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# CHELATION CONTROLLED ALDOL ADDITIONS OF THE ENOLSILANE DERIVED FROM tert-BUTYL THIOACETATE : A STEREOSELECTIVE APPROACH TO 1β-METHYLTHIENAMYCIN

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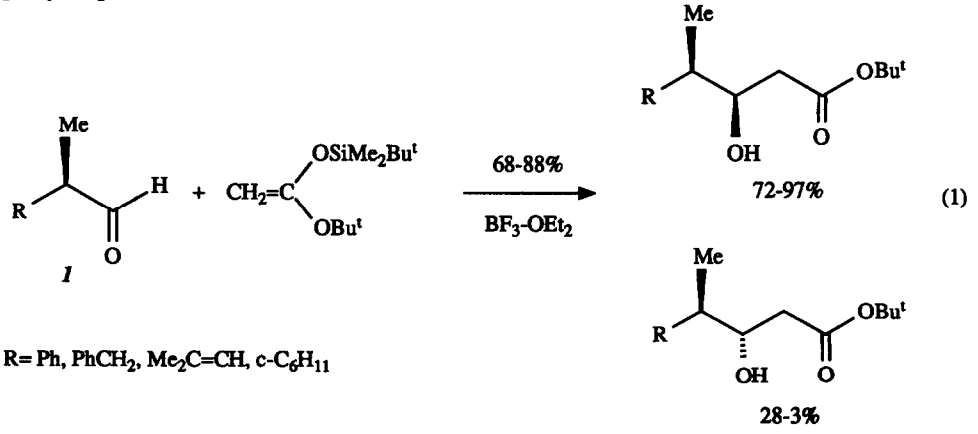
Abstract - The tert-butyldimethylenolsilane derived from tert-butyl thioacetate is a useful reagent for highly stereoselective chelation-controlled additions to chiral α-alkoxy and α-methyl-β-alkoxy aldehydes where the corresponding acetate fails. The aldol product deriving from the $TiCl_4$ mediated addition to α-methyl-β-alkoxy aldehyde 5 was elaborated in high yield to give the bicyclic β-lactam 11, an intermediate for the preparation of 1β-methylthienamycin. Problems associated with the partial racemization of aldehyde 5 during the $TiCl_4$ mediated condensations have not yet been completely resolved.

The Lewis acid mediated addition of silyl ketene acetals to chiral aldehydes is a well established methodology for carbon chain elongation with high diastereofacial selectivity.[1,2] In 1983 C.H. Heathcock and L.A. Flippin reported that enolsilanes show exceptional diastereofacial preferences in their Lewis acid mediated reactions with chiral α-methyl aldehydes 1: the most selective and preparatively useful reagent described in that study is the tert-butyldimethylenolsilane derived from tert-butyl acetate (Equation 1).[3] The reason for this high selectivity may be due to an approach trajectory of the nucleophile closer to the chiral center when the carbonyl group is bound to the Lewis acid.[3]

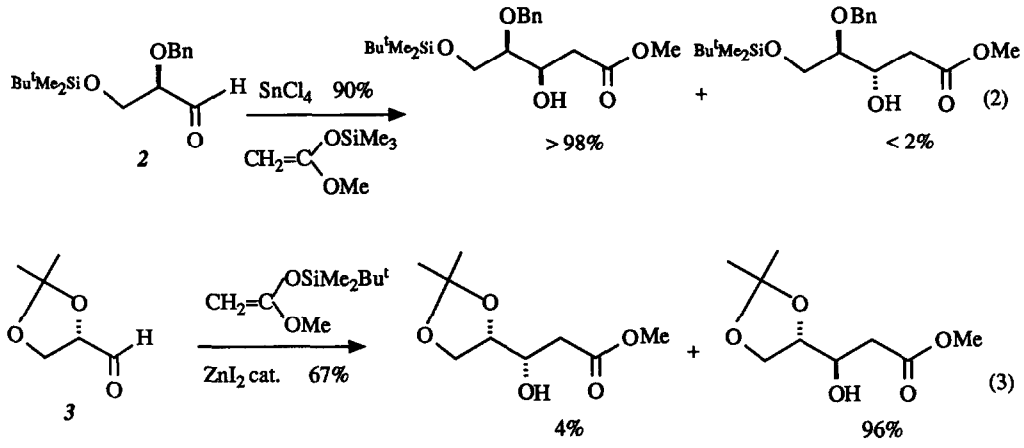



(1)

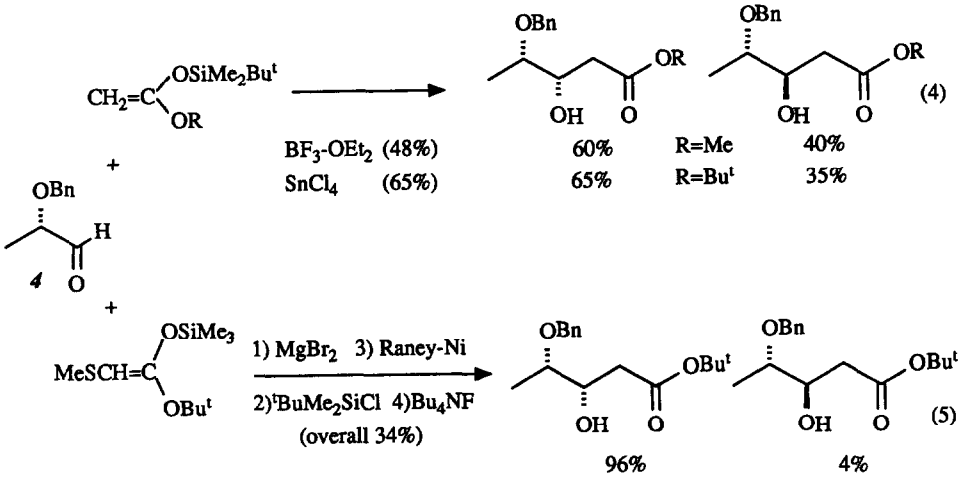
R= Ph, $PhCH_2$, $Me_2C=CH$, c-$C_6H_{11}$

With chiral α,β-dialkoxy aldehydes the methyl acetate derived silyl ketene acetal was reported to give remarkable chelation-controlled diastereofacial selectivities (Equations 2,3).[4,5] Reetz and Kesseler showed that excellent diastereofacial preferences in favor of the syn isomer can be achieved with aldehyde 2 and tin

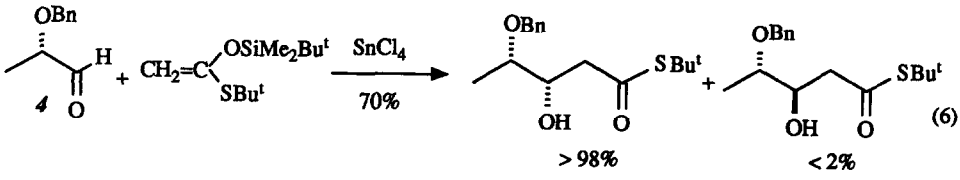
tetrachloride through the formation of the α-chelated complex.[4] Kita and coworkers showed that 2,3-O-isopropylidene glyceraldehyde 3 and catalytic $ZnI_2$ give high ratios of the anti isomer, possibly through the formation of the β-chelated complex.[5]




Unfortunately this high selectivity cannot be extended to chiral α-alkoxy aldehyde 4 (Equation 4).[6] A somewhat circuitous solution to this problem was proposed with the use of a methylthio-substituted silyl ketene acetal followed by protection, reductive desulfurization and deprotection (Equation 5).[7]




In this paper we show that the tert-butyldimethylenolsilane derived from tert-butyl thioacetate is a very effective reagent where the corresponding acetate fails. It is possible that the two oxygens of the acetate derived silyl ketene acetal somehow compete with the alkoxy aldehyde in the chelation of the Lewis acid with consequent loss of stereoselectivity.[6] With the thioanalog this undesirable effect is avoided and high chelation control is restored (Equation 6), in analogy with the similar behavior of propionates[6,8] and thiopropionates.[9]




We were also interested in the chelation-controlled enolsilane additions to chiral α-methyl-β-alkoxy aldehyde 5 for the stereoselective synthesis of 1β-methyl carbapenem antibiotics.[10] In this case too the thioacetate succeeds where the acetate fails (Equation 7, Fig.1).[11]

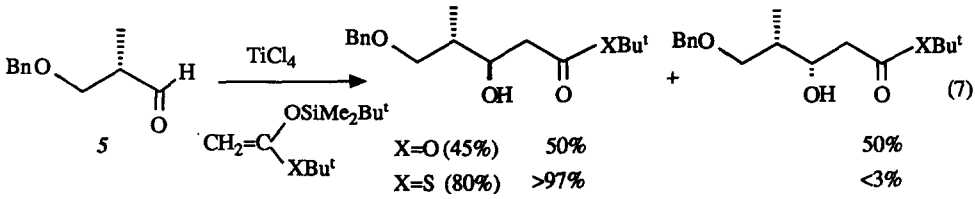
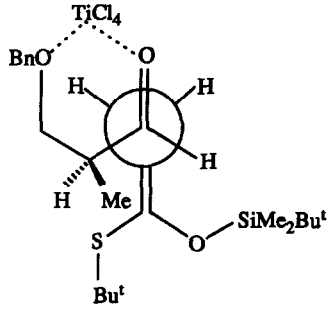



*figure 1*

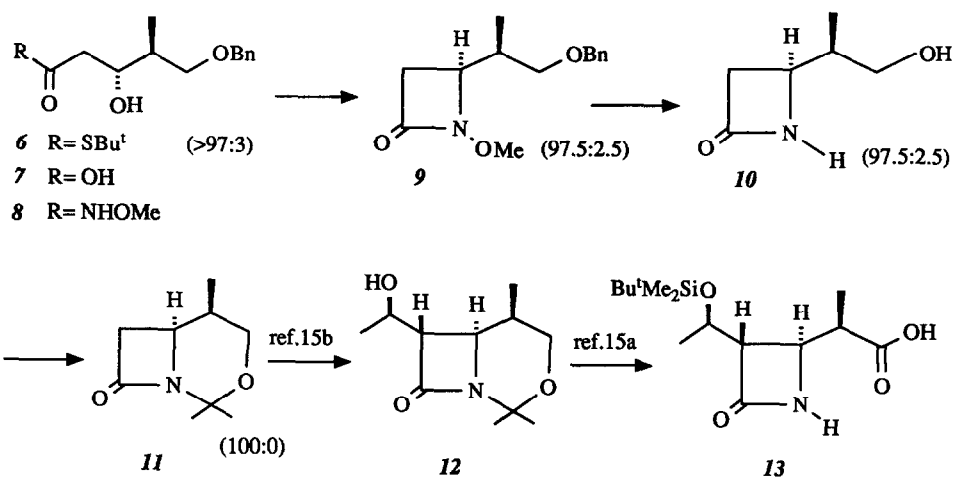



The aldol condensation product 6 (Scheme 1) was then hydrolized with $Hg(OCOCF_3)_2$ in acetonitrile-water[12] to give acid 7 in 88% yield which was treated with methoxyamine hydrochloride and the water-soluble carbodiimide[13] to give the desired hydroxamate 8 cleanly (80%). Treatment of 8 with methanesulfonyl chloride (pyridine, 0°C) gave the mesylate which was directly cyclized[14] to give N-methoxyazetidinone 9 in 75% overall yield from 8, as a 97.5:2.5 mixture of diastereoisomers (Scheme 1).

Both the phase transfer conditions ($CH_2Cl_2$-$H_2O$/$K_2CO_3$/n-$Bu_4NHSO_4$, 60°C, stirring) and $K_2CO_3$ in refluxing acetone under vigorous stirring proved suitable for the cyclization, but only the $K_2CO_3$-acetone reaction could be scaled-up from 0.2 to 2.0 mmol with no decrease in the yield due to competitive elimination of MsOH. The stereoisomeric ratio was confirmed at this stage by 200 MHz $^1H$ NMR spectroscopy in the presence of $Eu(fod)_3$.[15]

Dissolving metal reduction ($Na/THF-NH_3$/ -78°C, 1 hr)[14] cleanly effected both N-O and O-$CH_2$Ph bond cleavage to afford 10 in 75% yield.

*Scheme 1*




Finally, treatment with 2,2-dimethoxypropane in $CH_2Cl_2$ in the presence of $BF_3$-$OEt_2$[16a] gave the bicyclic acetonide 11 (80%) which was separated from the minor (2.5%) isomeric contaminant by flash chromatography. Bicyclic acetonide 11, characterized by the proton coupling pattern typical of 1$\beta$-methyl substitution,[16b] had previously been transformed into 12 [ a) LDA/$CH_3CHO$ b) $(CF_3CO)_2O$/DMSO c) K-Selectride][16b] and into 13 [ a) $^t$BuMe$_2$SiCl/DMF/Et$_3$N b) Jones].[16a] Acid 13 is a key intermediate for the preparation of the carbapenem antibiotic 1$\beta$-methyl thienamycin[16] which possesses improved chemical stability at high concentrations and decreased susceptibility to renal dipeptidase-I while retaining an excellent antibacterial profile.[17] The same sequence of reactions was repeated using aldehyde (S)(+)5 which was prepared in the enantiomerically pure form starting from (R)(-) methyl 3-hydroxy-2-methylpropionate.[18] Unfortunately, but not unexpectedly,[9d,10] $^1$H NMR analysis with Eu(hfc)$_3$[19] revealed the presence of variable amounts of the enantiomer of $\beta$-lactam 11 (up to 33%). This result is probably due to partial racemization of aldehyde 5 during the formation of the chelated complex with $TiCl_4$. Therefore a different mode of addition of the reagents was devised, i.e. $TiCl_4$ was added last to a premixed solution of the silyl ketene acetal and aldehyde 5. Following this experimental protocol both the yield of the condensation (from 80 to 60%) and the stereoselectivity ( from > 97:3 to 77:23) dropped. The synthetic sequence was then repeated and the 77:23 mixture was separated by flash chromatography to give compound 11 as a single isomer. $^1$H NMR analysis with Eu(hfc)$_3$[19] revealed that racemization of aldehyde 5 had been reduced but not eliminated (up to 16% of the enantiomer of 11 was detected).

In conclusion we have shown that the tert-butyldimethylenolsilane derived from tert-butyl thioacetate is a useful reagent for the substitution of the corresponding acetate. Problems associated with the partial racemization of aldehyde 5 during the $TiCl_4$ mediated condensations of the thioacetate derived silyl ketene acetal have not yet been completely resolved.

## EXPERIMENTAL

General. $^{1}H$ and $^{13}C$ NMR spectra were recorded with Varian XL-200 or Bruker WP-80 instruments in the FT mode. Optical rotations were measured in 1-dm cells of 1-ml capacity on a Perkin Elmer Model 241 polarimeter. IR spectra were recorded with a Perkin Elmer 681 spectrophotometer. Elemental analyses were performed with a Perkin Elmer Model 240 instrument. Silica gel 60 $F_{254}$ plates (Merck) were used for TLC; 273-400 mesh silica gel (Merck) was used for flash chromatography. Organic extracts were dried over $Na_2SO_4$. Dry solvents were distilled under nitrogen immediately before use: THF and ethyl ether from sodium/benzophenone, $CH_2Cl_2$ and diisopropylamine from $CaH_2$. All reactions were run under nitrogen atmosphere (from liquid nitrogen).

**Tert-Butyldimethylsilyl ketene acetal derived from tert-butyl thioacetate.** Tert-butyl thioacetate was prepared from acetyl chloride and tert-butyl mercaptan according to ref.20 and fractionally distilled. The yield was 80% of material with a b.p. of 135°C (760 mmHg). $^{1}H$ NMR ($CDCl_3$) δ 1.46 (s,9H), 2.20 (s,3H). Anal.Calcd for $C_6H_{12}OS$: C,54.50; H,9.15. Found: C,54.48; H,9.17%. A solution of diisopropylamine (0.77 ml, 5.5 mmol) in THF (6.7 ml) was treated with a 1.5 M solution of n-BuLi in n-hexane (3.67 ml, 5.5 mmol) at 0°C, under nitrogen, with stirring. After 20 min at 0°C the solution was cooled to -78°C and a solution of t-butyl thioacetate (0.83 g, 5.5 mmol) in HMPA (2.0 ml) was slowly added. After 30 min at -78°C a solution of tert-butyldimethylsilyl chloride (0.827 g, 5.5 mmol) in HMPA (2.0 ml) and n-hexane (1.0 ml) was added. Then the mixture was warmed to room temperature during 30 min, diluted with ice-cold pentane (30 ml), and washed with water. The organic phase was concentrated in vacuo and the resulting crude product was purified by Kugelrohr distillation (145°C, 20 mmHg) to give a colorless liquid in 75% yield. $^{1}H$ NMR ($CDCl_3$) δ 0.20 (s,6H), 0.96 (s,9H), 1.39 (s,9H), 4.68 (m,2H).

**Tert-Butyl (3S,4S)-3-hydroxy-4-(benzyloxy)thiopentanoate [Eq.6].** A solution of aldehyde 4 (0.121 g, 0.74 mmol) in methylene chloride (1.5 ml) was treated with a 1 M solution of $SnCl_4$ in methylene chloride (0.736 ml) at -80°C, under nitrogen, with stirring. After a few minutes, the tert-butyldimethylsilyl ketene acetal derived from tert-butyl thiacetate was added (0.271 g, 1.10 mmol). After 1 hr at -80°C the mixture was quenched with 1N KOH and the organic phase was washed with saturated brine, dried and evaporated. The crude product was analyzed by $^{1}H$ and $^{13}C$ NMR spectroscopy and shown to be a single (>98:2) stereoisomer. Then it was purified by flash chromatography (n-hexane-EtOAc 83:17) to give the title compound in 70% yield. $^{1}H$ NMR ($CDCl_3$) δ 1.20 (d,3H,J=6.25 Hz), 1.46 (s,9H), 2.67 (d,2H,J=6.2 Hz), 3.50 (dq,1H,J=6.25, 5.0 Hz), 4.00 (dt,1H,J=6.2, 5.0 Hz), 4.46 (AB,1H,J=11.7 Hz), 4.64 (AB,1H,J=11.7 Hz), 7.25-7.40 (m,5H). $^{13}C$ NMR ($CDCl_3$) δ 15.14, 29.77, 47.44, 48.31, 71.03, 71.41, 76.51, 127.72, 127.77, 128.41, 138.23, 199.25. Anal.Calcd for $C_{16}H_{24}O_3S$: C,64.83; H,8.16. Found: C,64.79; H,8.20%.

**Tert-Butyl ($3R^*,4S^*$) and ($3S^*,4S^*$)-3-hydroxy-4-methyl-5-(benzyloxy)pentanoate [Eq.7].** The tert-butyldimethylsilyl ketene acetal derived from tert-butyl acetate was prepared according to ref. 6. A solution of aldehyde 5 (0.356 g, 2.0 mmol) in methylene chloride (4.0 ml) was treated with a 1 M solution of $TiCl_4$ in methylene

chloride (2.0 ml) at -80°C, under nitrogen, with stirring. After a few seconds, the tert-butyldimethylsilyl ketene acetal derived from tert-butyl acetate was added (0.5 g, 2.2 mmol). After 1 hr at -80°C the mixture was quenched with 1 N KOH and the organic phase was washed with saturated brine, dried and evaporated. The crude product was analyzed by $^1$H NMR spectroscopy (yield by NMR : 45%) and shown to be a 50:50 mixture of stereoisomers. The compound could not be purified by chromatography because of extensive decomposition on silica gel. $^1$H NMR ($CDCl_3$)$\delta$ 0.94 (d,50% 3H,J=7.0 Hz), 0.95 (d,50% 3H,J=7.0 Hz), 1.46 (s,9H), 1.8-2.0 (m,1H), 2.27-2.55 (m,2H), 3.41-3.58 (m,2H), 3.89-4.01 (m,50% 1H), 4.10-4.21 (m,50% 1H), 4.50 (s,2H), 7.20-7.40 (m,5H).

**Tert-Butyl (3R$^*$,4S$^*$)-3-hydroxy-4-methyl-5-(benzyloxy)thiopentanoate (6) [Eq.7; Scheme 1].**

A solution of aldehyde 5 (0.946 g, 5.28 mmol) in methylene chloride (12.0 ml) was treated with a 1 M solution of $TiCl_4$ in methylene chloride (5.28 ml) at -80°C, under nitrogen, with stirring. After a few seconds, the tert-butyldimethylsilyl ketene acetal derived from tert-butyl thioacetate was added (2.238 g, 8.16 mmol). After 1.5 hr at -80°C the mixture was quenched with 1 N KOH and the organic phase was washed with saturated brine, dried and evaporated. The crude product was analyzed by $^1$H and $^{13}$C NMR spectroscopy, and then purified twice by flash chromatography (n-hexane-EtOAc 85:15; benzene-$Et_2O$ 95:5) to give the title compound in 80% yield. The (3R$^*$,4S$^*$)/(3S$^*$,4S$^*$) ratio was determined to be >97:3 by NMR spectroscopy. $^1$H NMR ($CDCl_3$)$\delta$ 0.925 (d,3H,J=7.0 Hz), 1.46 (s,9H), 1.8-2.0 (m,1H), 2.20-2.50 (b.s,1H,exchangeable), 2.54-2.74 (AB part of an ABX system, $J_{AB}$=15 Hz, $J_{AX}$=4.8 Hz, $J_{BX}$=7.5 Hz), 3.44-3.60 (AB part of an ABX system , $J_{AB}$=9.5 Hz, $J_{AX}$=5.0 Hz, $J_{BX}$=6.5 Hz), 4.02 (ddd,1H,J=4.8, 7.5, 7.25 Hz), 4.50 (s,2H), 7.20-7.40 (m,5H). $^{13}$C NMR ($CDCl_3$)$\delta$ 13.78, 29.78, 38.37, 48.24, 49.20, 72.04, 73.34, 73.50, 127.61, 127.67, 128.40, 138.00, 199.90. IR ($CHCl_3$)$\nu$ 3480, 2960, 1665, 1450, 1360, 1080, 970 cm$^{-1}$. Anal. Calcd for $C_{17}H_{26}O_3S$: C,65.77; H,8.44. Found: C,65.69; H,8.50%.

**Tert-Butyl (3R,4S)-3-hydroxy-4-methyl-5-(benzyloxy)thiopentanoate (6) [Eq.7; Scheme 1].**

The same procedure described above was followed with aldehyde (S)-(+) 5 which was prepared in the enantiomerically pure form starting from (R)-(-) methyl 3-hydroxy-2-methylpropionate according to ref. 18.

**Tert-Butyl (3R,4S) and (3S,4S)-3-hydroxy-4-methyl-5-(benzyloxy)thiopentanoate.**

A solution of the tert-butyldimethylsilyl ketene acetal derived from tert-butyl thioacetate (1.52 g, 6.16 mmol) and aldehyde (S)-(+) 5 (0.732 g, 4.11 mmol) in methylene chloride (8.22 ml) was treated with a 1 M solution of $TiCl_4$ in methylene chloride (4.11 ml) at -80°C, under nitrogen, with stirring. After stirring for 2 hr at -80°C the mixture was quenched with 1 N KOH and the organic phase was washed with saturated brine, dried and evaporated. The crude product was analyzed by $^1$H and $^{13}$C NMR spectroscopy, and then flash chromatographed twice (n-hexane-EtOAc 85:15; benzene-$Et_2O$ 95:5) to give the title compound as a 77:23 mixture of the (3R,4S) and (3S,4S) stereoisomers in 60% yield. Selected data of the minor (23%) (3S,4S) stereoisomer: $^1$H NMR ($CDCl_3$)$\delta$ 0.940 (d,3H,J=7.1 Hz), 1.46 (s,9H), 4.23 (ddd,1H,J=4.0, 4.0, 8.0 Hz), 4.50 (s,2H). $^{13}$C NMR ($CDCl_3$)$\delta$ 11.16, 29.78, 37.99, 48.24, 48.80, 70.16, 73.56, 138.11.

**(3R*,4S*)-3-hydroxy-4-methyl-5-(benzyloxy)pentanoic acid (7) [Scheme 1].**
A solution of thioester 6 (0.566 g, 1.81 mmol) in 4:1 acetonitrile-water (9.25 ml) was treated with $Hg(OCOCF_3)_2$ (1.08 g, 2.54 mmol) at 55-60°C under vigorous stirring. After 3 h at 55-60°C, the mixture was cooled to room temperature, diluted with ethyl acetate (30 ml) and filtered through Celite, washing the Celite cake with ethyl acetate (50 ml). The solution was then treated with $H_2S$ (10 min bubbling), and filtered again through Celite. The resulting solution was evaporated to give a crude compound which was purified by flash chromatography ($CH_2Cl_2$-MeOH from 94:6 to 80:20) to give acid 7 in 88-93% yield contaminated by small amounts (5%) of Hg-containing by-products. $^1H$ NMR ($CDCl_3$) δ 0.91 (d,3H,J=7.0 Hz), 1.88-2.04 (m,1H), 2.42-2.66 (AB part of an ABX system, $J_{AB}$= 16.0 Hz, $J_{AX}$= 4.0 Hz, $J_{BX}$= 8.0 Hz), 3.44-3.64 (AB part of an ABX system, $J_{AB}$= 9.5 Hz, $J_{AX}$= 4.5 Hz, $J_{BX}$= 7.5 Hz), 3.99 (ddd,1H,J=8.0, 8.0, 4.0 Hz), 4.52 (s,2H), 6.3 (b.s,1H,exchangeable), 7.25-7.40 (m,5H).

**Hydroxamate (8) [Scheme 1].**
A solution of acid 7 (0.433 g, 1.82 mmol) in 6:1 THF-water (18.2 ml) was treated with methoxyamine hydrochloride (0.275 g, 3.29 mmol) and the pH was adjusted to 4.5 with 1 N aqueous NaOH. A solution of WSC[13] (0.872 g, 4.55 mmol) in water (15 ml) was then added and the pH adjusted to 4.5 with 1 N HCl. After stirring for 1 h at room temperature, the mixture was acidified with 2 N HCl to pH 2, and extracted with ethyl acetate (3x20 ml). The combined organic extracts were washed with water, dried and evaporated to give a crude product which was purified by flash chromatography ($CH_2Cl_2$-MeOH 93:7) to give hydroxamate 8 in 80% yield. $^1H$ NMR ($CDCl_3$) δ 0.90 (d,3H,J=6.8 Hz), 1.75-2.10 (m,1H), 2.30-2.50 (AB part of an ABX system), 3.34-3.68 (AB part of an ABX system , $J_{AB}$= 9.1 Hz, $J_{AX}$= 1.8 Hz, $J_{BX}$= 3.8 Hz), 3.72 (s,3H), 3.75-3.95 (m,1H), 4.3 (b.s,1H), 4.50 (s,2H), 7.15-7.35 (m,5H), 9.2 (b.s,1H). IR ($CHCl_3$) ν 3480, 3400, 2890, 1690, 1460, 1090 $cm^{-1}$ (selected values). Anal. Calcd for $C_{14}H_{21}NO_4$: C,62.90; H,7.92; N,5.24. Found: C,62.83; H,7.98; N,5.19%.

**β-Lactam (9) [Scheme 1].**
A solution of hydroxamate 8 (0.402 g, 1.5 mmol) in dry pyridine (1.9 ml) at 0°C was treated with 4-(dimethylamino)pyridine (9 mg) and methanesulphonyl chloride (3.75 mmol). The mixture was stirred at 0°C for 3 hr then treated with 1 N HCl and ice and extracted with ethyl acetate (3x10 ml). The organic extracts were washed with 1 N HCl, saturated $NaHCO_3$, brine, dried and evaporated.
A solution of the crude mesylate (80 mg, 0.23 mmol) in dichloroethane (4.63 ml) was treated successively with water (0.5 ml), $K_2CO_3$ (128 mg, 0.93 mmol), and n-$Bu_4HSO_4$ (7.9 mg, 0.023 mmol) at 60°C under vigorous stirring. After 1 hr at 60°C, the mixture was diluted with $CH_2Cl_2$ (10 ml). The organic phase was washed with saturated brine, dried and evaporated to give a crude product which was flash chromatographed ($CH_2Cl_2$-EtOAc 92:8) to give the title compound 9 in 75% yield.
Alternatively a solution of the crude mesylate (0.932 g, 2.70 mmol) in dry acetone (12 ml) was added to a refluxing mixture of powdered $K_2CO_3$ (1.87 g, 13.54 mmol) in dry acetone (40 ml) under vigorous stirring. After refluxing for 1 hr, the mixture was cooled, diluted with ethyl acetate (100 ml) and filtered through Celite (washing with EtOAc). The solvent was evaporated to give a crude product which was purified by flash chromatography ($CH_2Cl_2$-EtOAc 92:8) to give the title compound 9 in 75% yield. Anal.Calcd for $C_{14}H_{19}NO_3$: C,67.45; H,7.68; N,5.62. Found: C,67.38;

H,7.70; N,5.57%. IR ($CHCl_3$) $\nu$ 2960, 2940, 2860, 1760, 1450, 1380, 1360, 1100 $cm^{-1}$ (selected values) $^1H$ NMR ($CDCl_3$) $\delta$ 1.06 (d,3H,J=6.7 Hz), 2.06 (septet,1H,J=ca.6.5 Hz), 2.49-2.74 (AB part of an ABX system, $J_{AB}$=14 Hz, $J_{AX}$=5.5 Hz, $J_{BX}$=2.8 Hz), 3.34-3.47 (AB part of an ABX system, $J_{AB}$=9.5 Hz, $J_{AX}$=6.0 Hz, $J_{BX}$=7.0 Hz), 3.73 (s,3H), 3.94 (ddd,1H,J=6.0, 5.5, 2.8 Hz), 4.42-4.55 (AB system, $J_{AB}$=12.5 Hz), 7.20-7.40 (m,5H).
A 97.5:2.5 ratio (mode of addition: aldehyde precomplexed with $TiCl_4$) and a 77:23 ratio (mode of addition: $TiCl_4$ added last) were determined by 200 MHz $^1H$ NMR spectroscopy with the aid of $Eu(fod)_3$.[15] Relevant $^1H$ NMR data of the minor stereoisomer :$\delta$ 0.984 (d,3H,J=6.7 Hz), 2.42-2.69 (AB part of an ABX system), 3.40-3.55 (AB part of an ABX system), 3.73 (s,3H), 4.0 (ddd,1H).

**$\beta$-Lactam (10) [Scheme 1].**
To a solution of Na (78 mg, 3.33 mmol) in 10:1 $NH_3$-THF (5 ml) at -78 °C a solution of N-methoxyazetidinone 9 (84.1 mg, 0.33 mmol) in THF (0.75 ml) was added. The resulting blue solution was stirred at -78 °C for 1h, then solid $NH_4Cl$ (360 mg, 6.72 mmol) was added, and the resulting colorless solution was diluted with ethyl acetate (3 ml). The ammonia was then allowed to distill off, while heating to room temperature, and 5 ml of ethyl acetate was added to the white slurry. After filtration (sintered glass funnel) and washing of the solids with additional ethyl acetate, the organic phase was concentrated to give a crude product which was purified by flash chromatography ($CH_2Cl_2$-MeOH 85:15) to give lactam 10 in 75% yield. IR (CHCl3) $\nu$ 3620, 3420, 2960, 2940, 1750, 1380, 1050 $cm^{-1}$ (selected values). $^1H$ NMR ($CDCl_3$) $\delta$ 0.98 (d,3H,J=6.7 Hz), 1.86 (septet,1H,J= ca.6.2 Hz), 2.82 (A part of an ABX system, $J_{AB}$=15 Hz, $J_{AX}$= 2.25 Hz), 3.07 (B part of an ABX system, $J_{AB}$=15 Hz, $J_{BX}$=5.25 Hz), 3.58 (A part of an ABX system, $J_{AB}$=11.0 Hz, $J_{AX}$=6.0 Hz), 3.66 (B part of an ABX system, $J_{AB}$=11.0 Hz, $J_{BX}$=5.7 Hz), 3.64-3.74 (m,1H), 4.2 (b.s,1H), 6.5 (b.s,1H). Anal.Calcd for $C_6H_{11}NO_2$: C,55.80; H,8.58; N,10.84. Found: C,55.75; H,8.62; N,10.74%.

**Acetonide (11) [Scheme 1].**
A solution of $\beta$-lactam 10 (330 mg, 2.56 mmol) in methylene chloride (5.12 ml) was treated with 2,2-dimethoxypropane (0.630 ml, 5.12 mmol) and with $BF_3$-$OEt_2$ (0.384 mmol, 0.048 ml) at room temperature, under nitrogen. After 1 hr the reaction was quenched with $Et_3N$ (3 drops), the mixture was evaporated and the crude product purified by flash chromatography (ethyl acetate/n-hexane 75:25) to give acetonide 11 in 80% yield. Anal.Calcd for $C_9H_{15}NO_2$: C,63.88; H,8.93; N,8.28. Found: C,63.80; H,8.99; N,8.19%. IR ($CHCl_3$) $\nu$ 2960, 1735, 1370, 1090, 900 $cm^{-1}$ (selected values). $^1H$ NMR ($CDCl_3$) $\delta$ 1.085 (d,3H,J=7.0 Hz), 1.38 (s,3H), 1.72 (s,3H), 1.80-1.95 (m,1H), 2.78 (A part of an ABX system, $J_{AB}$=15.0 Hz, $J_{AX}$=2.5 Hz), 2.85 (B part of an ABX system, $J_{AB}$=15 Hz, $J_{BX}$=4.6 Hz), 3.59 (A part of an AMX system, $J_{AM}$= 12.2 Hz, $J_{AX}$=2.6 Hz), 3.75 (ddd,1H,J=2.5, 4.6, 4.7 Hz), 3.95 (M part of an AMX system, $J_{AM}$= 12.2 Hz, $J_{MX}$=2.5 Hz).
A 97.5:2.5 ratio (mode of addition: aldehyde precomplexed with $TiCl_4$) and a 77:23 ratio (mode of addition: $TiCl_4$ added last) were determined by 200 MHz $^1H$ NMR spectroscopy. Relevant $^1H$ NMR data of the minor diastereoisomer: $\delta$ 0.865 (d,3H,J=6.7 Hz). The minor diastereoisomer was eliminated by flash chromatography.
$^1H$ NMR [$CDCl_3$ + $Eu(hfc)_3$][19]: $\delta$ 9.0 (0.16 H,dd, J=15.0, 2.5 Hz), 9.4 (0.84 H, dd, J=15.0, 2.5 Hz). Enantiomeric excess : 68%. $[\alpha]_D^{25}$= +24.7°(c 0.8, $CHCl_3$).

## NOTES AND REFERENCES


1) C.H.Heathcock, in "Asymmetric Synthesis", ed.J.D.Morrison, Academic Press, New York, 1984, vol.3, part B, p.111.

2) C.Gennari, in "Comprehensive Organic Synthesis", ed.C.H.Heathcock, Pergamon Press, Oxford, 1990, vol.2, in press.

3) C.H.Heathcock and L.A.Flippin, J.Am.Chem.Soc., 1983,105,1667.

4) M.T.Reetz and K.Kesseler, J.Org.Chem., 1985,50,5434.

5) Y.Kita, O.Tamura, F.Itoh, H.Yasuda, H.Kishino, Y.Yuan Ke and Y.Tamura, J.Org.Chem., 1988,53,554.

6) C.H.Heathcock, S.K.Davidsen, K.T.Hug and L.A.Flippin, J.Org.Chem., 1986,51,3027.

7) J.-i.Uenishi, H.Tomozane and M.Yamato, Tetrahedron Lett., 1985,26,3467.

8) a) M.T.Reetz, Angew.Chem.,Int.Ed.Engl., 1984,23,556. b) M.T.Reetz, K.Kesseler and A.Jung, Tetrahedron, 1984,40,4327.

9) a) C.Gennari, A.Bernardi, S.Cardani and C.Scolastico, Tetrahedron Lett., 1985,26,797. b) C.Gennari, A.Bernardi, G.Poli and C.Scolastico, Tetrahedron Lett., 1985,26,2373. c) C.Gennari, M.G.Beretta, A.Bernardi, G.Moro, C.Scolastico and R.Todeschini, Tetrahedron, 1986,42,893. d) C.Gennari, A.Bernardi, C.Scolastico and D.Potenza, Tetrahedron Lett., 1985,26,4129.

10) C.Gennari and P.G.Cozzi, J.Org.Chem., 1988,53,0000.

11) The $BF_3$-$OEt_2$ mediated addition of the tert-butyldimethylenolsilane derived from tert-butyl acetate to a chiral α-methyl-β-silyloxy aldehyde was reported to proceed with 100% non-chelation control, see: A.G.M.Barrett and T.M.Raynham, Tetrahedon Lett., 1987,28,5615.

12) S.Masamune, S.Kamata and W.Schilling, J.Am.Chem.Soc., 1975,97,3515. S.Masamune, Y.Hayase, W.Schilling, W.Kit Chan and G.S.Bates, J.Am.Chem.Soc., 1977,99,6756.

13) N-Ethyl-N'-[3-(dimethylamino)propyl]carbodiimide, see: a) M.J.Miller, J.S.Bajwa, P.G.Mattingly and K.Peterson, J.Org.Chem., 1982,47,4928. b) M.J.Miller, Acc.Chem.Res., 1986,19,49.

14) D.M.Floyd, A.W.Fritz, J.Pluscec, E.R.Weaver and C.M.Cimarusti, J.Org.Chem., 1982,47,5160.

15) Tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato)europium.

16) a) L.M.Fuentes, I.Shinkai, A.King, R.Purick, R.A.Reamer, S.M.Schmitt, L.Cama and B.G.Christensen, J.Org.Chem., 1987,52,2563. b) D.H.Shih, J.A.Fayter,

L.Cama, B.G.Christensen and J.Hirshfield, Tetrahedron Lett., 1985,26,583. c) D.H.Shih, L.Cama and B.G.Christensen, Tetrahedron Lett., 1985,26,587. d) T.Kawabata, Y.Kimura, Y.Ito, S.Terashima, A.Sasakki and M.Sunagawa, Tetrahedron Lett., 1986,27,6241.

17) D.H.Shih, F.Baker, L.Cama and B.G.Christensen, Heterocycles, 1984,21,29.

18) A.I.Meyers, K.A.Babiak, A.L.Campbell, D.L.Comins, M.P.Fleming, R.Henning, M.Heuschmann, J.P.Hudspeth, J.M.Kane, P.J.Reider, D.M.Roland, K.Shimizu, K.Tomioka and R.D.Walkup, J.Am.Chem.Soc., 1983,105,5015.

19) Tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato],europium(III) derivative.

20) P.N.Rylander and D.S.Tarbell, J.Am.Chem.Soc., 1950,72,3021.