Approaches toward the Total Synthesis of the Nine-Membered Thio-Lactone Core of Griseoviridin

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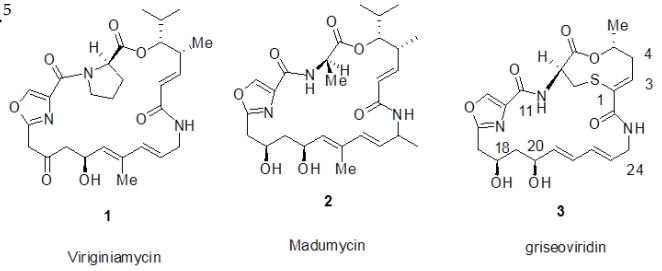
Abstract The synthetic potentialities of Jacobsen's hydrolytic kinetic resolution are demonstrated by the synthesis of a nine membered ring heterocycle component of Griseoviridin (3) in optically active form. The key step involves the stereospecific formation of the vinyl sulfide moiety using a combination system of ligand di phenyl phosphino ferrocin (DPPF), and base triethyl amin in NMP.

Index Terms chiral epoxide, Jacobsen's hydrolytic kinetic resolution, Horner salt generated from Wittig reaction (Wadsworth-Emmons reaction), macro lactone.

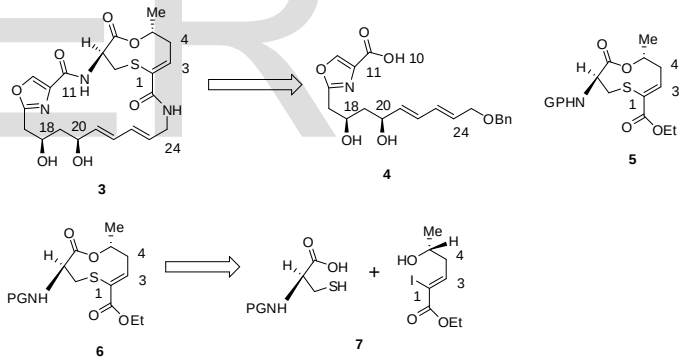
1 INTRODUCTION

The streptogramin antibiotics, for which the name streptogramin was derived from the soil microorganism *Streptomyces graminofaciens*, from which the antibiotic was first isolated in 1953,[1] have been known for the past five decades. During this time, they have proven to have many useful applications; in particular as a broad spectrum antibiotic with in vitro inhibitory activity toward various pathogenic bacteria and fungi.[2] These antibiotics occur as two distinctly different classes of compounds. The antibiotics of group A are complex macrocyclic lactam-lactones, for which six structures have been reported to date,[3] and their structures have been confirmed by X-ray crystallography.[4] Virginiamycin M1 (**1**), Madumycin II (**2**), and Griseoviridin (**3**) are representative examples of type A (Figure 1).[5]



As a synthetic challenge, we have been interested in one member of group A, Griseoviridin (3). The structure of Griseoviridin, the most structurally complex member of this class, was then determined and confirmed by single-crystal X-ray analysis.[6] Considerable progress has been reported in exploring novel synthetic routes to streptogramin of group A during these last years,[7] and the same synthetic effort has been recently applied to producing the key intermediates of Griseoviridin (3), for which, like Madumycin II (2),[8a] the total synthesis of Griseoviridin has recently been completed.[8b]

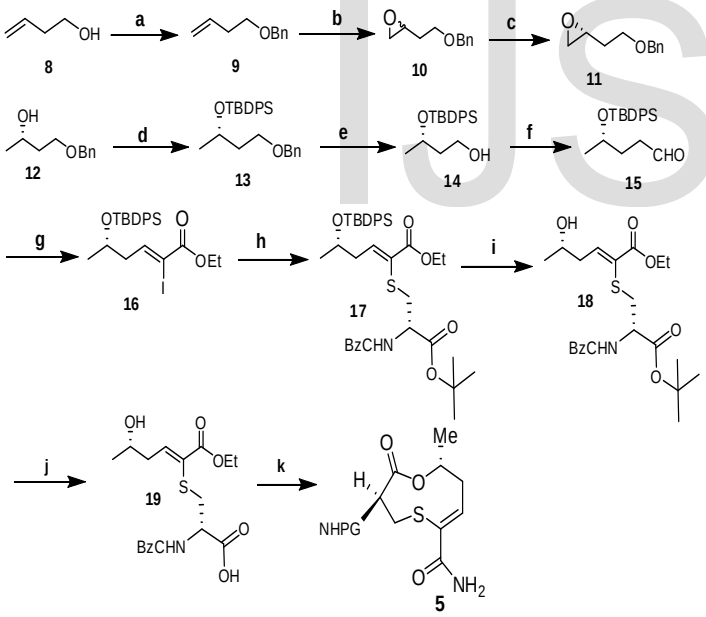
A retrosynthetic scheme to the Griseoviridin (**3**) is outlined in Scheme 1. The simple disconnection at the CBz protecting group has revealed two fragments, **4** and **5**.Further retrosynthetic analysis of the unusual sulphur containing nine-membered lactone system **6** of Griseoviridin (**3**) has shown the presence of the conjugated vinyl sulfide moiety (**7**). Recently, the vinyl sulfides have attracted special attention as important intermediates in various synthetic transformations, [9,10] and their stereospecific synthesis has been attempted.[11]



Results and Discussion

Griseoviridin **3**, one of the active compounds in the streptogramin family of antibiotics, has been the subject of synthetic studies for several years. The nine-membered ring heterocyclic component **6** has been previously prepared by three different approaches.[12-14] because the formation of the conjugated vinyl sulfide moiety in **7** has been the most important, and at the same time, the most difficult, step in the three precedent sequences, our approach was to obtain this moiety through use of 3-buten-1-ol. We began our synthesis with 3-buten-1-ol **8** as the starting material which was converted to its benzyl ether **9** using NaH and benzyl bromide with 96% yield and then epoxidized with mCPBA to result in racemic oxirane **10** in 84% yield, The oxirane **10** was hydrolyzed employing *(R,R)-salen-Co-(OAc)* catalyst to afford the chiral epoxide **11** in 45% yield with 98% ee. The chiral epoxide **11** was regioselectivity opened with $LiAlH_4$ to afford secondary alcohol **12** in 94%

yield. Secondary alcohol **12** OH group which was then protected as TBDPS ether **13** in 92% yield. Debenzylation of the benzyl ether **13** using Pd/C afforded alcohol **14** in 96% yield. Oxidation of alcohol was treated with PCC and using base sodium acetate to afford aldehyde **15** in 92% yield. Aldehyde **15** was subjected to a modified Wadsworth-Emmons reaction compound (ethyl 2-(diethoxyphosphoryl) acetate) in presence of NaH in THF and fallowed by the addition of N-iodo succinamide in dichloromethane to afford vinyl - iodide **16** in 78% yield. The vinyl - iodide **16** and Z-D-Cyst-O-t-Bu, led to the expected vinyl sulfide **17** in which was followed by the addition of ligand di phenyl phosphino ferrocin (DPPF), and base triethyl amin in NMP in 63% yield. Vinyl sulfide **17** in deprotection of TBDPS group followed by the addition of TBAF in THF **18** in 78% yield, Deprotection of tertiary butyl ester **18** was treated with trifloro acetic acid in dichloromethane; to afford seco-acid **19** in 70% yield, The nine membered thio lactonization of **5** was obtained from **19**, compound seco-acid **19** was treated with di isopropyl aza di carbaxylate in THF at 66 ^{0}C at 12 h to afforded macro lactone of Griseoviridin **5** in 58% yield. Spectral and analytical data obtained for **5** were consistent with those reported in the literature.



Scheme 2. Reagents, conditions and yields: (a) NaH, BnBr, THF, 0 ^{0}C, to rt, 3 h, (96%); (b)mCPBA, $NaHCO_3$, CH_2Cl_2, 0 ^{0}C, 2 h, (84%); (c)*(R,R)-salen-Co-(OAc)* catalyst, r.t, 20 ^{0}C to r.t, 24 h, 45%, 98% ee; (d) LiAlH4, THF 0 ^{0}C to r.t, 30 min (94%); (e) Imidazole, TBDPSCl, CH_2Cl_2 0 ^{0}C to r.t, 4 h (92%); (f) 10 % Pd/C, EtOAc, 12 h (under 55 psi pressure hydrogen atmosphere), 96%; (g) PCC,CH_3COONa, CH_2Cl_2 ,0 ^{0}C to r.t, 4 h (92%); (h) ethyl 2-(diethoxyphosphoryl)acetate, NaH, NIS, THF, CH_2Cl_2, 0^{0}C to r.t, 4 h,78%; (i) Z-D-Cyst-O-t-Bu,Pd_2dba_3, DPPF,Et_3N, NMP, r.t to 60^{0}C, 2h (63%).(j) TBAF,THF,r.t,2h,78% (k) TFA,CH_2CL_2, 0^{0}C to r.t, 2 h,74%; (crude material use for next step) TPP,THF, DIAD, 12h, 66^{0}C, (58%).

In conclusion, we have developed a simple and efficient route for the total synthesis of lactonization using Jacobsen's hydrolytic kinetic resolution as the key step and synthesized a common intermediate that can be further used for the total synthesis of Griseoviridin**.**

Experimental

Column chromatography was performed using silicagel 60-120/100-200 mesh. All the solvents were dried and distilled prior to use. IR spectra were recorded on a Perkin-Elmer Infrared spectrophotometer as KBr wafers or neat or in $CHCl_3$ as a thin film. ^{1}H, ^{13}C NMR were recorded on a Varian Gemini 200 or Bruker Avance 300 or Varian Unity 400 MH_Z instrument using TMS as an internal standard. Mass spectra were recorded on Micro mass VG 7070H mass spectrometer for EI, VG Autospec mass spectrometer for FABMS and micromass Quatro LC triple quadrupole mass spectrometer for ESI analysis. The optical rotations were recorded on JASCO DIP-360 digital polarimeter at 25 ^{o}C.

but-3-enyloxy) methyl (9). To a well-stirred suspension of freshly activated NaH (2.9 g, 123 mmol, 60% w/v dispersion in mineral oil) in anhydrous THF (50 mL), a solution of 5-hexene 1-ol (10 g, 100 mmol) in anhydrous THF (60 mL) was added dropwise at 0^{o}C. After 30 min, benzyl bromide (15.52 g, 120 mmol) was added and the reaction mixture was brought to room temperature for 3h. The reaction was quenched with ice pieces and product was extracted with Et_2O (3 x 100 mL). The combined organic layers were washed with water, brine and dried over anhydrous Na_2SO_4. After removing the volatiles under reduced pressure, crude benzyl ether was purified by column chromatography on silicagel (60-120 mesh, 5% EtOAc/hexane) to afford the pure product **9** (18.3 g, 96%) as a colorless-liquid.R_f=0.6(10% EtOAc/hexane).IR(KBr):3425,3069,3031,2924,2856,1718,1640,1454,1361,1310,1224,1101,1026,914,cm^{-1};^{1}HNMR 300MHz,$CDCl_3$), δ 7.39 -7.26 (m,5H),5.88-5.80 (m,1H), 5.12-5.04 (q, 2H, *J*=9.7Hz), 4.52 (d, 2H, *J*=19.5Hz),),3.52(t,2H,*J* = 6.8 Hz,),2.41-2.37(q,2H, *J*=6.8Hz); ^{13}C NMR(50 MHz,$CDCl_3$)δ135.2, 134.3, 127.5, 127.6, 126.9, 128.7, 128.9, 116.3, 72.8, 69.5, 33.5. Mass (ESI-MS) m/z 162(M+H)$^+$.

(*R*)-2-(2-(benzyloxy) ethyl) oxirane (11). A mixture of (*R,R*)-(-)-N, N'bis (3,5-ditert-butyl salicylidene)-1,2-cyclohexanediaminocobalt (143.0 mg, 0.24 mmol) toluene (1 mL) and AcOH (0.027 mL, 0.006 mmol) was stirred while open to the air for 1 h at room temperature. The solvent was removed under reduced pressure and the brown residue was dried over high vacuum. The oxirane **10** (16.38 g, 0.89 mmol) was added in one portion and the mixture was cooled in an ice water bath. Water (0.78 mL, 43.7 mmol) was slowly added and the temperature of the reaction mixture was maintained in such a way that it never rises more than 20 ^{o}C. After 1 h, addition was complete, the ice bath was removed and the reaction was stirred for 24 h. The product **11** was isolated by column chromatography on silicagel (60-120 mesh, 20% EtOAc/hexane) as a colorless liquid (7.4 g, 45%, 99% ee). Rf = 0.3 (15%

EtOAc/hexane). The column used was chiral cell OB (H) 250 x 4.6 mm, Daicel column, flow rate 1.0 mL/min. mobile phase used was 10% IPA in n-hexane, uv: 254 nm.Machine Shimadzu LC 10 AT pump, and SPD-10A UV detector. IR (KBr): 3458, 3032, 2923, 2861, 1720, 1632, 1452, 1362, 1261, 1101, 1026, 909, Cm-1, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30-7.23 (m, 5H), 4.49 (s, 2H), 3.60-3.55 (m, 2H), 3.00 (m, 1H), 2.73-2.70 (t, 1H, *J*= 4.5Hz), 2.47-2.44 (q, 1H, *J*=2.2,5.5Hz), 1.93-1.82 (m, 1H), 1.77-1.67 (m, 1H), Mass (ESI-MS) *m/z* 217 $(M+K)^+$.

(*S*)-4-(benzyloxy) butan-2-ol (12). To a well stirred suspension of $LiAlH_4$ (930 mg, 11.62 mmol) in anhydrous THF (15 mL), a solution of epoxide **11** (5.0 g, 24.15 mmol) in THF (30 mL) was added dropwise at 0 °C. The reaction mixture brought to room temperature and stirred for 30 min. The reaction mixture was quenched with aq. saturated NH_4Cl (40 mmol) at 0 °C. Reaction mixture was filtered, dried over anhydrous Na_2SO_4, and concentrated. Purification by column chromatography using silicagel (60-120 mesh, 15% EtOAc/hexane) afforded the product **12** (4.08 g, 94%) as a colourless oil. R_f = 0.3 (20% EtOAc/hexane). IR (KBr): 3409, 3030, 2966, 2927, 2864, 1636, 1453, 1368, 1310, 1208, 1098, 1028, 910, 849, 739 cm^{-1},^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25-7.17 (m, 5H), 4.42 (s, 2H), 3.94 (m, 2H), 3.66-3.62 (m, 1H), 2.88 (s, 1H,-OH),1.75-1.64 (m, 2H), 1.16 (d, 3H,-Methyl), Mass (ESI-MS) m/z180 (M+H) +, (M+Na) $^+$.

Butan-2- ylox (S)- (4-(benzyloxyy)(tert-butyl) diphenylsilane (13). To a stirred solution of alcohol **12** (3.80 g, 18.18 mmol) in anhydrous CH_2Cl_2 (50 mL) and Imidazole (1.85 g, 27.27 mmol) at 0 °C was added TBDPSCl (5.99 g, 21.81 mmol) dropwise and stirred for 4 h at room temperature. The reaction mixture was quenched with water and extracted with CH_2Cl_2 (3 x 40 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Purification by column chromatography using silicagel (100-200 mesh, 5% EtOAc/hexane) furnished the compound **13** (7.5 g, 92%) as a colorless liquid. R_f = 0.6 (5% EtOAc/hexane). IR (KBr): 3450, 3069, 2961, 2931, 2857, 1960, 1891, 1825, 1640, 1591, 1456, 1427, 1374, 1308, 1260, 1108, 1046, 1004, 948 cm^{-1}, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70-7.60 (m, 5H), 7.41-7.26 (m, 10H), 4.39 (s, 2H), 3.75-3.69 (m, 1H), 3.57-3.52 (m, 2H), 1.90-1.68 (m, 2H), 1.30 (t, 3H Methyl), 1.11-1.06 (t, 9H, Methyl), Mass (ESI-MS) *m/z* 441 $(M+Na)^+$.

(*S*)-3-(tert-butyldiphenylsiloxy)butan-1-ol (14). A solution of benzyl ether **13** (7.0 g, 0.0167 mmol) in EtOAc (45 mL) was mixed with 10% Pd/C and stirred for 12 h under 55 psi pressure hydrogen atmosphere. After catalyst filtration and subsequent solvent evaporation, the residue was chromatographed on silicagel (60-120 mesh, 30% EtOAc/hexane) to afford the alcohol **14** (5.37 g, 96%) as colorless oil. R_f = 0.5 (30% EtOAc/hexane. $[\alpha]_D^{25}$ +8.25 (c 1.1, $CHCl_3$). IR (KBr): 3404, 3070, 2961, 2932, 2890, 2858, 1588, 1467, 1427, 1380, 1108, 1027, 942, 821, 703 cm^{-1}, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71-7.68 (t, 4H, *J*=7.8 Hz), 7.42-7.35 (m, 6H), 4.13-4.09 (m, 1H), 3.81-3.76 (m,1H), 3.66-3.64 (m, 1H), 1.98 (s,1H, -OH), 1.82-1.75 (m,1H), 1.67-1.61 (m,1H), 1.10 (d, 3H, Methyl), 1.08 (s,9H Methyl), Mass (ESI-MS) *m*/z328 $(M+H)^+$& 351$(M+Na)^+$.

(*S*)-4-(tert-butyldiphenylsiloxy) pentanal (15). To a solution of alcohol **14** (5.0 g, 0.014 mol) in anhydrous DCM (50 mL) was added sodium acetate (2.41 g, 2.0eq), PCC (4.75 g, 1.5 mmol) at 0 °C. After 5 min, the cooling bath was removed and the reaction mixture was stirred for 2 h at room temperature where by the colour changed from brown to bright yellow and the mixture became highly viscous. Then the reaction was quenched with water solution (30 mL) and extracted with DCM (3 x 60 mL). The combined organic layers were washed with brine (40 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Purification of the crude product by column chromatography on silicagel (5% EtOAc/hexane) afforded the iodo compound **15** (6.34 g, 96%) as a colorless oil. $[\alpha]_D^{25}$ –15.5 (*c* 0.5, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.71 (s, 1H, Ald), 7.65 (d, 4H, J=6.2Hz), 7.40-7.33 (m, 6H), 4.36-4.25 (m, 1H), 2.54-2.38 (m, 2H), 1.33-1.25 (m, 2H), 1.18-1.16 (d, 3H, Methyl), 1.03 (s, 9H, Methyl), Mass (ESI-MS) *m*/z 341 $(M+H)^+$.

(*S,Z*)-Ethyl 5-(tert-butyldiphenylsilyloxy)-2-iodohex-2-enoate (16). To a solution of triethyl phosphonoacetate (750 µL, 3.78m mol) in anhydrous THF (16 mL) were added NaH (60% dispersion in mineral oil) (335 mg, 7.56 mmol) and N-iodo succinimide (1.1g, 4.91mmol). The solution was stirred for 1 h at room temperature, and crude aldehyde in CH_2Cl_2 (2 mL) was added dropwise. The stirring was maintained for an additional 15 min, and the solution was quenched with saturated solution of ammonium chloride (1ml). The mixture was filtered over silica gel (diethyl ether), the organic layer was washed with a saturated solution of $Na_2S_2O_3$ and dried with Na_2SO_4, and the solvent was evaporated under reduced pressure. Chromatography on silica gel (4/1heptane/ethyl acetate) gave **16** (750mg, 60%) as an inseparable z/e mixture (80/20), IR (KBr): 3483, 3069, 2960, 2931, 2857, 1716, 1615, 1467, 1427, 1368, 1250, 1110, 1038, 821, 703, 609 cm^{-1}, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64 (d, 1H, *J*=5.8Hz, olefin), 7.41-7.28 (m, 10Hz), 4.27-4.19 (m, 2H), 4.16-4.02 (m, 1H), 2.61-2.19 (m, 2H), 1.33 (d, 3H, Methyl), 1.25 (t, 3H), 1.05 (d, 9H, Methyl), Mass (ESI-MS) *m*/z 545 $(M+Na)^+$.

Tert-butyl 3-mercapto-2-(2-oxo-2-phenyl ethylideneamino) Propionate

D-Cysteine (1.92g, 8mmol) was dissolved in aqueous 60% perchloric acid (5.88g, 35.2mmol) with stirring in an ice bath. *Tert*-Butyl acetate (50ml) was added and the stirring and continued until a homogenous solution was obtained (2h). The mixture was kept at room temperature for 2 days, during which a white solid crystallized out. After cooling at 0 °C for 24h, the solid was filtered off and washed with ether. A portion of this Salt was dissolved in a mixture of ether and aqueous $NaHCO_3$.

The organic layer was washed in succession with aqueous $NaHCO_3$ and saturated NaCl solution, dried, and evaporated to give D-Cysteine di tertiary butyl ester as oil. Into the mixture of a saturated aqueous $KHCO_3$ solution (30mL) and $CHCl_3$ (30mL) in an ice bath were added D-Cysteine di tertiary butyl ester (3.40g, 10mmol) and carbobenzyloxy chloride (4mL, 4.78g 28mmol). After shaking the mixture for about 30 minute in an ice bath, the water layer was separated and discarded. To the $CHCl_3$ solution was added pyridine (1ml), and then the solution was washed successively with dilute sulphuric acid, distilled water, and dilute aqueous $KHCO_3$. The solution was dried over Na_2SO_4 and evaporated, and the residue crystallized from ethyl acetate- hexane to give *Z-D-Cyst-O-t-Bu***.**

(S,2Z)-ethyl-2-(S)-3-tert-butoxy-3-oxo-2-2-phenylethylidneamino) propyl thio)-5-(tert-butyl di phenyl silyloxy) hex-2-enoate (17). To a solution of **16** (175 mg, 0.53 mmol), Pd_2dba_3 (13.7 mg, 0.013 mmol), and dppf (30 mg, 0.053 mmol) in N-methylpyrrolidone (9 mL) was added triethylamine (150 μL, 1.06 mmol). The solution was stirred for 30 min at room temperature and then warmed to 60°C. Z-D-cysteine tert-butyl ester (231 mg, 0.74 mmol) in NMP (2.5 mL) was added over 1 h 30. The mixture was stirred for an additional 2 h, cooled at room temperature, and quenched with brine. After extraction with EtOAc, the organic layers were washed with brine and dried over Na_2SO_4, and the solvent was evaporated under reduced pressure. Chromatography on silica gel (7/1hexane/ethyl acetate) gave **17** (170 mg, 63% yield) as an inseparable Z/E mixture (80/20) and 15 mg of starting material (8.5%),^{1}H NMR (300 MHz, $CDCl_3$) δ. 7.72-7.55 (m, 4H), 7.38-7.24 (m, 10H), 7.06 -6.97 (1H), 6.65 (d, 1H, Olefin), 4.12-4.03 (m, 2H), 3.77 (m, 1H), 3.64 (m, 2H), 2.70 (t,1H) 2.88-2.01 (m, 2H), 1.25 (s,9H), 1.05 (s,6H, Methyl), 0.88 (d, 9H, Methyl), Mass (ESI-MS) *m*/z 705 $(M+H)^+$.

(R)-3-((S, Z)-1-ethoxy-5-hydroxy-1-oxohex-2-en-2-yl thio)-2-oxo-2-phenylethylidene amino) propanoic acid (18) To a solution of **17** (100 mg, 0.145 mmol), TBAF (30 mg, 0.045 mmol) in THF (5 mL) The solution was stirred for 1h at 0 ^{0}C to room temperature and Then the reaction was quenched with water solution (5mL) and extracted with ether (3 x 5 mL). The combined organic layers were washed with brine (5 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Purification of the crude product by column chromatography on silicagel (40 % EtOAc/hexane) afforded the compound **18.**

To a solution of **18** (98 mg, 0.19 mmol) in CH_2Cl_2 (1.2 mL) were added TFA (0.08 mL) dropwise. The mixture was stirred for 2 h at room temperature and treated with a saturated solution of $NaHCO_3$. After extraction with CH_2Cl_2, the aqueous layer was acidified with a few drops of concentrated HCl and extracted with CH_2Cl_2, The organic layers were washed with brine and dried over Na_2SO_4, and the solvent was evaporated under reduced pressure. The crude product **19.** (84 mg, 74% yield) was directly used for the next step

(3S, 6Z, 9R)-9-methyl-(2-oxo-2-phenylethylidene-amino)-3, 4, 8, 9-tetrahydro-2H-1, 5-oxathionine-6-carboxylic-acid (5). To a solution of crude material **19** (29 mg, 0.07 mmol) in THF (35 mL) were added triphenylphosphine (55 mg, 0.21 mmol) and isopropyl azodicarboxylate (43 μL, 0.21 mmol). The mixture was stirred overnight at reflux. The solvent was removed under reduced pressure. Chromatography on silica gel (3/1 heptane/ethyl acetate) gave **5** (16 mg, 58% yield).). IR (KBr) 2926, 2855, 1712, 1463, 1377, 1260, 1108, 1027, 803 cm-1, Mass (ESI-MS) m/z 388 (M+H) +.

Acknowledgements

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