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Preparation of the Key Intermediate in the Synthesis of GV143253A: The Anti-MRSA/E Injectable Trinem

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Abstract:

GV143253A is a broad-spectrum injectable β-lactam belonging to the class of trinem antibiotics. A key intermediate (3*S*,4*R*)-3-[(1*R*)-1-(*tert*-butyldimethyl- silyloxy)ethyl]-4-[-(6′*R*)-2′-[(*E*)-(pyrid-4yl)methylene]-1′-oxocyclohex-6′-yl]azetidin-2-one (10) was identified and synthesized via different enolate coupling approaches, using enol ether, lithium, sodium, magnesium, tin, zinc, zirconium, and titanium enolates. Among these approaches, the synthesis of (3*S*,4*R*)-3-[(1*R*)-1-(*tert*-butyldimethylsilyloxy)ethyl]-4-[-(6′*R*)-2′-[(*E*)-(pyrid-4yl)-methylene]-1′-oxocyclohex-6′-yl]azetidin-2-one (10) via a titanium enolate offered advantages in terms of greater diastereoselectivity, higher yield, robustness, and isolation of intermediates and was superior to the method previously used for preparing large quantities of drug substance for early development studies.

Introduction

In recent years, bacteria have enhanced their mechanism of resistance against the most common antibacterial drugs. In particular, methicillin-resistant staphylococci represent one of the most challenging and threatening diseases globally. Although confined to hospitals, it represents an important clinical problem, with up to 30% incidence in some U.S. hospitals and an average of 13% in Europe. GV143253A **1** (Figure 1) is a broad-spectrum injectable trinem antibiotic with satisfactory solubility and no nephrotoxic effects. The spectrum and activity are similar to those of the carbapenems. Activity against *Pseudomonas* is lost, but unlike carbapenems, GV143253A is active against MRSA/E pathogens. Pockets of resistance to the best treatment for MRSA (the glycopeptide vancomycin) have recently been reported, and no alternatives are currently available; hence, GV143253A represents an opportunity to become a first-line replacement, allowing the valuable glyclopeptide class held back as appropriate.

Background

The original synthesis of GV143253A was a linear process that started with the synthesis of the chiral intermediate GV97322X. The whole process required a multistep approach starting from the commercially available 4-acetoxyazetidinone. Introduction of the side-chain on the cyclohexanone moiety was then carried out, and synthesis

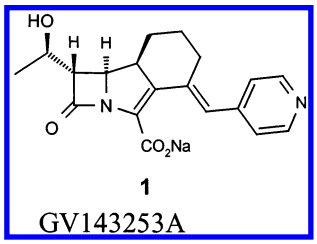

Figure 1.

and transformation of a transient phosphorane intermediate was used to selectively protect the nitrogen of GV97322X and to perform the subsequent cyclization (Scheme 1).

This synthetic approach was not ideal for further scale-up, as all of the intermediates possessed physical properties that were unsuitable for purification using standard crystallisation techniques.

An alternative convergent route was developed by the Chemical Development group which identified (3*S*,4*R*)-3-[(1*R*)-1-(*tert*-butyldimethylsilyloxy)ethyl]-4-[-(6′*R*)-2′-[(*E*)-(pyrid-4yl)methylene]-1′-oxocyclohex-6′-yl]azetidin-2-one, '*β*-enone- azetidinone' **2** (Figure 2) as a pivotal synthetic intermediate.

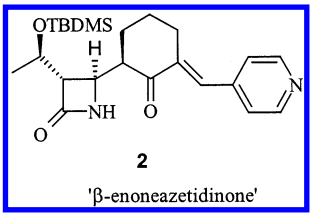

Figure 2.

Much effort was devoted to obtaining this intermediate in a single step starting from the commercially available 4-acetoxyazetidinone **3** and 2-[(*E*)-pyrid-4-yl)methylene]-cyclohexanone, "Pyridylenone" **4** (Scheme 2), thus allowing a convergent synthetic route.

Results and Discussion

"Pyridylenone" **4** was easily prepared following a literature procedure[1] starting from the commercial pyridine 4-carboxaldehyde **5** and 1-morpholine-1-cyclohexene **6** as depicted in Scheme 3. The mixture of the two diastereoisomers **7** (syn/anti 15/85) was converted to the desired intermediate and isolated as a salt of trifluoroacetic acid **8**.[2]

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(1) Sam, J.; Aparajithan, K. *J. Pharm. Sci.* **1967**, *56*, 664.

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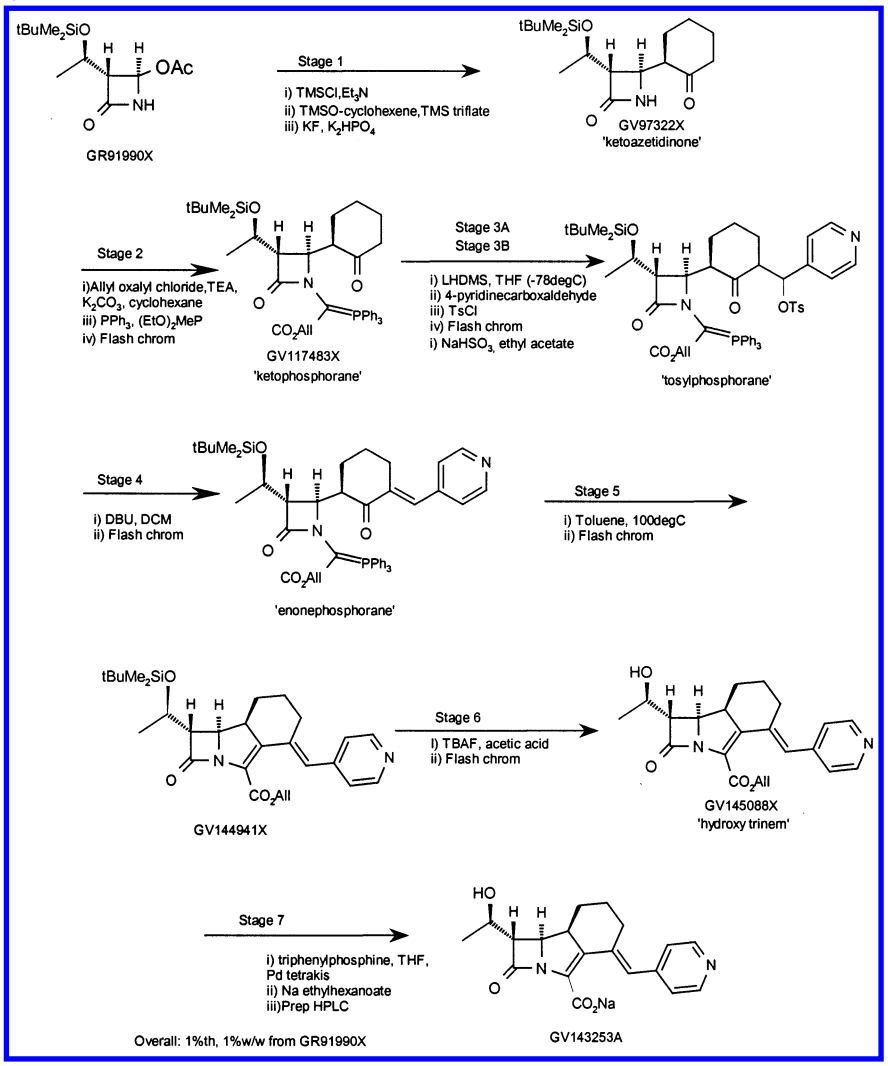
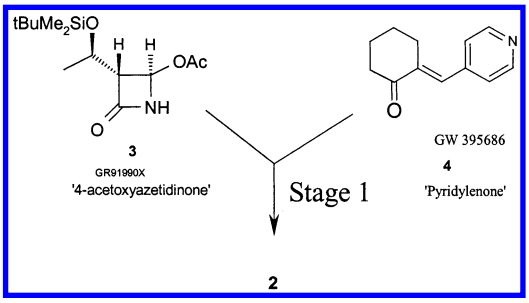
Scheme 1. **Original synthesis**

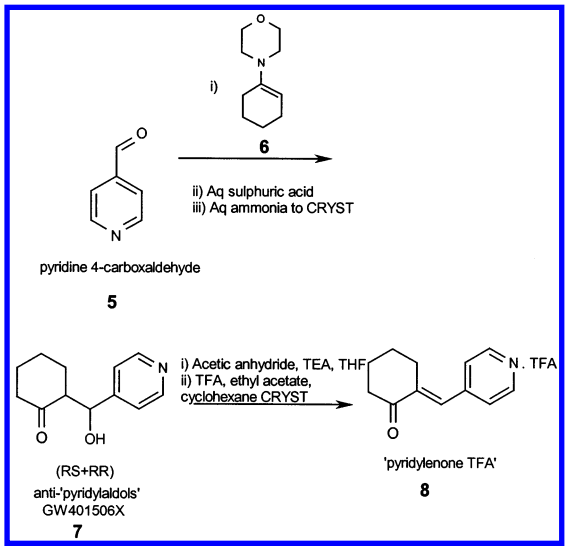


Scheme 2

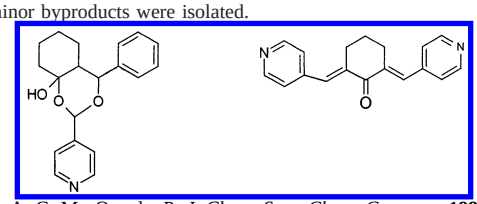


In a previous study[3] it was shown that a general approach to the synthesis of compounds such as **2** may be adopted by reacting the commercially available chiral "4-acetoxyazetidinone" **3** with suitably activated ketones. The first coupling approach (Scheme 4) was carried out by activating the pyridylenone **4** as a trimethylsilyl enol ether derivative **9** and reacting this with **3** under trimethylsilyl triflate catalysis. In this case the reaction afforded a mixture of α- and β-isomers **10** (α/β:50/50) in good yield.

Scheme 3. **"Pyridylenone" synthesis**

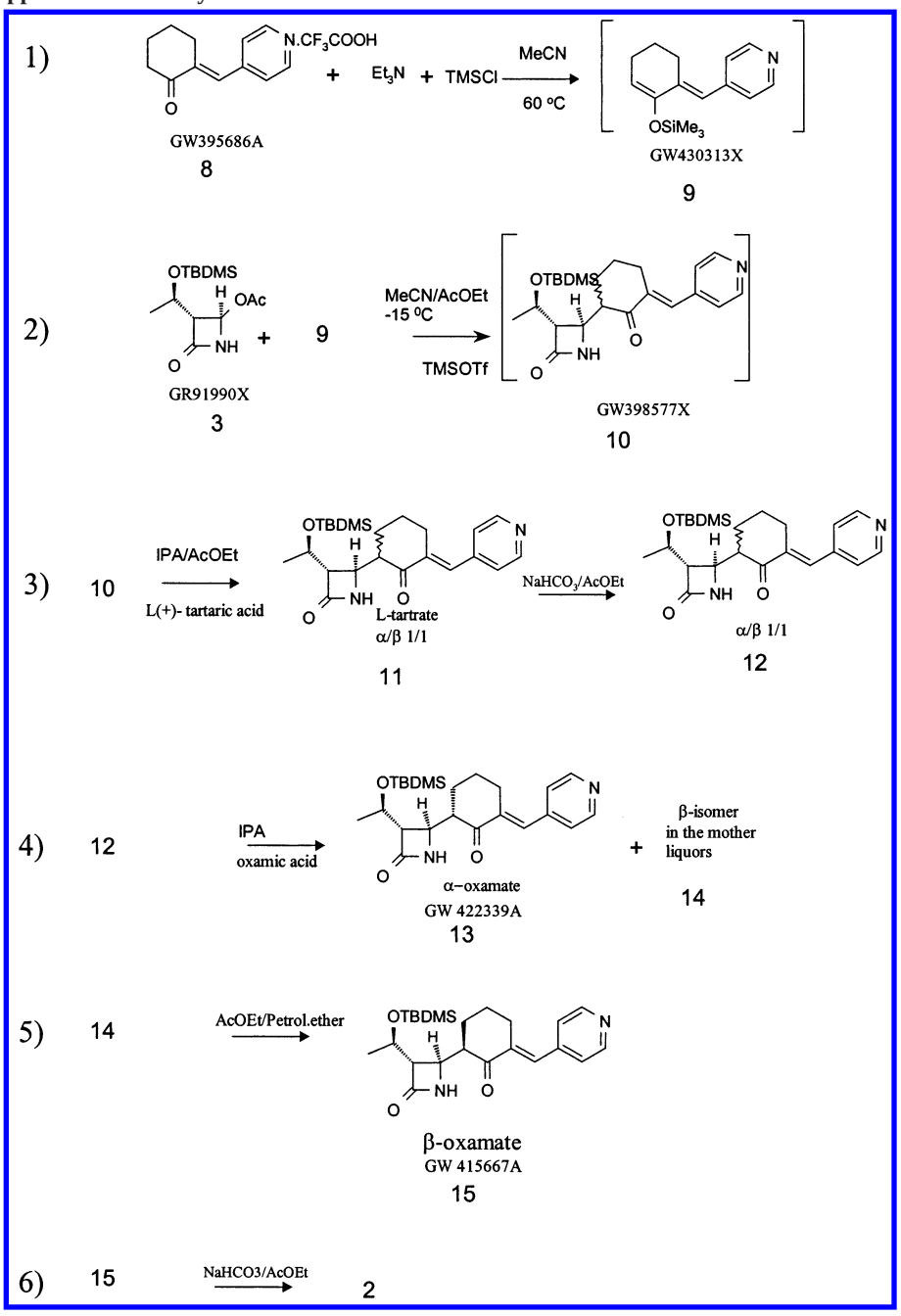


(2) Two minor byproducts were isolated.



(3) Barrett, A. G. M.; Quayle, P. *J. Chem. Soc., Chem. Commun.* **1981**, 1076.

Scheme 4. **Initial approach via the silyl enol ether**



The two isomers were isolated from the reaction mixture by precipitating them as the L-(+)-tartaric acid salts (α/β in a 1/1 ratio), allowing a first purification of the diasteroisomers **11** from the complex reaction mixture.

A breakthrough in this approach was achieved when it was found that oxamic acid in IPA was able to selectively precipitate the α-isomer as oxamate **13**, leaving the desired β-isomer **14** in the mother liquors and allowing its separation from the diasteromeric mixture **12**. The pure β-isomer was further precipitated as the oxamate from ethyl acetate, affording the desired compound as a yellow solid **15**.

Finally, it was found that the α-oxamate **13** could also be isomerised into a 60/40 α/β mixture, allowing a potential recycling of the α-isomer.

The whole process (Stage 1), depicted in Scheme 4, consisted of six steps for the isolation of the β-isomer.

(1) silyl enol ether formation
(2) coupling
(3) isolation of the α/β isomers as a 1/1 mixture of their L-tartrate salts
(4) separation of the α isomer from the α/β mixture
(5) isolation of the pure β isomer as oxamate
(6) isolation of the β-isomer

This nonstereoselective process was scaled up to a 200-L pilot-plant vessel achieving a 30% yield of the β-isomer **2** from 4-acetoxyazetidinone **3** without recycling.

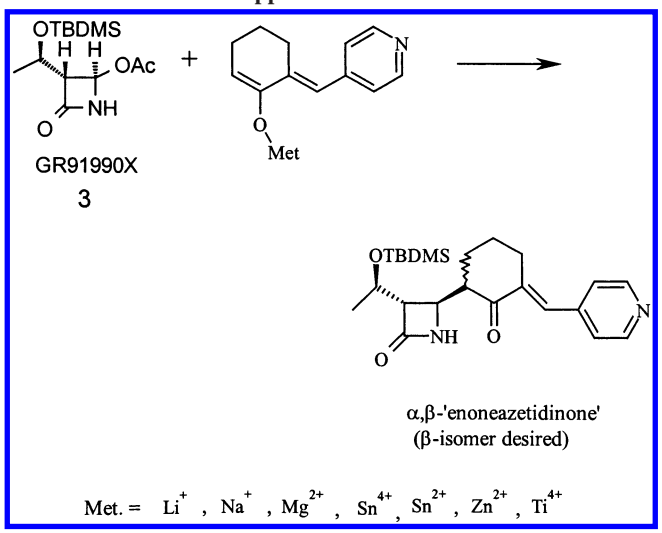
Although this procedure allowed the preparation of our target key intermediate in a good yield and within the deadline to produce the required amount of GV143253A for

Table 1

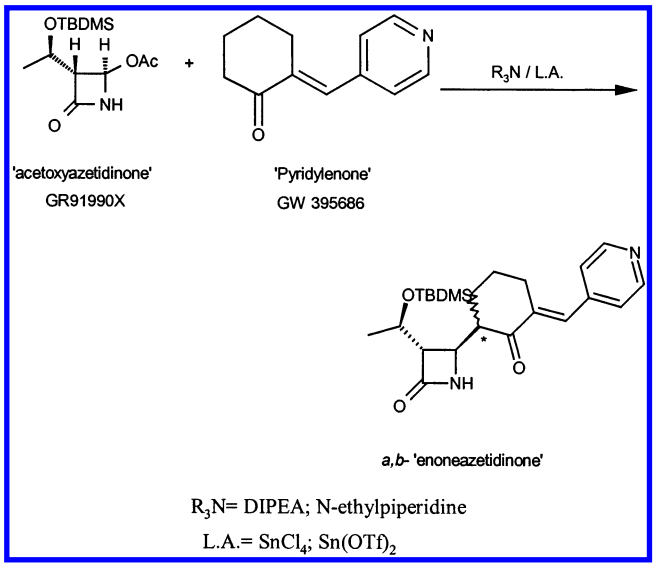
entry	method (equiv)	GW395686X (equiv)	base (equiv)	Lewis acid (°C)	conditions	α/β	yield
1	A[a]	2	DIPEA[f] (2.6)	$SnCl_4$ (5)	−20 → 0	68/32	15%
2	B[b]	2	DIPEA (2.9)	$SnCl_4$ (1 + 4)	−20 → 0 → 20	70/30	20%
3	B[b]	2	DIPEA (2.9)	$SnCl_4$ (1 + 4)	−20 → 0 → reflux	−	−
4	C[c]	2	1-ethylpiperidine (2.4)	$Sn(OTf)_2$ (2.2)	−20 → 0 → 20	−	−
5	B[b]	1.3	1-ethylpiperidine (1.8)	$Sn(OTf)_2$ (2.3)	−20 → 0 → 20	−	−
6	D[d]	2	LHMDS (2 + 1 equiv)	$ZnBr_2$ (2)	−20 → 0 → 20	40/60	10%
7	E	1.4	LHMDS (1.8)	$ClZr(O\text{-}n\text{-}Bu)_3$(1.8)	−5 → 0 → 20	60/40	20%

[a] **Method A:** base added to the mixture of GW395686X, GR91990X (1 equiv), and Lewis acid (5 equiv). [b] **Method B:** a mixture of GR91990X (1 equiv) and Lewis acid (1 equiv) added to a solution of GW395686X (2 equiv) and Lewis acid (4 equiv) and base (2.6−2.9 equiv). [c] **Method C:** GR91990X (1 equiv) added to a solution of GW395686X and Lewis acid and base. [d] **Method D:** base (1 equiv) and GR91990X added to the mixture of GW395686X and Lewis acid and base (2 equiv). [e] **Method E:** LHMDS added to GW395686X after transmetalation with $ClZr(O\text{-}n\text{-}Bu)_3$, GR91990X then added. [f] DIPEA = *N*,*N*-Diisopropylethylamine.

Scheme 5. **Enolates approach**



Scheme 6. **Tin enolates**



toxicology studies, a more streamlined process was investigated. The metal enolate chemistry of pyridylenone **4** was studied to find an efficient and stereoselective reaction (Scheme 5).

The study of the reactivity of the enolates started with the evaluation of the reactivity of the acetoxyazetidinone **3** and the lithium and sodium enolates of pyridylenone **4**.

Following the generation of the enolates in THF using LiHMDS, LDA, or solid NaHMDS, 4-acetoxyazetidinone **3** was added. Different equivalents, volumes, and temperatures were tried, resulting in no more than a 30% yield with an α/β ratio of approximately 1/1. This was probably due to the short lifetime of **3** under such basic reaction conditions. To increase the yields and to prevent degradation of **3**, the reactivity of a softer counterion was investigated. Magnesium enolates were generated according to two different protocols[4] by reacting pyridylenone **4** with either $Cl-Mg-N(i\text{-}Pr)_2$ or $Br-Mg-N(i\text{-}Pr)_2$ in THF at +5 °C or by a Mg/Li exchange with $MgBr_2$ on the lithium enolate formed with LiHMDS in THF.

Both of these approaches gave very low reaction yields (10%−15%) with a diastereoselectivity in favour of the α-isomer (α/β = 3/1). In addition a large amount of unreacted pyridylenone **4** was recovered.

Attempts were then aimed at increasing both the reactivity of acetoxyazetidinone **3** and the β-diasteroselectivity of the reaction; hence, enolates prepared from metal enolates whose salts are generally used as Lewis acids in enolate coupling reactions were studied. These metal enolates were generated following either a Mukaiyama-like procedure or a transmetalation protocol from the corresponding lithium enolates. Tin, zinc, zirconium, and titanium enolates were investigated. In the tin enolate case, the enolisation of pyridylenone **4** was carried out in the presence of a tertiary amine and a tin(IV)[5] or tin(II)[6] Lewis acid (Scheme 6). As clearly indicated in Table 1, when reaction occurred, the yields were low, and the α-isomer was generally the preferred one. Different addition orders were also tried to better activate the 4-acetoxyazetidinone, with no significant success (see entries 1−5 in Table 1).

The preparation of the zinc enolate[7] (entry 6, Table 1) was carried out by transmetalation of the lithium enolate with zinc bromide at 0 °C. Less than a 10% yield was obtained with a slight preference for the β-isomer. Similar results were obtained with the tri-*n*-butoxyzirconium enolate (entry 7, Table 1) generated by transmetalation from lithium enolates. However, when we focused our attention on other zirconium enolates, it was found that zirconium (IV) *tert*-butoxide[8] was

(4) Hobayashi, K.; Takabatake, H. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 1697.

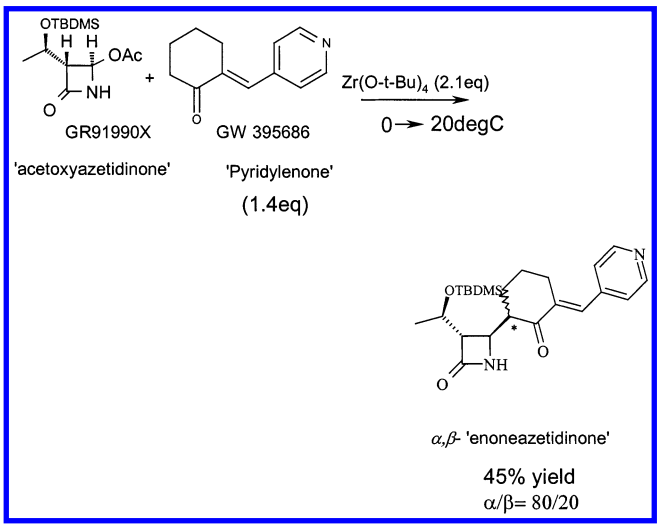
(5) Evans, D. A. *J. Am. Chem. Soc.* **1991**, *113*, 1047.
(6) Mukaiyama, T.; Stevens, R. W. *Chem. Lett.* **1982**, 353.
(7) Kennedy, G.; Rossi, T.; Tamburini, B. *Tetrahedron Lett.* **1996**, *37*, 7441.
(8) Shibasaki, M.; Kirio, Y.; Sasai, H. *J. Org. Chem.* **1990**, *55*, 5306.

Table 2[a]

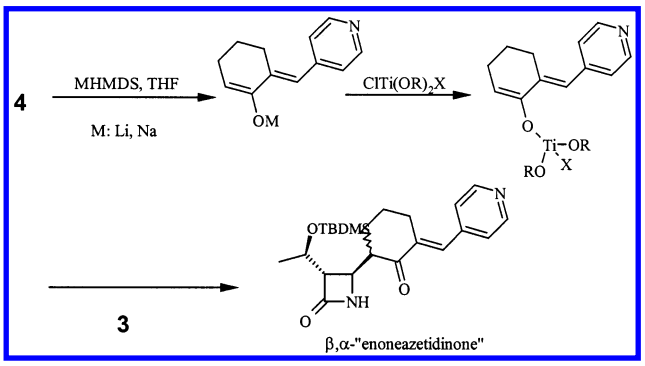
entry	Ti-complex	MHMDS	% yield	analytical data (by HPLC)	notes
1	A	Na	72[b]	β/α ratio = 49/51 (44/56 after work-up)	−
2	B	Na	18[c]	β/α ratio = 20/80	−
3	C	Na	No react.	−	−
4	C	Li	No react.	−	transmetalation at −25 °C → r.t.
5	D	Li	40[c]	β/α ratio = 48/52 (after 50 min) β/α ratio = 25/75 (after 2.5 h)	
6	E	Li	45[c]	β/α ratio = 42/58	
7	F	Li	45[c]	β/α ratio = 62/38 (after 10 min) β/α ratio = 57/43 (after 75 min)	transmetalation at −25 °C → rt
8	G	Li	0	−	LiHMDS 1.4 equiv $Ti(OMe)_4$ insoluble
9	H	Na	n.d.	β/α ratio = 55/45 (after 30 min)	$TiCl_4$·THF complex very insoluble

[a] Typical procedure: Lithium enolate was generated at 0 °C; transmetalation and quenching of the titanium enolate with **3** were carried out at rt GR91990X (1 equiv), GW395686X (1.4 equiv), Li(Na)HMDS (1.8 equiv), $ClTi(OR)_2X$ (1.8 equiv). [b] Yield calculated on the isolated product (by flash chromatography). [c] Yield in solution estimated by comparing %a/a of HPLC peaks.

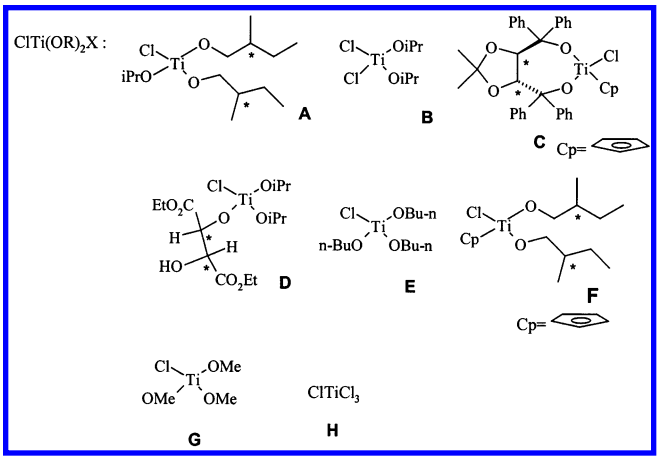
Scheme 7



Scheme 8



Scheme 9



a mild basic reagent that could be utilized in aldol reactions. It was described that treatment of $Zr(O\text{-}t\text{-}Bu)_4$ with some carbonyl compounds resulted in the direct formation of zirconium enolates and *tert*-butyl alcohol. These enolates were then reacted with aldehydes in cross and intramolecular aldol reactions. In our work we were attempting to directly generate the tri-*tert*-butoxyzirconium enolate on the pyridylenone **4** and to carry out the coupling with **3** as the electrophile. Contrary to the results obtained with $ClZr(O\text{-}n\text{-}Bu)_3$, Zr(IV) *tert*-butoxide gave the desired compound in medium-to-good yield but with a prevalence of the α-isomer (Scheme 7).

On the basis of some literature[9] findings showing the titanium enolate of cyclohexanone reacting with aldehydes *syn*-selectively, a more in-depth study was carried out on titanium enolates. After deprotonation of **4** with LiHMDS and transmetalation with chlorotitanium triisopropoxide[10] at ambient temperature, the azetidinone **3** was added (Scheme 8). The coupling gave both a promising yield (60%) and β-selectivity (β/α = 2/1).

Further work to increase the β/α stereoselectivity by reacting **3** with titanium enolates carrying different ligands was carried out. When not commercially available, the titanium complexes were prepared[11] via ligand exchange. These complexes (Scheme 9) were then reacted in situ with the Li/Na enolates of compound **4**, giving the desired titanium enolates which were finally treated with acetoxyazetidinone **3** to afford the desired compound as a mixture of β + α isomers.

Results are reported in Table 2.

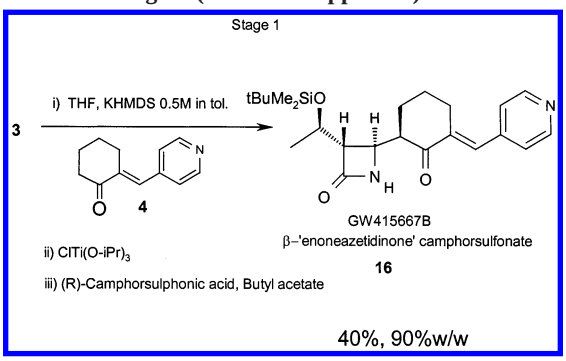
None of the reported enolates gave an enrichment in the β-isomer; therefore, a standard procedure with $ClTi(i\text{-}OPr)_3$ was developed by optimizing the equivalents of base and $ClTi(i\text{-}OPr)_3$. The resulting reaction protocol was set up,

(9) Reetz, M. T.; Peter, R. *Tetrahedron Lett.* **1981**, *22*, 4691.

(10) Wollmann, T.; Gerlach, U. In *Recent Advances in the Chemistry of Anti-infective Agents*; Bentley, P. H., Ed.; Royal Society of Chemistry: Cambridge, U.K., 1993; p 50.

(11) (a) Hafner, A.; Duthaler, R. O. *J. Am. Chem. Soc.* **1992**, *114*, 2321. (b) Mikami, K.; Matsukawa, S. *J. Am. Chem. Soc.* **1994**, *116*, 4077.

Scheme 10. **Stage 1 (Ti enolate approach)**



whereby pyridylenone **4** (1.3 equiv) was dissolved in dry tetrahydrofuran (THF, 5 mL/g) and added dropwise over 30 min to potassium hexamethyldisilazide (0.5 M in toluene, 1.69 equiv) at 0−5 °C. The suspension was stirred at 5 °C for 30 min and then treated with chlorotitaniumtrisisopropoxide (1.69 equiv) in THF (5 mL/g) over 2 min at 10−12 °C. The dark brown suspension was held at 15−20 °C for 45 min and then treated with **3** (33.8 g, 1 equiv) in one portion. The dark solution was then stirred at 20−25 °C for 60 min. (Notes: β/α ratio in the range 2/1 to 3/1; solution yield in the range 70−83% $\alpha + \beta$ isomers). The removal of residual titanium complexes from the crude reaction mixture and the isolation of the pure β-isomer was facilitated using acetic acid at low temperature (0−5 °C) which prevented the formation of an emulsion and allowed the β/α ratio to remain stable at around 2/1. The final solution was washed with aqueous 5% w/w $NaHSO_3$. Finally, (*R*)-(−)-10-camphorsulfonic acid was added to selectively precipitate (from ^{n}BuOAc) the desired β-isomer from the α/β mixture, thus allowing separation of the two isomers.

Stage 1 was therefore set as shown in Scheme 10, achieving a 40% overall yield from 4-acetoxyazetidinone. This process was successfully scaled up to a 5-L reactor.

Conclusions

A thorough investigation into the coupling between 4-acetoxyazetidinone **3** and pyridylenone **4** resulted in a stereoselective reaction using the Ti enolate where the maximum β/α ratio achievable was 2/1. The work-up was optimised with the aim of preventing emulsions and removing titanium complexes. The desired β-enoneazetidinone was isolated as the camphorsulfonate salt in a 40% overall yield which was an improvement of 10% over the original silyl enol ether approach and involved a much simplified isolation procedure. The whole method was successfully scaled-up to a 5-L reactor.

Experimental Section

Reagents were purchased from standard suppliers.

^{1}H NMR spectra were recorded at 300 or 500 MHz in $CDCl_3$ or d_6-DMSO and are reported in parts per million downfield.

HPLC analyses were conducted using a 5 μ Hypersil BDS C18 column, solvent system acetonitrile/buffer $NH_4H_2PO_4$ (0.05 M) 60/40 (v/v), flow rate 1 mL/min and detection at 270 λ. Retention time of α-enoneazetidinone **13** 10.1 min. Retention time of β-enoneazetidinone **14** 8.5 min.

Preparation of 'Pyridylaldol', GW401506X, 7. Pyridine-4-carboxaldehyde **5** (48 g, 0.9 equiv, 450 mmol) was added over 1.5 h to a solution of 1-morpholine-1-cyclohexene (1 equiv, 84.46 g, 505 mmol) in toluene (85 mL) at 5 °C. The solution was stirred for 1.5 h, and then 2 M H_2SO_4 (aq) (2.2 equiv, 500 mL) was added dropwise in 1 h and the mixture stirred at 15 °C for 30 min. The organic layer was run off, and 32% NH_3 (aq) was added at 15 °C until pH = 3.5. The mixture was seeded, and then further 32% NH_3 (aq) was added until pH = 5. The mixture was seeded again, stirred for 30 min, and then 32% NH_3 (aq) was added until pH = 7.5. The suspension was stirred at rt for 30 min, then filtered, washed with water (2 × 400 mL), and dried under vacuum to give **7** as a white solid: yield 61%. H^1 NMR ($CDCl_3$): 8.57 (2H, d), 7.26 (2H, d), 4.79 (1H, dd), 4.12 (1H, d), 2.59 (1H, m), 2.48 (1H, m), 2.36 (1H, m), 2.12 (1H, m), 1.84 (1H, m), 1.5−1.8 (3H, m), 1.39 (1H, m).

2-[(*E*)-(Pyrid-4-yl)methylene]cyclohexanone Trifluoroacetic Acid Salt, 8. Triethylamine (3 equiv, 76 g, 753 mmol) was added to a suspension of **7** (51 g, 251 mmol, 1 equiv) in THF (200 mL) at reflux (ca. 69 °C), and then a solution of acetic anhydride (51 mL, 2 equiv, 502 mmol) was added dropwise in over 30 min.The mixture was stirred at reflux (ca. 76 °C) for 1 h. The mixture was cooled to 10 °C, and 16% NaOH (aq) (140 mL) was added dropwise in 10 min. Water (100 mL) and EtOAc (300 mL) were added, and the resulting mixture was warmed to 25°. The organic layer was washed with saturated NH_4Cl (4 × 200 mL) and brine (200 mL) and then filtered through a silica pad, washing the silica with EtOAc (2 × 200 mL). The solution obtained was concentrated under vacuum to 50 mL. TFA (29 g, 251 mmol, 1 equiv) was added dropwise in over 30 min and then cyclohexane in 30 min. The resulting suspension was stirred for 1 h at 5 °C, filtered, washed with EtOAc/cyclohexane = 2/1 (2 × 70 mL), and dried under vacuum to give **8** as a pale yellow solid: yield 64.7%. H^1 NMR ($CDCl_3$): 8.80 (2H, d), 7.62 (2H, d), 7.38 (1H, m), 2.84 (2H, m), 2.62 (2H, t), 2.00 (2H, m), 1.86 (2H, m).

(3*S*,4*R*)-3(1′*R*)-1′-(*tert*-Butyldimethylsilyloxy)ethyl]4-[-2″-{(*E*)-(pyrid-4yl)methylene-l-oxocyclohex-6″-yl]-azetidin-2-one. 12. Triethylamine (6 equiv, 2.13 L, 15 mol) was added to a suspension of **8** (758 g, 2.51 mol, 1 equiv), in acetonitrile (6.06 L) at room-temperature resulting in complete dissolution. Trimethylsilyl chloride (3 equiv, 7.53 mol, 818 g) was then added over 15 min. The mixture was stirred at 60 °C for 2.5 h, cooled to 10 °C, and poured into a beaker containing ethyl acetate (9 L) and $NaHCO_3$ (5%, 3.64 L) with stirring. The organic layer was washed with cold saturated NH_4Cl (2 × 7.5 L) and brine (2 × 7.5 L). The organic phase was dried and concentrated at 40 °C in vacuo to give a solution of **9** in ethyl acetate (1.29 L). This solution was added to **3** (1 equiv, 2.50 mol, 720 g) dissolved in acetonitrile (5.87 L); the solution was cooled to 15 °C, and trimethylsilyl triflate (1 equiv, 2.50 mol, 550 g) was added over 30 min, keeping the temperature at <−2 °C. Further trimethylsilyl triflate (1 equiv, 2.50 mol, 550 g) was then added dropwise over 2 h. The resulting solution was stirred at 0 °C for l h and then poured into a mixture of cold

saturated $NaHCO_3$ (4.9 L) and ethyl acetate (8.6 L). The organic layer was washed with saturated $NaHCO_3$ (3.8 L), water (3 × 3.8 L), and brine (2 × 3.8 L). The organic phase was dried and concentrated at 45 °C in vacuo to 1.97 L. Isopropyl alcohol (2.58 L) and L-(+)-tartaric acid (0.5 equiv, 1.26 mol, 190 g) were then added to the concentrate. The resulting solution was warmed to 75 °C, stirred for 1 h, and then cooled to 2 °C for 1 h. The resulting yellow solid was filtered and washed with ethyl acetate (1.63 L) to give the tartrate salt **11** as a pale yellow solid; 711 g yield 90%. A portion of **11** (0.31 mol, 180 g) was suspended in ethyl acetate (900 mL), and an aqueous solution of $NaHCO_3$ (5%, 900 mL) was added over 30 min. After stirring for 1 h the two phases were separated, and the organic layer was washed with a 5% $NaHCO_3$ solution (450 mL) and water (450 mL), filtered over Celite, and evaporated to dryness to afford compound **12**: 150 g, yield 93%. H^1 NMR($CDCl_3$) 8.64 (2H, d + d), 7.23 (2H, m), 6.32 (1H, bs), 5.69 (1H, bs), 4.32 (1H, m), 4.26−4.16 (1H, m), 3.69 (1H, dd), 3.06 (1H, bs), 3.02−2 99 (1H, m), 2.98 (1H, bs), 2.78−2.76 (1H, m), 2.70−2.50 (1H, m), 2.45 (1H, m) 2.17 (1H, m), 1.99 (1H, m), 1.85 (1H, m), 1.65 (1H, m), 1.25 (3H, d), 0.88 (9H, s), 0.08 (6H, s). Selectivity: 1:1 β/α.

A solution of oxamic acid (1 equiv, 0.29 mol, 25 g) in methanol (6 L) was added in 20 min to a solution of **12** (1 equiv, 0.29 mol, 120 g) in IPA (6 L). After the mixture stirred for 5 min, the methanol was removed under vacuum (T < 25 °C), and the residual suspension was cooled to 0 °C and stirred for 1 h. The solid was filtered, washed with cold 2-propanol (0.2 L) and cold isopropyl ether (0.2 L) and dried under vacuum to afford compound **13**: 75 g, yield 51%. H^1 NMR (DMSO): 8.60 (2H, d), 8.11 (1H, bs), 7.94 (1H, s), 7.38 (2H, d), 7.09 (1H, m), 4.06 (1H, m), 3.58 (1H, d′d), 2.90 (1H, m), 2.87 (1H, dd), 2.68 (1H, m), 2.62 (1H, m), 2.04 (1H, m), 1.82 (1H, m), 1.68−1.60 (1H, m), 1.12 (1H, d), 0.84 (9H, s), 0.04 (3H, s), 0.02 (3H, s).

(3*S*,4*R*)-3-[(1′*R*)-1′-(*tert*-Butyldimethylsilyloxy)ethyl]-4-[(6″*S*)-2″-[(*E*)-(pyrid-4-yl)methylene]-oxocyclohex-6″-yl]-azetidin-2-one oxamate, 13; (3*S*,4*R*)-3-[(1′*R*)-1′-(*tert*-Butyldimethylsilyloxy)ethyl]-4-[(6″*R*)-2′-[(*E*)-(pyrid-4-yl)methylene]-oxocyclohex-6″-yl]-azetidin-2-one oxamate, 15. The solid **13** was filtered off, and the mother liquors **14** were concentrated, diluted with ethyl acetate and re-evaporated. Petroleum ether was added and the mixture was cooled to 5 °C. After stirring for 1 h the solid was filtered, washed with cold ethyl acetate/petroleum ether mixture (1/1; 1 L) and dried for 24 h under vacuum at 25 °C to give compound **15** as yellow/beige solid: 62 g, yield 42%. H^1 NMR (DMSO): 13.63 (1H, bs), 8.62 (2H, d), 8.10 (1H, bs), 7.94 (1H, s), 7.79 (1H, bs), 7.40 (2H, d), 7.18 (1H, m), 4.15 (1H, m), 3.98 (1H, dd), 2.94 (1H, dd), 2.90 (1H, m), 2.70 (1H, m), 2.63 (1H, m), 2.08 (1H, m), 1.86 (1H, m), 0.72−1.65 (2H, m), 1.16 (3H, d), 0.85 (9H, s), 0.06 (3H, s), 0.04 (3H, s).

(3*S*,4*R*)-3-[(1*R*)-1-(*tert*-Butyldimethylsilyloxy)ethyl]-4-[(6′*R*)-2′-[(*E*)-(pyrid-4yl)methylene]-1′-oxocyclohex-6′-yl]-azetidin-2-one, 2. 15 (62 g, 0.12 mol) was dissolved in ethyl acetate (1 L), washed with 5% aqueous bicarbonate solution (2 × 0.5 L) and brine (0.5 L), dried with Na_2SO_4, and evaporated to give compound **2**: 45 g, yield 91%. H^1 NMR (CD_3OD): 8.58 (2H, d), 7.43 (2H, d), 7.27 (1H, m), 4.30 (1H, m), 4.20 (1H, dd), 3.06 (1H, dd), 3.01 (1H, m), 2.75 (1H, m), 2.72 (1H, m), 2.20 (1H, m), 2.00 (1H, m), 1.75−1.85 (2H, m), 1.26 (3H, d), 0.92 (9H, s), 0.12 (3H, s), 0.11 (3H, s).

Procedure for the Reaction with Lithium and Sodium Enolates. Lithium or sodium enolates of 2[(*E*)-(pyrid-4-yl)-methylene]cyclohexanone were generated by using LiHMDS, LDA, and NaHMDS.

Example: 2[(*E*)-(pyrid-4-yl)methylene]cyclohexanone **4** (3 equiv, 6.15 mmol, 1.1 g) was added over 15 min to a solution of LiHMDS (2.1 equiv, 1 M in hexanes, 4.31 mmol) in THF (4 mL) at −78 °C. The solution was stirred for 40 min, keeping the temperature under −70 °C. 4-Acetoxy-azetidinone **3** (1 equiv, 2.05 mmol, 0.58 g) was then added, and the mixture was stirred at −78 °C over 60 min and then poured into an aqueous solution of ammonium chloride (5 mL), extracted with THF (2 × 5 mL), and distilled under reduced pressure to dryness to give the desired product as an oil: yield 15% a/a by HPLC.

Procedure for the Reaction with Magnesium Enolates. Example: EtMgBr 1 M in THF (2 equiv, 2.12 mmol, 2.12 mL) was added to a solution of *N*,*N*-diisopropylethylamine (2 equiv, 2.12 mmol, 0.27 g) in dry THF (1 mL) and the mixture heated to reflux for 1.5 h. The resulting white suspension was cooled to 0 °C, and 2[(*E*)-(pyrid-4-yl)-methylene]cyclohexanone **4** (2 equiv, 2.12 mmol, 0.4 g) was added. After stirring for 20 min 4-acetoxyazetidinone **3** (1 equiv, 1.06 mmol, 0.3 g) was poured into the mixture and stirred for 5 min. The crude reaction mixture was quenched into saturated aqueous NH_4Cl and extracted with ethyl acetate, and the organic layers were dried on Na_2SO_4. Removal of the solvent followed by flash chromatography on silica gel (ethyl acetate) gave the desired compound (0.06 g; yield 10−15%) as a mixture of $\alpha + \beta$ isomers. Selectivity: 1:3 β:α

Procedure for the Reaction with Tin (IV) and Tin (II) Enolates. Example: $SnCl_4$ 1 M in CH_2Cl_2 (5 equiv, 8.7 mmol, 8.7 mL) was added to a solution of 2[(*E*)-(pyrid-4-yl)methylene]cyclohexanone **4** (2 equiv, 3.5 mmol, 0.65 g) and 4-acetoxyazetidinone **3** (1 equiv, 1.74 mmol, 0.5 g) in CH_2Cl_2 (15 mL) at −20 °C. After stirring for 10 min at 0 °C, *N*,*N*-diisopropylethylamine (2.6 equiv, 4.5 mmol, 0.58 g) in CH_2Cl_2 (4 mL) was added over 20 min. The mixture was slowly warmed to room temperature and stirred for 1 h. The solution was quenched by pouring into a mixture of saturated aqueous potassium sodium tartrate (16 mL), saturated aqueous sodium bicarbonate (16 mL), and diethyl ether (54 mL). The mixture was stirred vigorously for 1 h, and then the two phases were separated, and the organic layer was dried with Na_2SO_4. The solvent was evaporated and the residue purified by flash chromatography to give a mixture of $\alpha + \beta$ isomers (0.1 g; yield 14%).

Procedure for the Reaction with Zinc Enolates. Example: LiHMDS 1 M in hexanes, (2 equiv, 2.08 mmol,2.08 mL) was added to a solution of 2[(*E*)-(pyrid-4-yl)methylene]-

cyclohexanone **4** (2 equiv, 2.08 mmol, 0.39 g) in dry THF (5 mL) at −20 °C. The mixture was stirred 15 min before heating to 0 °C, and then $ZnBr_2$ (2 equiv, 2.08 mmol, 0.47 g) dissolved in THF (5 mL) was added. After 10 min a solution of 4-acetoxyazetidinone **3** (1 equiv, 1.04 mmol, 0.3 g) in dry THF (4 mL) was added, the mixture was stirred for 1 h at 0 °C and then was quenched into a mixture of ethyl acetate and saturated aqueous NH_4Cl. The two phases were separated, and the organic layer was dried with Na_2SO_4. The solvent was evaporated and the residue purified by flash chromatography to give a mixture of $\alpha + \beta$ isomers (0.05 g, yield 11%).

Procedure for the Reaction with a Zirconium Enolate. A solution of **4** (1.3 equiv, 1.83 mmol, 0.344 g,) in dry THF (4 mL) and added dropwise over 5 min to a solution of zirconium(IV) *tert*-butoxide (1.06 g, 2.76 mmol, 2.1 equiv) in dry THF (4 mL) at −10/−5 °C. The mixture was stirred at −5 °C for 1.5 h and then treated with 4-acetoxyazetidinone **3** (1 equiv, 1.31 mmol, 0.378 g) in one portion. The dark mixture was held at 20−25 °C for 40 min and then poured into saturated sodium bicarbonate and ethyl acetate (80 mL). The biphasic mixture was filtered on Celite through a glass sinter washing, with ethyl acetate. The phases were separated and organics were washed with saturated sodium bicarbonate (30 mL), saturated ammonium chloride (30 mL), and brine (30 mL) and concentrated to give a mixture of $\alpha + \beta$ isomers: 0.25 g, yield 46%.

Procedure for the Reaction with Titanium Complex Enolates. Example: (2-Pyridylmethylene)cyclohexanone **4** (1.39 equiv, 3.37 mmol, 0.63 g) was added dropwise to a solution of sodium hexamethyldisilazide 1 M in THF (1.8 equiv, 4.35 mmol, 4.35 mL) at 0 °C.

In a separate flask, chlorotitaniumtrisisopropoxide (1.8 equiv, 4.38 mmol, 4.35 mL) in *n*-hexane (8 mL) was added to a solution of *S*-(−)-2-methyl-1-butanol (3.6 equiv, 8.76 mmol, 0.77 g) in toluene (80 mL). The mixture was stirred at room temperature for 30 min and then the mixture evaporated by distillation to give an oil which was diluted in dry THF (7 mL). This solution was then added dropwise to the preformed sodium enolate of (2-pyridylmethylene)-cyclohexanone **4** at room temperature and stirred for 1 h, and 4-acetoxyazetidinone **3** (1 equiv, 2.42 mmol, 8.43 g) was added. After stirring for 2 h the mixture was quenched by diluting with ethyl acetate (70 mL) and pouring into a saturated solution of $NaHCO_3$ (70 mL). The emulsion was filtered through a Celite pad and washed with ethyl acetate (2 × 30 mL). The organic layer was dried on Na_2SO_4 and concentrated in vacuo to give a dark red oil. The residue was purified by flash chromatography (ethyl acetate/cyclohexane: 75/35) to give a mixture of the two $\alpha + \beta$ isomers: 0.7 g, yield 71%. Selectivity: 1:1 β:α.

Procedure for the Reaction via a Simple Titanium Enolate. (3*S*,4*R*)-3-[(1*R*)-1-(*tert*-Butyldimethylsilyloxy)-ethyl]-4-[-(6′*R*)-2′-[(*E*)-(pyrid-4yl)methylene]-1′-oxocyclohex-6′-yl]azetidin-2-one. 2. Example: (2-Pyridylmethylene)-cyclohexanone **4** (1 equiv, 3.58 mmol, 0.67 g) was dissolved in THF (6.7 mL) and added dropwise over 30 min to potassium hexamethyldisilazide 0.5 M in toluene (8.5 mL) at 0−5 °C. The brown suspension was allowed to warm to 15 °C over 30 min, and then a solution of chlorotitanium-trisisopropoxide (1.1 mL) in THF (5 mL) was added over 20 min at 15−23 °C. The dark brown suspension was held at 20−23 °C for 45 min, and then treated with 4-acetoxyazetidinone **3** (1 equiv, 3.48 mmol, 1 g) in one portion. The dark mixture was held at 21−23 °C for 45 min and then poured into saturated sodium bicarbonate/ethyl acetate (1:1, 66 mL). The biphasic mixture was filtered through a glass sinter, the phases were separated and organics washed with brine (27 mL), dried, and concentrated to afford a red oil which was purified by chromatography (ethyl acetate: cyclohexane, 6:1) to give a mixture of **2** and its α-isomer (3*S*,4*R*)-3-[(1*R*)-1-(*tert*-butyldimethylsilyloxy)ethyl]-4-[-(6′S)-2′-[(*E*)-(pyrid- 4-yl)methylene]-1′-oxocyclohex-6′-yl]azetidin-2-one as a creamy white foam (1.29 g, yield 90%).

HPLC analysis of the product (Column: Hypersil BDS C18 (5 μm; 4.6 mm × 200 mm). Mobile phase: $NH_4H_2PO_4$ 0.05 M/CH_3CN = 40/60. Flow = 1.0 mL/min λ = 270 nm. Retention times: β-isomer = 8.5 min, α-isomer = 10.1 min) established that the product of the reaction was a 2.3:1 mixture of the title compound and the corresponding (6′*S*) compound (α-isomer): 1.1 g; yield 83%. Selectivity: 2:1 β:α.

(3*S*,4*R*)-3-[(1*R*)-1-(*tert*-butyldimethylsilyloxy)ethyl]-4-[-(6′*R*)-2′-[(*E*)-(pyrid-4yl)methylene]-1′-oxocyclohex-6′-yl]-azetidin-2-one camphorsulfonate. 16. (2-Pyridylmethylene)-cyclohexanone **4** (13.8 g, 1.3 equiv) in dry THF (75 mL) was added under nitrogen over 30 min to a solution 0.5 M of potassium bis(trimethylsilyl)amide in toluene (0.66 M, 176.4 mL, 1.69 equiv) at 0 °C. The mixture was stirred under nitrogen for 30−45 min at 0 °C, and then chlorotitaniumtri-isopropoxide (23 g, 1.7 equiv) in dry THF (75 mL) was added in 10 min. The resulting dark brown mixture was stirred for 45 min at 20−25 °C, and then solid **3** (15 g, 1 equiv) was added. The mixture was stirred for 1 h from 25 to 30 °C, and then the THF was removed under vacuum in 15 min and the mixture cooled to −10 °C. Glacial acetic acid (150 mL) was added dropwise, maintaining the temperature between −10 and 0 °C. The resulting mixture was stirred under nitrogen for 10 min at −5 °C, and then water (225 mL) and ethyl acetate (225 mL) were added over 20 min. After stirring for 10 min the mixture was separated, the aqueous layer was re-extracted with ethyl acetate (150 mL) at −5 °C, and the combined organics were washed with water (150 mL) at −5 °C. Citric acid disodium salt buffer pH = 5 0.1 M (150 mL) was added followed by 32% sodium hydroxide 10.8 M (about 100 mL) with stirring over 30 min at −5 °C to pH = 6.5. After stirring for 10 min the phases were separated, and the organic layer was washed with brine (150 mL) and then filtered through silica gel (Merck 60, 30 g).

The silica was washed with ethyl acetate (75 mL). The organic solution was extracted twice with sodium hydrogensulfite solution 5% w/w 0.54 M (150 mL) followed by aqueous sodium bicarbonate 5% 0.615 M (150 mL) and water (150 mL) to afford a yellow solution which was concentrated to dryness to give an oil that was dissolved in

n-butyl acetate (225 mL). The resulting solution was treated with 1*R*-(−)-camphorsulfonic acid (7.32 g, 0.6 equiv) and stirred 1 h at room temperature and 3 h at 0 °C. The resulting solid was filtered, washed with *n*-butyl acetate (30 mL), and dried under vacuum for 14 h at 20 °C to give **16** as a pale yellow solid: GW415667B, 14 g, yield 42%. ^{1}H NMR (CD_3-OD): 9.03 (2H, d), 7.82 (2H, d), 7.30 (1H, s), 5.93 (1H, bs), 4.30 (1H, dd), 4.25 (1H, q), 3.36 (1H, d), 3.02 (1H, m), 3.02 (1H, m), 2.94 (1H, d), 2.70 (1H, m), 2.70 (1H, m), 2.6 (1H, m), 2.35 (1H, m), 2.2 (1H, m), 2.1 (1H, m), 1.95 (1H, m), 1.8 (1H, m), 2.1−1.8 (4H, m), 1.4 (1H, m), 1.26 (3H, d), 1.09 (3H, s), 0.85 (3H, s), 0.88 (9H, s), 0.098 (3H, s), 0.092 (3H, s).

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