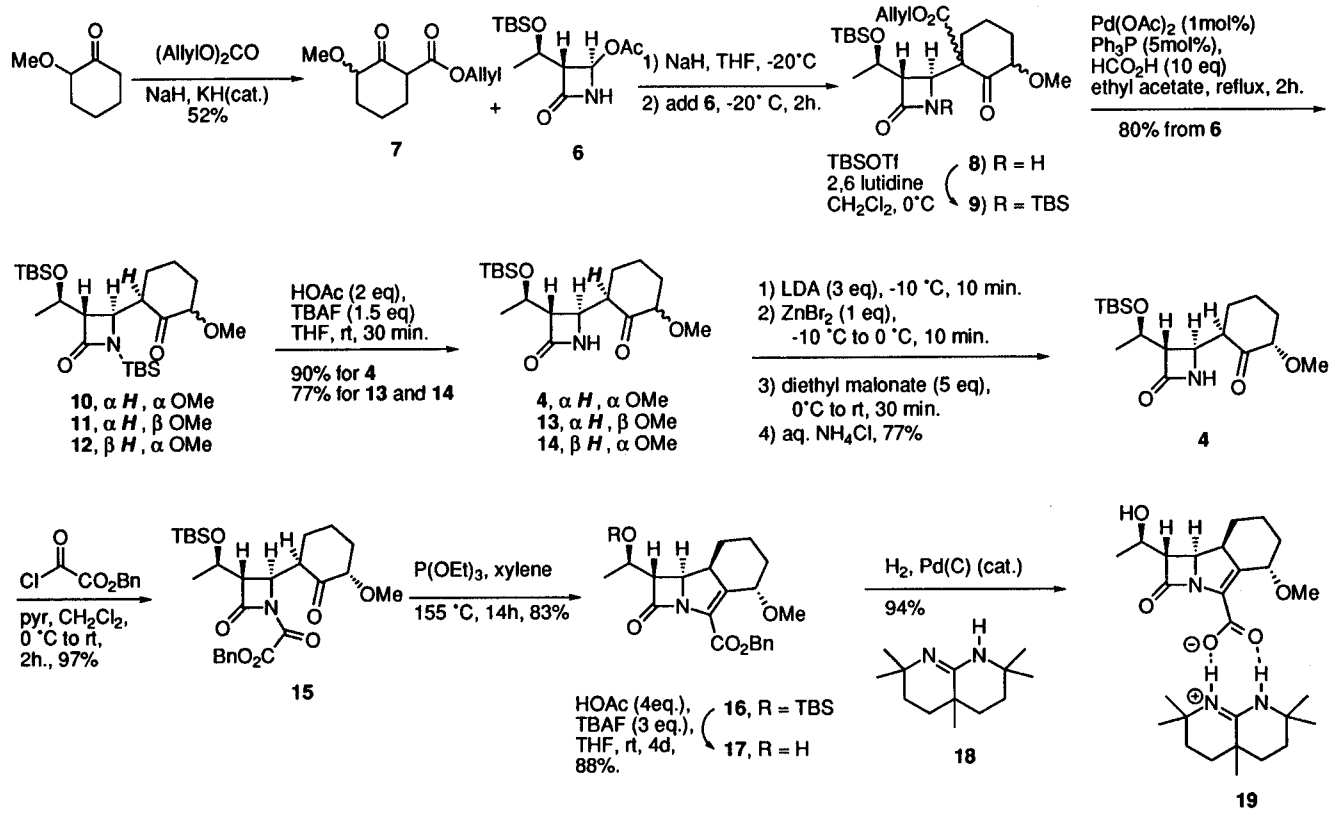

Table 1. Protonation of the Lithium Enolate of **5**

entry	proton source	α/β ratio[a]
1	D_2O	1:1.5[b]
2	methyl (*S*)-lactate	1.2:1
3	$(EtO_2C)_2CH_2$	1:1
4	TMEDA:$(EtO_2C)_2CH_2$	1:1.2
5	pyrrolidinone	1:1.5

[a] Determined by integrating the methoxy CH_3 resonances (α-methoxy, 3.29 ppm; *β*-methoxy, 3.46 ppm) in 1H NMR (300 MHz) spectrum of crude reaction mixture. [b] D incorporation >95%.

Table 2. Protonation of the Zinc Enolate of **5**

entry	proton source	α/β ratio[a]
1	D_2O	2.5:1
2	pyrrolidinone	1.5:1
3	diethyl malonate	>15:1
4	malononitrile	7:1
5	ethyl cyanoacetate	>15:1
6	nitromethane	2:1
7	2-pyridylacetonitrile	5:1[c]
8	2-mercaptopyridine	1:2
9	Meldrum's acid	3:1
10	diethyl methylmalonate	>15:1
11	ethyl acetoacetate	1:1.5[c]
12	di-*tert*-butyl malonate	9:1
13	bromozinc diethyl malonate[b]	3:1

[a] Determined by integrating the methoxy CH_3 resonances (α-methoxy, 3.29 ppm; *β*-methoxy, 3.46 ppm) in ^{1}H NMR (300 MHz) spectrum of crude reaction mixture. [b] Prepared by deprotonating diethyl malonate with LDA and adding zinc bromide (1 equiv). [c] Significant amounts of unidentified side products were also produced.

proton delivery. Formation of the lithium dianion followed by addition of $ZnBr_2$ (1.1 equiv) gave, after quenching the reaction with D_2O, a 2.5:1 mixture of **4** and **13**, respectively. Curiously, no deuterium was incorporated into the mixture of epimers, indicating the likehood of an internal proton quench. A series of experiments were then carried out in order to further improve the stereoselectivity in favor of **4**. We were thus pleased to find that addition of diethyl malonate (5 equiv) to the zinc dianion followed by aqueous workup gave the α- and *β*-methoxy isomers **4** and **13** in a ratio of >15:1 respectively, and that the α-methoxy isomer **4** could be isolated in a 77% yield. When subjected to the same conditions of dianion formation and protonation, the α-methoxy isomer **4** was recovered unchanged in 73% yield. Treatment of the *β*-methoxy isomer **13** under the same conditions resulted in a nearly total epimerization to **4** (72% yield). On a preparative scale, a mixture of methoxy isomers **4** and **13** isolated after condensation with the azetidinone **6** could be transformed to the desired α-methoxy isomer **4** in over 72% yield, with a major portion being obtained by direct crystallization before chromatography. A remarkably efficient and stereoselective route to the intended critical intermediate **4** was thus in hand.

To understand the nature of this highly selective protonation, a series of experiments were designed where the role of the zinc bromide, the role of the diethyl malonate, and the exact source of the proton were systematically studied. To prove the existence of the chelation to the zinc, we conducted two crucial experiments. Protection of the lactam nitrogen with TBS triflate and formation of the zinc enolate (LDA, 1.1 equiv) followed by addition of $ZnBr_2$ (1 equiv) and quenching the reaction with diethyl malonate resulted in a complete reversal of selectivity in protonation (<1:15, α/β). Also, all selectivity could be obliterated by performing the reaction in the presence of 10 equiv of zinc bromide. These experiments strongly suggested the presence of an intramolecular chelation of the enolate oxygen and the lactam nitrogen to the zinc.

In order to address the role of the diethyl malonate, a set of potential proton sources were selected and added to the zinc dianion of **4** and/or **13** given as **5**. The results are listed in Table 2.

With the exception of 2-mercaptopyridine (Table 2, entry 8) and ethyl acetoacetate (Table 2, entry 11), the protonation of

Table 3. Deuteration of the Zinc Enolate of **5**

entry	base	additive	time (h)	workup	α/β^a	% D[b]
1	LDA (3 equiv)	$(EtO_2C)_2CD_2$	10[c]	NH_4Cl	>15:1	0
2	LDA (3 equiv)	$(EtO_2C)_2CH_2$	10[c]	D_2O	>15:1	0
3	LDA (3 equiv)	$(EtO_2C)_2CD_2$	6	NH_4Cl	>15:1	65
4	LDA (3 equiv)	$(EtO_2C)_2CD_2$	6	D_2O	>15:1	65
5	LDA (3 equiv)	$(EtO_2C)_2CD_2$	6	NH_4Cl	>15:1	50
6	LTMP (3 equiv)	$(EtO_2C)_2CD_2$	6	NH_4Cl	>15:1	50
7	LiHMDS (3 equiv)	$(EtO_2C)_2CD_2$	6	NH_4Cl	>15:1	65
8	LiHMDS (3 equiv)	$(EtO_2C)_2CD_2$	6	D_2O	>15:1	65
9	LDA (1.9 equiv)	$(EtO_2C)_2CD_2$	6	NH_4Cl	>15:1	0
10	LDA (3 equiv)	$(EtO_2C)_2CMe_2$	6	D_2O	>15:1	30
11	LDA (3 equiv)	*i*-Pr2ND; $(EtO_2C)_2CMe_2$	6	NH_4Cl	>15:1	50
12	LDA (3 equiv)	*i*-Pr_2ND; $ZnBr_2$; $(EtO_2C)_2CMe_2$	6	NH_4Cl	>15:1	50
13	LDA (3 equiv)	$(EtO_2C)_2CMe_2$ (3 h); *i*-Pr_2ND	3	NH_4Cl	>15:1	20

[a] Determined by integrating the methoxy CH_3 resonances (α-methoxy, 3.29 ppm; β-methoxy, 3.46 ppm) in ^{1}H NMR (300 MHz) spectrum of crude reaction mixture. [b] Determined by integrating the disappearance of the resonance at 3.58 ppm; (H α to OMe) in the ^{1}H NMR (300 MHz) spectrum of crude reaction mixture. [c] Time is given in minutes.

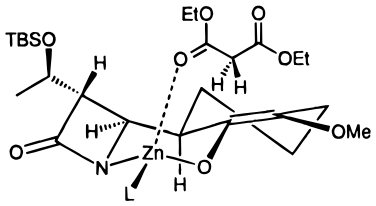

Figure 3.

the zinc enolate **5** leads preferentially to the formation of the α-methoxy derivative **4**. It is believed that the 2-mercaptopyridine and the ethyl acetoacetate are too strongly coordinating, which results in breaking the chelation of the zinc to the enolate oxygen and the lactam nitrogen. A weak preference for the β-methoxy epimer **13** over the desired **4** was in fact observed.

The remaining entries in Table 2 show that quenching the zinc enolate with a variety of other proton sources leads to a preferential formation of the α-methoxy epimer **4**. The highest diastereoselection was observed with diethyl malonate, ethyl cyanoacetate, and diethyl methylmalonate (Table 2, entries 3, 5, and 10, respectively). Other carbon acids such as malononitrile, 2-pyridylacetonitrile, and di-*tert*-butyl malonate (Table 2, entries 4, 7, and 12, respectively) showed modest to fairly good selectivities. Quenching with pyrrolidinone, nitromethane, and Meldrum's acid and using the bromozinc salt of diethyl malonate (Table 2, entries 2, 6, 9, and 12, respectively) gave poor selectivities, albeit always in favor of the α-methoxy isomer **4**. From this data, we hypothesized the existence of an intermediate where malonate could occupy the axial ligand position on the zinc enolate as shown in Figure 3. This would situate the methylene protons of the malonate moiety for optimum delivery to the β-face of the C-4 enolate atom. An equatorial disposition of the malonate places the methylene protons in a geometrically unfavorable position relative to the enolate α-carbon. The presence of excess malonate in solution would ensure the presence of the neutral molecule as a ligand, rather than as its enolate.

We now had to validate the proposed internal delivery of protons by the zinc-anchored malonate as shown in Figure 3. An obvious way to answer to this question was to perform a series of deuteration experiments, the results of which are shown in Table 3.

Diethyl malonate-d_2 was added to the zinc enolate **5** (Figure 2), the solution was stirred at room temperature for 10 min, and then the reaction was quenched with aqueous ammonium chloride (Table 3, entry 1). While examples of incomplete deuteration of enolates are known in the literature,[15] we were puzzled by the fact that *no deuterium* was incorporated in the product. This result suggested that the proton was actually being delivered by a source other than the malonate, for example during the aqueous workup or by the diisopropylamine generated upon formation of the lithium enolate. The zinc enolate was therefore treated with diethyl malonate, and subsequently the reaction was quenched with D_2O. Except for the excellent selectivity the product was once again devoid of deuterium (Table 3, entry 2), similar to when $ZnBr_2$ alone had been used (vide supra). The only other source of proton that remained was the diisopropylamine generated during the formation of the enolate, which could deliver a proton internally.[16]

Other researchers have found that the addition of butyllithium alleviates the problem of incomplete deuteration by metalating the liberated diisopropylamine.[15] Thus, addition of butyllithium to the lithium enolate, followed by the addition of zinc bromide and diethyl malonate-d_2 and aqueous NH_4Cl workup after 6 h of stirring at room temperature, provided the α-methoxy derivative **4**, in which 65% deuterium was introduced (Table 3, entry 3). A longer contact time with the deuterium source (malonate-d_2 or diisopropylamine-*d*) was required to reach this degree of deuteration. The same level of deuterium incorporation was also achieved when D_2O was used in the workup (Table 3, entry 4). When the conditions used in entry 1 were repeated with a longer reaction time, a 50% D incorporation was obtained (Table 3, entry 5). Reasonably good levels of deuterium incorporation could also be obtained with lithium tetramethylpiperidine (LTMP, Table 3, entry 6) and lithium hexamethyldisilazane (LiHMDS, Table 3, entries 7 and 8). However, when a substoichiometric quantity of LDA (Table 3, entry 9) was used in conjunction with deuterated malonate, the level of deuterium incorporation fell to zero while a high level of selectivity was maintained (Table 3, entry 9). Although these results show that deuteration is possible under specific conditions of stoichiometry, reaction time, and workup, they do not identify the exact source of the deuteron or, for that matter, the proton donor. A distinct possibility emerges where addition of diethyl malonate-d_2 to the solution which contains LDA produces deuterated diisopropylamine, which could be the enigmatic deuteron donor.

The longer reaction time in the presence of deuterated malonate and the remaining LDA (1 equiv) allows for deuterium exchange to take place with the diisopropylamine in solution. Evidently, a shorter reaction time does not allow for deuterated diisopropylamine to exchange with the initially coordinated diisopropylamine in the zinc enolate complex. In fact, deute-

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rium exchange between malonate-d_2 and diisopropylamine was only partially complete after 18 h at 25 °C, as evidenced by ^{1}H NMR. Although the exchange is expected to be instantaneous with the additional equivalent of LDA still present in the reaction mixture (Table 3, entries 1 and 2), the presence of excess malonate-d_2 (4 equiv) and the slower exchange of unbound diisopropylamine-*d* for the bound amine accounts for the nonincorporation of deuterium in entry 1. The result in entry 2 would argue in favor of a rapid internal proton transfer from bound diisopropylamine before the workup. The possible exchange of deuterium from D_2O for hydrogen on the coordinated diisopropylamine during the workup may be too slow to compete with internal delivery.

The decisive experiments were then to remove the protons from the malonate and to allow the diisopropylamine to be the only source of proton prior to the workup. Entries 10−13 of Table 3 show the results of these experiments. Replacing the diethyl malonate with diethyl 2,2-dimethylmalonate and quenching the reaction with D_2O produces the α-methoxy derivative **4** with the *same high level of diastereoselectivity* (>15/1) as before but with only 30% D incorporation (Table 3, entry 10). We then conducted the reaction in the presence of excess diisopropylamine-*d* prior to and after the addition of zinc bromide to the enolate (Table 3, entries 11 and 12). Again, a 50% D incorporation was observed with high selectivity in both cases, thus demonstrating that the order of addition of reagents to the initial enolate was not critical, as long as the zinc bromide and malonate were present in conjunction with diisopropylamine-*d*. It was thus clear that the only source of deuterium in these reactions was the diisopropylamine-*d* and that a contact time of at least 6 h was necessary for reasonable to good levels of deuterium incorporation. We should recall that a D_2O quench of the lithium enolate **5** (Figure 2) gave a mixture of **4** and the C-2 epimer **11**, in which >95% deuterium had been incorporated. Since the only difference is the presence of the malonate and the zinc enolate complex, the incomplete incorporation of deuterium in some of the experiments described above, even upon addition of D_2O (or 4 equiv of AcOH-d_4), must reflect upon the existence of a highly organized (and possibly aggregated) zinc enolate complex.

Entry 13 in Table 3 demonstrates the effect of contact time with diisopropylamine-*d* on deuterium incorporation. The reaction was conducted with diethyl 2,2-dimethylmalonate as the additive for 3 h, after which excess diisopropylamine-*d* was added and the reaction was continued for another 3 h. After the reaction was quenched with NH_4Cl, the deuterium content of the highly enriched **4**:**13** mixture was 20%. Thus, it is possible that a significant portion of protons had been transferred during the first 3 h period from internally coordinated diisopropylamine and that exchange with diisopropylamine-*d* was not efficient enough to produce more than 20% incorporation. Had the aqueous medium of the workup been solely responsible for the quenching of the enolate, no deuterium incorporation should have been observed. Furthermore, the origin of the stereochemical preference would still remain unresolved.

The questions that still remained were concerned with the spatial disposition of the diisopropylamine relative to the zinc enolate, the origin of the "directed" protonation and possibly the "timing" of such an event. Data from various experiments in Table 3 lead us to conclude that the malonate and diisopropylamine entities must adopt preferred coordination sites in the zinc enolate complex. We therefore propose a strongly coordinated "organized" intermediate, as shown in Figure 4, in which the axial coordination site on the zinc is occupied by the diisopropylamine and the equatorial site by the malonate. The

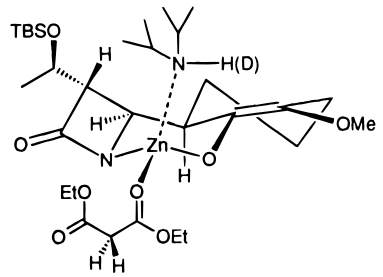

Figure 4.

Table 4. Quenching of the Zinc Enolate of **5** with Nonprotic Additives

entry	additive	α/β[a]
1	diethyl dimethylmalonate	>15:1
2	benzaldehyde	>15:1
3	benzophenone	6:1
4	tert-butyl acetate	5:1

[a] Determined by integrating the methoxy CH_3 resonances (α-methoxy, 3.29 ppm; β-methoxy, 3.46 ppm) in ^{1}H NMR (300 MHz) spectrum of crude reaction mixture.

amine moiety is favorably deployed to deliver a proton (or deuteron) to the β-face of the enolate leading to the desired product. To the extent that deuterium incorporation occurs in spite of a protic workup, we suggest a directed internal transfer from the coordinated amine. Although the level of deuterium incorporation increased with longer contact time (6 h vs 10 min or 1 h) before aqueous workup, reaching as high as 65% (Table 3, entries 7 and 8), we could not extend the reaction times longer at room temperature due to unwanted side reactions.

It is highly probable that, upon addition of water (or D_2O), there is an initial exchange of protons (or deuterons) on the coordinated axially disposed diisopropylamine ligand before the chelate breaks. The transfer may still take place internally, but the level of deuterium incorporation will depend to what extent the diisopropylamine is fully deuterated. An alternative proposal is that a significant amount of proton transfer must occur from the intermediate in Figure 4 prior to the workup. When deuterium transfer is involved, there must be enough contact time to allow the exchange to occur with bound and unbound diisopropylamine. Unfortunately, the exact timing of proton transfer cannot be ascertained because of the complexity of the exchange process, the lack of definitive structural information on the zinc enolate complex, and its stability in the reaction medium or upon workup. Regardless of the exact nature of the proton (or deuteron) transfer, the process is highly selective and must involve a geometrically well-organized complex which allows for a directed protonation.

We were intrigued by the fact that protons on the malonate were not required, and we briefly looked into other types of "carbon acids" (Table 4). Addition of benzaldehyde to the zinc enolate also gives a high selectivity of protonated α-methoxy ketone **4** with no trace of an aldol product (Table 4, entry 2). The addition of benzophenone (Table 4, entry 3) and *tert*-butyl acetate (Table 4, entry 4) also led to a relatively high degree of selectivity toward the α-methoxy ketone **4**. We assume that the role of the diisopropylamine as an internal proton source remains the same as that for malonates.

Having devised a highly selective and practical synthesis of the key intermediate **4**, we proceeded with the synthesis of the final target using standard protocols. Acylation of the lactam nitrogen with benzyl oxalyl choride produced the oxalimide **15** in 97% yield, which was subjected to triethyl phosphite-mediated ring closure[17] to provide the protected trinem **16** in 83% yield. Desilylation with tetrabutylammonium fluoride buffered with

acetic acid followed by hydrogenolysis in the presence of the bulky amidine **18**[18] afforded the final product **19** as a white amorphous solid. This was converted to the corresponding potassium salt using potassium ethylhexanoate, whose spectroscopic properties were in full agreement with those of an original sample data provided to us by Glaxo (Verona, Italy).

In conclusion, we have described a practical and novel nine-step synthesis of the Glaxo 4-methoxytrinem GV104326 in ca. 33% overall yield from a commercially available chiron. The highlight of the synthesis is a diastereoselective protonation of a zinc enolate complex which circumvents the use of an enantiomerically pure (S)-2-methoxycyclohexanone. Operationally, the synthesis is amenable to scaleup and it could be potentially applicable to a manufacturing protocol.

Experimental Section

General Procedure. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 300 instrument using deuteriochloroform as solvent ($CHCl_3$ standard, $\delta = 7.26$ ppm) (s, singlet; d, doublet; t, triplet; m, multiplet, br, broad). ^{1}H and ^{13}C NMR data are available upon request. Infrared spectra were recorded on a Perkin-Elmer 781 infrared spectrophotometer. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. Combustion analyses were performed by Guelph Laboratories Ltd., Guelph, Ontario, Canada. Column chromatography was performed using the flash method.[19] Melting points are uncorrected.

Allyl 3-Methoxy-2-oxocyclohexanecarboxylate (7). A slurry of 60% NaH in mineral oil (2.4 g) and 30% KH in mineral oil (~50 mg) was washed three times with hexanes (5 mL) and once with THF (5 mL) and then suspended in THF (20 mL) and diallyl carbonate (4.4 mL, 40 mmol). This mixture was then brought to reflux, and a solution of 2-methoxycyclohexanone (2.5 mL, 20 mmol) in THF (5 mL) was added dropwise over 15 min. After 12 h of reflux, the reaction mixture was cooled to room temperature, poured into a saturated aqueous solution of $NaHCO_3$ (100 mL) containing concentrated NH_4OH (2 mL), and stirred at room temperature for 30 min. The aqueous layer was acidified to pH 2 with concentrated HCl and extracted three times with ether (100 mL). The combined organic layers were washed three times with saturated $NaHCO_3$ (50 mL), once with water (50 mL), and once with brine (50 mL), and dried over Na_2SO_4. After filtration and concentration, the crude oil was purified by column chromatography (hexanes−ethyl acetate, 4:1), to afford the desired β-ketoester **7** as a mixture of tautomers and diastereomers (2.21 g, 52%).

(3*S*,4*R*)-1-*tert*-Butyldimethylsilyl-3-[(1*R*)-1-((*tert*-butyldimethylsilyl)oxy)ethyl]-4-[(1*R*,3*S*)-3-methoxy-2-oxocyclohexyl]azetidin-2-one (10). A slurry of 60% sodium hydride in mineral oil (540 mg, 13.5 mmol) was washed three times with hexane and suspended in THF (25 mL). This mixture was cooled to −20 °C and a solution of **7** (1.59 g, 7.5 mmol) in THF (10 mL) was added dropwise over 30 min. After 45 min of additional stirring at −20 °C, a solution of (3*S*,4*R*)-4-acetoxy-3-[(1*R*)-1-((*tert*-butyldimethylsilyl)oxy)ethyl]-azetidin-2-one (**6**, 2.15 g, 7.5 mmol) in THF (30 mL) was added dropwise at −20 °C over 30 min. After an additional 2 h at −20 °C, the reaction was quenched by the addition of acetic acid (2 mL), and the usual workup (saturated aqueous $NaHCO_3$, ethyl acetate) afforded the crude products **8** as a clear oil.

A solution of the crude products **8** prepared above in CH_2Cl_2 (20 mL) was cooled to 0 °C, 2,6-lutidine (1.7 mL, 15.0 mmol) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (2.6 mL, 11.3 mmol) were added. After 30 min of stirring, the reaction was poured into water (50 mL) and the aqueous layer was extracted three times with CH_2Cl_2 (100 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to give the crude N-TBS-protected products **9** as a pale yellow oil.

Palladium acetate (17 mg, 0.075 mmol, 1 mol %) and triphenylphosphine (100 mg, 0.38 mmol, 5 mol %) were suspended in ethyl acetate (15 mL), and formic acid (2.8 mL, 75 mmol) was added. After this mixture was refluxed for 30 min, a solution of the crude N-TBS-protected products **9** in ethyl acetate (35 mL) was added dropwise over 30 min. The mixture was heated at reflux for 2.5 h, cooled, diluted with ethyl acetate (200 mL), and washed with saturated aqueous $NaHCO_3$ (50 mL) and brine (50 mL). After the organic phase was dried over $MgSO_4$, it was filtered through a layer of silica gel. Concentration and flash chromatography (hexanes−ethyl acetate, 10:1 to 2:1) afforded **10** (1.32g, 37%) as a clear colorless oil and a 4:1 mixture of **11** and **12** (1.53 g, 43%). For **10**: $[\alpha]_D$ −2.5° (c 1.59, $CHCl_3$); IR ($CHCl_3$) 2950, 2870, 1740 (β-lactam CO), 1720 (cyclohexane (cHex) CO), 1520, 1110 cm^{-1}; MS (FAB, NBA), *m*/*e* (rel intensity) 470.5 (MH^+, 54), 454.4 (15), 412.4 (100), 185.2 (54), 153.2 (72); HRMS calcd for $C_{24}H_{48}O_4NSi_2$ 470.3122, found 470.3104.

(3*S*,4*R*)-3-[(1*R*)-1-((*tert*-Butyldimethylsilyl)oxy)ethyl]-4-[(1R,3S)-3-methoxy-2-oxocyclohexyl]azetidin-2-one (4). To a solution of **10** (912 mg, 1.94 mmol) in THF (10 mL) was added acetic acid (230 μL, 4.0 mmol) and a solution of tetrabutylammonium fluoride (2.0 mL, 2.0 mmol, 1 M in THF). The reaction was stirred for 30 min. and diluted with ethyl acetate (300 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ (50 mL), water (50 mL), 10% aqueous HCl (50 mL), water (50 mL), and brine (50 mL) and dried over $MgSO_4$. After filtration and removal of the solvents, the crude product was purified by flash chromatography (hexanes−ethyl acetate, 4:1 to 2:1) to afford the desired product **4** (619 mg, 90%) as a white crystalline solid: mp 127−129 °C (hexanes); $[\alpha]_D$ 31.9° (c 1.06, $CHCl_3$); IR ($CHCl_3$) 3440 (NH), 2950, 2870, 1770 (β-lactam CO), 1740 (cHex CO), 1520, 1100 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.76 (s, 1H, NH), 4.24−4.15 (m, 1H, TBSOC*H*), 4.02−4.00 (m, 1H, β-lactam α to N), 3.58 (apparent t, 1H, MeOC*H*), 3.29 (s, 3H, CH_3O), 3.10 (ddd, 1H, J = 3.8, 5.4, 12.4 Hz, *H*C1 cHex), 2.89 (dd, 1H, J = 2.5, 5.7 Hz, β-lactam α to CO), 2.28−2.21 (m, 1H, cHex), 2.15−1.96 (m, 2H, cHex), 1.73−1.52 (m, 3H, cHex), 1.26 (d, 3H, J = 6.2 Hz, CH_3CHOTBS), 0.88 (s, 9H, *t*-Bu), 0.09 (s, 3H, CH_3Si), 0.08 (s, 3H, CH_3Si); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 212.8, 168.6, 84.0, 65.9, 61.0, 56.9, 49.4, 48.7, 33.6, 28.4, 25.7, 22.4, 19.0, 17.8, −4.3, −5.1; MS (FAB, NBA), *m*/*e* (rel intensity) 356.3 (MH^+, 20), 298.2 (100), 181.2 (35), 156.2 (66); HRMS calcd for $C_{18}H_{34}O_4NSi$ 356.2257, found 356.2248. Anal. Calcd for $C_{18}H_{34}O_4NSi$: C, 60.81; H, 9.35; N, 3.94. Found: C, 60.60; H, 9.52; N, 3.85.

(3*S*,4*R*)-3-[(1*R*)-1-((*tert*-Butyldimethylsilyl)oxy)silyl)oxy)ethyl]-4-[(1*R*,3*R*)-3-methoxy-2-oxocyclohexyl]azetidin-2-one (13) and (3*S*,4*R*)-3-[(1*R*)-1-((*tert*-Butyldimethylsilyl)oxy)ethyl]-4-[(1*S*,3*S*)-3-methoxy-2-oxocyclohexyl]azetidin-2-one (14). To a solution of the mixture of **11** and **12** obtained above (1.25 g, 2.67 mmol) in THF (10 mL) were added acetic acid (300 μL, 5.2 mmol) and a solution of tetrabutylammonium fluoride (2.8 mL, 2.8 mmol, 1 M in THF). The reaction was stirred for 1 h and diluted with ethyl acetate (300 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ (50 mL), water (50 mL), 10% aqueous HCl (50 mL), water (50 mL) and brine (50 mL) and dried over $MgSO_4$. After filtration and removal of the solvents, the crude products were purified by flash chromatography (hexane−ethyl acetate, 4:1 to 1:2) to afford **13** (597 mg, 63%) and **14** (128 mg, 14%) as white crystalline solids. For **13**: mp 129−131 °C (hexane); $[\alpha]_D$ 83.4° (*c* 1.37, $CHCl_3$); IR ($CHCl_3$) 3470 (NH), 2990, 2930, 1770 (β-lactam CO), 1740 (cHex CO), 1470, 1140 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.76 (s, 1H, NH), 4.23−4.12 (m, 1H, TBSOC*H*), 4.09 (apparent t, 1H, β-lactam α to N), 3.81 (dd, 1H, J = 6.4, 12.1 Hz, MeOC*H*), 3.46 (s, 3H, CH_3O), 2.87 (dd, 1H, J = 2.5, 5.2 Hz, β-lactam α to CO), 2.62−2.54 (m, 1H), 2.47−2.40 (m, 1H), 2.16−1.99 (m, 2H, cHex), 1.81−1.57 (m, 3H, cHex), 1.25 (d, 3H, J = 6.2Hz, CH_3-CHOTBS), 0.88 (s, 9H, *t*-Bu), 0.09 (s, 3H, CH_3Si), 0.07 (s, 3H, CH_3-Si); ^{13}C NMR (75.5MHz, $CDCl_3$) δ 208.5, 168.5, 84.2, 65.6, 61.1, 57.6, 51.8, 48.7, 34.4, 28.2, 25.6, 22.4, 22.2, 17.7, −4.5, −5.2; MS (FAB,

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THIO), *m*/*e* (rel intensity) 356.3 (MH^+, 12), 298.5 (35), 181.1 (50), 156.2 (100), 114.9 (31); HRMS calculated for $C_{18}H_{34}O_4NSi$ 356.2257, found 356.2248. For **14**: mp 124−126 °C (hexane); $[\alpha]_D$ −17.5° (c 1.18, $CHCl_3$); IR ($CHCl_3$) 3470 (NH), 2980, 2930, 1760 (β-lactam CO), 1720 (cHex CO), 1470, 1140 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.07 (s, 1H, NH), 4.19−4.08 (m, 1H, TBSOC*H*), 3.82−3.76 (m, 1H, MeOC*H*), 3.69 (dd, 1H, J = 2.1, 9.7 Hz, β-lactam α to N), 3.46 (s, 3H, CH_3O), 2.71 (dd, 1H, J = 1.4, 5.7 Hz, β-lactam α to CO), 2.47−2.35 (m, 2H), 2.17−2.10 (m, 1H), 2.02−1.96 (m, 1H), 1.80−1.57 (m, 2H), 1.44−1.27 (m, 1H), 1.24 (d, 3H, J = 6.2 Hz, CH_3CHOTBS), 0.89 (s, 9H, *t*-Bu), 0.09 (s, 3H, CH_3Si), 0.07 (s, 3H, CH_3Si); ^{13}C NMR (75.5MHz, $CDCl_3$) δ 209.2, 167.6, 84.1, 65.6, 63.4, 57.8, 55.0, 50.2, 34.4, 31.4, 25.7, 22.8, 17.8, −4.5, −4.8; MS (FAB, THIO), *m*/*e* (rel intensity) 356.2 (MH^+, 14), 298.4 (25), 181.2 (18), 156.2 (100); HRMS calcd for $C_{18}H_{34}O_4NSi$: 356.2257, found 356.2252.

Preparation of 4 from the Epimerization of a 1:1 Mixture of 4 and 13. Following procedures described above, a ca. 1:1 mixture of **4** and **13** (1.47 g, 69%) was obtained from **7** (1.34 g, 6.3 mmol) and **6** (1.72 g, 6.0 mmol) after chromatography (hexanes−ethyl acetate, 4:1 to 0:1) to remove **14** (235 mg, 11%). The 1:1 mixture of **4** and **13** was subjected to epimerization as follows. To a solution of LDA prepared by adding *n*-BuLi (3.4 mL, 8.5 mmol, 2.5 M in hexanes) to a solution of diisopropylamine (1.3 mL, 9.3 mmol) in THF (10 mL) at 0 °C and stirring for 15 min, was added dropwise a solution of **4** and **13** (ca. 1:1, 1.0 g, 2.8 mmol) in THF (10 mL) over 15 min at −10 °C. After an additional 10 min, a solution of $ZnBr_2$, prepared by refluxing a solution of 1,2-dibromoethane (0.26 mL, 3.0 mmol) in THF (10 mL) over zinc powder (390 mg, 6.0 mmol) for 2 h, was added via cannula, and the reaction was allowed to warm to 0 °C over 10 min. Diethyl malonate (2.2 mL, 14 mmol) was added, and the reaction was warmed to room temperature over 30 min *and stirred for an addition 10−15 min (premature workup leads to lower ratios)*. The reaction mixture was then poured into saturated aqueous NH_4Cl (50 mL) and extracted twice with ethyl acetate (100 mL). The aqueous phase was made acidic by the addition of 10% HCl (10 mL) and extracted with ethyl acetate (100 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, and filtered, and the solvents were removed. Recrystallization of the residue from hexanes afforded **4** as a white crystalline solid mp 124−126 °C (510 mg, 51%). Chromatography of the mother liquor (hexane−ethyl acetate, 2:1) afforded an additional quantity (210 mg, 21%) of **4** as a white crystalline solid (total yield 72%, ^1H NMR of crude reaction mixture showed an α−β MeO ratio of 21/1).

General Procedure for the Protonation of the Lithium Enolates of 4 and/or 13. To a solution of LDA (0.38 mL, ca. 0.085 mmol), prepared by adding *n*-BuLi (0.4 mL, 1 mmol, 2.5 M in hexanes) to a solution of diisopropylamine (0.15 mL, 1.1 mmol) in THF (4 mL) at 0 °C and stirring for 15 min, was added dropwise over 1 min a solution of a mixture of **4** and **13** (ca 1:1, 10 mg, 0.028 mmol) in THF (1 mL). After stirring for 30 min, a solution of the proton source (5 equiv) in THF was added all at once. The solution was warmed to room temperature and then poured into ethyl acetate (50 mL) and saturated aqueous ammonium chloride (10 mL). The layers were separated, and the organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Integration of the methoxy CH_3 resonances (β-methoxy at 3.29 ppm, α-methoxy at 3.46 ppm) in the ^1H NMR spectra of the crude reaction mixtures gave the ratios listed in Table 1.

General Procedure for the Protonation or Deuteration of the Zinc Enolate of 4 and/or 13. To a solution of the lithium enolate prepared as above in THF was added at −78 °C a solution of zinc bromide (0.14 mL, 0.028 mmol, 0.2 M in THF). Stock solutions of 0.2 M zinc bromide were prepared by refluxing 1,2-dibromoethane (172 μL, 2.0 mmol) over zinc powder (320 mg, 5 mmol) for 2 h and diluting to a total volume of 10 mL with THF. The reaction mixture was warmed to 0 °C, and the proton source (5 equiv) was added either neat if it was a liquid or as a solution in THF if a solid. The reaction was then warmed to room temperature and stirred for approximately 30 min. Workup was as described above, and ^1H NMR analysis of the crude mixtures gave the ratios listed in Tables 2 and 4. Deuteration experiments were conducted in a similar manner. The additives were added to the zinc enolate at 0 °C, and the solution was stirred at room temperature for the specified times and workedup with ethyl acetate and either saturated aqueous ammonium chloride or D_2O as specified. Integrating the disappearance of the resonance at 3.58 ppm (H α to OMe) in the ^1H NMR spectra (300 MHz) of crude reaction mixtures gave the values in Table 3. In entries 3 and 4, the butyllithium was added to the lithium enolate at −78 °C and stirred for an additional hour before the addition of the zinc bromide.

Benzyl {(3*S*,4*R*)-3-[(1*R*)-1-((*tert*-butyldimethylsilyl)oxy)ethyl]-4-[(1*S*,3*S*)-3-methoxy-2-oxocyclohexyl]-2-oxoazetidin-1-yloxoacetate (15). To a solution of **4** (355 mg, 1.0 mmol) in CH_2Cl_2 (2 mL), was added a solution of benzyl oxalyl chloride (297 mg, 1.5 mmol) in CH_2Cl_2 (2 mL) and pyridine (160 μl, 2.0 mmol) at 0 °C. The reaction was warmed to room temperature, stirred for 3 h, poured into water (20 mL), and extracted three times with CH_2Cl_2 (25 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Purification by chromatography (hexanes−ethyl acetate, 4:1) afforded the desired product **15** (500 mg, 97%) as a colorless oil; $[\alpha]_D$ −42.3° (c 1.40, $CHCl_3$); IR ($CHCl_3$) 2940, 2880, 1820 (CO), 1760 (CO), 1740 (CO), 1700 (CO), 1400, 1110 cm^{-1}; MS (FAB), *m*/*e* (rel intensity) 518.4 (MH^+, 15), 486.4 (43), 460.3 (100), 159.2 (72); HRMS calcd for $C_{27}H_{40}O_7NSi$ 518.2574, found 518.2592.

Benzyl (4*S*,8*S*,9*R*,10*S*)-4-Methoxy-10-[(1*R*)-1-((*tert*-butyldimethylsilyl)oxy)ethyl]-11-oxo-1-azatricyclo[7.2.0.0^{3,8}]undec-2-ene-2-carboxylate (16). To a solution of **15** (485 mg, 0.94 mmol) in xylene (5 mL) was added triethyl phosphite (0.8 mL, 4.7 mmol). The resulting solution was heated to 155−160 °C for 14 h and then cooled to room temperature. The reaction mixture was then poured onto a silica gel column and eluted with hexanes to remove the xylene, followed by a hexanes−ethyl acetate (4:1) eluant to obtain the desired product **16** (378 mg, 83%) as a colorless oil: $[\alpha]_D$ 50.5° (*c* 1.26, $CHCl_3$); IR ($CHCl_3$) 2940, 2860, 1775 (β lactam CO), 1740 (ester CO), 1670, 1290, 1140 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.47−7.28 (m, 5H, aromatic), 5.35 (d, 1H, J = 12.6 Hz, benzylic H), 5.23 (d, 1H, J = 12.6, benzylic H), 4.96 (apparent t, 1H, MeOC*H*), 4.27−4.21 (m, 1H, TBSOC*H*), 4.16 (dd, 1H, J = 3.3, 10.5 Hz, β lactam α to N), 3.50−3.15 (m, 2H, *H*C8 and *H*C9), 3.24 (s, 3H, CH_3O), 2.10−2.03 (m, 1H, cHex), 1.88−1.81 (m, 2H, cHex), 1.69−1.27 (m, 3H, cHex), 1.24 (d, 3H, J = 6.2 Hz, CH_3CHOTBS), 0.88 (s, 9H, tBuSi), 0.08 (s, 6H, Me_2-Si); ^{13}C NMR (75.5MHz, $CDCl_3$) δ 175.6, 160.9, 148.5, 135.4, 128.3, 128.0, 127.8, 126.3, 72.1, 66.6, 65.9, 61.0, 56.0, 54.8, 43.8, 32.3, 30.6, 25.6, 22.3, 20.2, 17.8, −4.3, −5.0 ppm; MS (FAB), *m*/*e* (rel intensity) 486.3 (MH^+, 40), 428.2 (65), 286.1 (46), 159.1 (100); HRMS calcd for $C_{27}H_{40}O_5NSi$ 486.2676, found 486.2716.

Benzyl (4*S*,8*S*,9*R*,10*S*)-4-Methoxy-10-[(1*R*)-1-hydroxyethyl]-11-oxo-1-azatricyclo[7.2.0.0^{3,8}]undec-2-ene-2-carboxylate (17). To a solution of **16** (429 mg, 0.88 mmol) in THF (10 mL) were added acetic acid (230 μL, 2.7 mmol) and a solution of tetrabutylammonium fluoride (3 mL, 3 mmol, 300 MHz1 M in THF). The reaction mixture was stirred for 4 days at room temperature and then diluted with ethyl ether (300 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ (50 mL), saturated aqueousNH_4Cl (2 × 50 mL), and brine (50 mL), dried over $MgSO_4$, and filtered. After removal of the solvents, the crude product was purified by chromatography (hexanes−ethyl acetate, 1:1) to afford the desired product **15** (288 mg, 88%) as colorless oil: $[\alpha]_D$ +66.8° (*c* 2.82, $CHCl_3$); IR ($CHCl_3$) 2940, 2880, 1770 (CO, β-lactam), 1720 (CO, benzyl ester), 1640, 1380, 1090 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.46−7.27 (m, 5H, aromatic), 5.37 (d, 1H, J = 12.5 Hz, benzylic), 5.21 (d, 1H, J = 12.5 Hz, benzylic), 4.94 (apparent t, 1H, MeOC*H*), 4.26−4.22 (m, 1H, HOC*H*), 4.18 (dd, 1H, J = 3.2, 10.2 Hz, β lactam α to N), 3.28−3.19 (m, 2H, *H*C8 and *H*C9), 3.20 (s, 3H, CH_3O), 2.07−2.01 (m, 1H, cHex), 1.90−1.67 (m, 2H, cHex), 1.67−1.61 (m, 1H, cHex), 1.48−1.26 (m, 2H, cHex), 1.32 (s, 3H, J = 6.3 Hz, H_3CCOH) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 175.6, 161.0, 149.4, 135.3, 128.5, 128.2, 128.0, 126.1, 72.3, 66.9, 65.5, 60.4, 56.0, 54.9, 44.0, 32.4, 30.6, 21.5, 20.1 ppm; MS (FAB, NBA), *m*/*e* (rel intensity) 372.2 (MH^+, 20), 340.4 (20), 286 (20), 167.2 (22), 149.1 (100); HRMS calcd for $C_{21}H_{26}O_5N$ 372.18109, found 372.1824.

(4*S*,8*S*,9*R*,10*S*)-4-Methoxy-10-[(1*R*)-1-hydroxyethyl]-11-oxo-1-azatricyclo [7.2.0.0^{3,8}]undec-2-ene-2-carboxylic Acid Amidinium Salt (19). To a solution of **17** (241 mg, 0.65 mmol) in 1,4-dioxane (4 mL) were added 10% palladium-on-carbon (200 mg) and 3,3,6,9,9-pentamethyl-2,10-diazabicyclo[4.4.0]dec-1-ene (146 μL, 0.65 mmol). The resulting mixture was stirred under 1 atm of hydrogen for 1 h at room

temperature and then filtered through Celite. The solution of the amidinium salt was the lyophilized to obtain the desired product **19** (318 mg, 100%) as a white amorphous solid: $[\alpha]_D$ +60.4° (*c* 1.03, $CHCl_3$); IR ($CHCl_3$) 2930, 1770 (β-lactam CO), 1670 (carboxylate CO), 1400, 1150 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 11.35 (br, 2H, 2 amidinium NH), 5.27 (t, 1H, J = 2.8 Hz, MeOC*H*), 4.24−4.19 (m, 1H, HOC*H*), 4.09 (dd, 1H, J = 3.1, 10.2 Hz, β-lactam α to N), 3.28 (s, 3H, CH_3O), 3.16 (dd, 1H, J = 3.1, 6.9 Hz, β-lactam α to CO), 3.12−3.04 (m, 1H, C8), 2.04−1.90 (m, 4H), 1.89 (m, 6H), 1.59−1.50 (m, 4H), 1.39 (s, 6H), 1.32−1.30 (m, 12H) ppm; ^{13}C NMR (75.5MHz, $CDCl_3$) δ 175.5, 167.8, 166.8, 139.1, 133.4, 72.6, 66.9, 65.9, 59.8, 55.6, 55.0, 53.3, 53.2, 43.3, 32.3, 31.5, 31.3, 31.2, 30.8, 30.7, 30.3, 29.8, 29.7, 24.3, 21.8, 20.6 ppm.

(4*S*,8*S*,9*R*,10*S*)-4-Methoxy-10-[(1*R*)-1-hydroxyethyl]-11-oxo-1-azatricyclo[7.2.0.0^{3,8}]undec-2-ene-2-carboxylic Acid Potassium Salt. To a solution of the amidinium salt **19** (71 mg, 0.15 mmol) in ethyl ether (1 mL) and ethyl acetate (1 mL) was added at room temperature a solution of potassium 2-ethylhexanoate (310 μL, 0.16 mmol, 0.51 M in ethyl acetate). The resulting suspension of potassium salt was stirred for 15 min and placed in a centrifuge for 5 min, after which the supernatant was decanted. The residue was suspended in diethyl ether (1 mL), stirred for 1 min, and centrifuged, and the supernatant was decanted. This process was repeated three times, and the product was dried in vacuo to afford the title compound (24 mg, 54%) as a white amorphous solid. A ^1H NMR spectrum (300 MHz, D_2O) was identical to that of an authentic sample provided by Glaxo-Wellcome (Verona, Italy).

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Supporting Information Available: ^1H and ^{13}C NMR spectral data for most of the compounds in this paper (23 pages). See any current masthead for ordering and Internet access instructions. Ordering information is given on any current masthead page.

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