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An approach to the total synthesis of lankacidins: synthesis of advanced macrocyclic precursors

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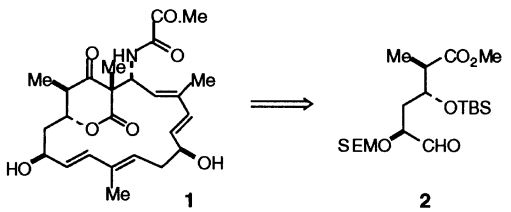
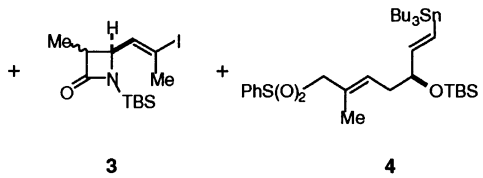
Abstract—The macrocyclic tetraenes **11** and **19**, possible precursors of lankacidin C **1**, have been prepared using intramolecular Stille reactions to close the macrocyclic rings. The Stille precursor **10** was prepared by stereoselective acylation of the azetidinone **3** using the thioester **7**. After reduction and deprotection, cyclisation gave the macrocyclic product **11** in 55% yield. Alternatively, the Boc-protected amino-ester **17** was prepared by ring-opening of the azetidinone, and cyclised to the macrocycle **19** in 48% yield.

Syntheses of the aldehyde **2**, azetidinone **3** and vinylstannane **4**, building blocks for a projected synthesis of the antitumour antibiotic, lankacidin C **1**[1–3] are reported in the accompanying communication.[4] We here describe the use of these intermediates to prepare complex macrocyclic tetraenes, possible precursors of lankacidin C **1**.





The conjugated dienyl ester **5** was prepared from the aldehyde **2** and the sulfone **4** using a Julia coupling and the methyl ester converted into the thioester **7** via the carboxylic acid **6**. Following the reaction conditions developed earlier,[3] acylation of the azetidinone **3** using the thioester **7** and lithium diisopropylamide as base was highly stereoselective, and gave mainly ($\geq$95:5) a single stereoisomer of the product. This was identified as the required isomer **8** by analogy with previous work[3] and the literature[2] although the yield, ca. 30–35%, was disappointing. Reduction of the ketone using potassium triethylborohydride was stereoselective and gave the alcohol **9**.[5] Since preliminary studies on the Stille reaction had shown that better results were obtained using vinylstannanes analogous to **9** when the silyloxy group allylic to the tributyltin substituent had been deprotected to give a free hydroxyl group,[6] the silyl ether **9** was treated with tetrabutylammonium fluoride to remove all three *tert*-butyldimethylsilyl groups. Cyclisation of the hydroxyvinylstannane **10** was then investigated. Initial studies were carried out using bis(acetonitrile)palladium(II) chloride as the catalyst[7] and modest yields, typically 25–30%, of the cyclised product **11** were obtained. However, significantly better yields, ca. 55%, of the required macrocyclic product **11** were obtained if the pre-reduced palladium(0) catalyst, $Pd_2(dba)_3$–$AsPh_3$, was used (Scheme 1).

The structure of the macrocyclic product was confirmed by extensive spectroscopic studies.[8] In particular, the mass spectrum of the product had a molecular ion corresponding to **11** and the position of the methyl group on the vinyl iodide moved from δ 2.48 to 1.87 in the ^{1}H NMR spectrum of the product, which also indicated the presence of two conjugated diene fragments.

The azetidinyl macrocycle **11** contains the intact nucleus of lankacidin C **1**. However, the presence of the three unprotected hydroxyl groups and the intact azetidinone meant that several selective functional group interconversions would be necessary to complete a syn-

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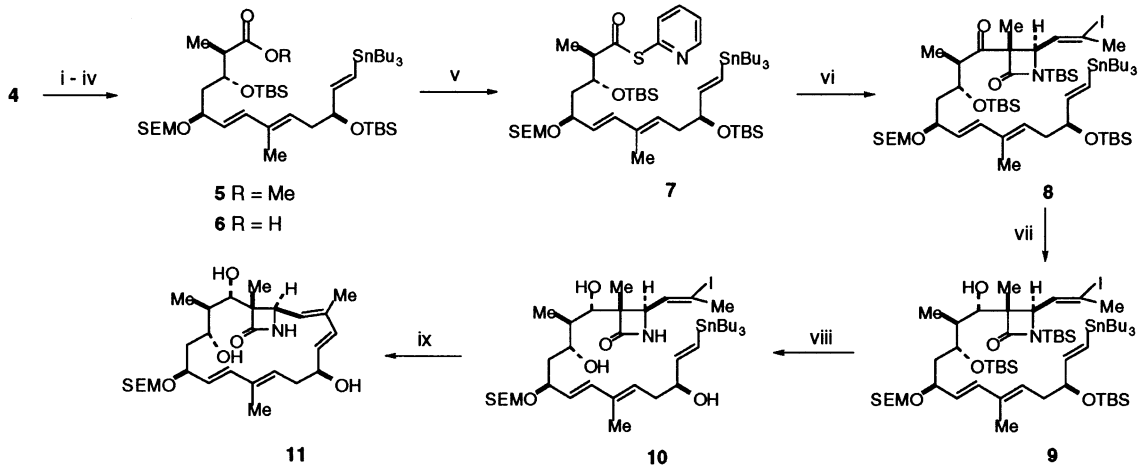
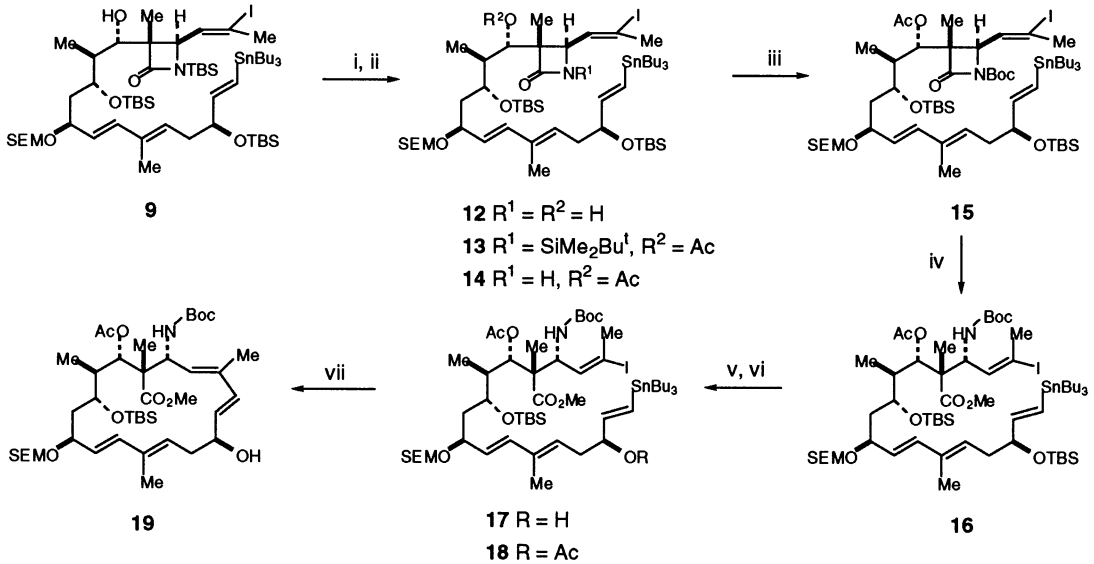
thesis of lankacidin C from **11**. Moreover, conformational modelling of the macrocyclic ring, indicated that it is difficult for the C(16)-hydroxyl group to reach the carboxyl carbon of the azetidinone ring to effect a one-step δ-lactone formation—azetidinone ring-opening. It was therefore decided to develop the chemistry of the vinylstannane **9** further to carry out some of these transformations before the macrocyclisation.

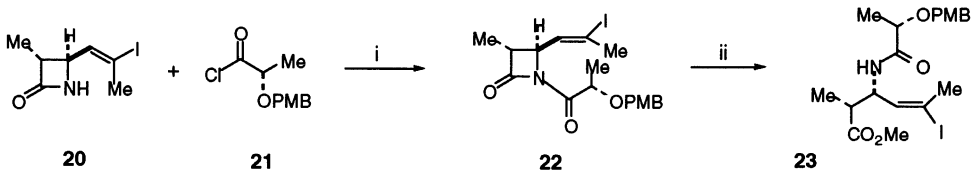
Treatment of the vinylstannane **9** with potassium fluoride in methanol–tetrahydrofuran removed the *N*-silyl group leaving the *O*-silyl groups unchanged.[3] However, conversion of the azetidinone **12** into its *tert*-butyloxycarbonyl (Boc) derivative was complicated by accompanying acylation of the C(18)-hydroxyl group. The vinylstannane was therefore converted into its acetate **13** before *N*-desilylation and conversion into the *N*-Boc azetidinone **15**. Ring-opening of the azetidinone was now carried out using potassium cyanide in methanolic *N*,*N*-dimethylformamide[9] to give the Boc-protected amino-ester **16**. The C(13)-hydroxyl was now deprotected selectively by treatment with tetrabutylammonium fluoride in tetrahydrofuran to give the alcohol **17**, since the presence of this silyl group was known to be detrimental to the Stille cyclisation,[6] and the regioselectivity of this mono-desilylation confirmed by conversion of the alcohol **17** into its acetate **18**.[10] Cyclisation of the hydroxyvinylstannane **17** was better carried out using the pre-reduced palladium catalyst $Pd_2(dba)_3$, and gave the 17-membered macrocycle **19** the structure of which was confirmed by spectroscopic studies (Scheme 2).[11]



Scheme 1. *Reagents and conditions*: i. LDA, **2**; ii. Ac_2O, Et_3N, DMAP; iii. Hg(Na), MeOH, EtOAc (67% of **5** from **2**); iv. NaOH, MeOH, THF, H_2O; v. 2-mercaptopyridine, DCC, DMAP (82% of **7** from **5**); vi. **3**, LiN^iPr_2 (30–35%); vii. $KBEt_3H$ (80%); viii. TBAF (90%); ix. $Pd_2(dba)_3$ (30 mol%), $AsPh_3$ (1.2 mol%), anhydrous DMF, THF (1:1), (55%).



Scheme 2. *Reagents and conditions*: i. Ac_2O, Et_3N, cat. DMAP (83%); ii. KF, MeOH (90%); iii. Boc_2O, DMAP, MeCN (89%); iv. MeOH, KCN, DMF (89%); v. TBAF, THF (70%); vi. Ac_2O, Et_3N, cat. DMAP (52%); vii. $Pd_2(dba)_3$ (30 mol%), $AsPh_3$ (1.2 mol%), anhydrous DMF, THF (1:1) (48%).



20 21 22 23

Scheme 3. *Reagents and conditions*: i. DMAP, Et_3N (50%); ii. MeOH, KCN, DMF, 48 h (88%).

The 17-membered macrocycle **19** contains all the functionality present in the large-ring system of lankacidin C **1**. The conversions that remain to be carried out include the deprotection of the C(16)-hydroxyl group with formation of the δ-lactone ring, and the introduction of the *N*-pyruvyl substituent. As a model study for this latter transformation, the *N*H-azetidinone **20** was acylated on nitrogen using the acid chloride **21** prepared from *p*-methoxybenzyl protected lactic acid.[12] Ring-opening of the *N*-acylated azetidinone **22** so obtained using potassium cyanide in methanol *N*,*N*-dimethylformamide gave the *N*-acylated amino-ester **23** in good yield (Scheme 3).

Present work is concerned with developing the chemistry described in this letter in order to complete a total synthesis of lankacidin C.

Acknowledgements

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4. Brain, C. T.; Chen, A.; Nelson, A.; Tanikkul, N.; Thomas, E. J. *Tetrahedron Lett.* **2001**, *42*, 1247–1250.
5. The configuration of the alcohol **9** was assigned by analogy with previous work in which 3-oxoalkylazetidinones analogous to **8** had been reduced and the structures of the products which were obtained confirmed after conversion into δ-lactones.[2,3]
6. Brain, C. T.; Thomas, E. J., unpublished observations.
7. Duncton, M. A.; Pattenden, G. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1235–1246.
8. *Experimental for **11***: Triphenylarsine (7 mg, 23 μmol) was added to a stirred solution of bis(dibenzylideneacetone)palladium (5.3 mg, 5.82 μmol) in a degassed mixture of anhydrous *N*,*N*-dimethylformamide/tetrahydrofuran (8 cm^3; 50:50) at room temperature. A solution of the azetidinone **10** (18 mg, 19 μmol) in degassed DMF/THF (4 cm^3; 50:50) was added dropwise to the yellow solution and the resulting dark green solution stirred at room temperature in the dark for 22 h. Water (5 cm^3) and ethyl acetate (10 cm^3) were then added and the aqueous phase separated and extracted with more ethyl acetate. The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using light petroleum/ethyl acetate (3:2) containing 1% triethylamine as eluent gave the macrocyclic fused azetidinone **11** (4.4 mg, 52%), as a white solid $[\alpha]_D$ −153 (*c* 0.43 in CH_2Cl_2) (found: M^++Na, 544.3071. $C_{28}H_{46}O_6SiNNa$ requires *M*, 544.3070); ν_{max} (cm^{-1}) 3319, 1745, 1621, 1451, 1380, 1249, 1089, 1020, 967, 859 and 835; δ_H (500 Mz; lankacidin numbering) ($CDCl_3$) 0.02 [9H, s, $Si(CH_3)_3$], 0.88 (2H, m, $SiCH_2$), 1.09 (3H, d, *J* 7.5, 17-CH_3), 1.26 (3H, s, 2-CH_3), 1.69 (3H, s, 11-CH_3), 1.72 (3H, s, 5-CH_3), 1.74 (1H, m, 15-H), 1.97 (2H, m, 15-H′ and 17-H), 2.43–2.61 (2H, m, 9-H_2), 2.72 (1H, br. s, OH), 3.37 (1H, br. s, OH), 3.47 (1H, m, O*H*CHCH_2Si), 3.76–3.71 (2H, m, 16-H and OHC*H*CH_2Si), 3.90 (1H, d, *J* 2, 18-H), 4.00 (1H, m, 14-H), 4.33 (1H, m, 8-H), 4.54 (1H, d, *J* 7, O*H*CHO), 4.61 (1H, d, *J* 10, 3-H), 4.84 (1H, d, *J* 7, OHC*H*O), 5.11 (1H, dd, *J* 12, 3.5, 10-H), 5.31 (1H, dd, *J* 15.5, 9.5, 13-H), 5.38 (1H, dd, *J* 15.5, 9.5, 7-H), 5.48 (1H, d, *J* 10, 4-H), 5.81 (1H, s, NH), 6.04 (1H, d, *J* 15.5, 12-H) and 6.05 (1H, d, *J* 15.5, 6-H); *m*/*z* (FAB) 544 (M^++Na, 48%).
9. Palomo, C.; Aizpurua, J. M.; Cuevas, C.; Mielgo, A.; Galarza, R. *Tetrahedron Lett.* **1995**, *36*, 9027–9030.
10. The regioselectivity of this monodesilylation contrasted with the preferred removal of the C(16)-silyl group if the C(18)-hydroxyl was unprotected (Chen, A.; Thomas, E. J., unpublished observations).
11. *Physical and spectroscopic data for **19***: $[\alpha]_D$ −131 (*c* 0.3 in CH_2Cl_2) (found: M^++Na, 832.4855. $C_{42}H_{75}O_{10}NSi_2Na$ requires *M*, 832.4827); ν_{max} (cm^{-1}) 3426, 1727, 1498, 1367, 1249, 1166, 1091, 1023, 909 and 836; δ_H (500 Mz; lankacidin numbering) ($CDCl_3$) 0.00 [9H, s, $Si(CH_3)_3$], 0.09 and 0.12 (each 3H, s, $SiCH_3$), 0.89 (2H, m, $SiCH_2$), 0.90 (3H, d, *J* 7, 17-CH_3), 0.93 [9H, s, $SiC(CH_3)_3$], 1.27 (3H, s, 2-CH_3), 1.39 [9H, s, $OC(CH_3)_3$], 1.57 (2H, m, 15-H_2), 1.70 (3H, s, 11-CH_3), 1.87 (3H, s, 5-CH_3), 2.01

(1H, m, 17-H), 2.00 (3H, s, CH_3CO), 2.49 (2H, m, 9-H_2), 3.28 (1H, dd, *J* 9.5, 2.5, 16-H), 3.45 and 3.64 (each 1H, m, O*H*CHCH_2Si), 3.70 (3H, s, OCH_3), 4.09–4.15 (2H, m, 8-H and 14-H), 4.46 (1H, br. s, OH), 4.55 and 4.67 (each 1H, d, *J* 6.5, OHC*H*O), 4.68 (1H, s, 18-H), 4.99 (1H, t, *J* 9.5, 3-H), 5.20 (1H, dd, *J* 16, 9, 7-H), 5.22 (1H, d, *J* 9.5, 4-H), 5.35 (1H, t, *J* 7.5, 10-H), 5.58 (1H, dd, *J* 15.5, 8.5, 13-H), 5.89 (1H, d, *J* 15.5, 12-H) and 5.81 (1H, d, *J* 16, 6-H); *m*/*z* (FAB) 832 (M^++Na, 85%).

12. The acid chloride **21** was prepared from methyl (*S*)-lactate by conversion to the *p*-methoxybenzyl ether using *p*-methoxybenzyl 2,2,2-trichloroacetimidate, saponification, and conversion of the carboxylic acid into the acid chloride using oxalyl chloride in DMF.