Tetrahedron Letters,Vol.30,No.47,pp 6503-6506,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Pergamon Press plc

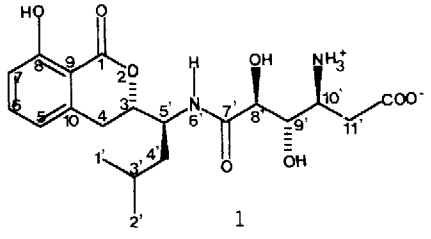
CHIRAL SYNTHESIS OF THE HYDROXY AMINO ACID MOIETY OF AI-77-B

J.P. GESSON*, J.C. JACQUESY and M. MONDON

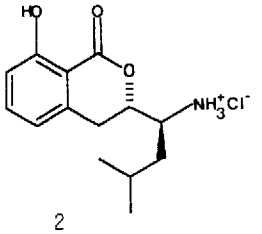
Laboratoire de Chimie XII, associé au CNRS
40, Avenue du Recteur Pineau - 86022 POITIERS (France)

ABSTRACT : Chiral synthons of the hydroxy amino acid moiety of AI-77-B, a potent antiulcerogenic compound, have been prepared from the known trifluoroacetamide **3** by reductive opening of the 4,6-O-benzylidene group followed by sequential oxidations at C-1 and C-6. Final oxidation at C-1 (after C-6) to a lactone is shown to proceed in better overall yield than the reverse process.

The AI-77s are a small group of related substances isolated from the culture broth of *Bacillus pumilus AI-77*. The major compound AI-77-B **1** has been shown to have a potent antiulcerogenic activity against stress ulcers without anticholinergic, antihistaminergic or central suppressive effects.[1,2] The absolute stereostructure of **1** has been determined from spectral data and by X-ray analysis together with chemical studies.[3]
The interest in this new class of antiulcer agents has led Shioiri[4] to complete the first total synthesis of AI-77-B by coupling the aminodihydroisocoumarin **2** to a protected hydroxy amino acid moiety (this author has also recently proposed a synthesis of another protected form of the latter[5]). We report here a new chiral synthesis of the amino acid part of **1**.



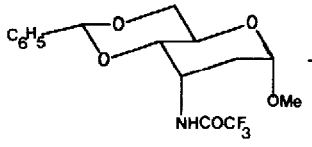
1



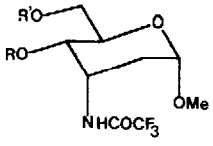
2

Trifluoroacetamide **3**, a known intermediate in the Horton synthesis of L-daunosamine (easily prepared from methyl-α-D-mannopyranoside[6] or from a methyl-α-D-glucopyranoside[7]) does have absolute configurations at C-3 and C-4 identical with those found respectively at C-10′ and C-9′ of **1** . Conversion of **3** to a suitably protected form of the amino acid

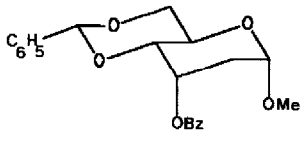
moiety of **1** requires therefore oxidation at C-1 and C-6 of **3**, after selective protection of the alcohol group at C-4. For this purpose the reductive cleavage of the 4,6-O-benzylidene group was considered. This reaction is known to depend on the nature of the substituent at C-3 and on the reducing agent : the presence of a bulky group at C-3 and/or the use of $NaBH_3CN$-HCl[8] favor the formation of a 6-O-benzyl derivative (e.g. **5**) while the presence of an OH group and/or the use of Lewis acid ($AlCl_3$) favor the 4-O-benzyl isomer[9] (e.g. **4**). Treatment of **3** with Et_3SiH-$TiCl_4$[10] for 30 min at -70°C affords a single compound **5**[11] in 89% isolated yield. The direction of hydrogenolysis is unambiguously demonstrated by benzoylation of the alcohol function at C-4 to **6**[11] (82%) which is characterized by a doublet of doublet ($J_{H-4,\ H-5}$=10.6 Hz and $J_{H-4,\ H-3}$=4.0 Hz) centered at 5.31 ppm for H-4. The unexpected formation of **5** results from complexation of the more hindered O-4. The presence of a vicinal nitrogen atom is crucial for this process since the opposite mode of opening has been observed for benzoate **8** using the same conditions.[12]



3



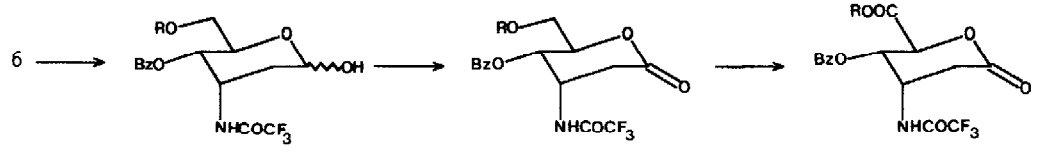
4 R = Bn, R' = H
5 R = H, R' = Bn
6 R = Bz, R' = Bn
7 R = Bz, R' = H



8

Starting from **6**, two strategies may be used to synthetize AI-77-B and analogs : either preparation of a fully oxidized chiron such as **13**, or preparation of acid **15** followed by oxidation at C-1 after derivatization. These will be successively discussed.

Hydrolysis of **6** to **9** turns out to be tedious : under the best conditions (CF_3COOH/H_2O : 80/20, 20°C, 6 days) there is obtained 61% of **9**[11], mp 166-167°C together with 26% of unreacted starting material.[13] Oxidation of **9** using Fétizon's reagent cleanly affords lactone **11**[11], mp 45°C (98%), whose benzyl group is then cleaved (H_2, Pd/C) to give **12**[11], mp 72-75°C (63%).[14]



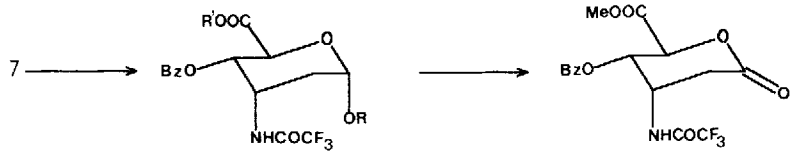
9 R = Bn
10 R = H

11 R = Bn
12 R = H

13 R = H
14 R = tBu

Final oxidation of the primary alcohol group to acid **13** was difficult to achieve[15] : the t-butyl ester **14**[11], mp 141-143°C, could be obtained in only 25% yield using Corey's conditions[16] (CrO_3/pyridin (1/2)-Ac_2O-tBuOH, CH_2Cl_2/DMF : 80/20, 20°C, 16h). The low yield in this last step[17] and the difficulties encountered in the hydrolysis of **6** prompt us to study the second strategy (vide infra).

Hydrogenolysis of **6** gives alcohol **7**[11] (H_2, Pd/C, 98%) which can be efficiently converted, using cat. $RuCl_3$-$NaIO_4$ (4.1 eq.)-($CH_3CN/CH_2Cl_2/H_2O$: 3/2/2, 20°C, 3h)[18], to acid **15** and then to ester **16**[11], mp 60-61°C, after treatment with CH_2N_2,(86% overall). After hydrolysis (CF_3COOH/H_2O : 80/20, 20°C, overnight) to **17**[11] (57% together with 17% of **16**)[12] the desired lactone **18**[11] is obtained in 98% yield after oxidation using excess Br_2-$CaCO_3$ (CH_3CN/H_2O : 5/1).[19]



15 R = Me, R' = H

16 R = R' = Me

17 R = H, R' = Me

18

In conclusion the conversion of the readily available amide **3** to useful chirons for synthesis of AI-77s has been completed in a few steps. Formation of the lactone after side-chain oxidation appears to be more efficient than the reverse process.

REFERENCES and NOTES

1.Shimojima,Y.;Hayashi,H.;Ooka,T.;Shibukawa,M. *Agric.Biol.Chem.***1982**,*46*,1823.
2.Shimojima,Y.;Hayashi,H.;Ooka,T.;Shibukawa,M.;Iitaka,Y. *Tetrahedron Lett.***1983**,*26*,1370.
3.Shimojima,Y.;Hayashi,H.;Ooka,T.;Shibukawa,M.;Iitaka,Y. *Tetrahedron*,**1984**,*40*,2519.
4.Hamada,Y.;Kawai,A.;Kohno,Y.;Hara,O.;Shioiri,T. *J.Am.Chem.Soc.***1989**,*111*,1524.
5.Kawai,A.;Hara,O.;Hamada,Y.;Shioiri,T. *Tetrahedron Lett.***1988**,*29*,6331.
6.Horton,D.;Weckerle,W. *Carbohydr.Res.***1975**,*44*,227.
7.Crugnola,A.;Lombardi,P;Gandolfi,C.;Arcamone,F. *Gazz.Chim.Ital.***1981**,*111*,395.
8.Garegg,P.J.;Hultberg,H.;Wallin,S. *Carbohydr.Res.***1982**,*108*,97.
9.Gelas,J. *Adv.Carbohydr.Chem.Biochem.***1981**,*39*,71.
10.Mori,A.;Ishihara,K.;Arai,I.;Yamamoto,Y. *Tetrahedron*,**1987**,*43*,755.
Doyle,M.P.;Debruyn,D.J.;Kooistra,D.A. *J.Am.Chem.Soc.***1972**,*94*,3659.
11.All new compounds have been characterized by elemental analysis and/or HRMS, IR and NMR. Chemical shifts relative to TMS (solvent : $CDCl_3$) as internal standard are given below (Bruker WP 200 SY).
5: oil, $[\alpha]_D$ +29° (c 1.5,$CHCl_3$). NMR : 2.00 (m,2H), 2.74 (s,OH), 3.41 (s,OMe), 3.74 (s,2H,H-6), 3.93 (m,1H), 4.49 (m,1H), 4.60 (ABq,2H), 4.83 (s,1H), 7.33 (s,5H), 7.95 (s,1H).
6 : oil, $[\alpha]_D$ +73° (c 1.2, $CHCl_3$). NMR : 2.0 (dd, J = 15 and 2.8 Hz, H-2), 2.23 (dt, J=15 and 3.7 Hz, H'-2), 3.49 (s,OMe), 3.66 (d, J = 3.2 Hz, O-CH2), 4.11 (dt, J = 10.6 and 3.2

Hz, H-5), 4.48 and 4.63 (ABq, J=12.3 Hz, CH_2-Ph), 4.81 (m, H-3), 4.92 (d, J = 2.8Hz, H-1), 5.31 (dd, J = 10.6 and 4 Hz, H-4), 7.1-7.9 (10H), 8.04 (d, J=8.5 Hz, NH).

7 : mp 85-87°C, $[\alpha]_D$ +31° (c 1, $CHCl_3$). NMR : 2.05 (dd, J = 14.6 and 2.8 Hz, H-2), 2.21 (dt, J = 14.6 and 3.7 Hz, H'-2), 3.49 (s, OMe), 3.69 (dd, J = 12.5 and 3.7 Hz, H-6), 3.81 (dd, J = 12.5 and 2.5 Hz, H'-6), 3.97 (dt, J = 10.6 and 3 Hz, H-5), 4.82 (m, H-3), 4.94 (d, J = 2.8 Hz, H-1), 5.23 (dd, J = 10.6 and 4 Hz, H-4), 7.43 (t, J = 7.4 Hz, 2H), 7.57 (t, J = 7.4 Hz, 1H), 7.93 (d, J = 7.4 Hz, 2H), 8.08 (d, J = 7.8 Hz, NH).

9 : mp 166-167°C, $[\alpha]_D$ +23° (c 1,$CHCl_3$). NMR : 2.03 (dd, J=15 and 2 Hz,H-2), 2.19 (d, J=15Hz,H'-2), 3.63 (d, J = 3.8Hz, 2H, H-6), 3.74 (OH), 4.4 (m, H-5), 4.48 and 4.60 (2d, J=12.2Hz, -CH_2Ph), 4.84 (m,H-3), 5.20 (dd, J=10.6 and 4 Hz, H-4), 5.48 (s, H-1), 7.23 (m, 5H), 7.42 (t, J= 7.3Hz, 2H), 7.57 (t, J = 7.3 Hz, 1H), 7.87 (d, J = 7.3 Hz, 2H), 8.18 (d, J = 8 Hz, NH).

11 : mp 45°C, $[\alpha]_D$ -53° (c 1, $CHCl_3$). NMR : 2.73 (dd, J = 17.6 and 10.5 Hz, H-2), 2.94 (dd, J = 17.6 and 6.6 Hz, H'-2), 3.77 (s, 2H, H-6), 4.58 (ABq, CH_2Ph), 4.71 (m, H-5), 5.08 (m, H-3), 5.54 (t, J = 2.6 Hz, H-4), 7.22 (NH), 7.33 (s, 5H), 7.43 (t, J = 7.4 Hz, 2H), 7.59 (t, J = 7.4 Hz, 1H), 7.98 (d, J = 7.4 Hz, 2H).

12 : mp 72-75°C, $[\alpha]_D$ - 73° (c 1, $CHCl_3$). NMR : 2.82 (dd, J = 17.7 and 9.4 Hz, H-2), 3.12 (dd, J = 17.7 and 6.2 Hz, H'-2), 3.89 (dd, J = 12.4 and 2 Hz, H-6), 3.98 (dd, J = 12.4 and 3 Hz, H'-6), 4.72 (q, J = 3 Hz, H-5), 5.03 (m, H-3), 5.55 (t, J = 3 Hz, H-4), 7.33 (d, NH), 7.47 (t, J = 7.5 Hz, 2H), 7.62 (t, J = 7.5 Hz, 1H), 7.99 (d, J = 7.5 Hz, 2H).

14 : mp 141-143°C, $[\alpha]_D$ - 46° (c 0.6, $CHCl_3$). NMR : 1.59 (s, 9H), 2.82 (dd, J = 17.8 and 11.5 Hz, H-2), 3.02 (dd, J = 17.8 and 7.1 Hz, H'-2), 4.55 (m, H-3); 5.11 (d, J = 2.4 Hz, H-5), 5.70 (t, J = 2.4 Hz, H-4), 7.18 (d, J = 7.4 Hz, NH), 7.47 (t, J = 7.4 Hz, 2H), 7.63 (t, J = 7.4 Hz, 1H), 8.02 (d, J=7.4 Hz, 2H).

16 : mp 122-123°C, $[\alpha]_D$ +53° (c 0.8, $CHCl_3$). NMR : 2.06 (dd, J = 14.6 and 2.8 Hz, H-2), 2.28 (dt, J = 14.6 and 3.7 Hz, H'-2), 3.52 (s, OMe), 3.71 (s, OMe), 4.51 (d, J = 10.4 Hz, H-5), 4.84 (m, H-3), 5.00 (d, J = 2.8 Hz, H-1), 5.37 (dd, J = 10.4 and 4 Hz), 7.42 (t, J = 7.4 Hz, 2H), 7.57 (t, J = 7.4 Hz, 1H), 7.92 (d, J = 7.4 Hz, 2H).

17 : mp 60-61°C, $[\alpha]_D$ -11° (c 1, $CHCl_3$). NMR : 3.70 (s, 3H), 4.76 (d, J = 10 Hz, H-5), 4.86 (m, 3H), 5.37 (dd, J = 10 and 4 Hz, H-4), 5.55 (s, H-1), 7.42 (t, J = 7.4 Hz, 2H), 7.56 (t, J = 7.4 Hz, 1H), 7.93 (d, J = 7.4 Hz, 2H), 8.04 (d, J = 8.5 Hz, NH).

18: mp 130-134°C, $[\alpha]_D$ -28° (c 0.6, $CHCl_3$). NMR : 2.81 (dd, J = 17.8 and 11.4 Hz, H-2), 3.15 (dd, J = 17.8 and 6.8 Hz, H'-2), 3.93 (s, OMe), 4.55 (m, H-3), 5.23 (d, J = 2.2 Hz, H-5), 5.72 (t, J = 2.2 Hz, H-4), 7.14 (NH), 7.50 (t, J = 7.5 Hz, 2H), 7.66 (t, J = 7.5 Hz, 1H), 8.04 (d, J = 7.5 Hz, 2H).

12.C. David, J.P. Gesson and J.C. Jacquesy, unpublished results.

13.Increase of the reaction time or of the temperature leads to complex mixtures, cleavage of the benzyl group being also observed in this case.

14.Hydrogenolysis of the corresponding acetate (instead of the benzoate) gives a mixture of products.

15.Complex mixtures were obtained using $RuCl_3$-$NaIO_4$, Swern or Jones reagents. No reaction was observed with Fétizon's reagent or CrO_3-2 Py.

16.Corey,E.I.;Samuelsson, B. *J.Org.Chem.***1984**,*49*,4735.

17.Attempted oxidation of both terminal functions of **10** using different systems was unsuccessful.

18.Carlsen,P.H.J.;Katsuki,T.;Martin,V.S.;Sharpless,K.B. *J.Org.Chem.***1981**,*46*,3936.

19.The crude mixture was rapidly filtered over Florisil. This material decomposes rapidly over silica and this instability may explain the low yield observed in the last oxidation step of the first sequence.

(Received in France 14 June 1989)