A Stereoselective Approach to the δ-Lactone Fragment of the Lankacidin Antibiotics

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An approach to the synthesis of the lactone fragment of the lankacidin antibiotics is described which is based upon stereoselective modification of an L-aspartic acid derived β-lactam.

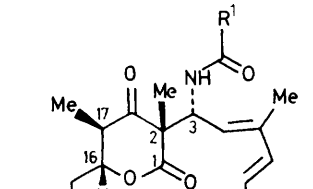
The lankacidins constitute a group of naturally occurring macrocyclic compounds which exhibit both antibiotic and antitumour activity, whilst being relatively non-toxic.[1] Structurally they are characterized by a 17-membered carbocyclic ring, bridged by a 6-membered lactone as found in lankacidin C (**1**) and the lankacidinols (**2**) and (**3**).

Any synthetic approach to the lankacidins has to address the question of stereochemical control,[2] particularly at the quaternary centre C(2) and at the adjacent nitrogen bearing centre C(3). One possible entry to this system involving acylation of a chiral β-lactam is shown in Scheme 1. The acylation of the β-lactam enolate anion would be expected to take place on its less hindered face, away from the bulky substituent at C(4), thereby establishing the required absolute configuration at C(3). Selective deprotection would then provide a hydroxy-β-lactam (**7**), which on intramolecular transacylation would give lactone (**8**) corresponding to the C(15)—C(4) fragment of the lankacidins. We now report preliminary studies which demonstrate the feasibility of this approach.

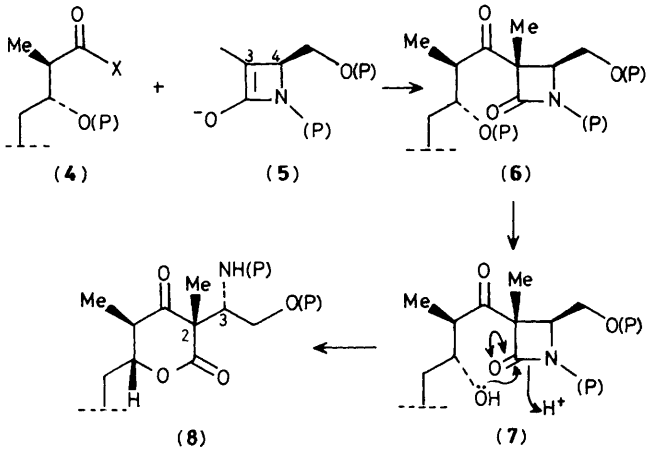
β-Lactam (**10**), available from dibenzyl aspartate (**9**),[3] was reduced using $NaBH_4$,[3,4] and protected, to provide the bis-TBDMS† derivative (**11**), $[\alpha]_D^{20}$ −26° (*c* 1.3, $CHCl_3$), lit.[4] $[\alpha]_D^{22}$ −25.3° (*c* 0.95, $CHCl_3$), which on methylation ($LiNPr_2^i$, MeI, −78 °C) gave predominantly the *trans*-3,4-disubstituted β-lactam (**12**) (Scheme 2).[5] This could be converted into its enolate anion efficiently using $LiNEt_2$, and the enolate anion trapped on its less hindered face by electrophiles. Thus alkyl halides (EtI, Bu^nI, or $PhCH_2Br$) gave the 3,3-disubstituted β-lactams (**23**)—(**25**) containing <10% of the alternative stereoisomers (**28**)—(**30**), and isobutyraldehyde and benzaldehyde gave, after oxidation, mixtures of ketones which contained more of the *trans*-ketones (**26**) and (**27**), selectivity *ca.* 4:1. Structures were assigned to these products on the basis of spectroscopic data; in particular nuclear Overhauser enhancement (n.O.e.) difference spectra were used to establish stereochemistry. Next the use of protected hydroxyaldehydes was investigated.

Aldol condensation of β-lactam (**12**), using $LiNEt_2$ as base, with the protected hydroxyaldehydes (**21**) and (**22**), followed by oxidation, was found to be more efficient than direct acylation, and gave mixtures of ketones containing more of the desired stereoisomers (**13**) and (**14**), stereoselectivities *ca.* 5:1, overall yields >80%. Structures were assigned to these products by analogy with the preliminary studies discussed above, and on the basis of spectroscopic data, the stereochemistry shown being supported by n.O.e. difference studies, *e.g.* irradiation of the 3-Me singlet caused enhancement (*ca.* 7%) of the CH_2OTBDMS peaks for the major adducts (**13**) and (**14**), and enhancement (12—14%) of the H(4) peaks for the minor adducts (**15**) and (**16**).

The β-lactams (**13**) and (**14**) were then activated towards ring-opening by selective *N*-deprotection and *N*-acylation to give the *N*-propionyl derivatives (**17**) and (**18**). Selective OH deprotection, either by mild acid treatment for the TBDMS-protected alcohol (**17**), which was found to be selective for the more accessible OTBDMS group,‡ or by hydrogenolysis for the BOM-protected alcohol (**18**), was accompanied by β-lactam opening and gave directly the β-keto-lactone (**19**) [9 steps from dibenzyl aspartate (**9**)]. The minor β-lactam ketones (**15**)



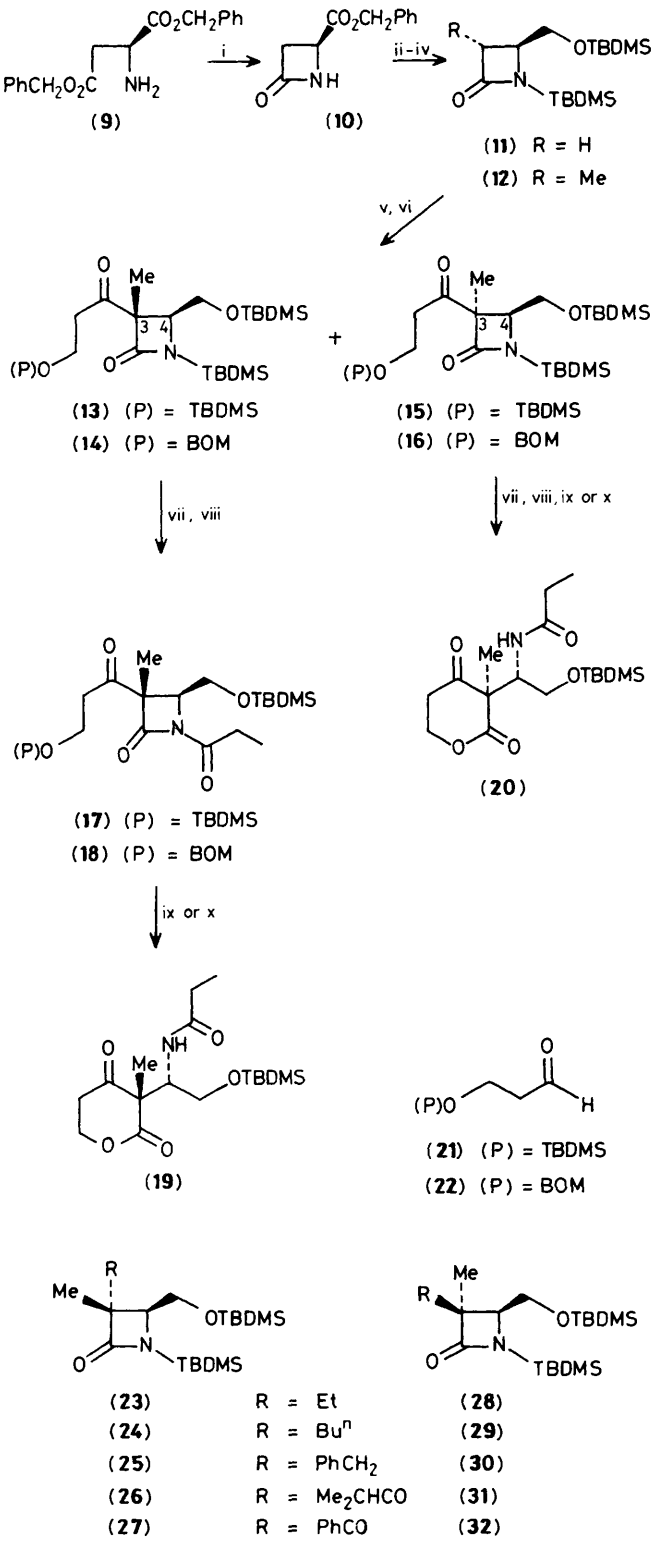
(**1**) R^1 = COMe, R^2 = H
(**2**) R^1 = CH(OH)Me, R^2 = H
(**3**) R^1 = CH(OH)Me, R^2 = COMe



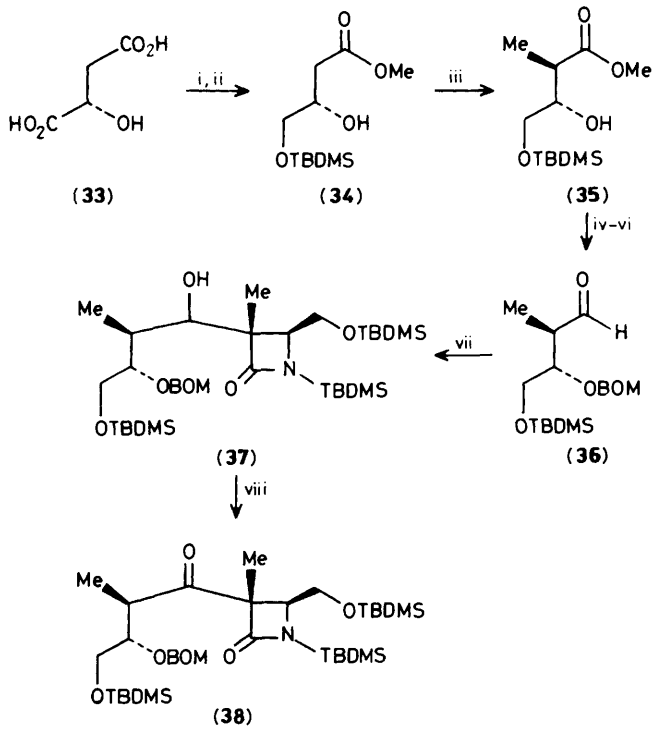
Scheme 1. (P) = protecting group.

† *Abbreviations:* TBDMS = Bu^tMe_2Si; DMAP = 4-*N*,*N*-dimethylaminopyridine; LDA = lithium di-isopropylamide; DDC = pyridinium dichromate; PTSA = *p*-$MeC_6H_4SO_3H$; THF = tetrahydrofuran; BOM = $PhCH_2OCH_2$; TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine; DIBAL = di-isobutylaluminium hydride; DMSO = dimethyl sulphoxide.

‡ The removal of one of the TBDMS groups by treatment of β-lactam (**17**) with mild acid [PTSA (cat.) in THF–H_2O, 20:1; room temp., 3 h] was quite selective and gave lactone (**19**), the same product as was obtained on deprotection of the BOM-ether (**18**), as the only product isolated after chromatography.



Scheme 2.† *Reagents:* i, Me_3SiCl, Et_3N, then Bu^{t}MgBr (79%); ii, $NaBH_4$, MeOH (71%); iii, TBDMS–Cl, Et_3N, DMAP,[8] CH_2Cl_2 (92%); iv, LDA (1.5 equiv.), −78 °C, 0.5 h, then MeI, −78 °C, 4 h (98%); v, $LiNEt_2$ (1.25 equiv.), −78 °C, 0.5 h, then (**21**) or (**22**) (1.25 equiv.), −78 °C, 4 h (*ca.* 95%); vi, PDC (3 equiv.), 3Å sieves [82% of (**13**) + (**15**), (**13**):(**15**) = 80:20; 92% of (**14**) + (**16**), (**14**):(**16**) = 85:15]; vii, KF, MeOH, 1 h, 0 °C (100%); viii, EtCOCl, Et_3N, DMAP, CH_2Cl_2, 0 °C (90—95%); ix, PTSA (0.1 equiv.), THF, H_2O (20:1), then $Ca(OH)_2$ (60—65%); x, 10% Pd-C, H_2 (83—87%).



Scheme 3.† *Reagents:* i, MeOH, HCl (85%); ii, $BH_3{\cdot}SMe_2$, $NaBH_4$, then TBDMS–Cl, Et_3N, DMAP, CH_2Cl_2[8] (73%); iii, LDA (2.2 equiv.), THF, −50 to −10 °C, then MeI (1.25 equiv.), TMEDA (1.1 equiv.), −70 °C, 4 h (86%); iv, BOM–Cl, Et_3N, DMAP, CH_2Cl_2, 24 h (92%); v, DIBAL (2.2 equiv.), THF, −25 °C, 16 h (94%); vi, $COCl_2$, DMSO (100%); vii, (**12**)· Li, −78 °C, 4 h [98% crude, 69% of (**37**) as a single isomer after chromatography]; viii, $COCl_2$, DMSO (96%).

and (**16**) were similarly converted into the isomeric β-keto-lactone (**20**). The two keto-lactones (**19**) and (**20**) were clearly different by high field ^1H n.m.r. spectroscopy, and were identified on the basis of spectroscopic data.

To check the compatibility of this approach with more heavily substituted aldehydes, the chiral protected hydroxy-aldehyde (**36**) was prepared from (*S*)-(−)-malic acid (**33**) (Scheme 3). Thus regioselective reduction of dimethyl (*S*)-malate using $BH_3{\cdot}SMe_2$–$NaBH_4$[6] followed by selective monoprotection of the primary hydroxy group gave the mono-TBDMS ether (**34**). Stereoselective enolate alkylation was then carried out using the procedure of Frater,[7] to provide the methylated ester (**35**), the only product isolated after chromatography (60%). The stereochemistry of (**35**) was assigned by analogy with the literature.[7] Protection of the hydroxy group, reduction, and Swern oxidation then gave aldehyde (**36**) which was added to the enolate of the methylated β-lactam (**12**). A single major aldol product (**37**) was isolated, and was oxidized to provide the desired ketone (**38**) so providing entry to a fully substituted lankacidin system.

This work would appear to demonstrate the feasibility of the proposed route to the δ-lactone fragment of the lankacidins, and illustrates the potential of readily available β-lactams for asymmetric synthesis. Present work is aimed at a synthesis of the natural products themselves.

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