Tetrahedron Letters, Vol.32, No.28, pp 3409-3412, 1991
Printed in Great Britain

0040-4039/91 $3.00 + .00
Pergamon Press plc

AN ENANTIOSPECIFIC APPROACH TOWARDS THE C_{10} SIDE-CHAIN OF BENGAMIDES

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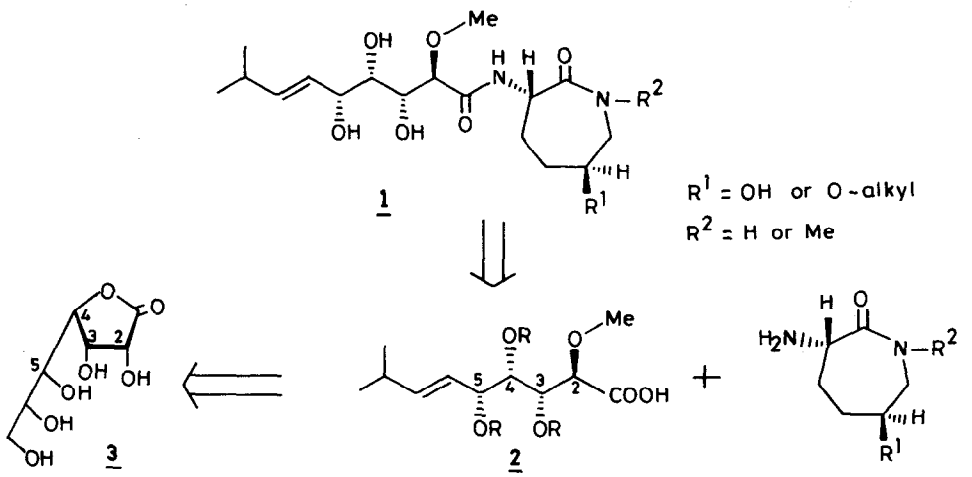
Abstract: An enantiospecific approach to the highly hydroxylated C_{10} side-chain, common to all bengamides, starting from α-D-gluco-heptonic γ-lactone, has been described.

Natural products, isolated from marine sponges, have attained special significance[1] due to novel structures and valuable biological profiles associated with them. During last few years, various families[2] of sponges have been systematically studied. For instance, from the Choristid sponge[3], a new category of amino acid derivatives, bengamides A-F (**1**), possessing anti-parasitic activity, were isolated. The structures of these amino acids were elucidated by chemical degradations and NMR spectral analysis. The novel chiral C_{10} side-chain [2-methoxy-3,4,5-trihydroxy-8-methylnon-6E-enoyl] (**2**), present in all bengamides, is a polyhydroxylated fatty acid containing E-3-methyl-1-buten terminal segment. The absolute stereochemical assignments were recently published[4]. Judging the nature of the side-chain (**2**), it seemed logical to utilise a carbohydrate as a precursor for its synthesis. We describe, therefore, the first approach towards the synthesis of C_{10} side-chain of bengamides starting from α-D-glucoheptonic γ-lactone (**3**). The idea



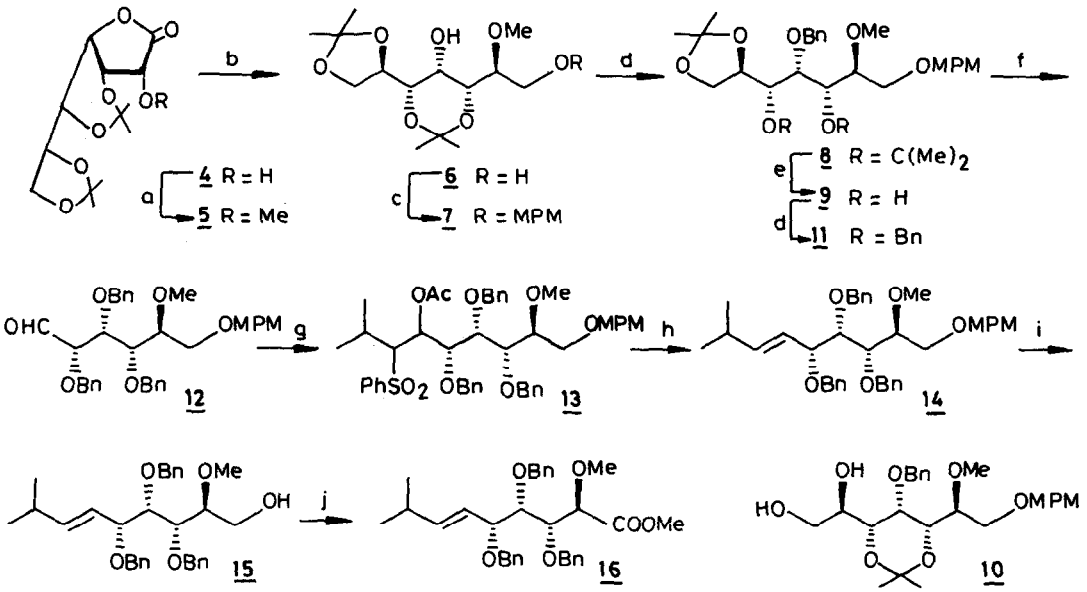
of selecting **3** for the present endeavour arises from the fact that chiralities at carbons C-2- to C-5 of the target molecule correlates with those of the starting material.

The synthesis began with conversion of **3** into the known[5] 3,5;6,7-di-O-isopropylidene derivative **4**, having a free OH group at C-2. The methyl group was introduced into **4** by stirring with excess of silver oxide-methyl iodide in CH_2Cl_2 under dark to give the 2-O-methyl derivative (**5**) (85%). The reduction of **5** with lithium aluminium hydride in dry THF under reflux gave the diol (**6**). In order to selectively protect the hydroxymethyl group, **6** was treated with 1 equivalent of sodium hydride and 1 equivalent of p-methoxybenzyl (MPM) bromide in dry THF to give **7** (70%). After conventional benzylation of **7**, the derived product **8** was subjected to selective hydrolysis with 0.8% sulfuric acid in methanol at room temperature to afford a chromatographically separable mixture of **9** and **10** in a ratio of 3:1. To determine the correct structures of **9** and **10**, periodate oxidation experiment was performed. For example, while compound **10** underwent smooth oxidation upon treatment with sodium periodate in ethanol compound **9** as expected resisted oxidation. Consequently, compound **9**[6] was benzylated and hydrolysed with PTSA in methanol. The resulting diol upon treatment with sodium periodate in ethanol at room temperature gave the aldehyde **12**.

The next critical step of the synthesis involved elaboration of (E)-3-methyl-1-butene terminal chain. The most reliable route for the problem in hand would be to utilise Julia's approach[7] of stereocontrolled elimination of acetoxysulfone (**13**) with sodium amalgam to generate E-geometry. Accordingly, isobutylphenylsulfone was treated with n-BuLi in THF at -30°C followed by the addition of **12** at the same temperature. After 1 h, the reaction mixture was worked-up and then acetylated in the presence of acetic anhydride, pyridine and a catalytic amount of DMAP to afford the acetoxysulfone (**13**). Subsequent elimination of acetoxysulfone functionality in **13** was performed in the presence of 6% sodium amalgam and sodium hydrogen phosphate in methanol at 0°C to afford **14** (50%). The stereochemical assignment of E-geometry was deduced by ^1H NMR spectrum in which the characteristic coupling constant (J = 15.7 Hz) was observed for the olefinic protons.

Further reaction was concerned with the cleavage of MPM group present in **14** by using DDQ in CH_2Cl_2 to get **15**. Compound **15** was oxidised by Jones reagent at 0°C in ether followed by esterification by diazomethane in ether to yield **16**[8]. The ^1H NMR and CI-MS were consistent with the structure.[9]

Scheme



a Moist Ag_2O, MeI, CH_2Cl_2, R T , 6h ; b . LAH , THF, Δ, 2h ; c . NaH (1eq), MPM-Br (1eq), THF, 0° - R T, 18h ; d . NaH , BnBr, THF, R T, 18h ; e . 0.8 % H_2SO_4, MeOH , R T, 48h ; f . i PTSA , MeOH, RT, 4h ; ii $NaIO_4$, EtOH , RT, 1h ; g i $PhSO_2$-$CH_2CH(Me)_2$, n-BuLi, THF, -30°C, 12 , 1h ; ii Ac_2O, Py, DMAP, R T, 3h ; h 6 % Na-Hg, Na_2HPO_4 , MeOH , 0°C, 2h ; i DDQ , CH_2Cl_2 , 1h ; j . i Jone's reagent , EtOEt , 0°C , 1h ; ii CH_2N_2 , EtOEt .

A simple and efficient chiron approach for the C_{10} side-chain framework of begamides starting from inexpensive and readily available α -D-glucoheptonic γ-lactone has been developed. Further work is in progress.

The authors wish to thank CSIR for the generous support under the 'Young Scientist Award Scheme'.

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4. Adamczeski, M., Quinoa, E. and Crews, P., J. Org. Chem., 1990, **55**, 240.
5. Brimacombe, J.S. and Tucker, L.C.N., Carbohydr. Res., 1965, **1**, 332.
6. Compound **10** could also be elaborated to the C_{10} side-chain segment of bengamide.
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8. All new compounds revealed satisfactory CH analysis.
9. Spectral Data: ^{1}H-NMR (δ,$CDCl_3$, 200 MHz): **7**; 1.34, 1.36 (2s, 6H), 1.45 (s, 6H), 3.30 (s, 3H), 3.80 (s, 3H), 3.48 (m, 2H), 3.68 (m, 3H), 4.09 (dd, 1H), 4.25 (dt, 1H), 4.70 (ABq, 2H), 6.85 (d, 2H), 7.35 (d, 2H); **9**; 1.28, 1.34 (2s, 6H), 3.30 (s, 3H), 3.70 (s, 3H), 4.50 (s, 2H), 4.60 (ABq, 2H), 6.80 (d, 2H), 7.22 (d, 2H), 7.35 (m, 5H); **14**; 0.95, 0.97 (2d, 2H, J=6.5 Hz), 2.25 (m, 1H), 3.29 (s, 3H), 3.76 (s, 3H), 4.55 (m, 6H), 5.38 (dd, 1H, J=15.7, 7.0 Hz), 5.55 (dd, 1H, J=15.7, 6.5 Hz), 6.82 (d, 2H), 7.5 (m, 17H); **15**; 0.95, 0.97 (2d, 6H, J=6.7 Hz), 2.31 (m, 1H), 2.94 (1H, OH), 3.41 (s, 3H), 4.50 (m, 6H), 5.32 (dd, 1H, J=15.7, 7.0 Hz), 5.57 (dd, 1H, J=15.7, 6.7 Hz), 7.30 (m, 15H); **16**; 0.98 (d, 6H, J=6.7 Hz), 2.31 (m, 1H), 3.30 (s, 3H), 3.46 (s, 3H), 4.50 (m, 6H), 5.37 (dd, 1H, J=15.7, 7.0 Hz), 5.73 (dd, 1H, J=15.7, 6.7 Hz); Mass Spectrum: **7**; MS:m/z 426 (M^+); **16**; CI-MS:m/z 533 (M^++1).

IICT COMMUNICATION NO. 2767

(Received in UK 23 April 1991)