Tetrahedron Letters,Vol.27,No.27,pp 3205-3208,1986 0040-4039/86 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

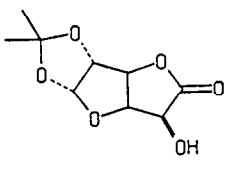
ENANTIOSPECIFIC SYNTHESES OF 2S,3R,4R,5S-TRIHYDROXYPIPECOLIC ACID, 2R,3R,4R,5S-TRIHYDROXYPIPECOLIC ACID, 2S,4S,5S-DIHYDROXYPIPECOLIC ACID, AND BULGECININE FROM D-GLUCURONOLACTONE

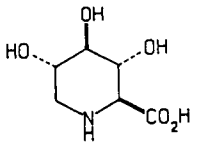
B. P. Bashyal, H.-F. Chow and G. W. J. Fleet

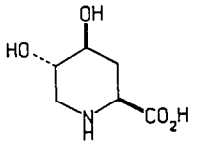
Dyson Perrins Laboratory, Oxford University, South Parks Road, Oxford, OX1 3QY, UK

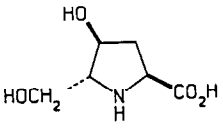
The potential of D-glucuronolactone as a starting material for the synthesis of polyfunctional amino acids is illustrated by its conversion to 2S,3R,4R,5S-trihydroxypipecolic acid, 2R,3R,4R,5S-trihydroxypipecolic acid, 2S,4S,5S-dihydroxypipecolic acid, and bulgecinine.

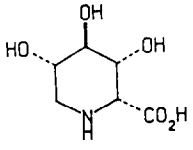
D-Glucuronolactone is a cheap chiral compound which reacts efficiently[1] with acetone to form the isopropylidene derivative (1) in which only the C-5 hydroxyl group is unprotected, allowing the introduction of a nitrogen function at C-5 with controlled stereochemistry.[2] This paper describes the synthesis from glucuronolactone of the naturally occurring L-amino acids, 2S,3R,4R,5S-trihydroxypipecolic acid (2),isolated from the seeds of Baphia racemosa[3] and shown to be a glucuronidase and iduronidase inhibitor,[4] 2S,4S,5S-dihydroxypipecolic acid (3), isolated from the leaves of Derris eliptica[5], and of bulgecinine [2S,4S,5R-4-hydroxy-5-(hydroxymethyl)proline] (4)[6], a constituent of the bulgecin glycopeptide antibiotics.[7] The synthesis of the D-amino acid, 2R,3R,4R,5S-trihydroxypipecolic acid (5) is also reported.


(1)

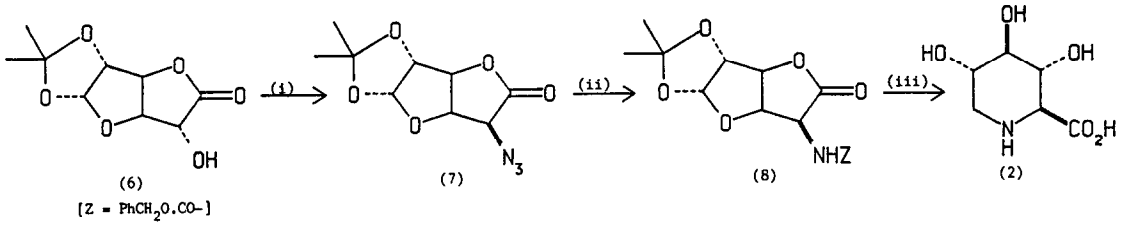

(2)


(3)


(4)


(5)

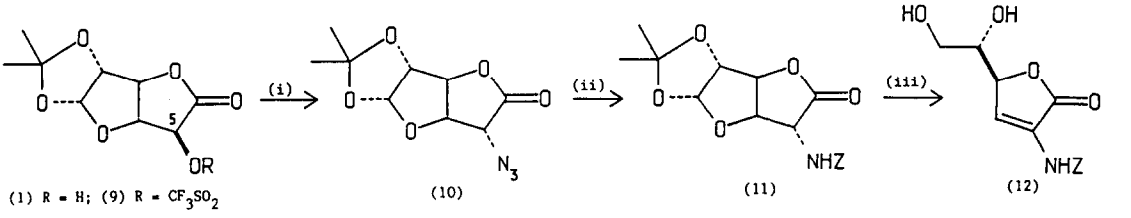
For the synthesis of the L-amino acid (2), it is necessary to introduce nitrogen with overall retention of configuration at C-5 of glucuronolactone, and then to connect the nitrogen function with C-1. Thus, (1) was first converted to the ido compound (6), m.p.137-138°, {lit.[8] m.p. 137-138°} in 78% yield as previously reported.[8] Conversion of (6) to the corresponding triflate followed by treatment with sodium azide in DMF gave the gluco-azide (7)[2] which on palladium catalysed hydrogenation and subsequent protection with benzyl chloroformate formed the carbamate (8)[9], m.p. 142-144°, $[\alpha]_D^{20}$ +40.4° (c, 0.9 in $CHCl_3$), in 44% yield from (6) [Scheme 1]. The isopropylidene protecting group in (8) was removed by aqueous trifluoroacetic acid; the resulting lactol on catalytic hydrogenation in the presence of palladium black in aqueous acetic acid underwent intramolecular



(i) $(CF_3SO_2)O$, pyridine, CH_2Cl_2,-20°; then NaN_3, DMF, -10° to -20°, 1h (ii) H_2, 10% Pd/C, EtOAc; then $PhCH_2OCOCl$, $NaHCO_3$, $EtOAc/H_2O$ (iii) CF_3COOH/H_2O, room temp; then H_2, palladium black, H_2O/AcOH (9:1), 4 days

SCHEME 1

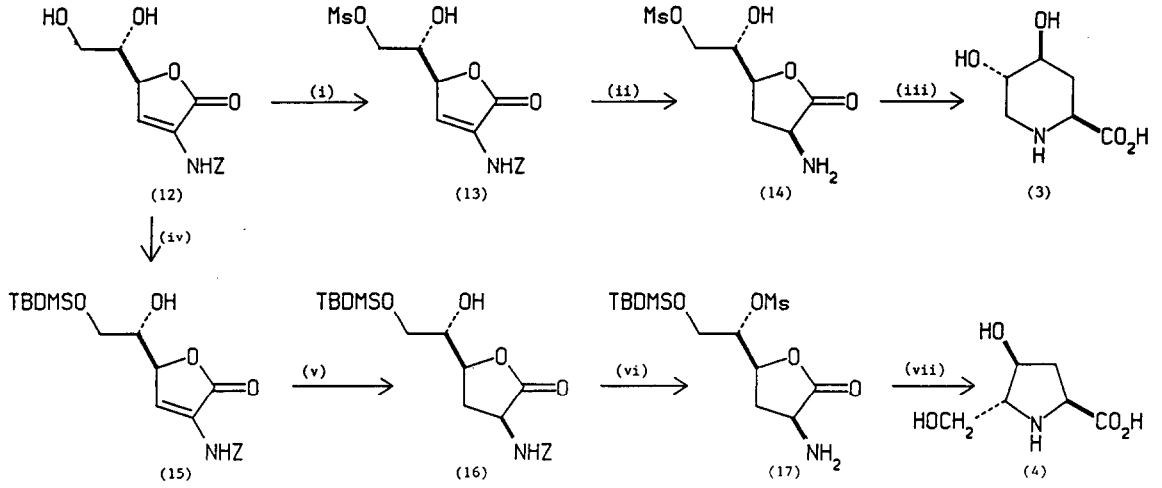
reductive amination and hydrolysis of the lactone to give, after purification by ion exchange chromatography, 2S,3R,4R,5S-trihydroxypipecolic acid (2), as white needles (from ethanol-water), m.p. 228-232°, (lit. m.p. 228-230°), in 60% yield, identical with an authentic sample.[10] A synthesis of (2) from glucose has been reported.[11]



(i)NaN_3, DMF, -20°, 5h (ii)H_2, Pd/C, EtOAc, 20°, 3h; then $PhCH_2OCOCl$, $NaHCO_3$, $EtOAc/H_2O$, 0°, 10 min (iii) MeONa/MeOH, 0°, 1 min; then $NaBH_4$, MeOH, 0°, 5min

SCHEME 2

The synthesis of the amino acids (3) -(5) involves introduction of nitrogen at C-5 with inversion of configuration. Thus the isopropylidene glucuronolactone (1) was reacted with trifluoromethane sulphonic anhydride in dichloromethane in the presence of pyridine at -30° to form the triflate (9)[8] which on treatment with sodium azide in DMF at -20° gave the azide, (10), m.p.114-116° $[\alpha]_D^{20}$ +243° (c, 1.1 in $CHCl_3$) {lit.[2] m.p. 115°, $[\alpha]_D^{20}$ +233° (c, 1.03 in $CHCl_3$)} in 84% yield [Scheme 2]. Hydrogenation of the azide (10) in the presence of palladium followed by protection as the benzyloxycarbonyl compound gave (11), $[\alpha]_D^{20}$ +83.6° (c, 0.58 in $CHCl_3$) {lit[12] $[\alpha]_D^{20}$ +85.5° (c, 0.4 in $CHCl_3$)} (72% yield). Treatment of the protected lactone (11) with base caused the anticipated fragmentation to give, after treatment with sodium borohydride, the unsaturated diol (12), m.p. 148-150° $[\alpha]_D^{20}$ +54.7° (c,0.17 in EtOH) (91% yield). The diol (12) is a suitable divergent intermediate for the synthesis of both the dihydroxypipecolic acid and of bulgecinine and may thus be readily prepared in an overall yield of 55% from (1) on a 5-10 gm scale.



[Ms = $MeSO_2$-; Z = $PhCH_2O.CO$-; TBDMS = t-$BuMe_2Si$-]

(i)$MeSO_2Cl$ (1.1 equiv), pyridine, -20°, 30h (ii) H_2, Pd black, EtOAc, pyridine, 20°, 11 h (iii) 0.1M KOH in EtOH-H_2O (1:1), 20°, 5 min (iv) t-$BuMe_2SiCl$, Et_3N, DMF, CH_2Cl_2, dimethylaminopyridine (v) Pd black, H_2, EtOAc, pyridine, 20°, 24 h; then $PhCH_2OCOCl$, $NaHCO_3$ in EtOAc -H_2O, 1 h (vi) $MeSO_2Cl$, pyridine, dimethylaminopyridine, 20°, 24 h; then 10% Pd/C, EtOAc - EtOH, (vii) $NaHCO_3$, EtOH/H_2O, room temp., 12h; then 2M HCl, room temp, 4h, THF

SCHEME 3

Selective esterification of (12) with methane sulphonyl chloride gave the primary mesylate (13), m.p.139-140°, $[\alpha]_D^{28}$ +30.7° (c, 0.30 in EtOAc) (80% yield) [Scheme 3] which was reduced with hydrogen in the presence of palladium black to give a single diastereomeric aminomesylate (14) (quantitative). Treatment of (14) with potassium hydroxide in aqueous ethanol, followed by purification by ion exchange chromatography gave 2S,4S,5S-dihydroxypipecolic acid (3) in 82% yield {66% from (6) and 37% from (1)}; bulgecinine (4) was formed as a minor product (about 6%) in this reaction. The synthetic dihydroxypipecolic acid (3) as the hydrochloride, $[\alpha]_D^{28}$ +23.5° (c, 0.32 in 2N HCl) {lit[5] $[\alpha]_D^{20}$ +19.5° (c, 0.15 in 2N HCl) had physical properties in agreement with those previously reported[5] and was identical to an authentic sample.[10]

Alternatively, protection of the primary alcohol in (12) as the tert-butyl dimethylsilyl ether (15), m.p. 107-107.5°, $[\alpha]_D^{28}$ +41° (c, 1.1 in EtOAc) (92% yield), followed by hydrogenation and then reprotection of the amine as the carbamate gave (16), (66% yield) in which only the original C-2 OH group of glucuronolactone is unprotected. Mesylation of (16), followed by removal of the benzyloxycarbonyl protecting group by hydrogenolysis, gave (17), m.p. 116-120° (quantitative yield). Sequential treatment of (17) with bicarbonate and dilute acid, gave after purification by ion exchange chromatography bulgecinine (4),

$[\alpha]_D^{24}$ -12° (c, 0.45 in water) {lit[6] $[\alpha]_D^{20}$ -13.1° (c, 0.95 in water)} in 75% yield [46% overall yield from (12); 26% yield from (1)]. The properties[13] of this synthetic (4), including the details of the 1H NMR spectrum, are in agreement with literature data for bulgecinine (4); a synthesis of (4) from glucose has been recently reported.[14]

The synthesis of the D-amino acid (5) was acheived by aqueous trifluoroacetic acid hydrolysis of the acetonide in the ido-azide (10) to the corresponding azidolactol, which on catalytic hydrogenation in aqueous acetic acid resulted in both hydrolysis of the lactone together with intramolecular reductive amination to form the D-amino acid, 2R,3R,4R,5S-trihydroxypipecolic acid (5),[12] [FAB MS, $(M+H)^+$ m/e 178] m.p.198-202°, $[\alpha]_D^{20}$ +34° (c, 0.25 in water) {35% from (10)}. The ido configuration is indicated by the small coupling constant (J, 2.5Hz) between H2 (on the carbon adjacent to the carboxyl group) and H3 in the 1H NMR of (5), while the 13C NMR spectrum of (5) is similar to, but significantly different from, the epimeric L-amino acid (2);[15] the biological properties of (5) will be reported elsewhere.

Although the yields in these syntheses have not been optimised, this work indicates that glucuronolactone may be of value in the synthesis of amino acids.[16]

REFERENCES

1. T.Kitihara, T.Ogawa, T.Naganuma and M.Matsui, Agr. Biol. Chem., 1974, 38, 2189.
2. J.Schweng and E.Zbiral, Tetrahedron Lett., 1978, 119.The Mitsonobu reaction of (1) with triphenylphosphine - diethylazodicarboxylate - hydrazoic acid gives a mixture of the two epimeric azides (7) and (10) in a ratio of 2:1 and a combined yield of 75%; this procedure is not attractive for the preparation of substantial amounts of the azides, since the epimers have to be separated by careful column chromatography and the use of hydrazoic acid on a large scale should be avoided. We are grateful to Professor Zbiral for providing full experimental details of this procedure and of the characterisation of the epimers.
3. K.S.Manning, D.G.Lynn, J.Shabanowitz, L.E.Fellows, M.Singh and B.D.Schrire, J. Chem. Soc., Chem. Commun.,1985, 127.
4. I.C.di Bello, P.Dorling, L.Fellows and B.Winchester, FEBS Lett., 1984, 176, 61.
5. M.Marlier, G.Dardenne and J. Casimir, Phytochemistry, 1976, 15, 183.
6. S.Shinagawa, F.Kasahara, S.Harada and M.Asai, Tetrahedron, 1984, 40, 3465.
7. A.Imada, K.Kintaka, M.Nakao and S.Shinagawa, J. Antibiot., 1985, 38, 17.
8. R.Cauk, H.Honig, J. Nimpf and H. Weidmann, Tetrahedron Lett., 1980, 21, 2135
9. Satisfactory spectral and/or analytical data have been obtained for all new compounds reported in this paper.
10.We are grateful to Dr. L.E.Fellows of the Royal Botanic Gardens at Kew for authentic samples of (2) and of the hydrochloride of (3).
11.R.C.Bernotas and B.Ganem, Tetrahedron Lett., 1985, 26, 4981.
12.H.Paulsen and E.Mackel, Chem. Ber., 1973, 106, 1525. The preparation of the D-amino acid (5) by hydrolysis of (11) and subsequent hydrogenation is indicated in this paper, but no isolation of (5), nor any characterisation of (5) is reported.
13.For example,for synthetic bulgecinine (4) 13C NMR (D_2O) δ 174.6(s), 71.2(d), 67.4(d), 60.0(d), 58.7(t), and 37.1(t). Reported values (ref.6) for (4) 13C NMR (D_2O) δ 174.4(s), 71.3(d), 67.6(d), 60.1(d), 58.8(t), and 37.3(t).
14.T.Wakamiya, K.Yamanoi, M.Nishikawa and T.Shiba, Tetrahedron Lett.,1985,26,4759.
15. 13C NMR (D_2O) of D-amino acid (5) δ 45.89 (t), 59.12 (d), 67.12 (d), 68.94 (d), 69.68 (d), 173.3 (s). Compare 13C NMR (D_2O) of L-amino acid (2) δ 45.99 (t), 61.86 (d), 67.78 (d), 70.96 (d), 76.54 (d), 172.52(s).

16. SERC Post-doctoral fellowships (to BPB and H-FC) are gratefully acknowledged.

(Received in UK 11 April 1986)