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An approach to the total synthesis of lankacidins: synthesis of the requisite building blocks

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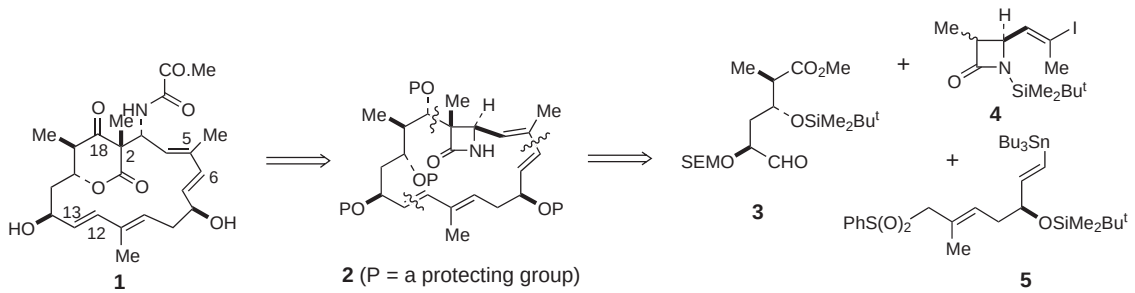
Abstract—A strategy for a total synthesis of lankacidin C **1** is outlined and the requisite building blocks synthesised. The azetidinone **4** was prepared from methyl but-2-ynoate **6** via a route which features the stereoselective addition of a tributyltin cuprate to the alkyne, an asymmetric aldol condensation and formation of the azetidinone by an intramolecular Mitsunobu reaction. The aldehyde **3** was prepared from dimethyl malate **18** and the sulfone **3** from prop-2-ynol **27** again using asymmetric aldol reactions as key steps. © 2001 Elsevier Science Ltd. All rights reserved.

The lankacidins, e.g. lankacidin C **1**, are a small group of antitumour antibiotics isolated from *Streptomyces* which have been of some interest to synthetic chemists because of their novel structures and biological activities.[1] Kende and ourselves independently conceived an approach to the δ-lactone component of the lankacidins using a stereoselective acylation of a 4-substituted azetidinone followed by rearrangement of a 3-(3-hydroxyalkyl)azetidinone to give the δ-lactone.[2,3] Kende subsequently completed a total synthesis of lankacidin C based on this chemistry using an intramolecular addition of a protected cyanohydrin anion to an aldehyde, a Stork–Takahashi cyclisation, to form the 17-membered ring.[4] We here describe an alternative strategy for the synthesis of lankacidins together with total syntheses of the necessary precursors.

Based on earlier work, the azetidinone **2** was identified as a possible precursor of lankacidin C.[2] Macrocyclic analogues of the lankacidins had been prepared by using a ketophosphonate–aldehyde condensation to form the 12,13-double-bond,[5] and this chemistry is known to be compatible with the presence of an azetidinone ring.[2] However, the yields of the macrocycle were only modest[5] and so it was decided to investigate an alternative strategy for formation of this ring. The Stille reaction has been used for macrocycle formation in complex syntheses[6] and model studies, vide infra, indicated that the formation of the 5,6-bond by a Stille process could be an option for ring formation. The 2,18-bond would be formed by a stereoselective azetidinone acylation[2,3] and the 12,13-double-bond could be introduced connectively, e.g. via a Julia reaction. Based



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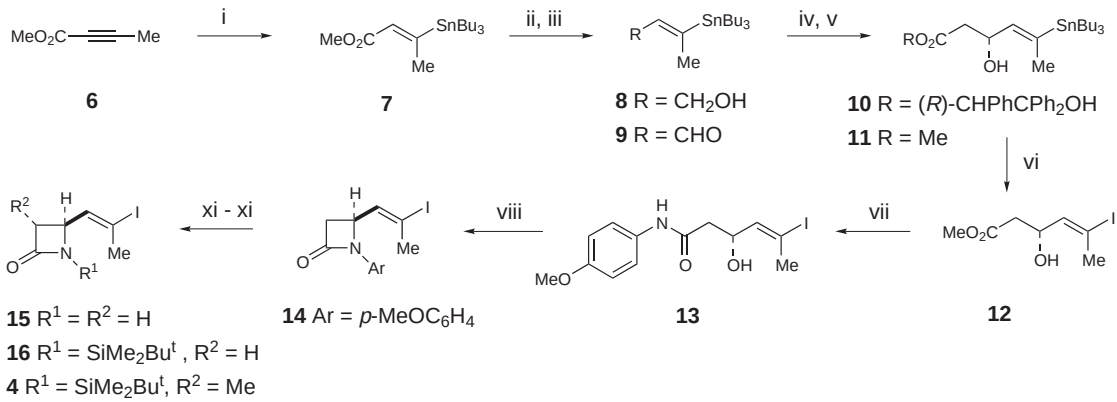
on this analysis, the azetidinone **4**, the aldehyde–ester **3** and the vinylstannane **5** were identified as potential precursors of lankacidin C **1**.

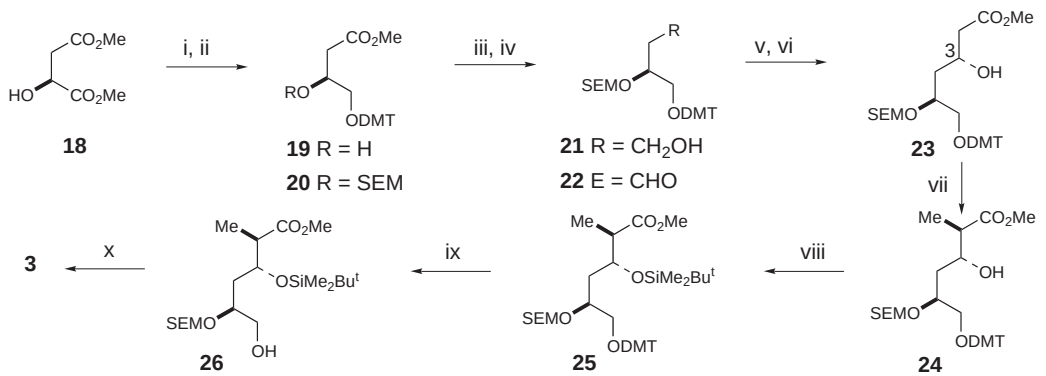
The (4*S*)-azetidinone **4** was prepared as outlined in Scheme 1, a racemic epimer being available by a shorter route.[7] Stereoselective conjugate addition[8] of a tributyltin cuprate to methyl but-2-ynoate **6** gave the (*E*)-vinylstannane **7** which was reduced to the alcohol **8**. Oxidation of the alcohol using Swern conditions (oxalyl chloride, dimethyl sulfoxide) gave a mixture of the (*E*)- and (*Z*)-aldehydes; however, manganese dioxide gave the required (*E*)-aldehyde **9**. An asymmetric aldol condensation with the chiral acetate, (*R*)-2-hydroxy-1,2,2-triphenylethyl acetate (*R*)-**17**,[9] followed by methanolysis gave the methyl ester **11** which was treated with iodine to give the (*E*)-vinyl iodide **12**. The methyl ester was then converted into the amide **13** which was cyclised under Mitsunobu conditions[10] to give the azetidinone **14**. Oxidative removal of the *p*-methoxyphenyl group gave the *N*H-azetidinone **15** which was reprotected as its *N*-*tert*-butyldimethylsilyl derivative **16**, shown to correspond to the (*S*)-enantiomer with an ee of 90(±5)% by correlation with known compounds.[11] Finally methylation gave the required azetidinone **4** containing ca. 10% of its epimer at C(3).[11]

The ester–aldehyde **3** was prepared as shown in Scheme 2. Selective reduction[13] and protection of dimethyl malate **18** gave the mono-dimethoxytrityl (DMT) ether **19**. This was further protected as its trimethylsilylethoxymethyl (SEM) ether **20** which was converted into the aldehyde **22** by reduction–oxidation. Aldol addition of (*S*)-2-hydroxy-1,2,2-triphenylethyl acetate (*S*)-**17**[9] followed by methanolysis gave the methyl ester **23** together with its epimer at C(3), ratio 75:25 which were separated by chromatography. The major isomer **23** was then methylated stereoselectively[14] to give the *anti*-2-methyl-3-hydroxy-ester **24**. After conversion into the *tert*-butyldimethylsilyl ether **25**, selective removal of the dimethoxytrityl ether gave the primary alcohol **26** and oxidation using TPAP gave the required aldehyde **3**.

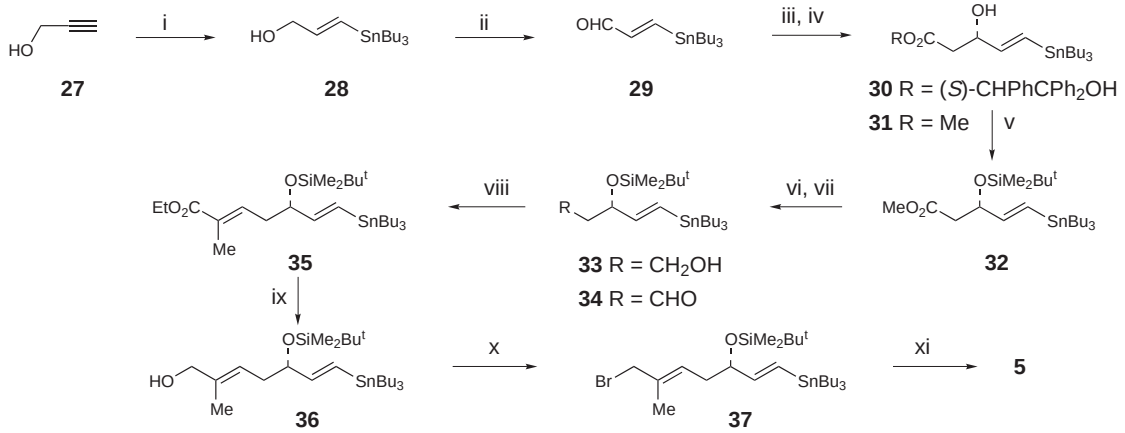
The vinylstannane **5** was prepared as outlined in Scheme 3. Free-radical addition of tributyltin hydride to propargyl alcohol **27** gave a mixture of (*E*)- and (*Z*)-vinylstananes from which the major (*E*)-isomer **28** was separated by chromatography.[15] Oxidation using activated manganese dioxide gave the aldehyde **29** which was converted into the hydroxy–ester **30** by a stereoselective aldol condensation with the acetate (*S*)-**17**.[9] Methanolysis gave the methyl ester **31**, ee 90(±5)%



Scheme 1. *Reagents and conditions:* (i) Li($Bu_3SnCuBr$)·DMS, –78°C (92%); (ii) DIBAL-H (98%); (iii) MnO_2, acetone (100%); (iv) (*R*)-**17**, 2LDA, $MgBr_2$ (98%); (v) MeONa, MeOH (85%); (vi) I_2, CCl_4 (87%); (vii) lithium *p*-methoxyphenylamide (70%); (viii) PPh_3, DEAD (90%); (ix) CAN, MeCN, H_2O; (x) *t*-$BuMe_2SiCl$, Et_3N (74% from **14**); (xi) LDA, MeI (95%).



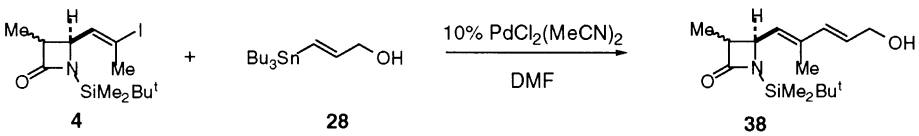
Scheme 2. *Reagents and conditions:* (i) BH_3·DMS, $NaBH_4$ then DMTCl, EtN^iPr_2 (93%); (ii) SEMCl, EtN^iPr_2 (100%); (iii) DIBAL-H; (iv) TPAP, NMO, 4A sieves (85% from **20**); (v) (*S*)-**17**, 2 LDA, $MgBr_2$; (vi) MeONa, MeOH (63% from **22**); (vii) 2 LDA, TMEDA, MeI (79%); (viii) $^tBuMe_2SiOTf$, 2,6-lutidine (98%); (ix) Cl_2CHCO_2H (83%); (x) TPAP, NMO, 4A sieves (86%).



Scheme 3. *Reagents and conditions:* (i) Bu_3SnH, AIBN, 100°C (83%; *E*:*Z* = 77: 23); (ii) MnO_2, acetone (98%); (iii) (*S*)-**17**, 2LDA, $MgBr_2$; (iv) MeONa, MeOH (95% from **29**); (v) $^tBuMe_2SiOTf$, 2,6-lutidine (97%); (vi) DIBAL-H (83%); (vii) TPAP, NMO, 4A sieves (87%); (viii) $Ph_3P{=}CMeCO_2Et$ (98%); (ix) DIBAL-H (97% from **34**); (x) MsCl, Et_3N, then LiBr (79%); (xi) $PhSO_2Na$, DMF (98%).

(Mosher's derivatives) which, after protection as its *tert*-butyldimethylsilyl ether **32**, was reduced to the alcohol **33**. Oxidation gave the aldehyde **34** which was taken through to the (*E*)-αβ-unsaturated ester **35**. Reduction gave the alcohol **36** and this was converted into the sulfone **5** via the bromide **37**.

Preliminary studies into the Stille condensation were carried out using the azetidinone **4**. For example, coupling with the (*E*)-vinylstannane **28** was very efficient using bisacetonitrile dichloropalladium(II) as catalyst and gave the conjugated diene **38** in 80% yield.



The accompanying communication describes the assembly of advanced macrocyclic precursors of lankacidin C **1** from the three building blocks **3**, **4** and **5**.

Acknowledgements

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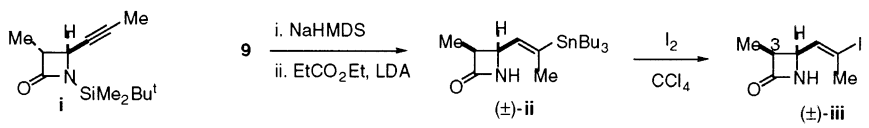
7. Preliminary attempts to hydrometalate the 4-alkynylazetidinone **i** gave mixtures of regio- and/or stereoisomers. However, the racemic azetidinone (±)-**iii** is available in two steps from the *N*-trimethylsilylimine prepared from aldehyde **9** by condensation with ethyl propanoate followed by metal–halogen exchange. The configuration at C(3) is unimportant for the synthesis since it is lost on enolate anion formation.



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11. The (4*S*)-configuration of the azetidinone **16** was established by ozonolysis followed by a reductive work up which gave (−)-4-hydroxymethyl-1-*tert*-butyldimethylsilylazetidinone, $[\alpha]_D$ −28 (*c* 1.3 $CHCl_3$), which is known to correspond to the (*S*)-enantiomer, $[\alpha]_D$ −31.5 (*c* 2.7, CH_2Cl_2).[12] The double-bond geometry of the azetidinone **4** was established by NOE observations.
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