Pergamon

Tetrahedron. Asymmetry Vol. 5, No. 11, pp. 2155-2162, 1994
Elsevier Science Ltd
Printed in Great Britain
0957-4166/94 $7.00+0.00

0957-4166(94)00294-0

The Use of Free Radical Cyclization in the Synthesis of Compounds related to the Mannostatins[1]

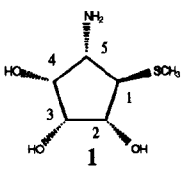
Anthony H. Ingall,[a] Peter R. Moore* [b] and Stanley M. Roberts [b]

a Research Laboratories, Fisons Pharmaceuticals, Bakewell Road, Loughborough, LE11 ORH
b Department of Chemistry, Exeter University, Exeter, Devon, EX4 4QD

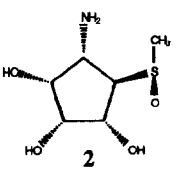
Abstract: A study of the potential use of 5-*exo* free radical cyclizations in the synthesis of carbocyclic compounds related to the mannostatins **1** and **2** is described. The dithioacetal **8** was prepared and the methyl oxime moiety utilised as an intramolecular radical trap. The stereochemistry of the products relating to the cyclization step, **10** and **11**, were determined with reference to extensive nOe studies, Figs 1 and 2.

INTRODUCTION

In 1989, the sugar hydrolase inhibitors mannostatin A **1**, and its corresponding sulfoxide mannostatin B **2**, were isolated from the fermentation broth of *Streptoverticillium verticillus*.[1] Both **1** and **2** were found to possess potent competitive inhibition properties against rat epididymal α-mannosidase. Mannostatin A was also found to competitively inhibit jack bean, mung bean and rat liver lysozymal α-mannosidase with IC_{50} values of 70, 450 and 160 nM respectively.[2]



1



2

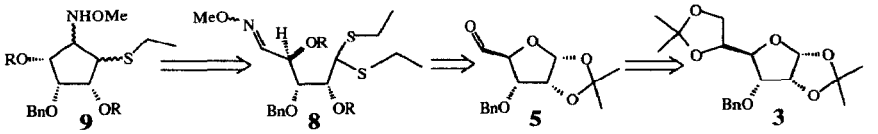
The first total syntheses of mannostatin A were reported simultaneously in 1991 by King and Ganem[3] and by Knapp and Dhar.[4] King and Ganem[3] employed an acylnitroso cycloaddition to prepare both enantiomerically pure and racemic **1**, whilst Knapp and Dhar [4] reported the stereocontrolled synthesis of both enantiomers of **1** from D- and L-ribonolactone. Two additional syntheses of racemic mannostatin A have also been reported by other groups.[5,6]

More recently, King and Ganem[7a] reported further synthetic studies including the synthesis of several analogues with interesting biological activity, whilst Li and Fuchs[7b] have described the synthesis of (+) mannostatin A in 39% overall yield fron D-ribonolactone.

In connection with our continuing studies[8] on the use of free radical cyclization reactions in the synthesis of carbocyclic compounds an investigation was undertaken into the use of such reactions in the synthesis of pentasubstituted cyclopentane compounds related to the mannostatins. We envisaged the formation of the C-1, C-5 bond (see numbering sequence on **1**) *via* a free radical reaction.

Retrosynthetic analysis (**Scheme 1**) shows that the key carbon-carbon bond forming reaction in the synthesis of the cyclopentane ring **9**, could arise *via* an intramolecular free radical cyclization of a radical derived

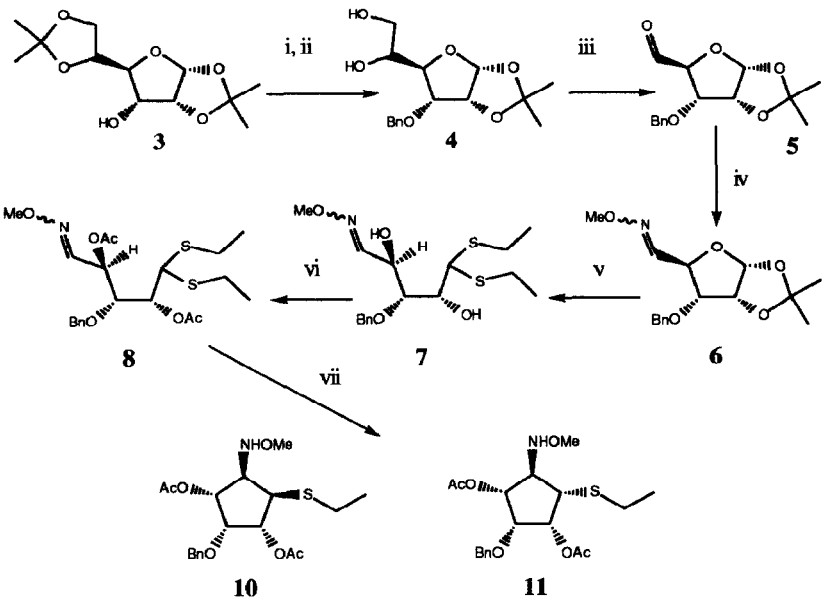
from a dithioacetal[9] onto an oxime.[10] The radical precursor **8** being formed from the known aldehyde **5**,[8a] which in turn can be derived from the protected D-allofuranose **3**.



Scheme 1

RESULTS AND DISCUSSION

The synthetic methodology employed for this investigation is outlined in **Scheme 2**.



Scheme 2. *Reagents and conditions*: i, $PhCH_2Br$, NaH, THF; ii, HCl, MeOH, r t, 12 h; iii $NaIO_4$, H_2O, MeOH; iv, $MeONH_2.HCl$, pyridine, CH_2Cl_2, r t, 2 h; v, EtSH, $ZnCl_2$, -10°C, 1 h; vi, Ac_2O, DMAP, pyridine, 40°C, 18 h; vii, Bu_3SnH (6 eq.), AIBN (2.5 eq.), toluene, 110°C, 1.5 h.

Thus, benzylation of the readily available protected D-allose **3**[11] followed by selective deprotection of the 5,6-*O*-isopropylidene group with hydrochloric acid in methanol,[12] gave the diol **4** in 70% yield. Sodium metaperiodate cleavage of this diol gave the aldehyde **5**,[8a] which was not vigorously purified but used crude in the next step. Reaction with *O*-methyl hydroxylamine hydrochloride gave the oxime **6** as an inseparable mixture of *E* and *Z* isomers in a ratio of 11:1 respectively (75% overall yield from the diol **4**). Ethanethiol in the presence of anhydrous zinc chloride[13] gave the dithioacetal **7** as a 3:1 mixture of *E* and *Z* isomers respectively, (isomerisation of the oxime being observed under the reaction conditions) in good yield (83%). Initial attempts to cyclize the dithioacetal **7** under the usual conditions[10] proved ineffective. Compound **7** was peracetylated

quantitatively to yield **8** as a 2:1 mixture of *E* and *Z* isomers. Again, attempts to cyclize the peracetylated radical precursor **8** by syringe pump addition of tributyltin hydride (2.14 equivalents) and AIBN (0.2 equivalents) to a refluxing solution of the dithioacetal **8** in toluene, only gave recovered starting material. However, the use of excess reagent (Bu_3SnH, 6 eq.) and excess initiator (AIBN, 2.5 eq.), resulted in complete reaction after 1.5 hours, giving the pentasubstituted cyclopentanes **10** and **11** in high yield (80%).

The product was obtained as a mixture (inseparable by flash chromatography over silica gel) of the diastereomers **10** and **11** in a ratio of 3:1 respectively (determined by ^1H nmr and GC-MS). Extensive nOe experiments on this mixture allowed for a conclusive assignment of relative stereochemistry of each diastereomer, the results of which are illustrated in Fig.1(for the major isomer, **10**) and Fig.2 (for the minor isomer, **11**).

The results from this cyclization can be interpreted using a similar model to that originally proposed by Wilcox and Thomasco.[14] The preferred conformation of the radical intermediate must be independent of the stereochemistry of the oxime moiety. The Fischer projection in Fig 3 illustrates a possible transient intermediate. The stereochemistry of the substituents at C-2, C-3 and C-4 in the cyclized product are fixed during the synthesis of the radical precursor. Steric interactions between the oxime ether and acetate on the β carbon and electronic repulsion between the electron pairs of the nitrogen atom and the oxygen atom on the β carbon atom, give rise to a *trans* arrangement of the oxime and protected alcohol moieties.

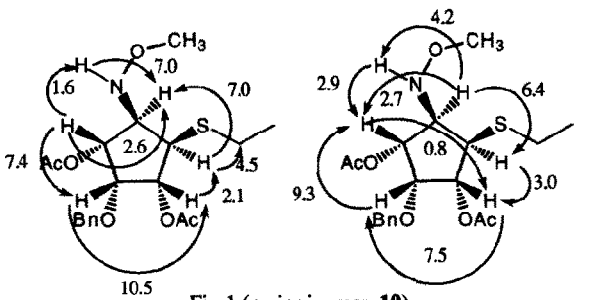


Fig.1 (major isomer, **10**)

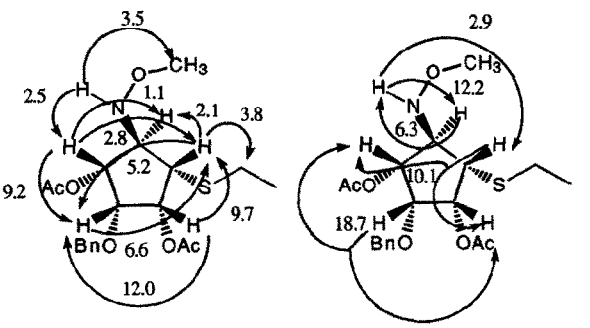


Fig.2 (minor isomer, **11**)

Note, all values are quoted as percentage enhancement

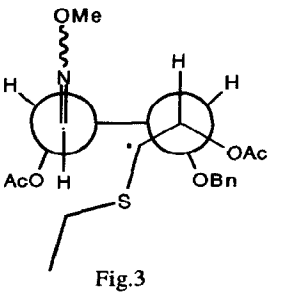


Fig.3

These results show that radicals derived from dithioacetals[8,9] can be cyclized in a 5-*exo* fashion onto *O*-protected oximes to form pentasubstituted cyclopentanes, which could prove useful for the synthesis of naturally occurring compounds, such as the mannostatins[1] and selected analogues.

EXPERIMENTAL

GENERAL: Ethyl acetate (EtOAc) and light petroleum (b.p. 40-60°C) were distilled prior to use. When anhydrous conditions were required the equipment was dried in an oven at 150°C overnight and allowed to cool in an atmosphere of dry nitrogen, the solvents being dried as follows. Dichloromethane, toluene and pyridine were distilled from calcium hydride, with pyridine and toluene being stored over 4 Å molecular sieves. THF was freshly distilled from sodium wire prior to use. Thin layer chromatography was performed on pre-coated glass plates (Merck silica gel 60F 254), the plates were visualised using UV light (254 nm) and/or phosphomolybdic acid in ethanol or *p*-anisaldehyde in glacial acetic acid or basic potassium permanganate or ninhydrin as appropriate. Flash chromatography performed over silica (Merck silica 60, 40-63 μm) was used to purify all products unless otherwise stated. IR spectra were obtained using a Perkin-Elmer 881 spectrophotometer. ^{1}H and ^{13}C NMR spectra were obtained using a Bruker AM 300 machine operating at 300 and 75.47 MHz respectively. *J* values are given in Hertz. Both low and high resolution mass spectra were obtained on a Kratos Profile HV3.

*(+)-3-*O*-Benzyl-1, 2-*O*-isopropylidene-α-D-allofuranose* **4**:[12]

A solution of *1,2;5,6-di-*O*-isopropylidene-α-D-allose* **3**[11] (5.0 g, 19.2 mmol) in dry THF (44 cm^3) was added dropwise with stirring under a nitrogen atmosphere to a suspension of sodium hydride (60% dispersion in oil, 1.74g, 43.5 mmol, washed with anhydrous di-ethyl ether) in THF (7 cm^3) at 0°C. Once the addition was complete, the mixture was allowed to warm to room temperature and stirred for a further 45 minutes to allow for complete deprotonation.The solution was recooled to 0 °C and tetrabutylammonium iodide (67 mg, 0.18 mmol) and benzyl bromide (2.38 cm^3, 3.42 g, 20 mmol) were added. The mixture was refluxed for 1 hour and then allowed to cool to room temperature. The mixture was filtered through a thick Celite plug, and the residue washed with dry THF. The combined filtrate and washings were concentrated under reduced pressure to give the crude product as a viscous, yellow oil.

A solution of the above crude benzyl derivative in a mixture of methanol (47 cm^3), water (45 cm^3) and concentrated hydrochloric acid (0.25cm^3) was stirred at room temperature for 12 hours. The mixture was neutralised with concentrated ammonia solution, filtered and concentrated under reduced pressure. Flash chromatography (EtOAc-light petroleum, 2:1) of this residue gave *(+)-3-*O*-benzyl-1, 2-*O*-isopropylidene-α-D-*

allofuranose **4**[12] (4.52g, 76%, R_f 0.2) as a viscous, clear oil; υ_{max}(neat)/cm^{-1} 3445 br s (OH_{str}), 3094, 3068 and 3036 (CH_{aryl}), 2990 and 2938 s (CH_{str}), 1374 s ($C(CH_3)_2$); δ_H(300 MHz; $CDCl_3$) 1.35 (3H, s, CH_3), 1.57 (3H, s, CH_3), 2.63-2.77 (1H, br s, OH), 2.78-2.95 (1H, br s, OH), 3.68 (2H, d, *J* 6, 6-CH_2), 3.89-4.03 (2H, m, 3-H and 5-H), 4.06-4.14 (1H, dd, *J* 3 and 9, 4-H), 4.52-4.63 (2H, m, $PhCH_A$ and 2-H), 4.76 (1H, d, *J* 11.5, $PhCH_B$), 5.75 (1H, d, *J* 4, 1-H), 7.29-7.37 (5H, m, Ph).
(Found $[M]^+$ 310.14114. $C_{16}H_{22}O_6$ $[M]^+$ requires 310.14164)

*(1R, 2R, 3R)-3-*O*-Benzyl-1,2-*O*-isopropylidene-α-D-*ribo*-pentodialdofuranose* **5**:[8a]

A solution of sodium metaperiodate (4.29g, 0.02 mol) in water (22 cm^3) was added dropwise , with stirring to a solution of the diol **4**[12] (3.34g, 0.011 mol) in methanol (44 cm^3). After 1 hour at room temperature, the solvent was removed under reduced pressure giving a solid white residue. This residue was dissolved in water (40 cm^3), which was then extracted with chloroform (3 x 40 cm^3). The organic layers were dried ($MgSO_4$), filtered and the filtrate concentrated under reduced pressure to yield the crude *(1R, 2R, 3R)-3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-*ribo*-pentodialdofuranose* **5**[8a] (3.21g) which was used directly in the formation of the oxime **6** without further purification.

*(1R,2R,3R)-3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-*ribo*-pentodialdofuranose-*O*-methyl oxime* **6**:

To a solution of the crude aldehyde **5**[8a] (1.0g) in anhydrous dichloromethane (22cm^3) was added anhydrous pyridine (0.9 cm^3 0.012 mol) and *O*-methyl hydroxylamine hydrochloride (456 mg, 5.46 mmol). The reaction mixture was stirred under an atmosphere of nitrogen at room temp. for 2 hours. The resulting mixture was poured onto ice cold dil. hydrochloric acid (38 cm^3), which was then extracted with ethyl acetate (3 x 40 cm^3). The combined organic layers were washed with saturated sodium hydrogen carbonate solution (40 cm^3), water (40 cm^3), brine (40 cm^3), and then dried ($MgSO_4$). Concentration under reduced pressure and flash chromatography (light petroleum-EtOAc, 5:1) of the residue gave the methyl oxime **6** (760 mg, 72% overall yield from the diol **4**, R_f 0.13, light petroleum-EtOAc, 4:1) as a viscous, clear oil being an inseparable mixture of *E* and *Z* isomers (11:1 respectively); υ_{max}(neat)/cm^{-1} 2988 and 2939 (CH_{str}), 1630 w ($C{=}N_{str}$), 1374 ($C(Me)_2$), 1026 s ($C\text{-}O_{str}$);

E isomer; δ_H($CDCl_3$) 1.36 (3H, s, CH_3), 1.61 (3H, s, CH_3), 3.75 (1H, dd, *J* 9 and 4.4, 3-H), 3.89 (3H, s, OCH_3) 4.56-4.66 (2H, m, 2-H and 4-H), 4.63 (1H, d, *J* 12, $PhCH_A$), 4.74 (1H, d, *J* 12, $PhCH_B$), 5.75 (1H, d, *J* 3.6, 1-H), 7.25 (1H, d, *J* 6.6, 5-H), 7.35 (5H, m, Ph); δ_C($CDCl_3$) 26.54 (CH_3), 26.78 (CH_3), 62.27 (OCH_3), 72.16 (CH_2, OCH_2Ph), 75.76 (CH, C-3), 77.58 (CH, C-2), 79.78 (CH, C-4), 104.08 (CH, C-1), 113.42 (C, $C(CH_3)_2$), 127.89, 128.0, 128.06 and 128.47 (all CH, all Ph for mixture of *E* and *Z* isomers), 137.25 (C, Ph), 146.75 (CH, C-5).

Z isomer; δ_H($CDCl_3$) 1.36 (3H, s, CH_3), 1.61 (3H, s, CH_3), 3.64-3.70 (1H, dd, *J* 9.1 and 4.4, 3-H), 3.90 (3H, s, OCH_3), 4.56-4.66 (1H, m, 2-H), 4.63 (1H, d, *J* 12, $PhCH_A$), 4.74 (1H, d, *J* 12, $PhCH_B$), 5.28 (1H, dd, *J* 9.1 and 6.8, 4-H), 5.73 (1H, d, *J* 3.6, 1-H), 6.6 (1H, d, *J* 6.8, 5-H), 7.35 (5H, m, Ph); d_C($CDCl_3$) 26.54 (CH_3), 26.78 (CH_3), 62.27 (OCH_3), 70.46 (CH, C-3), 72.29 (CH_2, OCH_2Ph), 78.08 (CH, C-2), 80.23 (CH, C-4), 104.08 (CH, C-1), 113.42 (C, $C(CH_3)_2$), 127.89, 128.0, 128.06 and 128.47 (all CH, all Ph, for mixture of *E* and *Z* isomers), 137.25 (C, Ph), 148.05 (CH, C-5).
(Found $[M]^+$ 307.14050. $C_{16}H_{21}NO_5$ $[M]^+$ requires 307.14197)

(2R,3R,4R)-3-O-Benzyl-1,1-diethylthio-2,4-dihydroxy-pentanal-O-methyl oxime **7**:

To a stirred solution of the methyl oxime **6** (441 mg, 1.44 mmol) in ethanethiol (4 cm^3) at -10°C was added anhydrous zinc chloride (752mg, 5.53 mmol). After 1 hour the excess ethanethiol was evaporated under reduced pressure at -10°C. The remaining white solid residue was dissolved in ethyl acetate (30 cm^3) and sodium hydrogen carbonate solution (6 cm^3) added. The precipitate which formed was filtered off through a Celite plug and the remaining solids were washed with ethyl acetate (30 cm^3). The combined filtrate and washings were washed with brine (2 x 30 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography (light petroleum-EtOAc, 3:1) gave the dithioacetal **7** (444 mg, 83%, R_f 0.11) as a clear, colourless oil. The product being an inseparable mixture of *E* and *Z* isomers (3:1 respectively);
υ_{max} (neat)/cm^{-1} 3440 br s (OH_{str}), 3033 (CH_{aryl}), 2967, 2930 and 2873 (CH_{str}), 1605 w ($C{=}N_{str}$), 1043 ($C\text{-}O_{str}$);

E isomer; δ_H($CDCl_3$) 1.21-1.28 (6H, t, *J* 7.5, 2 x CH_3), 2.56-2.72 (4H, m, 2 x SCH_2), 3.87 (3H, s, OCH_3), 3.95 (1H, dd, *J* 7.5 and 3.5, 2-H), 4.0 (1H, dd, *J* 7.5 and 4.0, 3-H), 4.18 (1H, d, *J* 3.5, 1-H), 4.68 (1H, dd, *J* 5.2 and 4.0, 4-H), 4.70 (1H, d, *J* 11, $PhCH_A$), 4.80 (1H, d, *J* 11, $PhCH_B$), 7.35 (5H, m, Ph), 7.56 (1H, d, *J* 5.2, 5-H); δ_C($CDCl_3$) 14.49 (CH_3), 14.54 (CH_3), 25.20 (CH_2, SCH_2), 25.68 (CH_2, SCH_2), 54.73 (CH, C-2), 61.83 (CH_3, OCH_3), 70.79 (CH, C-3), 72.84 (CH, C-1), 73.48 (CH_2, OCH_2), 81.11 (CH, C-4), 127.87, 127.92, 128.04 and 128.45 (all CH, all Ph, for mixture of *E* and *Z* isomers), 137.92 (C, Ph), 149.33 (CH, C-5).

Z isomer; δ_H($CDCl_3$) 1.25 (6H, t, *J* 7.5, CH_3), 2.56-2.72 (4H, m, SCH_2), 3.91 (3H, s, OCH_3), 4.0 (1H, m, 2-H), 4.09 (1H, dd, *J* 8.0 and 3.0, 3-H), 4.12 (1H, d, *J* 3.5, 1-H), 4.70 (1H, d, *J* 11, $PhCH_A$), 4.81 (1H, d, *J* 11, $PhCH_B$), 5.17 (1H, dd, *J* 5.3 and 3.0, 4-H), 6.91 (1H, d, *J* 5.3, 5-H), 7.35 (5H, m, Ph); δ_C($CDCl_3$) 14.49 (CH_3), 14.54 (CH_3), 25.20 (CH_2, SCH_2), 25.68 (CH_2, SCH_2), 54.77 (CH, C-2), 62.11 (CH_3, OCH_3), 66.85 (CH, C-3), 73.06 (CH, C-1), 73.91 (CH_2, OCH_2), 80.16 (CH, C-4), 127.87, 127.92, 128.04 and 128.45 (all CH, all Ph, for mixture of *E* and *Z* isomers), 137.92 (C, Ph), 151.25 (CH, C-5).

(Found $[M]^+$ 373.13710. $C_{17}H_{27}NO_4S_2$ $[M]^+$ requires 373.13816)

(2R,3R,4R)-3-O-Benzyl-2,4-diacetoxy-1,1-diethylthiol-pentanal-O-methyl oxime **8**:

To a stirred solution of the *O*-methyl oxime **7** (150 mg, 0.4 mmol) in anhydrous pyridine (3 cm^3) under a nitrogen atmosphere was added a catalytic amount of 4-dimethylaminopyridine (5 mg, 4.1 x 10^{-5}mol) followed by dropwise addition of acetic anhydride (0.18 cm^3, 0.19g, 1.9 mmol), the reaction was stirred at 40°C for 18 hours. The excess pyridine was removed by azeotroping the reaction mixture several times with toluene under reduced pressure. Flash chromatography (light petroleum-EtOAc, 6:1) of the resulting residue gave *(2R,3R,4R)-3-O-benzyl-2,4-diacetoxy-1,1-diethylthiol-pentanal-O-methyl oxime* **8** (155 mg, 84 %, R_f 0.2) as a colourless, clear oil, the product being an inseparable mixture of *E* and *Z* isomers (2:1, respectively); υ_{max} (neat)/cm^{-1} 3033 (CH_{aryl}), 2970 and 2933 (CHstr), 1753 ($C{=}O_{str}$), 1631 w ($C{=}N_{str}$), 1372 ($OCOCH_3$);

E isomer; δ_H($CDCl_3$) 1.17-1.26 (6H, m, 2 x CH_3), 2.08 (3H, s, OCOMe), 2.10 (3H, s, OCOMe), 2.52-2.72 (4H, m, 2 x SCH_2), 3.85 (3H, s, OMe), 4.12 (1H, d, *J* 4.2, 1-H), 4.30 (1H, dd, *J* 7.6 and 2.4, 3-H), 4.67 (1H, d, *J* 11.2, $PhCH_A$), 4.80 (1H, d, *J* 11.2, $PhCH_B$), 5.34 (1H, dd, *J* 7.6 and 4.2, 2-H), 5.65 (1H, dd, *J* 6.4 and 2.4, 4-H), 7.33 (5H, m, Ph), 7.38 (1H, d, *J* 6.4, 5-H); δ_C($CDCl_3$) 14.13 (CH_3), 14.32 (CH_3), 20.92 (CH_3, OCOMe), 25.10 (CH_2, SCH_2), 25.54 (CH_2, SCH_2), 51.81 (CH, C-1), 61.90 (CH_3, OCH_3), 70.74 (CH, C-3), 72.40 (CH, C-2), 73.60 (CH_2, OCH_2), 79.22 (CH, C-4), 127.95, 127.99,

128.03, 128.33 and 128.41 (all CH, all Ph, for mixture of *E* and *Z* isomers), 137.47 (C, Ph), 145.16 (CH, C-5), 169.31 (C=O), 169.37 (C=O).

Z isomer; $\delta_H(CDCl_3)$ 1.17-1.26 (6H, m, 2 x CH_3), 2.09 (6H, s, 2 x OCOMe), 2.52-2.72 (4H, m, 2 x SCH_2), 3.94 (3H, s, OCH_3), 4.10 (1H, d, *J* 3.0, 1-H), 4.40 (1H, dd, *J* 8.6 and 1.8, 3-H), 4.61 (1H, d, *J* 11.2, $PhCH_A$), 4.80 (1H, d, *J* 11.2, $PhCH_B$), 5.44 (1H, dd, *J* 8.6 and 3.0, 2-H), 6.29 (1H, dd, *J* 5.3 and 1.8, 4-H), 6.54 (1H, d, *J* 5.3, 5-H), 7.33 (5H, m, Ph); $\delta_C(CDCl_3)$ 14.32 (CH_3), 14.39 (CH_3), 20.79 (CH_3, OCOCMe), 25.54 (CH_2, SCH_2), 25.74 (CH_2, SCH_2), 52.08 (CH, C-1), 62.36 (CH_3, OCH_3), 66.55 (CH, C-3), 71.97 (CH, C-2), 72.62 (CH_2, OCH_2), 77.72 (CH, C-4), 127.95, 127.99, 128.03, 128.33 and 128.41 (all CH, all Ph, for mixture of *E* and *Z* isomers), 137.38 (C, Ph), 145.70 (CH, C-5), 169.16 (C=O), 169.82 (C=O).

(Found $[M]^+$ 457.15912. $C_{21}H_{31}NO_6S_2$ $[M]^+$ requires 457.15929)

*(1R,2R,3R,4R,5R) and (1S,2R,3R,4R,5R)-3-*O*-Benzyl-2,4-diacetoxy-1-ethylthiol-5-*O*-methyl hydroxylaminocyclopentane*, **10** and **11**:

Tributyltin hydride (0.19 cm^3, 7.22 x 10^{-4}m) and AIBN (49 mg, 3 x 10^{-4}m) were added to a solution of *(2R,3R,4R)-3-*O*-benzyl-2,4-diacetoxy-1,1-diethylthiol-pentanal-*O*-methyl oxime* **8** (55 mg, 1.2 x 10^{-4}m) in anhydrous toluene (3 cm^3) under dry nitrogen. After 90 minutes at 90°C the reaction mixture was allowed to cool and the solvent removed under reduced pressure. The resulting residue was dissolved in acetonitrile (10 cm^3) which was then washed with hexane (3 x 10 cm^3). The combined hexane layers were backwashed with acetonitrile (10 cm^3), and the combined acetonitrile layers were concentrated under reduced pressure to afford a crude residue (91 mg). Flash chromatography (light petroleum-EtOAc, 4:1) gave the product (33mg, 70%, R_f 0.16) as a viscous oil, being an inseparable mixture of the diastereomers *(1R,2R,3R,4R,5R)* and *(1S,2R,3R,4R,5R)-3-*O*-benzyl-2,4-diacetoxy-1-ethylthiol-5-*O*-methyl hydroxylaminocyclopentane* **10** and **11** (2.8:1 respectively); υ_{max}(neat)/cm^{-1} 3249 (NH_{str}), 2936 (CH_{str}), 1740 ($C=O_{str}$), 1375 ($OCOCH_3$), 1233, 1121 and 1040 ($C\text{-}O_{str}$);

Major isomer: *(1R,2R,3R,4R,5R)-3-benzyloxy-2,4-diacetoxy-1-ethylthiol-5-*O*-methyl hydroxylaminocyclopentane* **10**; $\delta_H(CDCl_3)$ 1.27 (3H, t, *J* 7, SCH_2CH_3), 2.03 (3H, s, $OCOCH_3$), 2.04 (3H, s, $OCOCH_3$), 2.58 (2H, q, *J* 7, SCH_2), 3.52 (1H, d, *J* 7.3, 1-H), 3.52 (3H, s, OCH_3), 3.58 (1H, m, 5-H), 4.34 (1H, t, *J* 5.3, 3-H), 4.50 (2H, s, $PhCH_2$), 5.01 (1H, dd, *J* 7.3 and 5.3, 2-H), 5.18 (1H, dd, *J* 5.9 and 5.3, 4-H), 6.13 (1H, d, *J* 3.7, NH), 7.33 (5H, m, Ph); $\delta_C(CDCl_3)$ 15.17 (CH_3), 20.90 (CH_3, $OCOCH_3$), 25.25 (CH_3, $OCOCH_3$), 27.09 (CH_2, SCH_2), 49.29 (CH, C-1), 62.29 (OCH_3), 63.52 (CH, C-5), 74.07 (CH, C-3), 74.34 (CH_2, OCH_2), 75.98 (CH, C-2), 77.53 (CH, C-4), 127.53, 127.66, 127.76, 127.90 and 128.30 (all CH, all Ph, for mixture of **10** and **11**), 138.0 (C, Ph), 170.35 (C=O), 170.36 (C=O).

Minor isomer: *(1S,2R,3R,4R,5R)-3-benzyloxy-2,4-diacetoxy-1-ethanethiol-5-*O*-methyl hydroxylaminocyclopentane* **11**; $\delta_H(CDCl_3)$ 1.23 (3H, t, *J* 7.5, SCH_2CH_3), 2.06 (3H, s, $OCOCH_3$), 2.13 (3H, s, $OCOCH_3$), 2.58 (2H, q, *J* 7.5, SCH_2), 3.10 (1H, dd, *J* 10.2 and 4.6, 1-H), 3.34 (1H, ddd, *J* 10.2, 4.7 and 2.2, 5-H), 3.55 (3H, s, OCH_3), 3.89 (1H, dd, *J* 7.0 and 4.0, 3-H), 4.50 (1H, d, *J* 11.3, $PhCH_A$), 4.60 (1H, d, *J* 11.3, $PhCH_B$), 5.28 (1H, dd, *J* 7.0 and 4.7, H-4), 5.48 (1H, dd, *J* 4.6 and 4.0, 2-H), 6.04 (1H, d, *J* 2.2, NH), 7.33 (5H, m, Ph); $\delta_C(CDCl_3)$ 14.95 (CH_3), 20.94 (CH_3, $OCOCH_3$), 26.12 (CH_3, $OCOCH_3$), 26.62 (CH_2, SCH_2), 44.59 (CH, C-1), 62.81 (OCH_3), 71.05 (CH, C-5), 72.32 (CH, C-3), 72.63 (CH_2, OCH_2), 73.32 (CH, C-4), 76.21 (CH, C-2), 127.53, 127.66, 127.76, 127.90 and 128.30 (all CH, all Ph, for mixture of **10** and **11**), 137.84 (C, Ph), 170.36 (C=O), 170.87 (C=O).

(Found $[M]^+$ 397.15437. $C_{19}H_{27}NO_6S$ $[M]^+$ requires 397.15591)

ACKNOWLEDGEMENT

We thank Fisons Pharmaceuticals for a studentship (to PRM) supporting this work. Also, Dr Vladimir Sik for recording the NMR measurements and E. Underwood for the mass spectroscopic data.

REFERENCES

1. (a) Aoyagi, T., Yamamoto, T.; Kojiri, K.; Morishima, H.; Nagai, M.; Hamada, M.; Takeuchi, T.; Umezawa, H. *J. Antibiot.*, **1989**, *42*, 883. (b) Morishima, H.; Kojiri, K; Yamamoto, T.; Aoyagi, T.; Nakamura, H.; Iitaka, Y. *J. Antibiot.*, **1989**, *42*, 1008.

2. Tropea, J. E.; Kaushal, G. P.; Pastuszak, I.; Mitchell, M.; Aoyagi, T.; Molyneux, R. J.; Elbein, A. D. *Biochemistry*, **1990**, *29*, 10062.

3. King, S. B.; Ganem, B. *J. Am. Chem. Soc.*, **1991**, *113*, 5089.

4. Knapp, S.; Dhar, T. G. M. *J. Org. Chem.*, **1991**, *56*, 4096.

5. (a) Trost, B. M.; VanVranken, D. L. *J. Am. Chem. Soc.*, **1991**, *113*, 6317. (b) Trost, B. M.; Van Vranken, D. L. *J. Am. Chem. Soc.*, **1993**, *115*, 444.

6. Ogawa, S.; Yuming, Y. *J . Chem. Soc., Chem. Commun.*, **1991**, 890.

7. (a) King, S. B.; Ganem, B. *J. Am. Chem. Soc.*, **1994**, *116*, 562. Also, of related interest see Goering, B. K.; Ganem, B. *Tetrahedron Lett.*, **1994**, *35*, 6997.(b) Li, C.; Fuchs, P. L. *Tetrahedron Lett.*, **1994**, *35*, 5121.

8. (a) Roberts, S. M.; Shoberu, K. M. *J. Chem. Soc., Perkin Trans. 1*, **1992**, 2625.(b) Jones, M. F.; Roberts, S. M. *J. Chem. Soc., Perkin Trans. 1*, **1988**, 2927.(c) Ingall, A. H.; Moore, P. R.; Roberts, S. M. *J. Chem. Soc., Chem. Commun.*, **1994**, 83.

9. Yadav, V.; Fallis, A. G. *Tetrahedron Lett.*, **1989**, *30*, 3283; Yadav, V.; Fallis, A. G. *Tetrahedron Lett.*, **1988**, *29*, 897.

10. Cyclization using a substituted oxime as the radical trap has precedent in the literature, see Corey, E. J.; Pyne, S. G. *Tetrahedron Lett.*, **1983**, *24*, 2821. Hart, D. J.; Seely, F. L. *J. Am. Chem. Soc.*, **1988**, *110*, 1631. Bartlett, P. A.; McLaren, K. L.; Ting, P. C. *J. Am. Chem. Soc.*, **1988**, *110*, 1633. Marco-Contelles, J.; Martinez, L.; Martinez-Grau, A.; Pozuelo, C.; Jimeno, M. L. *Tetrahedron Lett.* ,**1991**, *32*, 6437. Marco-Contelles, J.; Ruiz, P.; Martinez, L.; Martinez-Grau, A. *Tetrahedron*, **1993**, *49*, 30, 6669.

11.Austin, G. N.; Baird, P. D.; Fleet, G. W. J.; Peach, J. M.; Smith, P. W.; Watkin, D. J. *Tetrahedron*, **1987**, *43*, 3095.

12. Fleet, G. W. J.; Smith, P. W. *Tetrahedron*, **1987**, *43*, 971.

13. Juste, G.; Luthe, C. *Can. J. Chem.*, **1980**, *58*, 1799.

14. Wilcox, C. S.; Thomasco, L. M. *J. Org. Chem.*, **1985**, *50*, 546.

(*Received* 19 *September* 1994)