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ASYMMETRIC SYNTHESIS OF 3,4-CIS-SUBSTITUTED β-LACTAMS VIA CHIRAL NOREPHEDRINE-DERIVED OXAZOLIDINES.

S.Cardani, C.Gennari*, C.Scolastico*, R.Villa.

Dipartimento di Chimica Organica e Industriale, Centro CNR Sostanze Organiche Naturali, Università di Milano, Via Venezian 21, 20133 Milano, Italy

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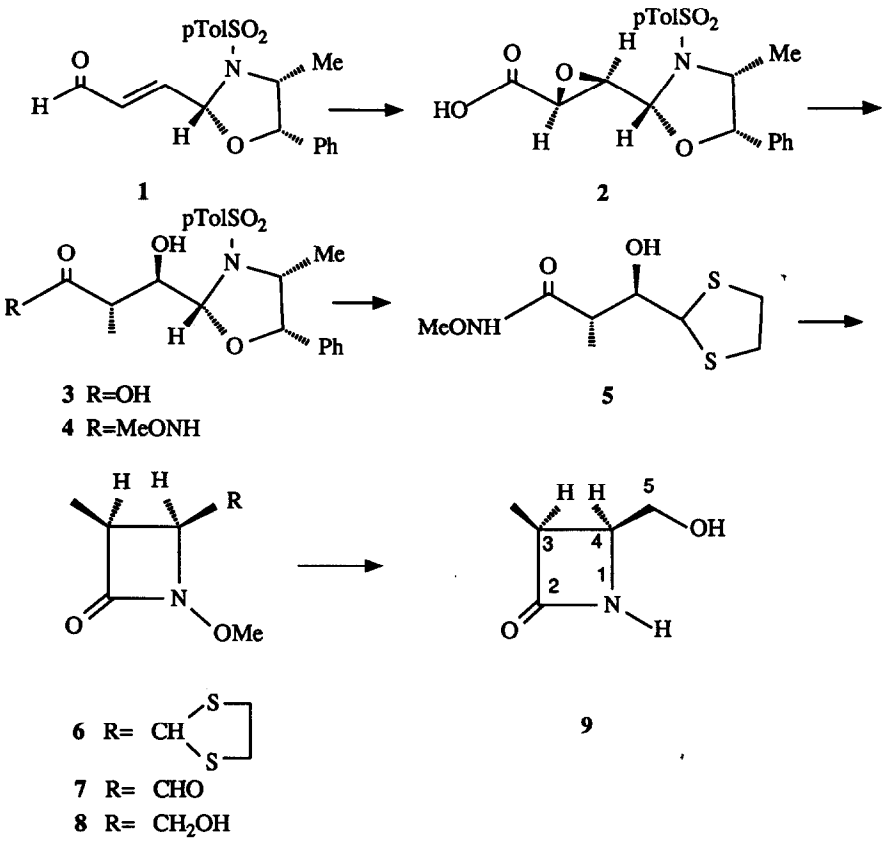
Abstract. A diastereo- and enantioselective approach to functionalized 3,4-cis-β-lactams 9 and 16 was developed based on the use of chiral norephedrine-derived oxazolidines. The key-steps in the synthesis of 9 (Scheme 1) are the potassium hypochlorite epoxidation of aldehyde 1 and the lithium dimethylcuprate addition to acid 2, both steps proceed regio- and stereoselectively (>98%) and in high yield. Standard synthetic methods and the Miller hydroxamate procedure for N-C cyclization were used to complete the synthesis of the target cis-β-lactam 9 (≥98% enantiomeric excess). In the synthesis of cis-substituted 3-amino-2-azetidinone 16 (Scheme 4) the key-step is the aqueous ammonia opening of epoxy acid 2 which proceeds regio- and stereoselectively (>98%). The Miller-type cyclization of hydroxamate 15a under Mitsunobu conditions failed to give 16a in a yield higher than 35%.

Since their discovery in 1980 5,6-cis-carbapenems[1a,b] e.g. C-19393 H_2 [2] (carpetymicin A),[3] have attracted much attention as synthetic targets due to their potent and broad antibacterial activity.

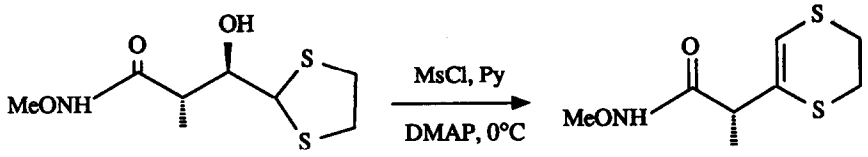
Several methods for constructing natural 5,6-cis-carbapenems and their synthetic intermediates (3,4-cis-β-lactams) have been reported.[4a-q] In the synthesis of carbapenem antibiotics, the control of the relative and absolute stereochemistry of the contiguous chiral centers and the enantioselective construction of the β-lactam ring remain difficult synthetic tasks, particularly in the case of the thermodynamically less stable cis-isomers.

Here we describe a diastereo- and enantioselective approach to a functionalized 3,4-cis-β-lactam (**9**) based on the use of chiral norephedrine-derived oxazolidines.[5] Our method starts with α,β-unsaturated aldehyde **1** which can be easily prepared on a large scale from one of the two commercially available norephedrine enantiomers (1S,2R). Aldehyde **1** was subjected to potassium hypochlorite in aqueous THF to give the epoxy acid **2**, obtained in 90% overall yield as a single isomer (> 98:2 by ^{1}H NMR spectroscopy) (Scheme 1).[5] Epoxy acid **2** was then treated with Me_2CuLi in Et_2O-THF to give regio- and stereoselectively (>98%) *anti* α-methyl-β-hydroxyacid **3** in 70% isolated yield.[6] Acid **3** was treated with N-hydroxybenzotriazole/DCC/methoxyamine hydrochloride and N-methylmorpholine in DMF[7] to give cleanly the desired hydroxamate **4** (84%). This method proved better and more reproducible than the use of the water-soluble carbodiimide (WSC).[4e] The chiral oxazolidine was than removed by treating **4** with ethanedithiol and BF_3OEt_2 in methylene chloride to give **5** (88%; 90% recovery of optically pure N-tosyl norephedrine).



Scheme 1

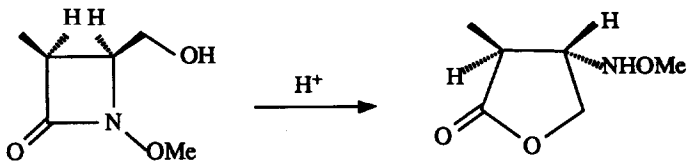
5 was then cyclized to cis-azetidinone **6** with DEAD and PPh_3[4e] with inversion of chirality at C-4 (β-lactam numbering), in accordance with the Miller hydroxamate procedure for N-C cyclization.[8] Attempts to use the mesylation-potassium carbonate ring closure procedure[9] failed because of the dithiolane expansion under mesylation conditions to give the unsaturated 1,4-dithiane **10** (Scheme 2). The cis-configuration of β-lactam **6** was confirmed by the value of the C(3)-H/C(4)-H coupling constant (5.66Hz).[10] Dithiolane **6** was then hydrolyzed (HgO, BF_3OEt_2, THF-H_2O)[11] to give aldehyde **7** which was, in turn, reduced ($NaBH_4$, MeOH/H_2O) to alcohol **8** in 60% overall yield. Alcohol **8** is very sensitive to acidic conditions (including silica gel) and rearranges to γ-lactone **11** (Scheme 3).[12] Dissolving metal reduction of crude alcohol **8** (Na/THF-NH_3/-78°C/1h)[9] smoothly effected N-O bond cleavage to afford the target cis-β-lactam **9** in 50% isolated yield and ≥98% enantiomeric excess (^1H NMR spectroscopy with $Eu(hfc)_3$ as chiral shift reagent) [[α]$_D$=+21.6° (c 0.6, $CHCl_3$)].[13]



5 **10**

Scheme 2

Functionalized cis-substituted 3-amino-4-alkyl-2-azetidinones have been shown to be versatile intermediates[14] for the synthesis of a number of biologically active β-lactam antibiotics, including O-2-isocephem and 2-isocephem,[15] carumonam (Ro-172301),[16] LY 163892.[17]

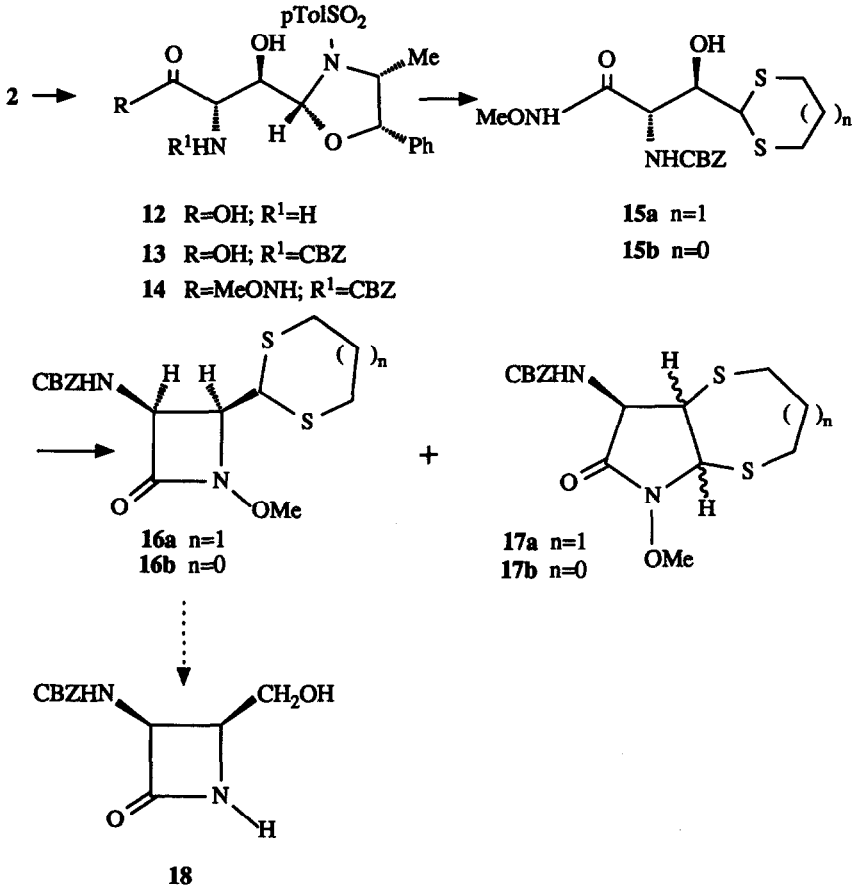


8 **11**

Scheme 3

Based on the use of chiral norephedrine-derived oxazolidines[5] we developed a diastereo- and enantioselective approach to the cis-substituted 3-amino-2-azetidinone **16** (Scheme 4). Our method starts with epoxy acid **2** which was treated with aqueous ammonia to give, regio- and stereospecifically (> 98:2), the *anti* α-amino-β-hydroxyacid **12** in quantitative yield.[5] α-Amino-β-hydroxyacid **12** was then transformed into the N-CBZ derivative **13** (CBZ_2O, Schotten-Baumann, 70%),[5] which was in turn treated with methoxyamine hydrochloride/N-methylmorpholine and N-hydroxybenzotriazole/DCC in DMF[7] to give the desired hydroxamate **14** cleanly (80%). The chiral oxazolidine was then removed by the treatment of **14** with propanedithiol and BF_3OEt_2 in methylene chloride to give dithiane **15a** in 55% isolated yield. Compound **15a** was then treated with DEAD and PPh_3[4e] to give the desired cis-azetidinone **16a** (35% yield) together with the undesired pyrrolidinone **17a** (two diastereoisomers, 35% yield). Any attempts to improve the yield of the β-lactam, including changing the solvent from THF to CH_2Cl_2 or benzene, the phosphine from PPh_3 to $(PhO)_3P$[18a] or $(Me_2N)_3P$[18b] and the experimental conditions, were uniformly unsuccessful. Pyrrolidinone formation was also greatly favored by the use of the dithiolane-derivative **15b** due to the ease of expansion from five- to six- vs. six- to seven-membered ring. Attempts to use the mesylation-potassium carbonate ring closure procedure[9] were unsuccessful for both the dithiolane **15b** and the dithiane **15a** due to ring expansion as reported in the case of compound **5** (see Scheme 2).

Needless to say, due to these unexpected results, this synthetic route, potentially leading to the useful intermediate **18**[14a,b] (Scheme 4), was not investigated further.



Scheme 4

In summary, it can be seen that new and interesting transformations of chiral norephedrine-derived oxazolidines have been developed for the synthesis of optically active 3,4-cis-substituted β-lactams without recourse to resolution. The exploitation of these findings for the synthesis of new biologically active β-lactam antibiotics is presently under investigation.

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EXPERIMENTAL

^{1}H NMR spectra were recorded with a Bruker AC-200 or WP-80, while ^{13}C NMR spectra were recorded with a Bruker AC-200 instrument in the FT mode with tetramethylsilane as internal standard. Optical rotations were measured in a 1 dm cell of 1 ml capacity by using a Perkin-Elmer 457 spectrophotometer. Silica gel 60 F_{254} plates (Merck) were used for analytical TLC, 270-400 mesh silica gel (Merk) for flash chromatography. "Dry" solvents were distilled under N_2 just before use: tetrahydrofuran (THF) and diethyl ether were distilled from sodium metal in the presence of benzophenone; dimethyl formamide (DMF) and methylene chloride from CaH_2. All reactions employing dry solvents were run under a nitrogen (from liquid N_2) atmosphere.

The α,β-unsaturated aldehyde **1**, the epoxy acid **2** ($[\alpha]_D^{25}$= -11.5° (c 1.58, $CHCl_3$) m.p.75-76 °C) and the N-CBZ-α-amino-β-hydroxyacid **13** were obtained as reported in ref.5.

α-Methyl-β-hydroxyacid **3**. A suspension of CuI (2.95 g, 15.5 mmol) in Et_2O (45 ml) was treated with 19 ml (30.4 mmol) of a 1.6 M solution of MeLi in Et_2O at 0°C. After 10 min a solution of epoxy acid **2** (2.08 g, 5.2 mmol) in THF (13 ml) was added dropwise under vigorous stirring at 0°C. After stirring for 5 hr at 0°C, the reaction mixture was acidified to pH=2 with 5% aqueous HCl. The resulting mixture was filtered on a celite pad and the filtrate was extracted with ethyl acetate. The organic layer was dried over sodium sulfate, filtered and the solvent evaporated under reduced pressure. The crude product was purified by flash chromatography (ethyl acetate-methanol 95:5) to give compound **3** as an oil in 79% yield. $[\alpha]_D^{25}$=+1.4° (c 0.98, $CHCl_3$). ^{1}H NMR (200MHz, $CDCl_3/D_2O$) δ: 0.92 (3H, d, J=7.12Hz), 1.49 (3H, d, J=7.98Hz), 2.50 (3H, s), 3.06-3.19 (1H, dq, J=7.98, 2.84Hz), 4.02-4.20 (2H, m), 4.23 (1H, d, J=5.70Hz), 5.12 (1H, d, J=5.98Hz), 7.08-7.88 (9H, m). ^{13}C NMR (50.3MHz, $CDCl_3$) δ: 15.7, 16.9, 21.4, 40.5, 58.8, 76.6, 81.4, 91.5, 181.6 (selected values). IR ($CHCl_3$): 3520, 1715, 1355, 1170 cm^{-1} (selected values). Anal.Calcd.for $C_{21}H_{25}NO_6S$: C,60.13; H,6.01; N,3.34. Found: C,60.10; H,6.03; N,3.33.

α-Methyl-β-hydroxy hydroxamate **4**. A solution of acid **3** (1.6 g, 3.70 mmol) in dry DMF (10.3 ml) was treated with N-hydroxybenzotriazole (525 mg, 3.90 mmol) and DCC (839 mg, 4.07 mmol) at room temperature. After stirring for 1 hr, the reaction mixture was cooled at 0°C and treated with methoxyamine hydrochloride (1.86 g, 22.2 mmol) and N-methylmorpholine (2.2 ml, 20.37 mmol). The reaction mixture was stirred at room temperature for 1 hr, then filtered on a celite pad , washing the filter cake with ethyl acetate. The filtrate was washed with a 5% HCl solution, water and brine. The organic extracts were dried over sodium sulfate, filtered and the solvent evaporated under reduced pressure. The crude product was purified by flash chromatography (ethyl acetate-n-hexane 6:4) to give **4** in 84% yield. $[\alpha]_D^{25}$=+7.7° (c 1, $CHCl_3$). ^{1}H NMR (200MHz, $CDCl_3/D_2O$) δ: 0.90 (3H, d, J=7.24Hz), 1.46 (3H, d, J=7.25Hz), 2.50 (3H, s), 2.80-3.00 (1H, m), 3.80-3.90 (1H, m), 3.85 (3H, s), 4.05-4.18 (1H, m), 4.24 (1H, d, J=5.03Hz), 5.03 (1H, d, J=6.67Hz), 7.05-7.89 (9H, m). ^{13}C NMR (50.3MHz, $CDCl_3$) δ: 16.3, 17.3, 21.6, 39.2, 59.1, 64.2, 76.1, 81.4, 91.7, 172.9 (selected values). IR ($CHCl_3$): 3700, 1675, 1600, 1345, 1160 cm^{-1} (selected values). Anal.Calcd.for $C_{22}H_{28}N_2O_6S$: C,58.91; H,6.29; N,6.25. Found: C,58.88; H,6.30; N,6.26.

Dithiolane **5**. A solution of hydroxamate **4** (1.38 g, 3.1 mmol) in dry methylene chloride (31 ml) was treated with ethanedithiol (3.1 ml) and boron trifluoride etherate (568 µl, 4.6 mmol) under nitrogen and stirred for 36 hr at room temperature. The reaction mixture was quenched with 5% $NaHCO_3$ aqueous solution and extracted with methylene chloride. The organic extracts were dried over sodium sulfate, filtered and the solvent evaporated in vacuo. The crude product was purified by flash chromatography (ethyl acetate-n-hexane 93:7) to give dithiolane **5** as an oil in 88% yield. $[\alpha]_D^{25}$=+9.35° (c 0.93, $CHCl_3$). ^{1}H NMR (200MHz, $CDCl_3/D_2O$) δ: 1.30 (3H, d, J=7.24Hz), 2.48-2.64 (1H, m), 3.19-3.30 (4H, m), 3.61 (1H, t, J=6.39Hz), 3.80 (3H, s), 4.61 (1H, d, J=6.39Hz). ^{13}C NMR (50.3MHz, $CDCl_3$) δ: 15.3, 38.4, 38.9, 41.3, 57.1, 64.1, 77.3, 172.7. IR ($CHCl_3$): 3700, 3400, 1680 cm^{-1} (selected values). Anal.Calcd.for $C_8H_{15}NO_3S_2$: C,40.49; H,6.37; N,5.90. Found: C,40.53; H,6.30; N,5.91.

1,4 Dithiane **10**. A solution of **5** (40 mg, 0.169 mmol) in pyridine (340 µl) was treated with DMAP (1.03 mg, 8.4 10^{-3} mmol) and mesyl chloride (20 µl, 0.253 mmol) at 0°C and stirred for 6 hr. During this period more mesyl chloride (3x20 µl, 3x0.253 mmol) was added. The reaction mixture was diluted with ethyl acetate and washed with 1 N HCl. The organic layer was dried over sodium sulfate, filtered and the solvent evaporated under reduced pressure. The crude product was purified by flash chromatography (n-hexane-ethyl acetate 65:35). ^{1}H NMR (80MHz, $CDCl_3$) δ: 1.35 (3H, d, J=7.50Hz), 2.95-3.20 (5H, m), 3.75 (3H, s), 6.10 (1H, s), 8.45 (1H, bs).

Anal.Calcd.for $C_8H_{13}NO_2S_2$: C,43.81; H,5.97; N,6.39. Found: C,43.78; H,5.99; N,6.35.

β-Lactam **6**. A solution of hydroxamate **5** (240 mg, 1.01 mmol) in dry THF (6.8 ml) was treated with Ph_3P (400 mg, 1.53 mmol) and DEAD (235 µl, 1.50 mmol) and stirred for 1.5 hr at 0°C. The solvent was evaporated under reduced pressure and the crude product was purified by flash chromatography (n-hexane-ethyl acetate 6:4) to give β-lactam **6** as an oil in 45% yield. $[\alpha]_D^{25}$=-38.1° (c 1.05, $CHCl_3$). ^1H NMR (200MHz, $CDCl_3$) δ: 1.45 (3H, d, J=7.25Hz), 3.09 (1H, dq, J=7.25, 5.66Hz, C<u>H</u>CH_3), 3.26-3.31 (4H, m), 3.87 (3H, s), 4.00 (1H, dd, J=5.66, 10.60Hz, C<u>H</u>NOMe), 4.51 (1H, d, J=10.60Hz, SC<u>H</u>S). ^{13}C NMR (50.3MHz, $CDCl_3$) δ: 9.8, 38.6, 38.7, 44.0, 51.3, 63.9, 66.1, 167.1. IR ($CHCl_3$): 2980, 2930, 1770 cm^{-1} (selected values). Anal.Calcd.for $C_8H_{13}NO_2S_2$: C,43.81; H,5.97; N,6.39. Found: C,43.78; H,5.96; N,6.37.

Aldehyde **7**. A suspension of red HgO (310 mg, 1.43 mmol) in 85:15 THF-H_2O (1.1 ml) was treated with boron trifluoride etherate (120 µl, 0.98 mmol) and stirred for 2 min at room temperature. A solution of β-lactam **6** (104 mg, 0.47 mmol) in THF (800 µl) was added at once and, after stirring at room temperature for 24 hr, the reaction mixture was filtered on a celite pad washing the filter cake with ethyl acetate. The aqueous layer was neutralized with a 5% $NaHCO_3$ aqueous solution and evaporated under reduced pressure. The crude mixture was taken up with ethyl acetate and the solvent evaporated. The crude product was quickly purified by flash chromatography (ethyl acetate-n-hexane 95:5) to give aldehyde **7** in 60% yield. ^1H NMR (200MHz, $CDCl_3$) δ: 1.28 (3H, d, J=7.24Hz), 3.40 (1H, dq, J=7.24, 6.13Hz, C<u>H</u>CH_3), 3.90 (3H, s), 4.45 (1H, dd, J=6.13, 2.23Hz, C<u>H</u>CHO), 9.80 (1H, d, J=2.23Hz, C<u>H</u>O). IR ($CHCl_3$): 1775, 1730, 1455 cm^{-1} (selected values).

Alcohol **9**. A solution of aldehyde **7** (191 mg, 1.33 mmol) in 10:1 MeOH-H_2O (6.7 ml) was treated with $NaBH_4$ (63.7 mg, 1.60 mmol) at 0°C. After stirring for 15 min, the reaction mixture was neutralized with a saturated aqueuos solution of NaH_2PO_4. The solvent was evaporated and the residue was taken up with methylene chloride. The solvent was evaporated in vacuo to give crude alcohol **8** which was not purified further. ^1H NMR (200MHz, $CDCl_3$) δ: 1.27 (3H, d, J=7.50Hz), 2.25 (1H, bs), 3.09 (1H, dq, J=5.20, 7.50Hz, C<u>H</u>CH_3), 3.82 (3H, s), 3.89-3.95 (2H, m), 3.98-4.06 (1H, m). IR ($CHCl_3$): 3620, 3000, 1765, 1260, 1190 cm^{-1} (selected values).

Characterization of γ-lactone **11**: ^1H NMR (200MHz, $CDCl_3$) δ: 1.30 (3H, d, J=7.30Hz), 2.58 (1H, dq, J=6.54, 7.30Hz, C<u>H</u>CH_3), 3.51-3.66 (1H, m), 3.54 (3H, s), 4.12 (1H, dd, J=5.88, 9.41Hz, C<u>H</u>OH), 4.39 (1H, dd, J=6.80, 9.41Hz, C<u>H</u>OH), 5.65 (1H, bs). IR ($CHCl_3$) ν_{max}:1780 cm^{-1}.

To a solution of Na (300 mg, 13.0 mmol) in 12:1 NH_3-THF (13 ml) at -78°C, a solution of crude alcohol **8** in THF (1.7 ml) was added. The resulting blue solution was stirred at -78°C for 1hr, then solid NH_4Cl (1.09 g, 20.37 mmol) was added, and the resulting colorless solution was diluted with ethyl acetate. The ammonia was then allowed to distill off, while the solution was heated to room temperature. After filtration 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 (methylene chloride-methanol 9:1). Compound **9** was obtained in 45% yield. $[\alpha]_D^{25}$=+21.6° (c 0.57, CH_2Cl_2). ^1H NMR (200MHz, $CDCl_3$) δ: 1.25 (3H, d, J=7.80Hz), 3.02 (1H, bs), 3.36 (1H, dq, J=7.80, 4.09Hz, C<u>H</u>CH_3), 3.68-3.90 (3H, m), 6.70 (1H, bs, N<u>H</u>). ^{13}C NMR (50.3MHz, $CDCl_3$) δ: 8.3, 46.3, 52.5, 62.2, 173.3. IR ($CHCl_3$): 3420, 2930, 1760, 1600, 1420, 1225, 1200, 1040 cm^{-1} (selected values). Anal.Calcd.for $C_5H_9NO_2$: C,52.16; H,7.88; N,12.17. Found: C,52.15; H,7.85; N,12.19.

<u>N-CBZ-α-amino-β-hydroxy hydroxamate **14**</u>. A solution of N-CBZ-α-amino-β-hydroxyacid **13** (1.0 g, 1.80 mmol) in dry DMF (1 ml) was treated with N-hydroxybenzotriazole (255 mg, 1.89 mmol) and DCC (408 mg, 1.98 mmol) at room temperature. After 1 hr stirring methoxyamine hydrochloride (902 mg, 10.8 mmol) and N-methylmorpholine (1.08 ml, 9.9 mmol) were added. The reaction mixture was stirred for 30 min at room temperature and then filtered on a celite pad washing the filter cake with ethyl acetate. The filtrate was washed with a 5% HCl solution, water and brine. The organic extracts were dried over sodium sulfate, filtered and the solvent evaporated under reduced pressure. The crude product was purified by flash chromatography (ethyl acetate-n-hexane 65:35) to give **14** in 82% yield. $[\alpha]_D^{25}$= -5.7° (c 1.46, $CHCl_3$). m.p.80°C. ^1H NMR (80MHz, $CDCl_3/D_2O$) δ: 0.85 (3H, d, J=6.7Hz), 2.56 (3H, s), 3.75 (3H, s), 3.91-4.17 (1H, m), 4.01 (1H, dd, J=3.65, 6.41Hz), 4.25 (1H, d, J=5.13Hz), 4.54 (1H, dd, J=3.65, 9.33Hz), 5.15 (2H, s), 5.27 (1H, d, J=6.41Hz), 5.39 (1H, d, J=9.33Hz), 7.00-7.90 (14H, m). Anal.Calcd.for $C_{29}H_{33}N_3O_8S$: C,59.68; H,5.70; N,7.20. Found: C,59.65; H,5.71; N,7.23.

<u>Dithiane **15a**</u>. A solution of hydroxamate **14** (380 mg, 0.652 mmol) in dry methylene chloride (6.5 ml) was treated with propanedithiol (655µl) and boron trifluride etherate (84 µl, 0.652 mmol) and stirred at room

temperature for 4.5 hr. The reaction mixture was quenched with phosphate buffer, then the organic layers were dried over sodium sulfate, filtered and the solvent evaporated under reduced pressure. The crude product was purified by flash chromatography (ethyl acetate-methanol 95:5) to give **15a** as an oil in 55% yield. ^{1}H NMR (200MHz, $CDCl_3/D_2O$) δ: 1.86-2.18 (2H, m), 2.62-2.75 (2H, m), 2.75-3.04 (2H, m), 3.78 (3H, s), 4.03-4.17 (2H, m), 4.53 (1H, dd, J=8.46, 4.23Hz, CHNHCBZ), 5.15 (2H, s), 6.03 (1H, d, J=8.46Hz, NH), 7.35 (5H, s). Anal.Calcd.for $C_{16}H_{22}N_2O_5S_2$: C,49.72; H,5.74; N,7.25. Found: C,49.69; H,5.75; N,7.23.

Dithiolane **15b**. A solution of hydroxamate **14** (334 mg, 0.6 mmol) in dry methylene chloride (6 ml) was treated with ethanedithiol (472 µl) and boron trifluoride etherate (106 µl, 0.9 mmol) at room temperature. After stirring for 4.5 hr, the reaction mixture was treated with a 5% $NaHCO_3$ aqueous solution. The aqueous layer was extracted with methylene chloride. The organic extracts were dried over sodium sulfate, filtered and the solvent evaporated under reduced pressure. The crude product was purified by flash chromatography (methylene chloride-methanol 95:5) to give dithiolane **15b** as an oil in 77% yield. ^{1}H NMR (80MHz, $CDCl_3/D_2O$) δ: 3.20 (4H, s), 3.65-3.88 (4H, m), 4.20-4.45 (1H,m), 4.70 (1H, d, J=6.7Hz, SCHS), 5.12 (2H, s), 5.82 (1H, d, J=8.66Hz), 7.35 (5H, s). Anal.Calcd.for $C_{15}H_{20}N_2O_5S_2$: C,48.37; H,5.41; N,7.52. Found: C,48.36; H,5.43; N,7.54.

β-Lactam **16a**. A solution of Ph_3P (257 mg, 0.979 mmol) in dry THF (3 ml) was treated with DEAD (120 µl, 0.688 mmol) and a solution of dithiane **15a** (122 mg, 0.316 mmol) in THF (2 ml) at 0°C. After stirring for 10 min at 0°C, the solvent was evaporated under reduced pressure and the crude product purified by flash chromatography (ethyl acetate-methanol 95:5) to give β-lactam **16a** as an oil in 35% yield and two diastereoisomeric pyrrolidinones **17a** (35% yield) [the order of product elution is **17a** (first diastereoisomer),**16a**, **17a** (second diastereoisomer)]. **16a**: ^{1}H NMR (200MHz, CD_3COCD_3) δ: 1.90-2.03 (2H, m), 2.70-3.05 (4H, m), 3.84 (3H, s), 4.21 (1H, d, J=9.30Hz, SCHS), 4.46 (1H, dd, J=5.50, 9.30Hz, CHNOMe), 5.05 (1H, d, J=12.50Hz, CHPh), 5.12 (1H, dd, J=5.50, 10.0Hz, CHNHCBZ), 5.17 (1H, d, J=12.50Hz, CHPh), 6.95 (1H, d, J=10.0Hz), 7.30-7.45 (5H, m). IR ($CHCl_3$): 3400, 1785, 1725, 1520 cm^{-1} (selected values).Anal.Calcd.for $C_{16}H_{20}N_2O_4S_2$: C,52.15; H,5.47; N,7.60. Found: C,52.19; H,5.48; N,7.61. **17a** (first eluted diastereoisomer): ^{1}H NMR (200MHz, CD_3COCD_3) δ: 1.90-2.60 (2H, m), 2.78-3.20 (4H, m), 3.58 (1H, dd, J=11.83, 9.68Hz), 3.63 (3H, s), 4.78 (1H, dd, J=11.83, 9.25Hz, CHNHCBZ), 5.12 (2H, s), 5.40 (1H, d, J=9.68Hz, MeONCHS), 6.78 (1H, d, J=9.25Hz, NHCBZ), 7.38-7.50 (5H, m). **17a** (second eluted diastereoisomer): ^{1}H NMR (200MHz, CD_3COCD_3) δ: 2.70-3.12 (6H,m), 3.47 (1H, dd, J=11.44, 8.65Hz), 3.80 (3H, s), 4.14 (1H, dd, J=11.44, 8.15Hz, CHNHCBZ), 4.73 (1H, d, J=8.65Hz, MeONCHS), 5.12 (2H, s), 6.92 (1H, d, J=8.15Hz, NHCBZ), 7.25-7.42 (5H, m).

Pyrrolidinone **17b**. A solution of dithiolane **15b** (76 mg, 0.205 mmol) in dry THF (1.1 ml) was treated with Ph_3P (58 mg, 0.221 mmol) and DEAD (34 µl, 0.217 mmol) at 0°C. After 1 hr, the solvent was evaporated and the crude product purified by flash chromatography (n-hexane-ethyl acetate 6:4) to give **17b** in 45% yield. ^{1}H NMR (80MHz, $CDCl_3$) δ: 2.90-3.30 (4H, m), 3.50 (1H, dd, J=11.2, 8.2Hz, CHCHNH), 3.82 (3H,s), 4.03 (1H, dd, J=11.2, 7.0Hz, CHNH), 4.67 (1H, d, J=8.2Hz, CHNOMe), 5.12 (2H, s), 5.26 (1H, d, J=7.0Hz,NH), 7.35 (5H, s). IR ($CHCl_3$): 3440, 1730, 1510 cm^{-1} (selected values).

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