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Synthesis of 3α-Alkoxy-4β–Substituted-2-Azetidinones from L(+)-Tartaric Acid.

Derek H. R. Barton[a], Jeanine Cléophax[b], Alice Gateau-Olesker[b], Stephan D. Géro*[b] and Catherine Tachdjian[a].

a) Department of Chemistry, Texas A&M University, College Station, Texas 77843, U.S.A.
b) Institut de Chimie des Substances Naturelles, C.N.R.S., 91198 Gif-sur-Yvette, France .

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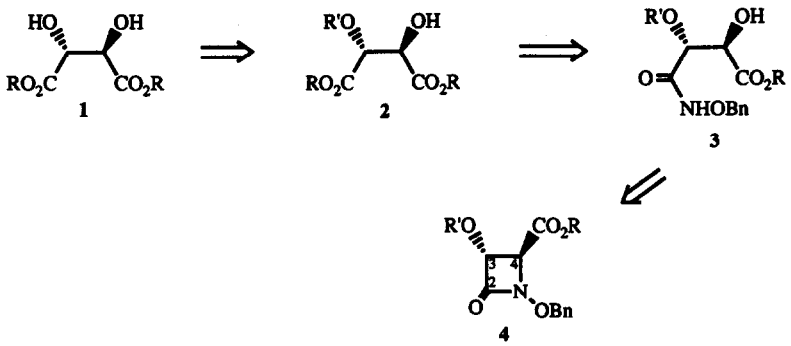
Abstract: *The synthesis of 3α-alkoxy-4β-azetidinones from L(+) tartaric acid is described. Regioselective saponification and methylation along with a stereo selective radical decarboxylative alkylation are key steps leading to optically pure trans-β-lactams.*

In the last two decades important progress has been made in the field of β-lactams to improve their activities as they constitute the most important therapeutic agents against bacterial infection.[1] The structural features believed to be essential for antibacterial activity and increased stability towards β-lactamases have undergone considerable revision owing to the discovery of cephamycin,[2] carbapenems,[3] clavulanic acids,[4] nocardicin,[5] monobactams[6] and so on. Since 1982 our laboratory's interest in this area was focused on the synthesis of monocyclic β-lactams with non classical substitution at C-3 and C-4 that could further easily be transformed to a wide variety of bicyclic β-lactams. Penicillin, cephalosporin and monobactams having a methoxy group at C-6α, C-7α and C-3α respectively were shown to have a better stability toward β-lactamases.[7] Also a new concept appeared dealing with the use of β-lactams in the treatment of degenerative diseases with the discovery that modified substituted cephalosporins and 2-azetidinones have been shown to inhibit human leukocyte elastase (HLE).[8] Interestingly from these studies 7-α methoxy cephalosporins have been reported to be very potent inhibitors of HLE.[9]

Some time ago we have communicated the synthesis from L(+)-tartaric acid of 3α-alkoxy-4β-alkoxycarbonyl-2-azetidinones.[10] Herein we describe in full this work along with the synthesis of monobactam **24** using a similar approach.

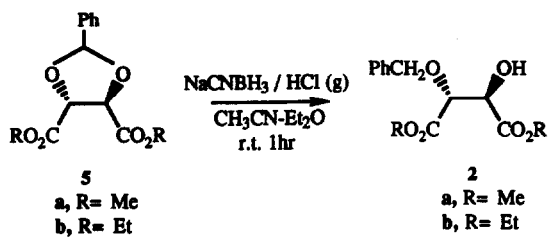
Miller and coworkers[11] have previously reported simple approaches to the synthesis of monocyclic β-lactams based on the direct cyclisation of a β-hydroxamate under Mitsunobu conditions[12] or by transforming the hydroxyl group into a leaving group, the cyclisation taking place in presence of a weak base.[13]

The naturally abundant and cheap tartaric acid is a valuable starting material for natural products syntheses.[14] We conceived that the preparation of 3α-alkoxy-2-azetidinones **4** can easily be effected starting from the diester **1** by N-C_4 ring closure of the corresponding β-hydroxamate **3**. The monoalkoxy derivative **2** of L(+)-tartaric diester **1** could be prepared taking advantage of the symmetry of this system that has equivalent hydroxyl groups. The key step of this synthesis would be the conversion of **2** into the hydroxamate **3** that will require the differentiation of the two carboxylic esters (Scheme 1).



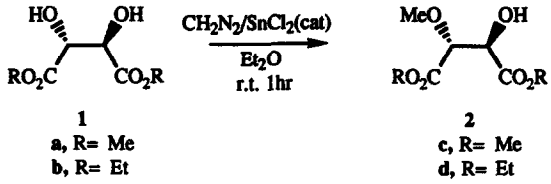
Scheme 1

We initially choose to prepare the monobenzyl derivatives **2a,b** from the dimethyl and diethyltartrates **1a,b** using selective benzylation with benzyltrichloro-acetamidate.[15] However treatment of **1** in hexane-dichloromethane (1:1) solution using a catalytic amount of triflic acid gave a mixture of products from which the required monobenzyl ethers **2a,b** were isolated in only poor yield (30%). Likewise, treatment of **1** with benzyl bromide and sodium hexamethyl disilazane in tetrahydrofuran was inefficient. Finally the preparation of the benzyloxy derivatives **2a,b** was easily achieved by reductive opening[16] of the *O*-benzylidene tartrate **5**. Thus treating **5a,b** with sodium cyanoborohydride in acetonitrile in presence of hydrogen chloride in diethyl ether at room temperature for one hour afforded the crystalline monobenzyl ethers **2a,b** (Scheme 2).



Scheme 2

We also turned our attention to the selective monomethylation of dimethyl or diethyl tartrates **1a,b**. This transformation was based on the regioselective enhancement of the nucleophilicity of the hydroxyl groups in the starting materials by complexation with tin (II) chloride prior to methylation with diazomethane.[17] Accordingly, reaction of **1a,b** in acetonitrile with an ethereal solution of diazomethane provided the syrupy monomethyl ethers **2c,d** in 80% yield .

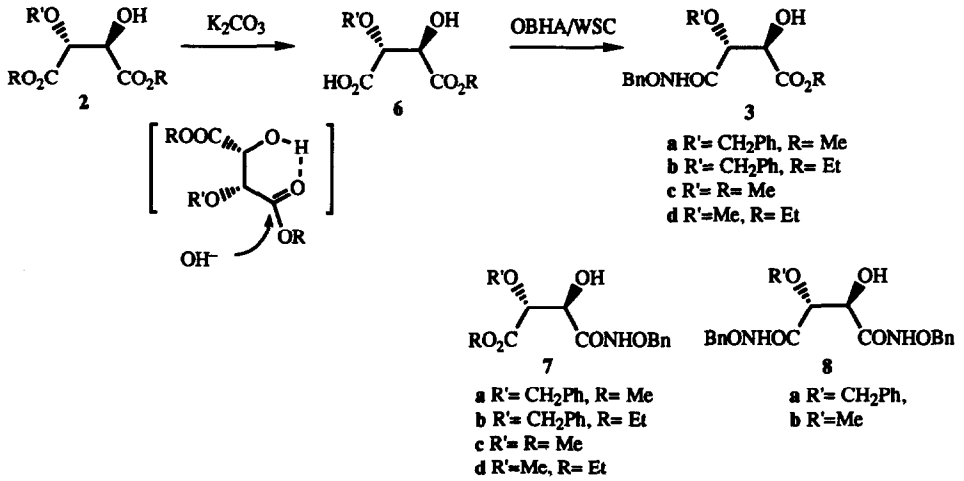


1
a, R= Me
b, R= Et

2
c, R= Me
d, R= Et

Scheme 3

The next step of the synthesis consists in the preparation of the hydroxamate **3** by regioselective mono saponification of the diester **2** followed by treatment of the carboxylic acid intermediate **6** with benzylhydroxylamine. We first examined the possibility of obtaining the desired monoester **6** by using potassium carbonate in dioxane-water (1:1) solution. We obtained better result than we had expected as the desired half ester **6** was present in the reaction mixture in 65-75% among with some undesired monoester and dicarboxylic acid as determined by ^{1}H NMR. The chemoselective hydrolysis of the diester **2** leading to the monoester **6** may be explained by an anchimeric assistance through hydrogen bonding of the β-hydroxyl group with the carbonyl of the ester group as depicted in Scheme 4. The crude **6** was further treated with *O*-benzyl hydroxylamine hydrochloride (OBHA) in presence of 1-ethyl-3-(dimethylamino)propylcarbodiimide hydrochloride [the *so called* water soluble carbodiimide (WSC)] at room temperature for one hour in a water-tetrahydrofuran solution at pH 4.5. Chromatography of the crude product on silica gel permitted only the separation of the monohydroxamates **3** and **7** (55-65%) from the dihydroxamate **8** (6-10%). Unfortunately we were not able to obtain the pure desired hydroxamate **3** even after repeated chromatography on silica gel. Its structure was unequivocally assigned only at a later stage.



2

6

3
a R'= CH2Ph, R= Me
b R'= CH2Ph, R= Et
c R'= R= Me
d R'=Me, R= Et

7
a R'= CH2Ph, R= Me
b R'= CH2Ph, R= Et
c R'= R= Me
d R'=Me, R= Et

8
a R'= CH2Ph,
b R'=Me

Scheme 4

Although the saponification using potassium carbonate gave satisfactory yields we were interested to improve this transformation by using a chemoenzymatic approach. We were curious to know, whether a cofactor independent hydrolase such as pig liver esterase[18] (PLE) could be exploited for the preparation of the β-hydroxy half ester **6**. In the event when the dimethyl-*O*-benzyl tartrate **2a** was incubated with pig liver

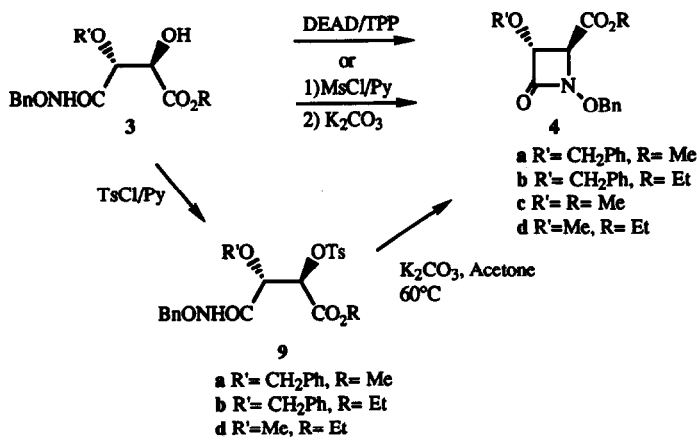
esterase (Sigma) in a 0.1 M phosphate buffer (pH 8.0) the corresponding half ester **6a** was obtained exclusively and was transformed to the β-hydroxamate **3a** required for β-lactam formation in 66% overall yield. As shown in Table 1 the method employing the pig liver esterase is slightly superior to the one using K_2CO_3.

Table 1: Yields and ratio[a] of monohydroxamates 3,7 and dihydroxamate 8 from the diester 2.

Diester 2	Method[b]	Monohydroxamates 3+7 (yield%)	3/7 (ratio)	Dihydroxamate 8 (yield%)
2a	A	3a+7a (65%)	3a/7a 6/1	8a (6%)
2a	B	3a (66%)	-	-
2b	A	3b+7b (60%)	3b/7b 7/3	8a (12%)
2c	A	3c+7c (62%)	3c/7c 6.5/3.5	8b (10%)
2d	A	3d+7d (55%)	3d/7d 7/1	8b (4%)

[a] Calculated by ^{1}H NMR.
[b] Method A: 1) K_2CO_3, 2) OBHA/WSC; Method B: 1) PLE, 2) OBHA/WSC

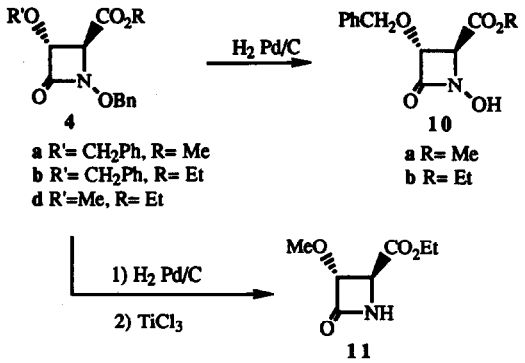
The cyclization of **3** to the corresponding β-lactam **4** was finally performed either on the mixture of **3** and **7** previously obtained from the monosaponofication using K_2CO_3 or from the pure **3a** obtained from the pig liver esterase catalyzed hydrolytic reaction (Scheme 5).



Scheme 5

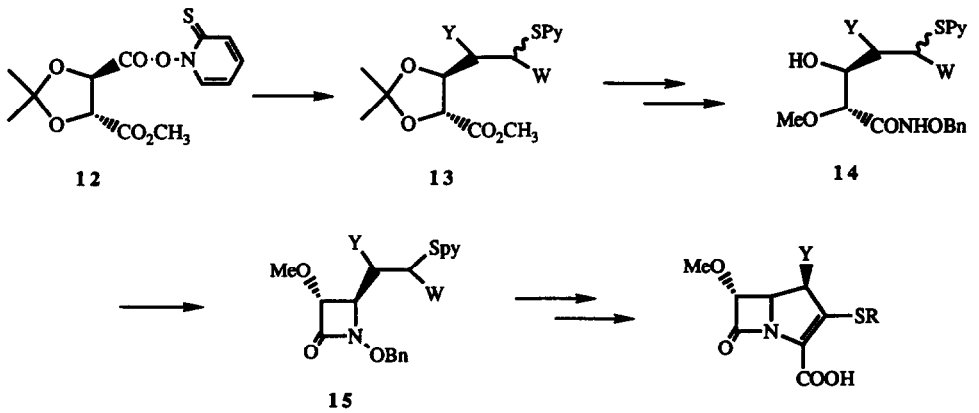
We first effected this transformation under the usual Mitsunobu conditions (DEAD/TPP) or by mesylation followed by treatment with potassium carbonate in acetone as described by Miller.[11] Under these conditions we were able to obtain the desired azetidinones **4** but in low yields (20-35%). Tosylation in pyridine of the monohydroxamate **3** furnished the desired sulfonate ester **9** in excellent yield. At this stage we were able to

separate by column chromatography the tosylate **9** from the undesired ester derived from the tosylation of **7**. Finally selective catalytic hydrogenation of **4a,b** afforded the *N*-hydroxy-β-lactam **10a,b** in 80% yield. The target 2-azetidinone **11** was obtained by further $TiCl_3$ mediated reduction of the *N-O* bond[19] when starting from **4d** (Scheme 6).



Scheme 6

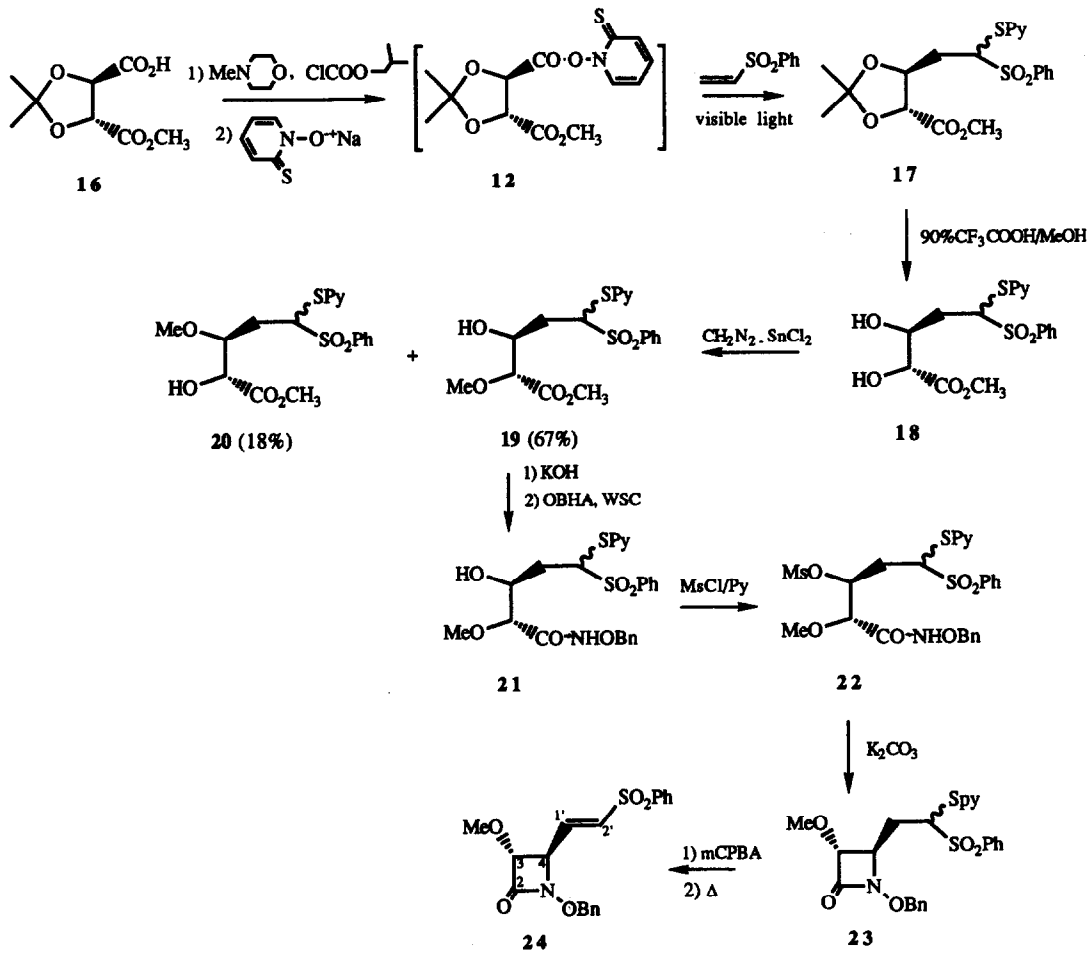
As a continuation to this work we next investigated the possibility of obtaining the monocyclic β-lactam **15** with a highly functionalized side chain at C-4 that could allow further elaboration especially into the carbapenem system.[20] This approach was based on the radical decarboxylative alkylation of tartaric acid developed in our laboratory.[21] This involves the visible light photolysis of the *N*-hydroxy-2-thiopyridone derivative **12** in presence of an electron deficient olefin to give the addition product **13** with retention of configuration. The elaboration of the β-lactam **15** could be effected by employing the method previously described via the β-hydroxamate **14** (Scheme 7).



Scheme 7

We chose to prepare the sulfone derivative **17** obtained in 70% yield from the *in situ* photolysis of the *N*-hydroxy-2-thiopyridone derivative **12** in presence of phenyl vinyl sulfone (Scheme 8). The Barton ester **12** was prepared by the usual mixed anhydride method[22] at low temperature (-20°C) in THF by treating the half ester **16** with *N*-methylmorpholine and isobutyl chloroformate followed by addition after 15 min of the sodium

salt of the *N*-hydroxy-2-thiopyridone. After 1hr 30 min at -20 °C, phenyl vinyl sulfone was added to the solution and the mixture was photolyzed (tungsten light) for about 30 min. The addition product was obtained as a mixture of two stereoisomers at C-5 that were not separated. Removal of the isopropylidene group was effected in the presence of 90% trifluoroacetic acid in methanol at room temperature and gave the diol **18** in 71% yield. Preparation of the desired monomethyl derivative **19** was achieved using diazomethane in the presence of tin (II) chloride as already described for the preparation of the **2c,d**. Although in this case the diol **18** is not symmetrical we were able to obtain the required monomethyl derivative **19** in 67% yield along with the undesired monomethyl derivative **20** in only 18% yield which were easily separated by column chromatography.



Scheme 8

The monomethyl derivative **19** was converted to the hydroxamate **21** by saponification of the methylester group with potassium hydroxide in a mixture of dioxane-water (1:1) followed by treatment of the crude material with OBHA and WSC in a usual manner. Under theses conditions the β-hydroxamate **21** was obtained in 88% yield. Mesylation of the hydroxyl group in **21** using mesyl chloride in pyridine afforded the desired mesyl derivative **22** in 69% yield. The different attemps in obtaining the tosyl derivative were unsuccessful in this case probably due to steric hindrance. The cyclization of **22** was carried out following the general procedure of treatment with potassium carbonate in refluxing acetone which lead to the *trans*-lactam **23** (72%). Finally oxidation of the thiopyridyl group with metachloroperbenzoic acid (mCPBA) followed by thermolysis in refluxing toluene gave the *trans*-β-lactam **24** enantiomerically pure in 75% yield (Scheme 8). This result was also a supplementary proof of the retention of configuration during the radical decarboxylative alkylation of tartaric acid.[23]

To conclude we have realized the synthesis of optically pure *trans*-3α-alkoxy-2-azetidinones from L(+)-tartaric acid. Interestingly the optically active β-lactams **22** and **23** described herein present the particularity to have a side chain at C-4 that can be further manipulated to generate other functional groups of interest for the preparation of the carbapenem skeleton. Also we can easily imagine the use of more sophisticated olefins during the radical decarboxylative alkylation of tartaric acid which could allow the preparation of wide variety of monocyclic β-lactams.

Experimental

Melting points were taken on a Reicher apparatus and are not corrected. IR spectra were recorded on a Perkin Elmer 297 spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on Bruker WP200 SY (200 MHz) or on a HS80 (80 MHz) in $CDCl_3$. Chemical Shifts are in p.p.m. downfield from tetramethylsilane used as an internal standard (δ values). Mass spectra were run on AEI MS-9 and AEI MS-50 spectrometers. Microanalyses were performed at the Service for Microanalysis of the CNRS at Gif-sur-Yvette. Solvents were dried and purified by standard methods. All the reactions were effected under an inert atmosphere of argon. Column chromatography was carried out on silica gel 60 (0.040-0.060 mm). Preparative thin-layer chromatographic plates were laboratory-made using silica gel 60 PF_{254} (Merck).

Monoethers 2a-d

Dimethyl 2-*O*-benzyl-L-tartrate 2a:

To a solution of dimethyl-2,3-*O*-benzylidene-L(+)-tartrate **5a** (3g, 11 mmol) and sodium cyanoborohydride ($NaBH_3CN$, 3 g) in dry acetonitrile (35 ml) was added dropwise a saturated solution of HCl in ether until the pH of the solution reached pH 2. After stirring for 2 hrs at room temperature the mixture was poured over a saturated aqueous solution of $NaHCO_3$ and extracted with dichloromethane. The organic layer was washed with water dried over $MgSO_4$ and evaporated under reduced pressure. The residue was chromatographed on a

short column of silica gel. The monobenzyl derivative **2a** (2.55 g, 85%) was obtained pure by recrystallization from cyclohexane. ^{1}**H** (60 MHz) 3.2 (1H, OH); 3.7 (3H, s); 3.85 (3H, s); 4.3 (1H, d); 4.6 (1H, m); 4.58 (2H, q); 7.1 (5H, m); **m.p.** 69°C (cyclohexane); $[\alpha]_D^{25}$ = +87° (c=0.98, $CHCl_3$); **Anal.** Calcd. for $C_{13}H_{16}O_6$: C, 58.20; H, 6.01 Found C, 58.27; H, 6.03.

Diethyl 2-*O*-benzyl-L-tartrate 2b:

This compound was prepared in a manner analogous to that of **2a** starting from diethyl-2,3-*O*-benzylidene-L(+)-tartrate **5b** (3g, 9.9 mmol) and $NaBH_3CN$ (3 g). Rapid filtration of the residue on silica gel gave **2b** (2.24 g, 77%). ^{1}**H** (60 MHz) 1.2 (3H, s); 1.4 (3H, s); 3.1 (1H, OH); 3.7 (3H, s); 3.9 to 4.4 (6H, m); 4.5 (1H, q); 7.1 (5H, m);^{13}C 14 (CH_3); 14.2 (CH_3); 61.4 (CH_2); 61.9 (CH_2); 72.4 (CH); 73.0 (CH); 78.5 (CH_2); 128.0 (CH); 128.2 (CH); 128.3 (CH); 136.9 (Cq); 169.3 (C=0); 171.1(C=0); $[\alpha]_D^{25}$ = +73° (c=1.35, $CHCl_3$); **Anal.** Calcd. for $C_{15}H_{20}O_6$; C, 60.80; H, 6.80 Found C, 60.70; H, 6.80.

Dimethyl 2-*O*-methyl-L-tartrate 2c:

To a solution of dimethyl-L(+)-tartrate **1a** (450 mg, 2.5 mmol) and anhydrous $SnCl_2$ (50 mg) in dry acetonitrile (10 ml) was added an ethereal solution of diazomethane at 0°C until the color of the mixture remained yellow. The solvents were removed under reduced pressure and the residue was chromatographed on a short column of silica gel (ethyl acetate/hexane, 1/2). Further Kugelrohr distillation furnished the pure **2c** (292 mg, 60%). **b.p.** 35°C/ 0.4 mmHg; $[\alpha]_D^{25}$ = +32° (c=1.14, $CHCl_3$); **Anal.** Calcd. for $C_7H_{12}O_6$: C, 43.75; H, 6.29 Found C, 43.63; H, 6.38.

Diethyl-2-*O*-methyl-L-tartrate 2d:

This compound was prepared in a manner analogous to that of **2c** starting from diethyl-L-tartrate **1b** (1.5 g, 7.3 mmol).Chromatography of the residue on silica gel (ethyl acetate/hexane, 1/3) and Kugelrohr distillation gave **2d** (1.2 g, 75%). **b.p.** 115°C/ 0.5 mmHg; $[\alpha]_D^{25}$ = +37° (c=1.09, $CHCl_3$); **Anal.** Calcd. for $C_9H_{16}O_6$: C, 49.09; H, 7.32 Found C, 48.82; H, 7.27.

Monohydroxamates 3a-d:

General Procedure: To a solution of the monoether **2** (1 mmol) in dioxane-water (5 ml, 1/1) is added K_2CO_3 (2.5 mmol) and the mixture was stirred at room temperature for 5 hrs. The solution was then treated with Amberlite IRN 77 (H^+), filtered and evaporated under reduced pressure. To the residue dissolved in water (10 ml) was added a solution of OBHA (3 mmol) and WSC (3 mmol) in water (5 ml), the pH of the solution being kept at pH 4.5 by adding HCl (1N) dropwise. After 30 min the dihydroxamate **8** was isolated by simple filtration. The aqueous layer was then extracted with dichloromethane. The organic layer was dried over $MgSO_4$, filtered and evaporated. The crude material was chromatographed on silica gel (ethylacetate/hexanes, 8/2) to give the mixture of the monohydroxamates **3** and **7**.

From 2a: Dihydroxamate 8a (6%): ^{1}**H** (60 MHz) 4.3-4.6 (5H, m); 4.7 (2H, s); 4.78 (2H, s); 7.1 (15H, m); 8.85 (1H, m); 9.2 (1H, m); **Anal.** Calcd. for $C_{25}H_{26}O_6N_2$: C, 66.65; H, 5.81; N, 6.21 Found C,

66.20; H, 5.61; N, 6.11. **Monohydroxamates 3a+7a** (65 %, **3a/7a**, 6/4): ^{1}**H** (60 MHz) 3.58 (3H, s); 3.7 to 4.6 (5H, m); 4.85 (1H, s); 7.1 (10H, m); 8.98 and 9.78 (1H, 2 br, 6/4).**IR** (cm^{-1}) 1730 and1670; **Anal.** Calcd. for $C_{19}H_{21}O_6N$: C, 63.49; H, 5.89; N, 3.89 Found C, 63.23; H, 6.05; N, 3.91.

From 2b: Dihydroxamate 8a (12%). **Monohydroxamates 3b+7b** (60 %, **3b/7b**, 7/3): ^{1}**H** (60 MHz) 1.2 (3H, 2t); 3.75-3.85 (9H, m); 7.18 (10H, m); 9.13 and 9.33 (1H, 2 s, 7/3).

From 2c: Dihydroxamate 8b (10%): ^{1}**H** (60 MHz) 3.22 (3H, s); 4.22 (1H, br); 4.55 (1H, br); 4.84 (2H, s); 4.9 (2H, s); 7.3 (10H, s); 9.14 (1H, s); 9.38 (1H, m); **Anal.** Calcd. for $C_{18}H_{22}O_6N_2$; C, 59.65; H, 6.11; N, 7.73 Found C, 59.91; H, 6.33; N, 7.96. **Monohydroxamates 3c+7c** (62 %, **3c/7c**, 6.5/3.5):.^{1}**H** (60 MHz) 3.3 and 3.4 (3H, 2s, 6.5/3.5); 3.6 and 3.8 (3H, 2s); 4.15 (1H, br); 4.3-4.5 (2H, m); 4.8 (2H, s, br); 4.9 (2H, s); 7.2 (5H, s); 9.31 (1H, m).

From 2d: Dihydroxamate 8b (4%). **Monohydroxamates 3d+7d** (55 %, **3d/7d**, 7/1). ^{1}**H** (60 MHz) 1.25 (3H, t); 2.8 (1H, s); 3.22 and 3.35 (3H, 2s); 4.0-4.85 (6H, m); 7.18 (5H, s); 8.75 and 9.25 (1H, 2s, 7/1); **Anal.** Calcd. for $C_{14}H_{19}O_6N$; C, 56.55; H, 6.44; N, 4.71 Found C, 56.45; H, 6.32; N, 4.51.

Tosylates 9a,b,d

Tosyl derivative 9a:

Method A: (From the monohydroxamates 3 previously obtained by monosaponification of 2 with K_2CO_3). To the mixture of the monohydoxamates **3a** and **7a** (**3a/7a** 6/4, 440 mg, 1.22 mmol) in dichloromethane (2 ml) and pyridine (3 ml) was added tosyl chloride (580 mg) at - 10°C. After 2 days at - 10°C, the mixture was poured over a cold aqueous solution containing 3.1 ml of HCl (12N) and extracted with dichloromethane. The organic layer was dried over $MgSO_4$, filtered and evaporated under reduced pressure. Chromatography of the residue on silica gel (ethyl acetate/hexane, 2/8) gave the starting monohydroxamates **3a+7a** (90 mg) and the tosylate **9a** (420 mg, 85% determined with respect of **3a**). ^{1}**H** (60 MHz) 2.3 (3H, s); 3.55 (3H, s); 4.3 (2H, s); 4.4 (1H, d, J = 2 Hz); 4.6 (2H, s); 5.25 (1H, d, J = 2 Hz); 7.0-7.25 (12H, m); 7.6 (2H, d); 8.77 (1H, br).

Method B (From the monohydroxamate 3 via monosaponification of 2 with PLE) : To a solution of the diester **2a** (3g, 10 mmoles) in phosphate buffer (19 ml, 0.1 M, pH 8) was added Pig Liver Esterase (200 u/mM). The pH of the solution was kept at pH 8 by addition of an aqueous solution of NaOH (1N) using a pH-stat. When the required quantity of NaOH was added, the solution was extracted with ether thus allowing the separation of the unreacted starting material (136 mg). The aqueous layer was then acidified with Amberlite IRN 77 (H^+), filtered and further extracted with ethyl acetate. The organic layer was dried over $MgSO_4$, filtered and evaporated under reduced pressure to give the desired monoester in 73% yield. 240 mg of this derivative was further reacted in 5 ml of aqueous tetrahydrofuran with OBHA (150 mg) and WSC (300 mg). After 30 minutes the mixture was extracted with dichloromethane. ^{1}H NMR of the residue obtained after evaporation of the solvent showed the presence of the monohydroxamate **3a** in 90% yield. Tosylation of the

crude material with tosyl chloride (400 mg, 3 eq) in pyridine-dichloromethane (5 ml, 1/1) at - 10°C gave, after chromatography of the residue on silica gel, the tosylate **9a** in 80% yield identical to the product obtained by the Method A.

Tosyl derivative 9b:

9b was prepared following the Method A: To the mixture of the monohydoxamate **3b** and **7b** (**3b/7b** 7/3, 560 mg, 1.5 mmol) in dichloromethane (2 ml) and pyridine (3 ml) was added tosyl chloride (710 mg) at - 10°C. After 3 days at - 10°C, the mixture was poured over a cold aqueous solution containing 3.1 ml of HCl (12N) and extracted with dichloromethane. The organic layer was dried over $MgSO_4$, filtered and evaporated under reduced pressure. Chromatography of the residue on silica gel (ethyl acetate/hexane, 1/1) gave the starting monohydroxamates **3b+7b** (100 mg, 17.8%), the tosylate **9b** (390 mg, 85% determined with respect of **3b**). **m.p.** 83-84°C (dichloromethane/hexane); $[\alpha]_D^{25}$ = +20° (c= 0.87, $CHCl_3$); **^{1}H** (60 MHz) 1.15 (3H, t); 2.3 (3H, s); 4.0 (2H, dq); 4.35 (2H, s); 4.4 (1H, d, J = 2.5 Hz); 4.58 (2H, s); 5.25 (1H, d, J = 2.5 Hz); 7.05-7.25 (12H, m); 7.6 (2H, d); 8.77 (1H, br); **Anal.** Calcd. for $C_{27}H_{29}O_8NS$; C, 61.46; H, 5.54; N, 2.65; H, 6.10 Found C, 61.24; H, 5.38; N, 2.62; H, 5.80.

Tosyl derivative 9d:

9d was prepared following the Method A: To the mixture of the monohydoxamate **3d** and **7d** (**3d/7d** 7/1, 475 mg, 1.6 mmol) in dichloromethane (2 ml) and pyridine (5 ml) was added tosyl chloride (457 mg) at - 10°C. After one day at - 10°C, the mixture was poured over a cold aqueous solution containing 5.2 ml of HCl (12N) and extracted with dichloromethane. The organic layer was dried over $MgSO_4$, filtered and evaporated under reduced pressure. Chromatography of the residue on silica gel (ethyl acetate/hexane, 1/1) gave the starting monohydroxamates **3d+7d** (110 mg, 23%), the tosylate **9d** (430 mg, 80% determined with respect of **3d**). **m.p.** 101-102°C (dichloromethane/hexane); $[\alpha]_D^{25}$ = +12° (c= 1.03, $CHCl_3$); **^{1}H** (60 MHz) 1.25 (3H, t); 2.34 (3H, s); 3.3 (3H, s); 4.2 (2H, q); 4.30 (1H, d, J = 3 Hz); 4.68 (2H, d); 5.35 (1H, d, J = 3 Hz); 7.1-7.3 (7H, m); 7.7 (2H, d); 8.8 (1H, br); **Anal.** Calcd. for $C_{21}H_{25}O_8NS$; C, 55.86; H, 5.58; N, 3.10; S, 7.10 Found C, 55.62; H, 5.49; N, 3.13; S, 6.80.

2-Azetidinones 4a-d

2-azetidinone 4a:

Method A (MsCl/K_2CO_3, acetone): typical procedure: To a solution of the mixture of the hydroxamate **3a** and **7a** *(previously obtained by monosaponification of 2a with K_2CO_3)* (150 mg, 0.4 mmol) in pyridine-dichloromethane (5 ml, 1/1) at - 10°C was added mesyl chloride (0.6 ml). After 2 hrs at 0°C the mixture was extracted with dichloromethane. The crude was then dissolved in acetone and added to a suspension of K_2CO_3 (83 mg) in acetone at 60°C. The reaction mixture was stirred for 1 hr and filtered. Evaporation of the solvent followed by chromatography of the residue on silica gel (ethyl acetate/hexane, 1/1) gave the azetidinone **4a** (20 mg, 20%). $[\alpha]_D^{25}$ = +51° (c= 0.69, $CHCl_3$); **IR** (cm-1) 1740 and 1790; **^{1}H** (400 MHz) 3.75 (3H, s); 4.04 (1H, d, J = 1.5 Hz); 4.54 (1H, d, J = 1.5Hz); 4.67 (2H, q); 5.07 (2H, q); 7.38 (10H, m); **Anal.** Calcd. for $C_{19}H_{19}O_5N$; C, 66.84; H, 5.61; N, 4.10 Found C, 66.82; H, 5.72; N, 3.96.

Method B (DEAD/TPP): typical procedure: To a solution of the mixture of the hydroxamate **3a** and **7a** *(previously obtained by monosaponification of 2a with K_2CO_3)* (300 mg, 0.8 mmol) in dry THF (5 ml) was added triphenylphosphine (435 mg) and diethylazodicarboxylate (0.26 ml). After 2 hrs the solution was evaporated under reduced pressure and the residue was chromatographed on silica gel (ethyl acetate/hexane, 1/1) and gave the starting hydroxamate (50 mg) and the azetidinone **4a** (96 mg, 50% with respect to the reacted starting **3a**).

Method C ($TsCl/K_2CO_3$, acetone): typical procedure: A solution of the tosylate **9a** (57 mg, 0.1 mmol) in acetone (3 ml) was added to a suspension of K_2CO_3 in refluxing acetone. After 1 hr the reaction mixture was filtered and the solvent evaporated under reduced pressure. The β-lactam **4a** was, under these conditions, obtained in quantitative yield.

2-azetidinone 4b:
The azetidinone **4b** was obtained in 80% from the tosylate **9b** by method C. $[\alpha]_D^{25}$ = + 40° (c= 0.63, $CHCl_3$); ^1H (80 MHz) 1.6 (3H, t); 4.01 (1H, d, J = 1.5 Hz); 4.23 (2H, q); 4.55 (1H, d, J = 1.5 Hz); 4.68 (2H, s); 5.1 (2H, s); 7.4-7.6 (10H, m); **Anal.** Calcd. for $C_{20}H_{21}O_5N$; C, 67.59; H, 5.96; N, 3.94 Found C, 67.33; H, 5.93; N, 3.88.

2-azetidinone 4c:
The azetidinone **4c** was obtained in 22% yield from the hydroxamate **3c** by method A. $[\alpha]_D^{25}$ = + 37° (c= 0.54, $CHCl_3$); ^1H (200 MHz) 3.43 (3H, s); 3.76 (3H, s); 4.04 (1H, d, J = 1.5 Hz); 4.40 (1H, d, J = 1.5 Hz); 5.08 (2H, q); 7.34 (5H, s); **Anal.** Calcd. for $C_{13}H_{15}O_5N$; C, 58.85; H, 5.70; N, 5.28 Found C, 58.83; H, 5.74; N, 3.53.

2-azetidinone 4d:
The azetidinone **4d** was obtained in a quantitative yield from the tosylate **9d** by method C. $[\alpha]_D^{25}$ = + 37° (c= 1.6, $CHCl_3$); ^1H (60 MHz) 1.3 (3H, t); 3.40 (3H, s); 4.0 (1H, d, J = 1.5 Hz); 4.20 (2H, q); 4.3 (1H, d, J = 1.5 Hz); 4.98 (2H, s); 7.25 (5H, s); **Anal.** Calcd. for $C_{14}H_{17}O_5N$; C, 60.20; H, 6.13; N, 5.01 Found C, 60.05; H, 6.21; N, 5.05.

N-Hydroxy-2-Azetidinones 10a,b
General Procedure: The azetidinone **4** (0.5 mmoles) was dissolved in ethyl acetate (10 ml) and hydrogenated at (3 bars) in presence of 5% Pd/C (170 mg) for 1 hr. Filtration and evaporation of the solvent followed by chromatography of the residue on silica gel afforded the desired product **10**.

From 4a: The *N*-Hydroxy-2-azetidinone **10a** was obtained in 80% yield. ^1H (60 MHz) 3.7 (3H, s); 4.28 (1H, d, J = 1.5 Hz); 4.55 (1H, d, J = 1.5 Hz); 4.62 (2H, s); 7.2 (5H, s).

From 4b: The *N*-Hydroxy-2-azetidinone **10b** was obtained in 77% yield. ^{1}**H** (60 MHz) 1.9 (3H, t); 4.22 (2H, q); 4.29 (1H, d, J = 1.2 Hz); 4.52 (1H, d, J = 1.2 Hz); 4.70 (2H, q); 7.59 (5H, s).

2-Azetidinone 11:

A solution of the azetidinone **4d** (270 mg, 1 mmole) in ethyl acetate (25 ml) was quantitatively hydrogenated (3 bars) in presence of 5% Pd/C (270 mg) for 1hr. After filtration and evaporation, the residue was dissolved in methanol (5 ml) and added, under argon, to an aqueous solution containing $NaHCO_3$ (2.35 gr, 17 eq) and 4 ml of a 20% aqueous solution of $TiCl_3$ (771 mg, 5 mmoles). The solution was then adjusted to pH 6.5 by addition a 10% aqueous solution of Na_2CO_3. After stirring for 1hr, the mixture was extracted with ethyl acetate and chromatographed on silica gel (EtOAc/hexane, 2/8). The azetidinone **11** (50 mg) was obtained in 30% yield

$[\alpha]_D^{25}$ = +15° (c= 1.3, $CHCl_3$); **IR** (cm-1) 1740 and 1795; ^{1}**H** (400 MHz) 1.32 (3H, t); 3.55 (3H, s); 4.15 (1H, d, J = 2 Hz); 4.27 (2H, q); 4.63 (1H, t, J = 1.5Hz); 6.49 (1H, br); **Anal.** Calcd. for $C_7H_{11}O_4N$; C, 48.55; H, 6.40; N, 8.09 Found C, 48.01; H, 6.39; N, 7.88.

Addition product 17:

To a degassed solution of the 2,3-*O*-isopropylidene monomethyl tartrate **16** (1g, 4.9 mmol) in anhydrous THF (40 ml) was added, at -20°C and under argon, *N*-methyl morpholine (0.54 ml, 4.9 mmol) and isobutyl chloroformate (0.64 ml, 4.9 mmol). The mixture was stirred for 15 minutes and the sodium salt of *N*-hydroxy-2-thiopyridone (805 mg, 5.39 mmol) was added. The reaction mixture was stirred at - 20°C, in the dark, for 90 minutes and then phenyl vinyl sulfone (1.3 g) was added and the resulting yellow solution was irradiated with a tungsten lamp (250 W) for 30 minutes at - 20°C. The mixture was extracted with ether and washed successively with $NaHCO_3$ (0.1N), H_2O and brine. The organic layer was dried over $MgSO_4$, filtered and evaporated to dryness under reduced pressure. Flash chromatography of the residue on silica gel (ethyl acetate-hexane 6:4) gave the addition product **17** as a mixture of isomers. This was obtained as an oil; **IR** (film) 1750-1580-1560-1440-1405 cm^{-1}; ^{1}**H** NMR (200 MHz) 1.36 (6H, m), 2.32 to 2.93 (2H, m), 3.7 (3H, s), 3.83 (3H, s), 4.36 (2H, m), 5.96 (1H, m), 7 (2H, m), 7.43 (4H, m), 7.96 (2H, m), 8.26 (1H, m); ^{13}**C** NMR 26 (CH_3), 27.2 (CH_3), 32.5 (CH_2), 52.1 (CH_3), 62.4 63.5 (CH), 75.9 76.5 (CH), 77.9 79 (CH), 111.5 111.6 (Cq), 120.6 (CH), 122.4 (CH), 128.4 (CH), 129.9 (CH), 133.5 (CH), 136.3 (CH), 137.6 (CH), 149.1 (CH), 154.6 (Cq), 170.4 (C=O); **MS** (EI, m/z): 437 $(M)^+$, 422 $(M\text{-}CH_3)^+$; **Anal.** Calcd for $C_{20}H_{23}NO_6S_2$: C, 54.89; H, 5.29; N, 3.20; S, 14.65 Found: C, 54.64; H, 5.14; N, 3.12; S, 14.72.

Diol 18:

The addition product **17** (290 mg, 0.66 mmol) was dissolved in trifluoroacetic acid (2.7 ml) and methanol (0.3 ml). The mixture was stirred at room temperature for 30 min and the solvents were removed under reduced pressure by coevaporation with toluene. The residue was taken up in methanol and treated with Amberlite IRN 45 (OH^-) to remove the residual traces of trifluoroacetic acid. The solution was then filtered and the solvent evaporated. Column chromatography of the residue on silica gel (ethylacetate/hexane, 1/1) afforded the diol **18** (186 mg, 71%). This was obtained as an oil; **IR** (film) 3500-1740-1580-1560-1420 cm^{-1}; ^{1}**H** NMR (200

MHz) 1.96 -2.83 (2H, m), 3.13 (2H, OH, m), 3.8 (3H, 2s), 4.2 (1H, m), 4.46 (1H, m), 5.33-5.78 (1H, m), 7.1 (2H, m), 7.46 (4H, m), 7.96 (2H, m), 8.33 (1H, m); ^{13}C NMR 32.2 32.7 (CH_2), 52.6 (CH_3), 63 66.2 (CH), 69 70.6 (CH), 72.7 73.7 (CH), 120.7 121.5 (CH), 122.9 123.9 (CH), 128.4 128.7 (CH), 129.5 129.7 (CH), 133.8 133.8 (CH), 136.7 137.2 (CH), 136.9 (Cq), 149.2 149.6 (CH), 155.1 155.2 (Cq), 173.0 173.2 (C=O); **MS** (EI, m/z): 398 $(MH)^+$, 366 $(M\text{-}OCH_3)^+$, 338 $(M\text{-}CO_2CH_3)^+$, 256 $(M\text{-}SO_2Ph)^+$; **Anal.** Calcd for $C_{17}H_{19}NO_6S_2$: C, 51.38; H, 4.82; N, 3.52; S, 16.16 Found: C, 51.46; H, 5.04; N, 3.63; S, 15.96.

Methylation of 18:

To a solution of diol **18** (342 mg, 0.86 mmol) in acetonitrile (10 ml) was added a catalytic amount of $SnCl_2$ followed by dropwise addition of an ethereal solution of diazomethane until a yellow coloration persisted. The excess of diazomethane was destroyed by addition of few drops of acetic acid and the solvent was removed under reduced pressure. The residue was chromatographed on silica gel (preparative plates) (EtOAc/Hexane, 6/4). The desired methoxy derivative **19** (270 mg, 67%) was isolated along with **20** (77 mg, 18%) .

Compound 19:

^1H NMR (200 MHz) 1.96 -2.75 (2H, m), 3.5 (3H, s), 3.7 (3H, 2s), 3.86 (1H, m), 4.38 (1H, m), 5.56-5.81 (1H, m), 7.0 (2H, m), 7.41 (4H, m), 7.96 (2H, m), 8.31 (1H, m); ^{13}C NMR 31.1 31.8 (CH_2), 51.8 (CH_3), 58.7 (CH_3), 62.3 65.3 (CH), 68.7 70.3 (CH), 81.5 82.9 (CH), 121.0 121.4 (CH), 122.9 123.6 (CH), 128.8 (CH), 129.9 (CH), 134.1 (CH), 137.4 (CH), 149.6 150 (CH), 154.7 155.5 (Cq), 171.5 (C=O); **MS** (EI, m/z): 412 $(MH)^+$, 380 $(M\text{-}OCH_3)^+$, 352 $(M\text{-}CO_2CH_3)^+$, 270 $(M\text{-}HSO_2Ph)^+$; **Anal.** Calcd for $C_{18}H_{21}NO_6S_2$: C, 52.53; H, 5.14; N, 3.40; S, 15.58 Found: C, 52.60; H, 5.40; N, 3.22; S, 15.74.

Compound 20:

IR (film) 3500-1740-1580-1560-1420 cm^{-1}; ^1H NMR (200 MHz) 2.0 -2.73 (2H, m), 3.26-3.36 (3H, 2s), 3.8 (3H, 2s), 4(1H, m), 4.16-4.35 (1H, m), 5.9 (1H, m), 7.03 (2H, m), 7.41 (4H, m), 7.95 (2H, m), 8.3 (1H, m); ^{13}C NMR 27.0 29.3 (CH_2), 52.2 (CH_3), 57.8 59 (CH_3), 62.1 62.7 (CH), 71.1 72.1 (CH), 78.8 79.3 (CH), 120.6 120.7 (CH), 122.3 122.4 (CH), 128.2 128.3 (CH), 129.3 129.5 (CH), 133.5 (CH), 136.3 136.4 (CH), 136.6 (Cq), 148.9 149 (CH), 153.7 153.8 (Cq), 173 (C=O); **MS** (EI, m/z): 411 $(M)^+$, 352 $(M\text{-}CO_2CH_3)^+$, 270 $(M\text{-}HSO_2Ph)^+$; **Anal.** Calcd for $C_{18}H_{21}NO_6S_2$: C, 52.53; H, 5.14; N, 3.40; S, 15.58 Found: C, 52.66; H, 5.34; N, 3.68; S, 15.29.

Hydroxamate 21:

To a solution of **19** (623 mg, 1.52 mmol) in dioxane (10 ml) was added KOH (102 mg, 1.2 eq) in water (5 ml). After 15 min the solution was acidified with HCl (1N, 1.5 ml). To this solution was added OBHA (485 mg, 2 eq) and WSC (584 mg, 2 eq) and the pH was brought to pH 4 by adding NaOH (1N). The mixture was stirred for 30 min and the solution finally neutralized. After evaporation of the solvents the residue was taken up in dichloromethane and the solution was washed with brine, dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Column chromatography of the residue on silica gel (EtOAc/Hexane, 8/2) gave 675 mg of the hydroxamate **21** (88%) as a white solid. **IR** (film) 3300-1680-1580-1560-1440-1410 cm^{-}

^{1}; ^{1}H NMR (200 MHz) 1.96 (1H, m), 2.76 (1H, m); 3.38 (3H, OCH_3, s), 3.7 (1H, m), 4.36 (1H, m), 4.93 (2H, s), 5.4 (1H, m), 7.03 (2H, m), 7.36 (9H, m), 7.9 (2H, m), 8.26 (1H, m), 9 (1H, NH); **MS** (EI, m/z): 502 $(M)^+$.

Mesyl derivative 22:

To a solution of **21** (512 mg, 1.35 mmol) in anhydrous pyridine (7 ml, 87 mmoles) was added at 0°C mesyl chloride (80 µl, 1 eq). The mixture was stirred for 8 hrs at 0°C and poured over a solution of HCl (12N, 4ml, 48 mmoles) in cold water (75 ml). The aqueous layer was extracted with dichloromethane. The organic layer was dried over $MgSO_4$, filtered and evaporated. Column chromatography of the residue on silica gel afforded the mesyl derivative **22** (512 mg, 65%). **IR** (film) 3400-1730-1640-1580-1560-1460-1420 cm^{-1}; ^{1}H NMR (200 MHz) 2.43 (2H, m), 2.96 3.05 (3H, 2s),3.38 3.45 (3H, 2s), 3.6 (1H, m), 4.2 (1H, m), 4.93 (2H, 2s), 5.8 (1H, m), 7.03 (2H, m), 7.46 (9H, m), 7.95 (2H, m), 8.26 (1H, m), 9.1 (1H, NH, 2s); ^{13}C NMR 29.2 (CH_2), 38.1 38.5 (CH_3), 59.6 60.1 (CH_3), 61.3 62.1 (CH), 77.8 (CH), 78.4 (CH_2), 79.4 (CH), 80.6 81.5 (CH), 120.9 121.1 (CH), 122.6 122.9 (CH), 128.4 128.6 (CH), 129.3 129.5 (CH), 133.9 (CH), 134.8 (CH), 136.1 (Cq), 136.6 136.9 (CH), 148.9 149 (Cq), 153.3 (Cq), 165.3 165.7 (C=O); **MS** (EI, m/z): 581 $(MH)^+$, 485 $(MH\text{-}OMs)^+$.

β-Lactam 23:

A solution of the mesyl derivative **22** (512 mg, 0.88 mmoles) in acetone (30 ml) was added to a suspension of K_2CO_3 (500 mg, 4 eq) in refluxing acetone (5 ml). The mixture was stirred for 1 hr at 60°C and the solvent removed under reduced pressure. Column chromatography of the residue on silica gel (EtOAc/Hexane, 1/1) afforded the monocyclic β-lactam **23** (310 mg, 72%). **IR** (film) 1780-1580-1560-1450-1420 cm^{-1}; ^{1}H NMR (200 MHz) 2.16-2.75 (2H, m), 3.5 (3H, s), 3.85 (1H, m), 4.13 4.21 (1H, 2d, J = 1Hz), 4.96 (2H, m), 5.76 5.83 (1H, 2m), 6.93 (2H, m), 7.33 (9H, m), 7.83 (2H, m), 8.08 (1H, m); **MS** (EI, m/z): 484 $(M)^+$.

β-Lactam 24:

To a solution of **23** (310 mg, 0.64 mmoles) in anhydrous chloroform (10 ml) was added, at 0°C, mCPBA (133 mg, 1.2 eq). The mixture was stirred for 1 hr at 0°C and the solution was diluted with dichloromethane and washed successively with $NaHCO_3$ (0.1N), H_2O and brine. The organic layer was dried over $MgSO_4$, filtered and evaporated to dryness. The residue was dissolved in anhydrous toluene (30 ml) and refluxed for 30 min. The solvent was then removed under reduced pressure and the residue chromatographed on silica gel (EtOAc/Hexane, 2/8). The β-lactam **24** (180 mg) was isolated in 75% yield. **m.p.** 62°C (dichloromethane/hexane); $[\alpha]_D^{25}$ = +2.5° (c= 2.05, $CHCl_3$); **IR** (film) 1780-1440-1310-1300-1140 cm^{-1}; ^{1}H NMR (200 MHz) 3.41 (3H, OCH_3, s); 3.9 (1H, H_4, m, $J_{4\text{-}3}$=1Hz, $J_{4\text{-}1'}$=6Hz, $J_{4\text{-}2'}$=1 Hz); 4.15 (1H, H_3, d, $J_{3\text{-}4}$=1Hz); 4.93 (2H, CH_2, s); 6.46 (1H, $H_{2'}$, dd, $J_{2'\text{-}1'}$=15Hz, $J_{2'\text{-}4'}$=1Hz); 6.78 (1H, $H_{1'}$, dd, $J_{1'\text{-}4}$= 6Hz, $J_{1'\text{-}2'}$=15Hz); 7.28 (6H, m); 7.61 (3H, m); 7.9 (1H, m); ^{13}C NMR 58 (CH_3), 64.2 (C-4), 78.7 (CH_2), 85.6 (C-3), 127.8 (CH), 128.8 (CH), 129.3 (CH), 129.5 (CH), 134.5 (Cq), 134.8 (CH), 138.4 (CH), 139.7 (Cq), 161.4 (C=O); **MS** (EI, m/z): 374 $(MH)^+$; **Anal.** Calcd for $C_{19}H_{19}NO_5S$: C, 61.10; H, 5.13; N, 3.75; S, 8.58 Found: C, 61.37; H, 5.06; N, 3.31; S, 8.36.

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