Tetrahedron Letters,Vol.23,No.43,pp 4509-4512,1982 0040-4039/82/434509-04$03.00/0
Printed in Great Britain

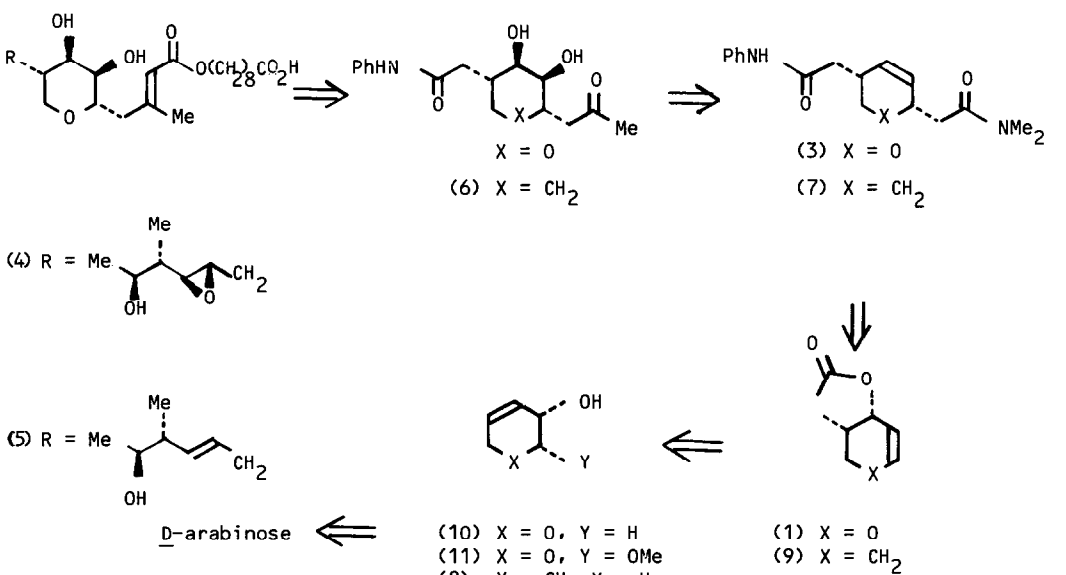
ENANTIOSPECIFIC SYNTHESES OF INTERMEDIATES IN THE TOTAL SYNTHESIS OF PSEUDOMONIC ACIDS

G.W.J. Fleet and M.J. Gough

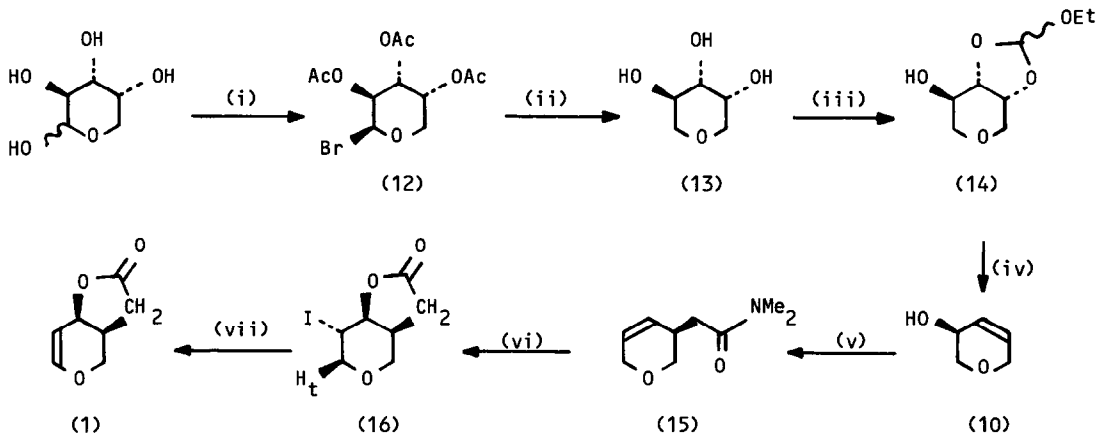
Dyson Perrins Laboratory, Oxford University, South Parks Road, Oxford.

Abstract: Enantiospecific syntheses of 1S,6S-3,7-dioxabicyclo[4,3,0]non-4-en-8-one (1) and of the enantiomer (2) from D- and L-arabinose respectively have been achieved by two different routes. The conversion of (1) to 6S-(3R-acetanilido)-3,6-dihydro-2H-pyranyl-N,N-dimethylacetamide (3), a key intermediate in the synthesis of pseudomonic acids, is described.

Several approaches to the total synthesis[1] of racemic pseudomonic acids, a group of compounds with interesting antimicrobial and antimycoplasmal activity,[2] have appeared. Work on the early stages of an enantiospecific route involving nucleophilic attack by an allyl silane on an oxonium ion derived from a carbohydrate precursor has been



SCHEME 1

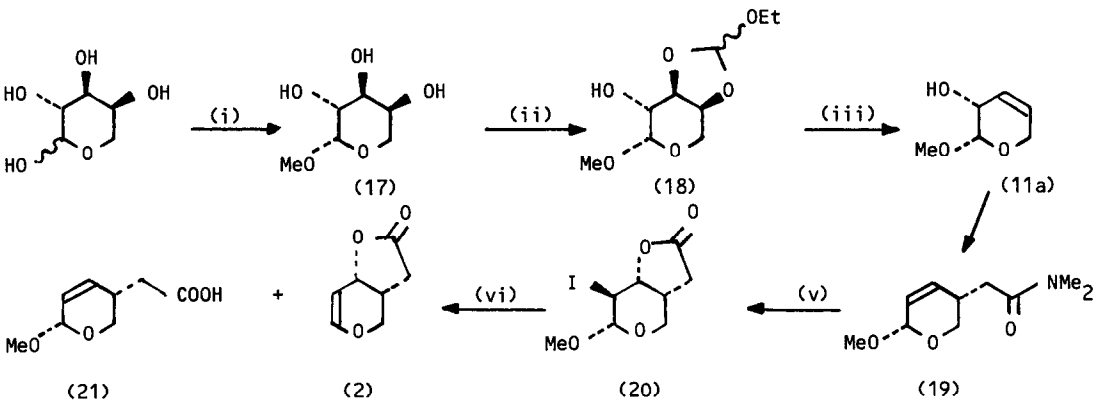


(i) Ac_2O/HBr (ii)H_2/Pd/Et_3N followed by MeONa/MeOH (iii) $HC(OEt)_3$/AcOH

(iv) heat (v) $MeC(OMe)_2NMe_2$ (vi) I_2/aqueous THF (vii) DBU

SCHEME 2

reported.[3] Recently we described studies on the total synthesis of carbocyclic analogues[4] of pseudomonic acids A (4) and C (5); a key intermediate (6), which might be elaborated by suitable ylid reactions to the natural product analogues, was prepared from (7) by successive treatment with methyl lithium and osmium tetroxide/N-methylmorpholine-N-oxide. The two cis side chains were introduced by two suitable Claisen rearrangements, starting from cyclohexenol (8) and involving the intermediate lactone (9).[4] (Scheme 1). This strategy has now been used in the enantiospecific synthesis of the bisamide (3) from lactone (1) which was prepared by two routes from arabinose via the allylic alcohols (10) and (11); both enantiomers of arabinose are readily and cheaply available and this approach would allow the synthesis of the naturally occurring pseudomonic acids and of their enantiomers. Treatment of D-arabinose with acetic anhydride followed by hydrogen bromide gives bromotriacetate (12)[5] (Scheme 2). Although lithium aluminium hydride reduction gives 1,5-anhydro-D-arabinitol (13) directly,[6] it was found more convenient on larger scales to hydrogenolyse the bromine in (12) by palladium in the presence of triethylamine[7] to the corresponding triacetate[8] (86% yield) which on methanolysis by a trace of sodium methoxide in methanol gave triol (13) in 91% yield. Elimination of the cis-diol unit in (13) to give the chiral allylic alcohol (10) was achieved by conversion to the cyclic orthoesters (14) by treatment of the triol with triethylorthoformate in ethyl acetate with a catalytic amount of acetic acid; pyrolysis[9] of (14) at 200° under

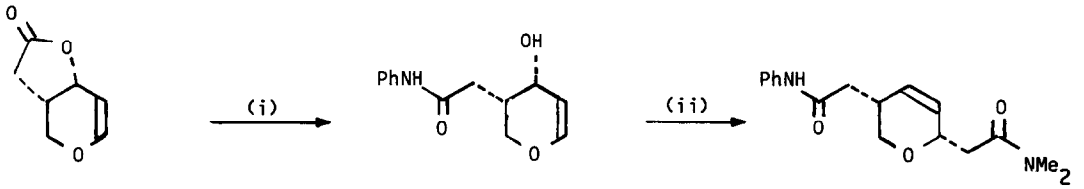


(i) $MeOH/H^+$ (ii) $HC(OEt)_3/H^+$ (iii) heat @ 200° (iv) $MeC(OMe)_2NMe_2$
(v) iodine in aqueous THF (vi) Zn/NaI in pyridine

SCHEME 3

nitrogen gave the previously unknown[10] (S)-3,6-dihydro-2H-pyran-3-ol (10), $[\alpha]_D^{20}$ -7.4 (c 0.015 in $CHCl_3$) in 72% yield from 1,5-anhydro-D-arabinitol (57% yield from bromotriacetate (12)). The pyran-3-ol (10) was heated with N,N-dimethylacetamide in xylene to give, after Claisen rearrangement of an intermediate ketene aminoacetal,[11] the transposed allylic amide, 3R-3,6-dihydro-2H-pyranyl-N,N-dimethylacetamide (15) (60% yield) which on treatment with iodine in aqueous THF at 0° formed 5S-iodo-1S,6S-3,7-dioxabicyclo-[4,3,0]nonan-8-one (16), isolated by flash chromatography[12] m.p. 111-113° (64% yield), $[\alpha]_D^{20}$ + 97.6° (c 0.01 in $CHCl_3$). Hydrogen iodide was eliminated from iodolactone (16) on treatment with 1,5-diazabicycloundecene in refluxing benzene to form 1S,6S-3,7-dioxa-bicyclo[4,3,0]non-4-en-8-one (1) in 94% yield (27% overall yield from bromotriacetate (12)); the elimination occurs regiospecifically as only H_t in (16) can become antiperiplanar to the iodide leaving group. The unsaturated lactone (1) has a characteristic low field doublet, δ 6.6 (J 6.2 Hz) due to the olefinic proton on C-3; no trace of any other elimination product was found.

An alternative approach to the unsaturated lactone from arabinose is illustrated by the conversion of L-arabinose to the enantiomer of (1), 1R,6R-3,7-dioxabicyclo[4,3,0]-non-4-en-8-one (2) shown in Scheme 3. L-Arabinose on treatment with methanol/hydrogen chloride gave methyl-β-L-arabinopyranoside (17)[13] which was converted by triethyl-orthoformate in the presence of acid catalyst to the orthoesters (18) (94% yield). Pyrolysis of (18) gave the enantiomer of (11), 3,4-dideoxy-methyl-β-L-arabinopyranoside (11a)



(1) (22) (3)

(i) PhNHLi in THF @ -78° (ii) MeC/OMe)$_2$NMe$_2$ in refluxing xylene.

SCHEME 4

(41% yield), which with N,N-dimethylacetamide dimethyl acetal in refluxing xylene formed 3S-(6S-methoxy)-3,6-dihydro-2H-pyranyl-N,N-dimethylacetamide (19) (87% yield). Reaction of (19) with iodine in aqueous THF gave (4S-methoxy) (5S-iodo)-1R,6R-3,7-dioxabicyclo[4,3,0]-nonan-8-one (20), (56% yield; 19% from methyl pyranoside (17)), m.p. 126-128°, $[\alpha]_D^{20}$-18.8° (c 0.01 in Me_2CO). Anti-elimination of iodine and methoxy from iodolactone (21) on treatment with zinc dust[14] in pyridine to the required lactone (2) (26% yield) was accompanied by the formation of unsaturated acid (21) as the major product; work is currently in progress to optimise the yield of (2) in this reaction.

Ring opening of the unsaturated lactone (1) with anilide ion (derived from treatment of aniline with n-butyl lithium in THF) gave the amido allylic alcohol (22), m.p.137-139°, $[\alpha]_D^{20}$-11.3° (c 0.005 in Me_2CO) (low field doublet at δ 6.4) in 85% yield which was converted to the bisamide (3) by heating with N,N-dimethylacetamide dimethyl acetal in xylene to effect a further Claisen amide acetal rearrangement (Scheme 4). Although yields of several reactions in the above sequences have yet to be optimised, this work demonstrates the viability of the strategy of double Claisen rearrangements[4] in controlling the stereochemistry of the substituents on the pyran ring in the total synthesis of pseudomonic acids and their analogues.

References:

1. R.A. Raphael, J.H.A. Stibbard, and R. Tilbury, Tetrahedron Lett., 23, 2407, (1982; A.P. Kozikowski, R.J. Schmiesing and K.L. Sorgi, Tetrahedron Lett.,22, 2059 (1981); B.B. Snider, D.J. Rodini, T.C. Kirk and R. Cordova, J. Am. Chem. Soc., 104, 555 (1982).
2. S. Coulton, P.J. O'Hanlon and N.H. Rogers, J. Chem. Soc. Perkin Trans. 1, 1982, 729.
3. A.P. Kozikowski and K.L. Sorgi, Tetrahedron Lett., 23, 2281 (1982).
4. G.W.J. Fleet and C.R.C. Spensley, Tetrahedron Lett., 23, 109 (1982).
5. F. Weygand, Methods in Carbohydrate Chemistry, 1, 182 (1962).
6. H.G. Fletcher, Methods in Carbohydrate Chemistry, 2, 197 (1963).
7. L. Zervas and C. Zioudrou, J. Chem. Soc., 1956, 214.
8. H.G. Fletcher and C.S. Hudson, J. Am. Chem. Soc., 69, 1672 (1947).
9. G. Crank and F.W. Eastwood, Aust. J. Chem., 17, 1385 (1964); ibid., 21, 2013 (1968).
10. All new compounds referred to have satisfactory analytical and/or spectral data.
11. P.R. Jenkins, R. Gut, H. Wetter and A. Eschenmoser, Helv. Chim. Acta, 62, 1922 (1979)
12. W.C. Still, M. Kahn and A. Mitra, J. Org. Chem., 43, 2923 (1978).
13. J. Honeyman, J. Chem. Soc., 1946, 986.
14. L.F. Fieser and M. Fieser, Reagents for Organic Synthesis, 1, 1276 (1968).

(Received in UK 16 August 1982)