Tetrahedron Vol 44, No 13, pp 4221 to 4232, 1988
Printed in Great Britain

0040-4020/88 $3.00 + .00

$TiCl_4$-MEDIATED REACTIONS OF SILYL KETENE ACETALS DERIVED FROM N-METHYLEPHEDRINE ESTERS: ASYMMETRIC SYNTHESIS OF β-LACTAMS

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(*Received in UK 27 October 1987*)

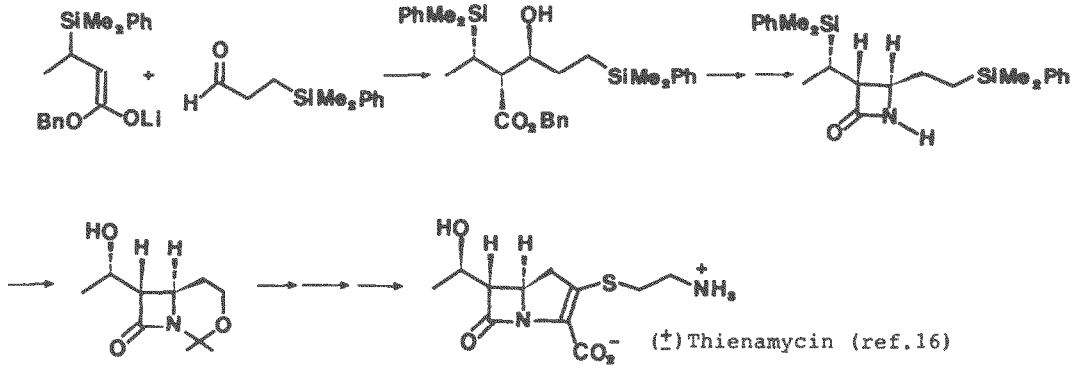
Abstract - $TiCl_4$ mediated addition of silyl ketene acetals derived from N-methylephedrine esters to various aldehydes and imines was used as the key-step in the enantio- and diastereo-controlled synthesis of β-lactams. Thus 3,4-trans and cis substituted-2-azetidinones were synthesized in good yield and high enantiomeric purity, and transformed by using established methods to known precursors of carbapenem antibiotics.

Since the discovery of a new β-lactam antibiotic, thienamycin, by the Merck research group in 1976, more than 40 carbapenem and carbapenam antibiotics have been isolated from microorganisms.[1,2] The unique broad spectrum activity of these antibiotics and the low fermentation yields have stimulated a great deal of interest for the total synthesis of this family of compounds. Moreover, as naturally occurring carbapenems are extremely sensitive to renal dipeptidase-I, an enzyme responsible for the metabolic inactivation, only a few semi-synthetic carbapenem drugs are available for clinical use at present. This unfortunate circumstance has generated considerable activity directed toward the total synthesis of carbapenem analogs possessing enhanced chemical and metabolic stability.[3-14] In the synthesis of carbapenem antibiotics, the control of the relative and absolute stereochemistry of the contiguous chiral centers, and the enantioselective construction of the β-lactam ring remain difficult synthetic tasks.[15]

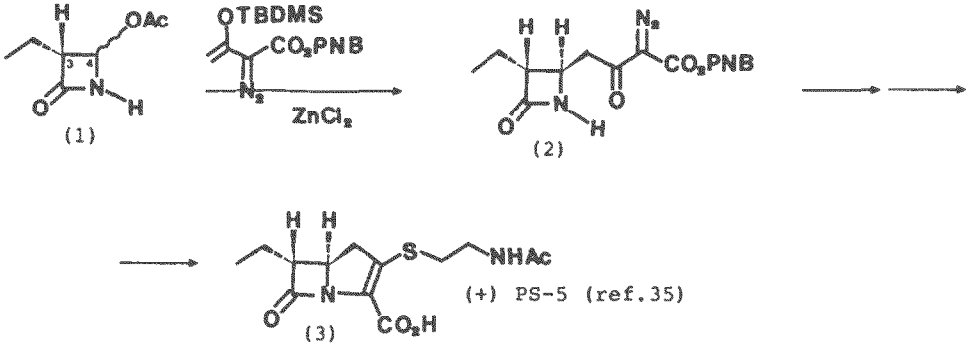
Organosilicon chemistry has been largely used as a tool for the solution of these problems. Fleming and Kilburn[16] used a β-silylenolate in an aldol reaction to assemble three contiguous stereocenters with high selectivity. After being used to control stereochemistry the phenyldimethylsilyl group was converted to a hydroxy group with retention of configuration. A known precursor of thienamycin was then synthesized using conventional chemistry (Scheme 1).

Silyl ketene acetals and silyl enol ethers were used by several research groups in the Lewis acid-catalyzed addition to 4-acetoxy-2-azetidinones.[17-37] By the use of this method, the proper side chains were added to various 4-acetoxy-2-azetidinones with good 3,4-trans stereoselectivity. In Hart's synthesis of PS-5,[35] starting from a 2:1 mixture of 4-acetoxy epimers (1) only the 3,4-trans β-lactam (2) was obtained in 63% yield (Scheme 2).

Following the pioneering work of Ojima,[38,39] silyl ketene acetals were also used by several research groups in the Lewis acid-catalyzed addition to imine-type

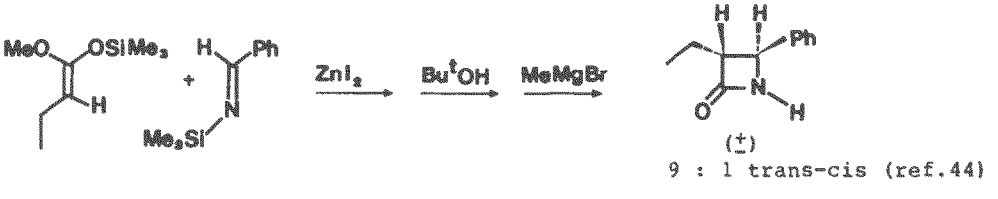


Scheme 1



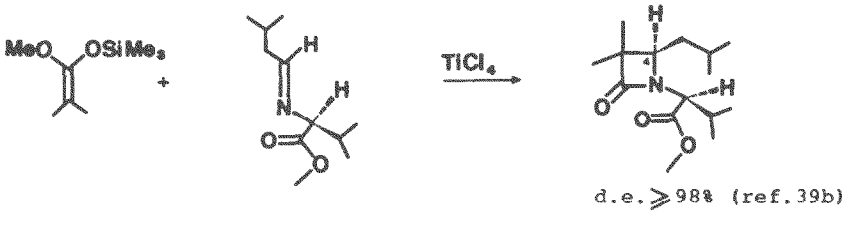
Scheme 2

compounds to synthesize β-lactams.[40-46] Although the reaction was studied in some detail, only the trimethylsilyl trifluoromethansulphonate catalyzed condensation with imines[46] and the ZnI_2 promoted addition to N-trimethylsilylimines[44] were reported to proceed with any stereoselectivity (Scheme 3).



Scheme 3

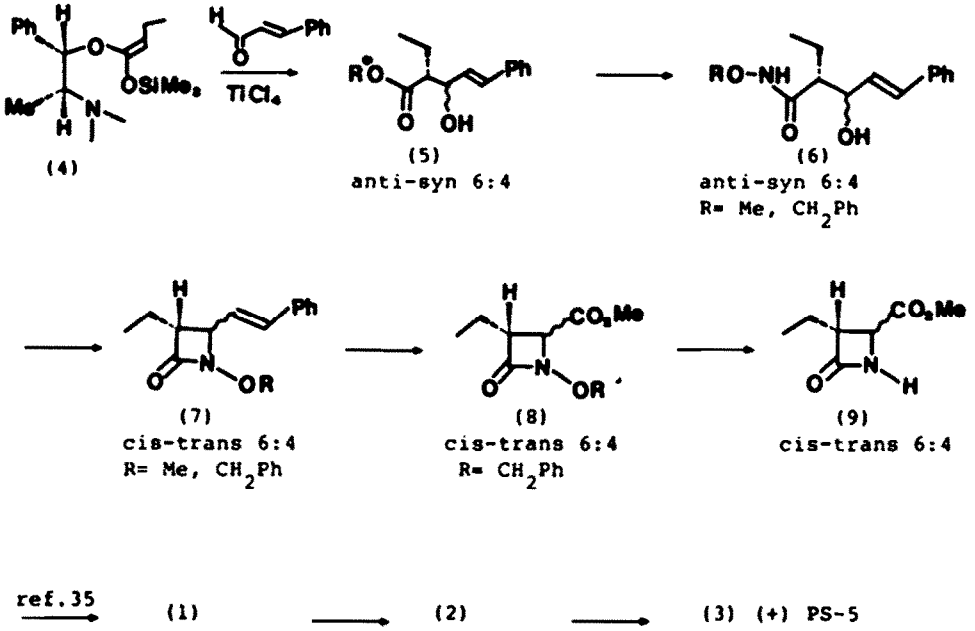
On the other hand quite high asymmetric induction at carbon-4 was reported by Ojima and Inaba in the construction of the β-lactam ring via addition to chiral optically active imines[39b] (Scheme 4).



Scheme 4

In this paper we report our studies in this field, regarding the enantio- and diastereo-controlled synthesis of β-lactams using silyl ketene acetals derived from N-methylephedrine esters.[47,48] We recently introduced an asymmetric variant of the "Mukaiyama reaction" using $TiCl_4$ as a stereochemical template and silyl ketene acetals derived from N-methylephedrine esters:[49] by this route anti α-methyl-β-hydroxy esters,[50] 3-benzyloxy-2-methylpropionaldehyde,[51] and α-amino- and α-hydrazinoacids[52] were synthesized in high enantiomeric excess and good chemical yield.

Our first approach to chiral β-lactams was based on our enantioselective Lewis acid-mediated aldol methodology[49,50] in combination with the Miller hydroxamate procedure for N-C cyclization[53] (Scheme 5).

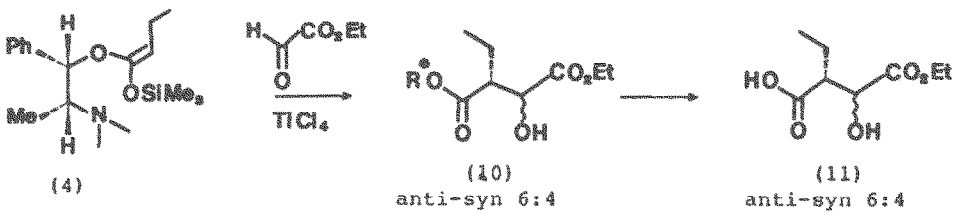


Scheme 5

(1S,2R)-N-Methylephedrine butyrate was treated with LDA and the enolate trapped with Me_3SiCl to give the E silyl ketene acetal (4) in quantitative yield. Addition of 1 mol.equiv. of the silyl ketene acetal in methylene chloride to 1 mol.equiv. of $TiCl_4$-cinnamaldehyde complex at -78 deg C in CH_2Cl_2 gave the aldol condensation product (5) as a mixture of two epimers at the C-OH stereocenter (anti-syn 6:4) in 70% yield. As usual, while the silyl ketene acetal π-facial selectivity is very high (⩾50:1), the aldehyde π-facial selectivity is poor, and there is only a moderate preference (6:4) for the anti vs. the syn isomer.[49,50] However this is not as unfortunate as it looks, because the epimeric stereocenter is to undergo demolition and stereoselective reconstruction further in the synthetic sequence (vide infra). Displacement of the chiral auxiliary from (5) to give the hydroxamate (6) was achieved in good yield (80%) without detectable epimerization using the aluminum amide reagent derived from benzyloxyamine (or methoxyamine) hydrochloride and triethylaluminum (3 equiv. of each, 0 deg C, THF).[54] Cyclization with triphenylphosphine and DEAD[53] gave β-lactam (7) in good yield (80%) with inversion of chirality at C-4. The cis and trans isomers could be separated at this stage by simple flash-chromatography and their enantiomeric excesses were shown to be ⩾96% by ^1H NMR spectroscopy in the presence of the chiral shift reagent $Eu(hfc)_3$. Oxidative cleavage of the double bond with catalytic osmium tetroxide and sodium periodate[55] yielded an aldehyde, which was further oxidized without purification

with potassium permanganate and K_2CO_3[55] to give an acid, which was isolated as its methylester (CH_2N_2) in 86% overall yield. Optical purity and absolute configuration were confirmed at this stage by comparison with the known cis and trans methylesters (8) previously synthesized from malic acid by Miller and coworkers.[56] N-O Reduction was achieved by subsequent treatment with H_2/Pd-C and buffered $TiCl_3$[53] to give, in good yield (73%), β-lactam (9), which had already been converted into (+)PS-5 (3) by Hart and coworkers[35,57] (see also scheme 2). As already mentioned in the introductory section, the $ZnCl_2$ catalyzed addition to epimeric 4-acetoxy-azetidinones is trans stereoselective, therefore there is no need to separate the cis and trans stereoisomers, and the reaction sequence outlined above can be conveniently carried through using the epimeric mixture.

A much shorter route that avoids the tedious oxidative demolition of the double bond was then developed using ethyl glyoxylate (Scheme 6). Addition of 2 mol.equiv. of $TiCl_4$ to a mixture of 1 mol.equiv. of freshly distilled ethyl glyoxylate and 1 mol.equiv. of silyl ketene acetal (4) in methylene chloride at -78 deg C gave the condensation product (10) in 80% yield as a 6:4 anti-syn mixture of epimers at the



(4) (10) anti-syn 6:4 (11) anti-syn 6:4

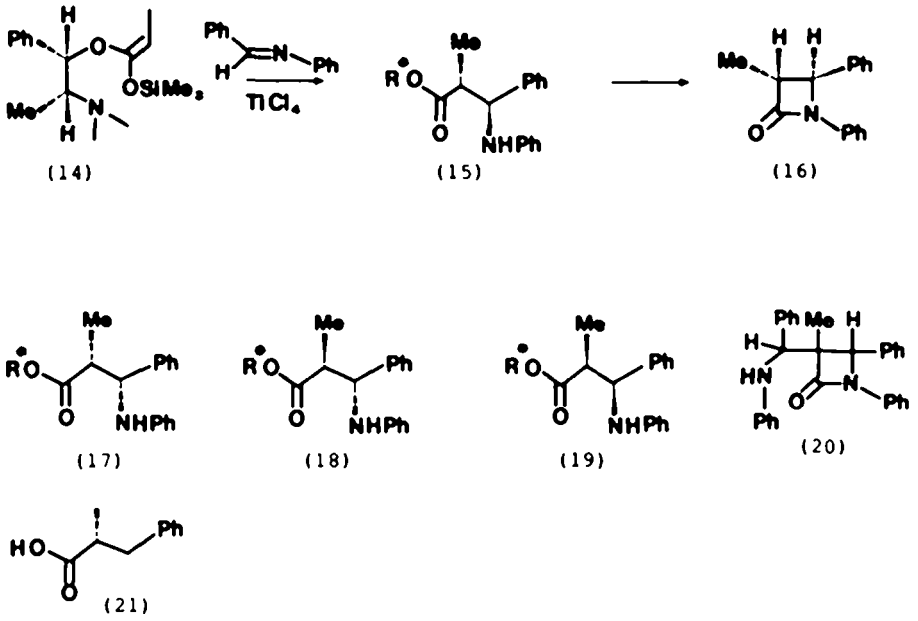
(12) cis-trans 6:4 (13) cis-trans 6:4

Scheme 6

C-OH stereocenter. Hydrogenolysis (HCOOH, MeOH, Pd-C)[58] followed by filtration through Dowex 50W-X8 (SO_3H) with water gave a 70% yield of the epimeric mixture of acids (11). Treatment with benzyloxyamine hydrochloride and the water-soluble carbodiimide[56] provided the desired hydroxamate cleanly (70%), which was cyclized to azetidinone (12) with DEAD and PPh_3[56] in 80% yield. Final treatment with H_2/Pd-C and buffered $TiCl_3$[53] gave the epimeric β-lactams (13)(cis-trans 1.5:1) in 70% yield. These were separated by flash-chromatography and their enantiomeric excesses were shown to be 91% (cis) and 70% (trans) by the ^{1}H-NMR-chiral shift reagent technique.

Our second approach to chiral β-lactams was based on our enantioselective Lewis acid-mediated methodology using imines as electrophiles.

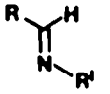
Reaction of the silyl ketene acetal (14) with benzylideneaniline in the presence of 2 mol.equiv. of $TiCl_4$ gave one of the four possible stereoisomers, anti-(15), as the major product in 67% yield (Scheme 7).



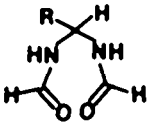
Scheme 7

The minor isomer detectable by 200 MHz-^{1}H-NMR spectroscopy in the crude reaction mixture was syn-(17) [anti-(15)/syn-(17) ratio ⩾10:1], while anti-(18) was present only in traces [anti-(15)/anti-(18) ⩾38:1] and syn-(19) could not be detected. An authentic mixture of the four stereoisomers was synthesized by LDA enolization of (1S,2R)-N-methylephedrine propionate (THF-HMPA, -78 deg C) and subsequent addition to benzylideneaniline.[59] The enolate addition in THF (without HMPA) gave low yields of the cis β-lactam (e.e. 30%),[59,60] together with a mixture of the syn adducts (17) and (19) (ratio 5.25:1), and the bis-adduct (20) as a single diastereoisomer (^{1}H, ^{13}C NMR). The absolute configuration was proved by hydrogenolysis (H_2, $PdCl_2$, AcOH) of the product mixture derived from the $TiCl_4$-mediated reaction to give the known acid (21).[61] The same mixture was cyclized with $LiN(TMS)_2$ in THF to give, after flash-chromatography, trans β-lactam (16) in 79% yield and 95% e.e. [⩾38:1 by ^{1}H-NMR-Eu(hfc)$_3$], which could be obtained optically pure by single recrystallization.

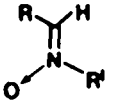
The same $TiCl_4$-mediated condensation was attempted with several different imines and imine-derivatives with either no results (22-30) or low yields (31) (Scheme 8).



(22) R,R'= alkyl
(23) R= Ph-CH=CH-; R'= Ph
(24) R= Ph-; R'= CH_2Ph
(25) R= Ph-CH=CH-; R'= p-MeO-C_6H_4-
(26) R= Ph-CH=CH-; R'= O(O=)CPh
(27) R= Ph-CH=CH-; R'= OCH_2Ph



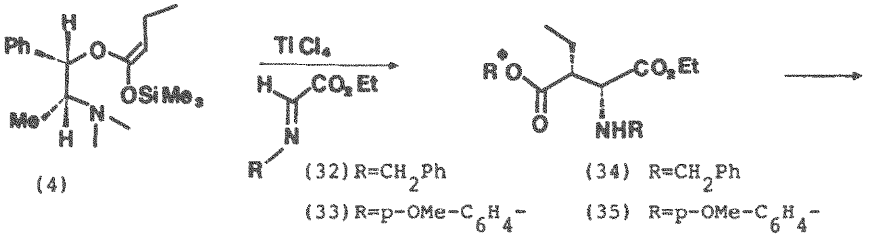
(28) R= Ph-CH=CH-



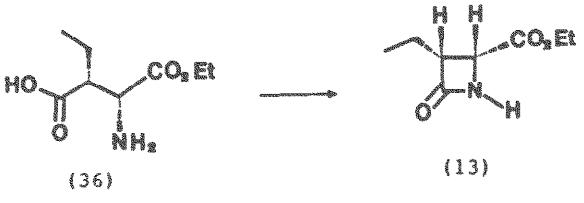
(29) R= n-Pr; R'= Ph
(30) R= Ph-CH=CH-; R'= Ph
(31) R=R'= Ph

Scheme 8

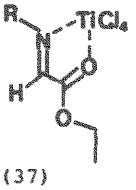
Eventually we turned our attention to more reactive imines, namely the ethoxycarbonyl substituted imines (32) and (33)[55,62] (Scheme 9). Addition of 1 mol.equiv. of a 1:1 mixture of silyl ketene acetal (4) and iminoester (32) to 2 mol.equiv. of $TiCl_4$ in CH_2Cl_2 at -78 deg C gave the condensation product (34), which was hydrogenolized without purification (HCOOH, MeOH, Pd-C)[58] to yield the β-aminoacid (36). Filtration through Dowex 50W-X8 (SO_3H) with 5% NH_4OH gave pure (36) as a ca. 8:1 syn-anti epimeric mixture in 53% overall yield. Ring closure using the Mukaiyama procedure (2-chloro-1-methylpyridinium iodide, Et_3N, CH_3CN)[63] gave the cis β-lactam (13) in good yield (87%) and 50% enantiomeric excess.



(4) (32) R=CH_2Ph (33) R=p-OMe-C_6H_4- (34) R=CH_2Ph (35) R=p-OMe-C_6H_4-



(36) (13)



(37)

Scheme 9

The stereochemical outcome of this reaction [syn-anti 8:1; e.e.(syn) 50%] is quite different from that of the previous reaction with benzylideneaniline [anti-syn 92:8; e.e.(anti) 95%]. This is probably the result of a different reaction mechanism due to the formation of a 5-membered ring chelate complex (37) in the case of the iminoesters.

Iminoester (33) gave a higher yield of condensation product under the same reaction conditions (70%). Adduct (35) was then hydrogenolized (HCOOH, MeOH, Pd-C)(95%) and the resulting β-aminoacid treated with ceric ammonium nitrate (CAN) (CH_3CN, H_2O,-25 deg C)[64] to give, after filtration through the Dowex 50W-X8, compound (36) in 82% yield as a 7:1 syn-anti epimeric mixture. Ring closure under the previously described conditions[63] gave cis β-lactam (13) in good yield (85%) and 75% enantiomeric excess.

Our new procedure can therefore be useful for the synthesis of cis carbapenem antibiotics,[1,2] successfully complementing other available methods.[62,65] Efforts to expand the scope and utility of this method further are presently being made in our laboratory.

EXPERIMENTAL SECTION

(1S,2R)-(+)-N-methylephedrine butyrate. $[\alpha]_D$ +42.2 ($CHCl_3$, c 1.2); ^1H NMR ($CDCl_3$)δ 0.93 (t,3H,J=7.7 Hz), 1.06 (d,3H,J=6.6 Hz), 1.4-1.9 (m,2H), 2.2-2.5 (m,2H), 2.3 (s,6H), 2.87 (dq,1H,J=5.4,6.6 Hz), 5.95 (d,1H,J=5.4 Hz), 7.30 (s,5H). ^{13}C NMR ($CDCl_3$)δ 9.47, 13.67, 18.37, 36.56, 41.30, 63.67, 75.17, 126.31, 127.38, 128.18, 140.34, 172.50. IR (liquid film) 1740, 1495, 1455, 1175, 740, 695 cm^{-1} (selected values). Anal.Calcd. for $C_{15}H_{23}NO_2$: C,72.28; H,9.23; N,5.62. Found: C,72.20; H,9.30; N,5.58%.

E Silyl ketene acetal(4) from (1S,2R)-N-methylephedrine butyrate. A solution of diisopropylamine (1.45 ml, 10.2 mmol) in THF (20.5 ml) was treated with n-BuLi (1.5 N in n-hexane, 6.8 ml,10.2 mmol), at 0 deg C under nitrogen, with stirring. After 30 min at 0 dec C, the solution was cooled to -78 deg C, and a solution of (+)-N-methylephedrine butyrate (8.5 mmol) in THF (17.0 ml) was slowly added. After 1 h at -78 deg C, TMSCl (1.29 ml, 10.2 mmol) was slowly added. After 1 h at -78 deg C the mixture was slowly warmed-up to room temperature (during 1 h). The mixture was then evaporated and pumped. The residue (THF free !) was taken-up in methylene chloride (8.5 ml), and the 0.8 M solution so obtained could be stored at -20 deg C for several weeks and used as stock solution. ^1H NMR ($CDCl_3$)δ 0.00 (s,9H), 0.90 (t,3H,J=6.9 Hz), 1.09 (d,3H,J=6.7 Hz), 2.05 (m,2H), 2.30 (s,6H), 2.80 (m,1H), 3.48 (t,1H,J=6.9 Hz), 5.25 (d,1H,J=4.0 Hz), 7.25 (s,5H). Spectroscopic yield (^1H NMR) : ⩾ 95%; E-Z ratio (^1H NMR) ⩾ 95:5, based on an authentic E-Z mixture obtained using $LiN(SiMe_3)_2$ as base instead of LDA.

Aldol condensation product (5). A solution of cinnamaldehyde (9 mmol) in methylene chloride (27 ml) was treated with a 1.0 M solution of $TiCl_4$ in methylene chloride (9 ml), at -78 deg C, under nitrogen, with stirring. Immediately after, a 0.8 M solution of silyl ketene acetal (4) in methylene chloride (11.25 ml) was slowly added at -78 deg C. After 2 h at -78 deg C, the mixture was quenched with 5% $NaHCO_3$ and 1.5 N NaOH aqueous solution and filtered through Celite. The aqueous phase was extracted with methylene chloride and the combined organic extracts were dried and evaporated. The crude product was then filtered through silica gel (CH_2Cl_2-MeOH 97:3) to give the aldol condensation product in 70% yield as a 6:4 anti-syn mixture. ^1H NMR ($CDCl_3$)δ 0.9-1.13 (m,6H,anti+syn), 1.5-1.9 (m,2H,anti+syn), 2.32 (s,6H,syn), 2.38 (s,6H,anti), 2.60 (m,1H,anti+syn), 2.90 (m,1H,anti+syn), 4.43 (ddd,1H,anti,J=8.3,6.7,0.7 Hz), 4.58 (ddd,1H,syn,J=3.85,5.20,1.3 Hz), 6.0-6.3 (d,1H,anti+syn), 6.20 (dd,1H,anti,J=16.0,6.7 Hz), 6.25 (dd,1H,syn,J=16.0,5.20 Hz), 6.67 (dd,1H,anti,J=16.0,0.7 Hz), 6.67 (dd,1H,syn,J=16.0,1.3 Hz), 7.27 (s,10H,anti+syn).

Hydroxamate (6). A suspension of benzyloxyamine (or methoxyamine) hydrochloride (3.45 mmol) in dry THF (7 ml) was treated at 0 dec C under nitrogen , with stirring, with a 1.9 M solution of Et_3Al in toluene (1.83 ml, 3.45 mmol). After 30 min a solution of ester (5) (0.44 g, 1.15 mmol) in THF (1.15 ml) was slowly added at 0 deg C. After 1 h at 0 deg C the mixture was acidified with diluted HCl to pH 4.5, extracted with EtOAc, and worked-up as usual. Flash-chromatography (n-hexane-EtOAc 55:45) gave the hydroxamate (6) in 80% yield as a 6:4 anti-syn mixture. ^1H NMR (6,R=CH_2Ph)($CDCl_3$)δ 0.92 (t,3H,J=6.6 Hz,anti+syn), 1.5-2.2 (m,2H,anti+syn), 2.6-3.1 (m,1H,anti+syn), 4.4 (m,1H,anti+syn), 4.87 (s,2H,syn), 4.89 (s,2H,anti), 6.12 (dd,1H,J=6.5,15.8 Hz,anti), 6.15 (dd,1H,J=6.36,15.8 Hz,syn), 6.62 (d,1H,J=15.8 Hz,anti), 6.63 (d,1H,J=15.8 Hz,syn), 7.3 (m,10H,anti+syn), 8.3 (b.s,1H,anti+syn). ^1H NMR (6,R=Me)($CDCl_3$)δ 0.96 (t,3H,J=6.7 Hz,anti+syn), 1.5-2.3 (m,2H,anti+syn), 2.4-3.0 (m,1H,anti+syn), 3.75 (s,3H,anti+syn), 4.35-4.55 (m,1H,anti+syn), 6.14 (dd,1H,J=6.40,16.25 Hz,anti), 6.18 (dd,1H,J=6.49,16.25 Hz,syn), 6.64 (d,1H,J=16.25 Hz,anti+syn), 7.3 (m,5H,anti+syn), 8.6 (b.s,1H,anti+syn).

β-Lactam (7). A solution of hydroxamate (6) (0.465 g, 1.44 mmol) in dry THF (10 ml) was treated with PPh_3 (0.378 g, 1.44 mmol), and then with DEAD (0.226 ml, 1.44 mmol).After 1.5 h at room temperature the solvent was evaporated and the crude mixture was flash-chromatographed (n-hexane-EtOAc 75:25) to give (7) in 80% yield as a 6:4 cis-trans mixture. The cis and trans isomers were separated by flash-chromatography (n-hexane-EtOAc 85:15) and analized separately.
^1H NMR (7,R=CH_2Ph,cis)($CDCl_3$)δ 0.95 (t,3H,J=7.5 Hz), 1.55 (m,2H), 2.9 (m,1H), 4.2 (dd,1H,J=8.8,5.6), 4.92 (s,2H), 5.85 (dd,1H,J=16.0,8.8 Hz), 6.5 (d,1H,J=16.0 Hz), 7.35(m,10H). ^1H NMR [$CDCl_3$ + Eu(hfc)$_3$] racemic : δ 6.6 (50% CH_2O, AB system); 6.4 (50% CH_2O,s); optically active : 6.6 (100% CH_2O, AB system).
^{13}C NMR (7,R=CH_2Ph,cis)($CDCl_3$) δ 12.3,19.0,51.7,63.5,78.0,167.0 selected values.
IR($CHCl_3$) ν max. 1770 cm^{-1}. $[\alpha]_D$ = +76.7 (c 1.6,$CHCl_3$).
^1H NMR (7,R=CH_2Ph,trans)($CDCl_3$) δ 0.97 (t,3H,J=7.2 Hz), 1.7 (m,2H), 2.63 (ddd,1H,J=2.1,6.0,8.1 Hz), 3.8 (dd,1H,J=8.6,2.1 Hz), 4.93 (s,2H), 5.91 (dd,1H,J=16.0,8.6 Hz), 6.49 (d,1H,J=16.0 Hz), 7.30 (s,5H), 7.32 (s,5H).
^1H NMR [$CDCl_3$ + Eu(hfc)$_3$] racemic : δ 6.60 (50% CH_2O,s), 6.64 (50% CH_2O,s); optically active : 6.64 (100% CH_2O,s).
^{13}C NMR (7,R=CH_2Ph,trans) ($CDCl_3$) δ 12.0,21.2,54.4,66.2,78.0,166.4 selected values.
IR ($CHCl_3$) ν max. 1770 cm^{-1}. $[\alpha]_D$ = -34.3 (c 1.2,$CHCl_3$).
^1H NMR (7,R=Me,cis)($CDCl_3$)δ 1.02 (t,3H,J=7.5 Hz), 1.70 (m,2H), 3.0 (m,1H), 3.8 (s,3H), 4.56 (dd,1H,J=8.0,5.33 Hz), 6.19 (dd,1H,J=16.0,8.0 Hz), 6.76 (d,1H,J=16.0),

7.35 (m,5H). ^{1}H NMR [$CDCl_3$ + Eu(hfc)$_3$] racemic : δ 4.64 (50% MeO,s), 4.77 (50% MeO,s); optically active : 4.77 (100% MeO,s).
^{13}C NMR (7,R=Me,cis) ($CDCl_3$) δ 12.3,19.1,51.9,62.5,63.9,166.6 selected values. IR ($CHCl_3$) ν max.=1770 cm^{-1}. $[\alpha]_D$= +54.2 (c 1.0,$CHCl_3$).
^{1}H NMR (7,R=Me,trans)($CDCl_3$) δ 1.02 (t,3H,J=7.5 Hz), 1.78 (m,2H), 2.70 (ddd,1H,J=2.1,5.3,8.0), 3.8 (s,3H), 4.13 (dd,1H,J=8.0,2.1 Hz), 6.20 (dd,1H,J=16.0,8.0), 6.75 (d,1H,J=16.0), 7.35 (m,5H). ^{1}H NMR [$CDCl_3$ + Eu(hfc)$_3$] racemic : δ 6.50 (50% MeO,s), 6.56 (50% MeO,s); optically active : 6.56 (100% MeO,s). ^{13}C NMR (7,R=Me,trans) ($CDCl_3$) δ 11.4,21.2,54.1,63.9,65.2,166.1 selected values. IR ($CHCl_3$) ν max.=1770 cm^{-1}. $[\alpha]_D$=-3.0 (c 1.0,$CHCl_3$).

Methylester (8). A solution of compound (7,R=CH_2Ph)(0.566 g, 1.85 mmol)in THF-water (74 ml, 1.8:1) was treated with a 0.039 M solution of OsO_4 in t-BuOH (4.74 ml, 0.185 mmol) and then with sodium periodate (1.58 g,7.4 mmol). The mixture was stirred under nitrogen for 8 h at room temperature. The precipitate was then filtered off and washed twice with ether. The organic layer was separated, washed twice with 5% sodium bicarbonate solution, dried over sodium sulfate, and evaporated to give the crude aldehyde. The crude aldehyde was dissolved in THF-water (33 ml, 1.8:1) and then treated with potassium permanganate (7.2 mmol, 1.16 g) and potassium carbonate (11.6 mmol,1.63 g) at room temperature, under nitrogen. The mixture was stirred for 5 h, then the brown precipitate was filtered off, and the tetrahydrofuran was evaporated under reduced pressure. The aqueous layer was washed twice with ether and then acidified with 6 N HCl to pH 4. Extraction of the aqueous layer with ether, drying of the combined organic extracts over sodium sulfate and evaporation of the ether yielded the crude acid. The crude acid was dissolved in ether and treated with diazomethane. The crude compound was then purified by flash-chromatography (n-hexane-EtOAc 7:3) to give the methyl ester (8,R=CH_2Ph) in 86% overall yield. ^{1}H NMR (8,R=CH_2Ph,trans)($CDCl_3$) δ 1.0 (t,3H,J=7.0 Hz), 1.7 (m,2H), 2.89 (ddd,1H,J=2.4,6.35,7.84 Hz), 3.74 (s,3H), 3.79 (q,1H,J=2.4 Hz), 5.05 (AB system,2H), 7.4 (s,5H). IR ($CHCl_3$) ν max.= 1750,1780 cm^{-1}. $[\alpha]_D$= +5.6 (c 4.4, MeOH); lit. (ref.56)= +5.6 (c 4.4, MeOH). ^{1}H NMR (8,R=CH_2Ph,cis)($CDCl_3$) δ 0.97 (t,3H,J=7.0 Hz), 1.6 (m,2H), 3.07 (dt,1H,J=6.0,7.5 Hz), 3.75 (s,3H), 4.23 (d,1H,J=6.0 Hz),5.1 (AB system,2H), 7.37 (s,5H). IR ($CHCl_3$) ν max.= 1750,1780 cm^{-1}. $[\alpha]_D$= +2.8 (c 3.5, MeOH); lit. (ref.56)= +2.8 (c 3.5, MeOH).

Methylester (9). A solution of compound (8)(0.4 g, 1.5 mmol) in methanol (10 ml) was treated with 5% Pd-C (20 mg) and stirred for 2 h under hydrogen atmosphere. The catalyst was removed by filtration and the filtrate evaporated to give the N-hydroxy compound (260 mg,100%). ^{1}H NMR (N-hydroxy compound,trans)($CDCl_3$) δ 1.0 (t,3H,J= 6.7 Hz), 1.78 (m,2H), 2.92 (ddd,1H,J=2.2,6.4,8.0), 3.8 (s,3H), 4.04 (d,1H,J= 2.2 Hz), 7.65 (b.s,1H). IR ($CHCl_3$) ν max.= 3100-3500,1780,1750 cm^{-1}. ^{1}H NMR (N-hydroxy compound,cis)($CDCl_3$) δ 0.98 (t,3H,J= 6.7 Hz), 1.59 (m,2H), 3.18 (dt,1H,J= 7.75,5.64 Hz), 3.8 (s,3H), 4.65 (d,1H,J= 5.64 Hz), 5.65 (b.s,1H). IR ($CHCl_3$) ν max. = 3100-3500,1780,1750 cm^{-1}.
A solution of the N-hydroxy compound (260 mg, 1.5 mmol) in methanol (40 ml) was added to a solution of $TiCl_3$ (15% aqueous, 8.0 ml, 7.89 mmol) and sodium bicarbonate (2.21 g, 26.84 mmol) in 79 ml of water adjusted to pH 6.5 with 10% aqueous sodium carbonate. The mixture was stirred for 1.5 h under argon, then filtered through Celite. Methanol was then evaporated under reduced pressure, and the resulting aqueous layer was extracted several times with EtOAc and methylene chloride. The combined organic extracts were dried over sodium sulfate and evaporated to give a crude product which was flash-chromatographed (n-hexane-EtOAc 1:1) to give methylester (9) in 73% yield. ^{1}H NMR (9,trans)($CDCl_3$) δ 1.0 (t,3H,J= 7.2 Hz), 1.8 (m,2H), 3.19 (m,1H), 3.73 (s,3H), 3.85 (d,1H,J= 2.4 Hz), 6.5 (b.s,1H). IR ($CHCl_3$) ν max. = 3415,1765,1740 cm^{-1}. ^{1}H NMR (9,cis)($CDCl_3$) δ 1.02 (t,3H,J= 7.0 Hz), 1.62 (m,2H), 3.43 (m,1H), 3.78 (s,3H), 4.26 (d,1H,J= 5.60 Hz), 6.2 (b.s,1H). IR ($CHCl_3$) ν max. = 3415,1765,1740 cm^{-1}.

Aldol condensation product (10). A solution of freshly distilled ethyl glyoxylate[66] (9 mmol) in methylene chloride (27 ml) was treated with a 0.8 M solution of silyl ketene acetal (4) in methylene chloride (11.25 ml), at -78 deg C, under nitrogen, with stirring. Immediately after a 1.0 M solution of titanium tetrachloride in methylene chloride (18 ml) was slowly added at -78 deg C. After 2 h at -78 deg C the mixture was quenched and worked-up as described for the preparation of (5) to give the condensation product (10) in 80% yield as a 6:4 anti-syn mixture. ^{1}H NMR ($CDCl_3$) δ 0.8-1.1 (m,6H,anti+syn), 1.22;1.23 (t,3H,J= 7.23 Hz,anti;syn), 1.5-2.0 (m,2H,anti+syn), 2.30;2.32 (s,6H,anti;syn), 2.55;2.70 (m,1H,anti;syn), 2.8-2.9 (m,1H,anti+syn), 4.17;4.18 (q,2H,J= 7.23 Hz, anti;syn), 4.33 (d,1H,J= 5.5 Hz,anti), 4.51 (d,1H,J= 3.5 Hz, syn), 6.15;6.20 (d,1H,J= 5.0 Hz; d,1H,J= 3.0 Hz; anti;syn), 7.2-7.35 (m,5H,anti+syn).

Acid (11). A solution of the aldol condensation product (10)(3.4 g, 9.6 mmol) in 10:1 methanol-formic acid (106 ml) was treated with 10% Pd-C (2.035 g) under nitrogen, with stirring. After 3 h the catalyst was filtered off, washed with warm methanol, and the mixture was evaporated in vacuo. The resulting crude product was passed through a column of Dowex 50W-X8 by elution with water. The resulting aqueous solution was then evaporated to dryness under reduced pressure to give acid (11) in 70% yield. ^{1}H NMR (11,syn)($CDCl_3$) δ 0.97 (t,3H,J= 7.3 Hz), 1.28 (t,3H,J= 7.0 Hz), 1.75 (m,2H), 2.70 (m,1H), 4.25 (q,2H,J= 7.0 Hz), 4.48 (d,1H,J= 5.0 Hz), 5.0 (b.s,2H). IR (neat) ν max. 3100-3500, 1740 cm^{-1}.

^{1}H NMR (11,anti)($CDCl_3$) δ 1.02 (t,3H,J= 7.3 Hz), 1.28 (t,3H,J=7.0 Hz), 1.75 (m,2H), 2.80 (m,1H), 4.25 (q,2H,J= 7.0 Hz), 4.30 (d,1H,J= 3.85 Hz), 5.0 (b.s,2H). IR (neat) ν max. 3100-3500, 1740 cm^{-1}.

β-Lactam (12). A solution of acid (11) (1.3 g, 6.28 mmol) in 5.2:1 THF-water (62 ml) was treated with O-benzylhydroxylamine hydrochloride (1.5 g, 9.42 mmol) at pH 4.5. A solution of water-soluble carbodiimide (N-ethyl-N'-(3-(dimethylamino)propyl)carbodiimide) (2.4 g, 12.6 mmol) in water (41.9 ml) was then added and the pH maintained at 4.5. After 3 h stirring, the mixture was extracted with ethyl acetate. The combined organic extracts were washed with water, dried (sodium sulfate), and evaporated. The crude product was flash-chromatographed (methylene chloride-MeOH 97:3) to give the hydroxamate in 70% yield (1.37 g). ^{1}H NMR ($CDCl_3$)(syn) δ 0.90 (t,3H,J= 7.5 Hz), 1.30 (t,3H,J=7.0 Hz), 1.65 (m,2H), 2.45 (m,1H), 4.20 (q,2H,J= 7.0 Hz), 4.30 (b.s, 1H), 4.90 (s,2H), 7.40 (s,5H), 8.5 (b.s,1H). IR ($CHCl_3$) ν max. 3090,1730,1685 cm^{-1}. ^{1}H NMR ($CDCl_3$)(anti) δ 0.95 (t,3H,J= 7.5 Hz), 1.28 (t,3H,J= 7.0 Hz), 1.70 (m,2H), 2.45 (m,1H), 4.20 (q,2H,J= 7.0 Hz), 4.25 (d,1H), 4.87 (s,2H), 7.40 (s,5H), 8.5 (b.s,1H). IR ($CHCl_3$) ν max. 3400,1740,1680 cm^{-1}.
The hydroxamate (1.37 g) was cyclized with triphenylphosphine and DEAD in THF using a modification of the procedure described for the preparation of (7) : the mixture was stirred at room temperature for 7 h. Flash-chromatography (n-hexane-EtOAc 75:25) gave β-lactam (12) in 80% yield.
^{1}H NMR ($CDCl_3$)(12 trans) δ 0.98 (t,3H,J= 7.5 Hz), 1.29 (t,3H,J= 7.3 Hz), 1.65 (m,2H), 2.88 (ddd,1H,J=2.4,6.3,8.0), 3.78 (d,1H,J=2.4 Hz), 4.19 (q,2H,J= 7.3 Hz), 5.05 (s,2H), 7.35 (s,5H). IR ($CHCl_3$) ν max. = 1740,1780 cm^{-1}.
^{1}H NMR ($CDCl_3$)(12 cis) δ 0.98 (t,3H,J= 7.5 Hz), 1.30 (t,3H,J=7.3 Hz), 1.65 (m,2H), 3.06 (dt,1H,J= 5.9,7.5 Hz), 4.20 (d,1H,J= 5.9 Hz), 4.21 (q,2H,J= 7.3 Hz), 5.1 (s,2H), 7.35 (s,5H). IR ($CHCl_3$) ν max. 1740,1780.

β-Lactam (13). Compound (12) was reduced with hydrogen and Pd-C as described for the preparation of (9) to give the N-hydroxy compound in quantitative yield.
^{1}H NMR ($CDCl_3$)(N-hydroxy compound,trans) δ 1.0 (t,3H,J= 6.7 Hz), 1.30 (t,3H,J=7.0 Hz), 1.75 (m,2H), 2.88 (ddd,1H,J= 2.2,6.0,8.0), 4.02 (d,1H,J= 2.2 Hz), 4.22 (q,2H,J= 7.0 Hz), 5.7 (b.s,1H). IR ($CHCl_3$) ν max. 3100-3500, 1780,1750 cm^{-1}.
^{1}H NMR ($CDCl_3$)(N-hydroxy compound,cis) δ 0.98 (t,3H,J= 6.7 Hz), 1.30 (t,3H,J= 7.0 Hz), 1.60 (m,2H), 3.12 (dt,1H,J= 7.80,5.60), 4.22 (q,2H,J= 7.0 Hz), 4.45 (d,1H,J= 5.60 Hz), 5.7 (b.s,1H). IR ($CHCl_3$) ν max. 3100-3500, 1780, 1750 cm^{-1}.
The N-hydroxy compound was reduced with titanium trichloride as described for the preparation of (9) to give β-lactam (13) in 70% yield as a 6:4 cis-trans mixture. The two isomers were separated by flash-chromatography (n-hexane-EtOAc 1:1).
^{1}H NMR (13,cis) δ 1.05 (t,3H,J= 6.7 Hz), 1.29 (t,3H,J= 7.2 Hz), 1.60 (m,2H), 3.40 (ddt,1H,J= 5.78,0.95,7.90 Hz), 4.21 (q,2H,J= 7.2 Hz), 4.22 (d,1H,J= 5.78 Hz), 6.33 (b.s,1H). IR ($CHCl_3$) ν max. = 3415,1765,1740 cm^{-1}. $[\alpha]_D$ = +31.6 (c 1, $CHCl_3$). ^{1}H NMR [$CDCl_3$ + Eu(hfc)$_3$] racemic : δ 6.70 (50% CH,d,J=5.78 Hz), 6.90 (50% CH,d,J=5.78 Hz); optically active : 6.70 (95.5% CH,d,J=5.78 Hz), 6.90 (4.5% CH,d,J=5.78 Hz).
^{1}H NMR (13,trans) δ 1.05 (t,3H,J= 6.9 Hz), 1.30 (t,3H,J= 7.2 Hz), 1.80 (m,2H), 3.20 (m,1H), 3.83 (d,1H,J= 2.5 Hz), 4.22 (q,2H,J= 7.2 Hz), 6.2 (b.s,1H). IR ($CHCl_3$) ν max. = 3415,1765,1740 cm^{-1}. $[\alpha]_D$= +8.8 (c 1, $CHCl_3$). ^{1}H NMR [$CDCl_3$ + Eu(hfc)$_3$] racemic : δ 5.50 (50% CH,d), 5.85 (50% CH,d); optically active : 5.50 (15% CH,d), 5.85 (85% CH,d).

(1S,2R)-(+)-N-methylephedrine propionate. $[\alpha]_D$ +46.3 ($CHCl_3$, c 1.2); ^{1}H NMR ($CDCl_3$) δ 1.05 (d,3H,J= 6.7 Hz), 1.15 (t,3H,J=7.7 Hz), 2.25 (s,6H), 2.38 (q,2H,J= 7.7 Hz), 2.88 (dq,1H,J=5.4,6.7 Hz), 5.94 (d,1H,J=5.4 Hz), 7.25 (s,5H). ^{13}C NMR ($CDCl_3$) δ 9.02, 9.36, 27.95, 41.11, 63.73, 75.00, 126.13, 127.27, 128.07, 140.12, 172.81. IR ($CHCl_3$) 2980, 2940, 1735, 1460, 1450, 1375, 1185 cm^{-1} (selected values). Anal. Calcd. for $C_{14}H_{21}NO_2$: C, 71.45; H,9.00; N,5.95. Found: C,71.30; H,9.11; N,5.87.

E Silyl ketene acetal (14) from (1S,2R)-N-methylephedrine propionate. The reaction was run under the same experimental conditions described for the preparation of (4). ^{1}H NMR ($CDCl_3$) δ 0.00 (s,9H), 1.10 (d,3H,J= 6.7 Hz), 1.55 (d,3H,J=6.7 Hz), 2.30 (s,6H), 2.80 (dq,1H,J=4.0,6.7 Hz), 3.48 (q,1H,J=6.7 Hz), 5.29 (d,1H,J=4.0 Hz), 7.27 (s,5H). Spectroscopic yield (^{1}H NMR) : ≥ 95%; E-Z ratio (^{1}H NMR) ≥95:5, based on an authentic E-Z mixture obtained using $LiN(SiMe_3)_2$ as base instead of LDA.

Condensation via silyl ketene acetal (14). A solution of benzylideneaniline (15.6 mmol) and of silyl ketene acetal (14) (15.6 mmol) in methylene chloride (62.8 ml) was slowly added (during 1 h) to a 1 M solution of titanium tetrachloride in methylene chloride (31.2 ml) at -78 deg C, under nitrogen, with stirring. After 1 h at -78 deg C, the mixture was slowly warmed up to -40 deg C (during 2 h), then quenched and worked-up as described for the preparation of (5). Filtration through silica gel (methylene chloride, then 97:3 methylene chloride-MeOH) gave the condensation product (15,17,18) in 75% yield.
^{1}H NMR ($CDCl_3$ + D_2O) δ 0.96 (d,3H,J=6.7 Hz), 1.22 (d,3H,J=6.9 Hz), 2.21 (s,6H), 2.15-2.40 (m,1H), 2.88 (dq,1H,J=6.7,5.2 Hz), 4.47 (d,1H,J=7.00 Hz, isomer anti-15, 89.2%), 4.83 (d,1H,J=4.66 Hz, isomer syn-17, 8.5%), 4.51 (d,1H,J=7.56 Hz, isomer anti-18, 2.3%), 5.88 (d,1H,J=5.2 Hz), 6.3-6.7 (m,2H), 6.9-7.4 (m,13H).

Condensation via LDA-THF-HMPA. A solution of diisopropylamine (0.45 ml,3.2 mmol), in dry THF (6.4 ml) was treated at 0 deg C, under nitrogen, with stirring with a

1.5 M solution of n-BuLi (2.14 ml, 3.2 mmol). After 30 min the mixture was cooled to -78 deg C and 3.0 ml of HMPA and then a solution of (1S,2R)-N-methylephedrine propionate (0.63 g,2.7 mmol) in THF (5.4 ml) were added. After 1 h at -78 deg C, a solution of benzylideneaniline (0.58 g,3.2 mmol) in THF (6.4 ml) was added. The mixture was stirred at -78 deg C for 1 h, then warmed up to -20 deg C (during 1 h), then diluted with ether (100 ml) and quenched with saturated brine. Usual work-up and flash-chromatography (methylene chloride-MeOH 96:4) gave the condensation product (15,17,18,19) in 25% yield.
^{1}H NMR ($CDCl_3$ + D_2O) δ 0.8-1.4 (6H), 2.1-2.3 (6H), 2.1-3.2 (2H), 4.47 (d,1H,J=7.00 Hz, isomer anti-15, 33%), 4.51 (d,1H,J=7.56 Hz, isomer anti-18, 33%), 4.83 (d,1H,J=4.66 Hz, isomer syn-17,17%), 4.75 (d,1H,J=5.12 Hz, isomer syn-19,17%), 5.8-5.95 (1H), 6.3-6.7 (m,2H), 6.9-7.4 (m,13H).

Condensation via LDA-THF. The reaction was run under the same experimental conditions described above without adding HMPA. The condensation product (17,19) was obtained in 20% yield. ^{1}H NMR ($CDCl_3$ + D_2O) δ 1.01 (d,3H,J=6.7 Hz), 1.15 (d,3H,J=6.5 Hz), 2.1-2.3 (m,1H), 2.26 (s,6H), 2.6-3.2 (m,1H), 4.75 (d,1H,J= 5.12 Hz, isomer syn-19, 16%), 4.83 (d,1H,J=4.66 Hz, isomer syn-17, 84%), 5.88 (d,1H,J=4.0 Hz), 6.3-6.8 (m,2H), 6.9-7.4 (m,13 H).
The cis β-lactam was obtained in 20% yield. ^{1}H NMR ($CDCl_3$) δ 0.85 (d,3H,J=8.0 Hz), 3.68 (dq,1H,J=8.0,5.60 Hz), 5.18 (d,1H,J=5.60 Hz), 6.9-7.4 (m,10H).
^{1}H NMR [$CDCl_3$ + Eu(hfc)$_3$] racemic : δ 2.25 (50% CH_3,d), 2.50 (50% CH_3,d); optically active : 2.25 (65% CH_3,d), 2.50 (35% CH_3,d).
The bis-adduct (20) was obtained in 20% yield. ^{1}H NMR ($CDCl_3$) δ 0.89 (s,3H), 4.75 (2H,s,one exchanges with D_2O), 5.30 (s,1H), 6.5-7.7 (m,20 H). ^{13}C NMR ($CDCl_3$) δ 13.15, 62.21, 62.75, 63.77, 114.57, 117.41, 118.40, 124.10, 126.76, 128.05, 128.63, 129.02, 134.45, 137.23, 139.06, 147.43, 169.56. IR ($CHCl_3$) 3690, 3100-3600, 1735, 1600, 1500 cm^{-1} (selected values).

Acid (21). A solution of adduct (15,17,18) obtained from the titanium tetrachloride mediated condensation (2.9 g, 6.99 mmol) in AcOH (70 ml) was treated with $PdCl_2$ (0.372 g, 2.1 mmol) and stirred for 5 days under hydrogen atmosphere. The catalyst was removed by filtration , washed with AcOH and methylene chloride, and the filtrate evaporated to give a crude compound which was flash-chromatographed (n-hexane-EtOAc 9:1) to give acid (21) in 52% yield. $[\alpha]_D$ = -23.0 (neat), absolute conf. R; Ref.61a: -25.4 (neat), R; Ref.61b: -24.6 (neat), R. ^{1}H NMR ($CDCl_3$) δ 1.15 (d,3H,J=6.4 Hz), 2.4-3.2 (m,3H), 7.21 (s,5H), 8.2 (b.s,1H). ^{13}C NMR ($CDCl_3$) δ 16.43, 39.37, 41.33, 126.44, 128.44, 129.04, 139.10, 182.58.

Trans β-lactam (16). A solution of adduct (15,17,18) obtained from the titanium tetrachloride mediated condensation (11.7 mmol) was dissolved in dry THF (19.5 ml) and then slowly added to a solution of LiN(TMS)$_2$ (12.8 mmol) in THF (32 ml) at -10 deg C under nitrogen, with stirring. After 45 min at -10 deg C the mixture was quenched with NH_4Cl sat. solution and worked-up as usual. Flash-chromatography (n-hexane-EtOAc 9:1) gave pure trans β-lactam (16) in 79% yield and 95% enantiomeric excess. Recrystallization (n-hexane-EtOAc) gave optically pure (16) as white crystals, m.p. = 136 deg C, $[\alpha]_D$ = - 64.8 (c 1.0, $CHCl_3$).
^{1}H NMR ($CDCl_3$)δ1.47 (d,3H,J= 7.6 Hz), 3.12 (dq,1H,J= 7.6,2.5 Hz), 4.58 (d,1H,J=2.5 Hz), 6.95-7.40 (m,10H). ^{1}H NMR [$CDCl_3$ + Eu(hfc)$_3$] racemic : δ 2.75 (50% CH_3,d), 2.90 (50%, CH_3,d); optically active : 2.75 (2.5%, CH_3,d), 2.90 (97.5% CH_3,d).

Condensation product (34). A solution of iminoester (32)[55,62] (1.486 g, 7.8 mmol) and of silyl ketene acetal (4) (7.8 mmol) in methylene chloride (33.5 ml) was slowly added to a 1 M solution of titanium tetrachloride in methylene chloride (15.6 ml) at -78 deg C, under nitrogen, with stirring. After 1 h at -78 deg C and 1 h at -40 deg C the mixture was quenched and worked-up as described for the preparation of (5) to give the crude condensation product (34).

β-Aminoacid (36). A solution of the crude condensation product (34) (7.8 mmol) in 10:1 methanol-formic acid (86 ml) was treated with 10% Pd-C (1.652 g) under nitrogen, with stirring. After 3 h the catalyst was filtered off, washed with warm methanol, and mixture was evaporated in vacuo. The resulting crude product was passed through a column of Dowex 50W-X8 by elution with water and then with 5% aqueous NH_4OH. The resulting 5% NH_4OH eluate was then evaporated to dryness under reduced pressure to give acid (36)[4] in 53% overall yield as a 8:1 syn-anti mixture. ^{1}H NMR ($CDCl_3$)(36,syn) δ 0.92 (t,3H,J= 6.7 Hz), 1.25 (t,3H,J= 7.20 Hz), 1.60 (m,2H), 2.65 (m,1H), 4.18 (d,1H,J= 4.8 Hz), 4.25 (q,2H,J= 7.20 Hz), 7.35 (b.s,1H).

Condensation product (35). A solution of iminoester (33)[55,62] (0.994 g, 4.8 mmol) and of silyl ketene acetal (4) (4.8 mmol) in methylene chloride (20.5 ml) was added to a 1 M solution of titanium tetrachloride in methylene chloride (9.6 ml) as previously described for the preparation of (34). The condensation product was isolated by flash-chromatography (methylene chloride-MeOH 99:1) in 70% yield as a mixture of epimers. ^{1}H NMR ($CDCl_3$ + D_2O) δ 1.0 (t,3H,J=7.0 Hz), 1.05 (d,3H,J=7.4 Hz), 1.10 (t,3H,J=7.4 Hz), 1.5-2.1 (m,2H), 2.22 (s,6H), 2.70-3.0 (m,2H), 3.70 (s,3H), 4.0 (q,2H,J=7.4 Hz), 4.20 (d,1H,J=4.45, minor isomer), 4.25 (d,1H,J=5.65 Hz, major isomer), 5.90 (d,1H,J=5.80 Hz), 6.4-6.8 (AA'BB',4H), 7.25 (s,5H). ^{13}C NMR ($CDCl_3$)δ9.41, 12.26, 14.05, 21.00, 41.25, 50.06, 55.63, 59.27, 61.21, 63.25, 76.71, 114.72, 115.65, 126.77, 127.59, 128.16, 139.71, 140.65, 152.96, 171.84, 172.17 (major isomer).

β-Aminoacid (36). A solution of the condensation product (35) (1.5 g,3.275 mmol) in 10:1 methanol-formic acid (35.75 ml) was treated with 10% Pd-C (0.695 g) under nitrogen, with stirring. After 5 h the catalyst was filtered off, washed with warm methanol, and the mixture was evaporated in vacuo. The resulting crude product was flash-chromatographed (methylene chloride-MeOH 97:3) to give the p-methoxy amino acid as a 7:1 syn-anti mixture. ^{1}H NMR ($CDCl_3$) δ 0.99 (t,3H,J=7.3 Hz, anti), 1.01 (t,3H,J=7.3 Hz, syn), 1.19 (t,3H,J= 7.5 Hz, anti), 1.20 (t,3H,J=7.5 Hz, syn), 1.6-1.9 (m,2H), 2.80 (m,1H), 3.73 (s,3H), 4.15 (q,2H,J= 7.5 Hz), 4.25 (d,1H,J=5.65 Hz), 6.3 (b.s,1H), 6.65-6.80 (AA'BB',4H). A solution of p-methoxy amino acid (0.917 g, 3.11 mmol) in CH_3CN (77.8 ml) was treated with a solution of CAN (5.1 g, 9.31 mmol) in water (11.3 ml) at -25 deg C, under nitrogen, with stirring. After 10 min the two phases were separated, and the organic phase was washed with water. The combined aqueous extracts were passed through a column of Dowex 50W-X8. The column was eluted with water and then with 5% aqueous NH_4OH. The resulting 5% NH_4OH eluate was then evaporated in vacuo to give β-aminoacid[4] (36) in 82% overall yield as a 7:1 syn-anti mixture. ^{1}H NMR (D_2O)(36,syn) δ 0.73 (t,3H,J=7.0 Hz), 1.05 (t,3H,J= 7.0 Hz), 1.37 (m,2H), 2.43 (m,1H), 3.94 (m,1H), 4.05 (q,2H,J= 7.0 Hz).

β-Lactam (13). A solution of β-aminoacid (36)(0.596 g, 3.155 mmol) in dry CH_3CN (315.5 ml) was treated with 2-chloro-1-methylpiridinium iodide (0.887 g, 3.47 mmol) and then with a 1 M solution of triethylamine in CH_3CN (6.94 ml) at reflux temperature, under nitrogen, with stirring. After 7 h at reflux, the solvent was evaporated in vacuo and the crude mixture was flash-chromatographed (n-hexane-EtOAc 1:1) to give β-lactam (13) as a 8:1 cis-trans mixture (from adduct 34) or 7:1 cis-trans mixture (from adduct 35) in 85-87% yield. Cis β-lactam (13) was isolated by flash-chromatography (n-hexane-EtOAc 1:1) and the enantiomeric excess (50% from adduct 34 and 75% from adduct 35 respectively) was determined as described previously.

REFERENCES AND NOTES

1 Fukagawa,Y.; Okabe,M.; Yoshioka,T.; Ishikura,T. The Proceedings of the Third International Symposium on "Recent Advances in the Chemistry of β-lactam Antibiotics", Cambridge, England, 2-4 July 1984, The Royal Society of Chemistry, Special Publication No.52, p.163-182.
2 Nagahara,T.; Kametani,T. Heterocycles 1987,25,729-806.
3 Shih,D.H.; Baker,F.; Cama,L.; Christensen,B.G. Heterocycles 1984,21,29.
4 Nagao,Y.; Kumagai,T.; Tamai,S.; Abe,T.; Kuramoto,Y.; Taga,T.; Aoyagi,S.; Nagase,Y.; Ochiai,M.; Inoue,Y.; Fujita,E. J.Am.Chem.Soc. 1986,108,4673.
5 Fuentes,L.M.; Shinkai,I.; Salzmann,T.N. J.Am.Chem.Soc. 1986,108,4675.
6 Yoshioka,T.; Watanabe,A.; Isshiki,K.; Fukagawa,Y. Tetrahedron Lett. 1986,27,4335.
7 Iimori,T.; Shibasaki,M. Tetrahedron Lett. 1986,27,2149.
8 Kawabata,T.; Kimura,Y.; Ito,Y.; Terashima,S.; Sasaki,A.; Sunagawa,M. Tetrahedron Lett. 1986,27,6241.
9 Kim,C.U.; Luh,B.; Partyka,R.A. Tetrahedron Lett. 1987,28,507.
10 Deziel,R.; Favreau,D. Tetrahedron Lett. 1986,27,5687.
11 Hatanaka,M. Tetrahedron Lett. 1987,28,83.
12 Siva Prasad,J.; Liebeskind,L.S. Tetrahedron Lett. 1987,28,1857.
13 Fuentes,L.M.; Shinkai,I.; King,A.; Purick,R.; Reamer,R.A.; Schmitt,S.M.; Cama,L.; Christensen,B.G. J.Org.Chem. 1987,52,2563.
14 Brown,P.; Southgate,R. Tetrahedron Lett. 1986,27,247.
15 Different from the real world, in β-lactam chemistry construction of the garage (the β-lactam) is often more important than that of the house (the 5-membered ring).
16 Fleming,I.; Kilburn,J.D. J.Chem.Soc.,Chem.Commun. 1986,1198.
17 Mickel,S. Aldrichimica Acta 1985,18,95.
18 Reider,P.S.; Rayford,R.; Grabowski,E.J.J. Tetrahedron Lett. 1982,23,379.
19 Karady,S.; Amato,J.S.; Reamer,R.A.; Weinstock,L.M. J.Am.Chem.Soc. 1981,103,6765.
20 Kametani,T.; et al. Heterocycles 1979,13,523.
21 Kametani,T.; et al. Heterocycles 1980,14,575.
22 Kametani,T.; Honda,T.; Nakayama,A.; Fukumoto,K. Heterocycles 1980,14,1967.
23 Ernest,J. Tetrahedron 1977,33,547.
24 Bachi,M.D.; Goldberg,O.; Gross,A. Tetrahedron Lett. 1978,4167.
25 Oida,S.; Yoshida,A.; Ohki,E. Chem.Pharm.Bull. 1980,28,3494.
26 Onoue,H.; et al. Tetrahedron Lett. 1979,3867.
27 Barrett,A.G.; Quayle,P. J.Chem.Soc.,Chem.Commun. 1981,1076.
28 Tajima,Y.; Yoshida,A.; Takeda,N.; Oida,S. Tetrahedron Lett. 1985,26,673.
29 Kraus,G.A.; Neuenschwander,K. J.Chem.Soc.,Chem.Commun. 1982,134.
30 Buynak,J.D.; Pajouhesh,H.; Lively,D.L.; Ramalakshmi,Y. J.Chem.Soc.,Chem.Commun. 1984,948.
31 Ueda,Y.; Maynard,S.C. Tetrahedron Lett. 1985,26,6309.
32 Ueda,Y.; Roberge,G.; Vinet,U. Can.J.Chem. 1984,62,2936.

33 Maruyama,H.; Shiozaki,M.; Hiraoka,T. Bull.Chem.Soc.Jpn. 1985,58,3264.
34 Reider,P.J.; Grabowsky,E.J. Tetrahedron Lett. 1982,23,2293.
35 Hart,D.J.; Lee,C.S.; Pirkle,W.H.; Hyon,M.H.; Tsipouras,A. J.Am.Chem.Soc. 1986,108,6054.
36 Habich,D.; Hartwig,W. Tetrahedron Lett. 1987,28,781.
37 Hart,D.J.; Ha,D.C. Tetrahedron Lett. 1985,26,5493.
38 Ojima,I.; Inaba,S.; Yoshida,K. Tetrahedron Lett. 1977,3643.
39 (a) Ojima,I.; Inaba,S. Tetrahedron Lett. 1980,21,2077. (b) Ojima,I.; Inaba,S. Tetrahedron Lett. 1980,21,2081.
40 (a) Ikeda,K.; Achiwa,K.; Sekiya,M. Tetrahedron Lett. 1983,24,4707. (b) Tetrahedron Lett. 1983,24,913.
41 Dubois,J.E.; Axiotis,G. Tetrahedron Lett. 1984,25,2143.
42 (a) Okano,K.; Morimoto,T.; Sekiya,M. J.Chem.Soc.,Chem.Commun. 1984,883. (b) Morimoto,T.; Sekiya,M. Chem.Lett. 1985,1371.
43 Shono,T.; Tsubata,K.; Okinaga,N. J.Org.Chem. 1984,49,1056.
44 Colvin,E.W.; McGarry,D.G. J.Chem.Soc.,Chem.Commun. 1985,539.
45 Cainelli,G.F.; Contento,M.; Drusiani,A.; Panunzio,M.; Plessi,L. J.Chem.Soc.,Chem.Commun. 1985,240.
46 (a) Guanti,G.; Narisano,E.; Banfi,L. Tetrahedron Lett. 1987,28,4331. (b) Tetrahedron Lett. 1987,28,4335.
47 For a preliminary communication on part of this work, see : Gennari,C.; Venturini,I.; Gislon,G.; Schimperna,G. Tetrahedron Lett. 1987,28,227.
48 Both enantiomers of N-methylephedrine are commercially available (Fluka).
49 Gennari,C.; Colombo,L.; Bertolini,G.; Schimperna,G. J.Org.Chem. 1987,52,2754.
50 (a) Gennari,C.; Bernardi,A.; Colombo,L.; Scolastico,C. J.Am.Chem.Soc. 1985,107,5812. (b) Palazzi,C.; Colombo,L.; Gennari,C. Tetrahedron Lett. 1986,27,1735.
51 Gennari,C.; Bernardi,A.; Scolastico,C.; Potenza,D. Tetrahedron Lett. 1985,26,4129.
52 Gennari,C.; Colombo,L.; Bertolini,G. J.Am.Chem.Soc. 1986,108,6394.
53 Miller,M.J. Acc.Chem.Res. 1986,19,49. For other examples of the aldol/N-C cyclization approach, see : (a) ref. 16 of this paper. (b) Hsiao,C.N.; Ashburn,S.P.; Miller,M.J. Tetrahedron Lett. 1985,26,4855. (c) Evans,D.A.; Sjogren,E.B. Tetrahedron Lett. 1986,27,3119. (d) Hsiao,C.N.; Liu,L.; Miller,M.J. J.Org.Chem. 1987,52,2201. (e) Evans,D.A.; Sjogren,E.B. Tetrahedron Lett. 1986,27,4961.
54 Levin,J.I.; Turos,E.; Weinreb,S.M. Synth.Commun. 1982,12,989. For applications of this reagent to carbapenem synthesis, see ref. 53 c,e of this paper.
55 Georg,G.I.; Kant,J.; Gill,H.S. J.Am.Chem.Soc. 1987,109,1129.
56 Miller,M.J.; Bajwa,J,S.; Mattingly,P.G.; Peterson,K. J.Org.Chem. 1982,47,4928.
57 For total syntheses of (+)PS-5, see : Favara,D.; Omodei-Sale,A.; Consonni,P.; DePaoli,A. Tetrahedron Lett. 1982,23,3105. Okano,K.; Izawa,T.; Ohno,M. Tetrahedron Lett. 1983,24,217. Ref. 35, 53b, 53c of this paper. Shibasaki,M.; Ishida,Y.; Iwasaki,G.; Iimori,T. J.Org.Chem. 1987,52,3488.
58 El Amin,B.; Anantharamaiah,G.M.; Royer,G.P.; Means,G.E. J.Org.Chem. 1979,44,3442.
59 Ha,D.C.; Hart,D.J.; Yang,T.K. J.Am.Chem.Soc. 1984,106,4819.
60 Gluchowski,C.; Cooper,L.; Bergbreiter,D.E.; Newcomb,M. J.Org.Chem. 1980,45,3413.
61 a) Helmchen,G.; et al. Angew.Chem.,Int.Ed.Engl. 1979,18,63. b) Schrecker,A.W. J.Org.Chem. 1957,22,33.
62 Mukaiyama,T.; Suzuki,H.; Yamada,T. Chem.Lett. 1986,915. Chem.Lett. 1987,293.
63 Huang,H.; Iwasawa,N.; Mukaiyama,T. Chem.Lett. 1984,1465.
64 Georg,G.I.; Gill,H.S. J.Chem.Soc.,Chem.Commun. 1985,1433.
65 Tamura,N.; Kawano,Y.; Matsushita,Y.; Yoshioka,K.; Ochiai,M. Tetrahedron Lett. 1986,27,3749, and references therein.
66 Blake,J.; Tretter,J.R.; Juhasz,G.J.; Bouthrone,W., Rapoport,H. J.Am.Chem.Soc. 1966,88,4061.