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Synthetic Studies on the Azinothricin Family of Antitumour Antibiotics. 5. Asymmetric Synthesis of Two Activated Esters For the Northern Sector of A83586C

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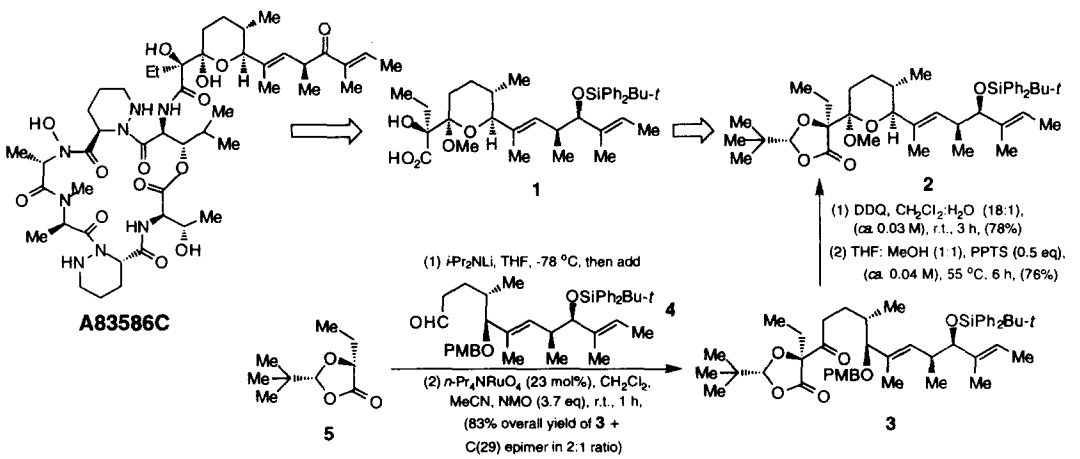
Abstract: An asymmeric synthesis of the activated esters **20** and **21** is reported. Both molecules equate with the C(28)-C(47) region of A83586C, and contain functionality appropriate for future unification with the hexapeptide unit. A useful new reaction is described for converting a methyl ester directly into a thioethyl or HOBT ester that operates under very mild conditions.

A83586C is an architecturally novel cyclodepsipeptide isolated from the antibiotic beer of *Streptomyces karnatakensis* by Smitka and coworkers.[1] Although A83586C is itself highly toxic to mice at doses of 9.3 mg/kg, and unlikely ever to be used clinically, it remains an interesting drug design lead for the following reasons. First, it has an unprecedented molecular structure; second, it exhibits pronounced antitumour properties *in vitro* against a CCRF-CEM human T-cell leukaemia line (IC_{50} = 0.0135 μg/ml), and; third, it has a devastating biocidal profile against resistant strains of Gram-positive bacteria at very low drug concentrations. Moreover, A83586C has a sister molecule, citropeptin, which can confer 123% life-extension on mice bearing P388 lymphocytic leukaemia when administered at 2 mg/kg/day,[2] although high toxicity is again a problematic feature. If the structural domains responsible for the observed toxicity of A83586C and citropeptin could be identified, through detailed structure-toxicity work, then it might prove possible to delete or modify these regions so as to create new analogues with enhanced antitumour effects and much lower toxicity *in vivo*. One way of gaining access to such analogues would be to develop a total synthesis of A83586C itself and then to make adjustments as required.[3]

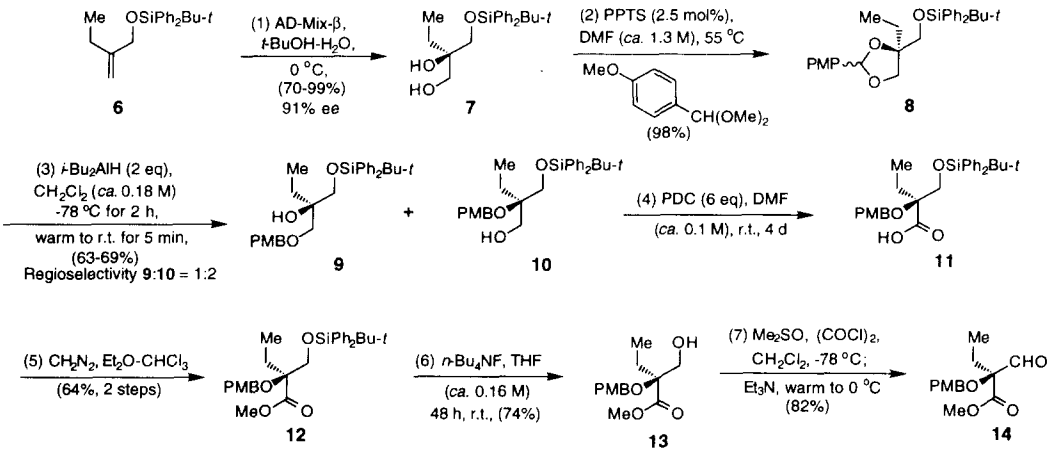
Scheme 1



Some time ago, we reported the preparation of β-keto ester **3**, an advanced intermediate with a structure corresponding to the C(28)-C(47) segment of the target molecule.[3d] While it transpired that β-keto ester **3** could be readily manipulated into glycoside **2** (Scheme 1), subsequent elaboration of **2** into acid **1** proved troublesome.[4] More specifically, we were unable to devise conditions for the successful hydrolysis of the *t*-butyl 1,3-dioxolane ester in **2** to obtain **1**. In light of this set-back, we reluctantly modified our strategy to the northern half of A83586C, and now describe a route that provides the activated esters **20** and **21**, two northern sector intermediates with functionality appropriate for unification with the hexapeptide sequence.

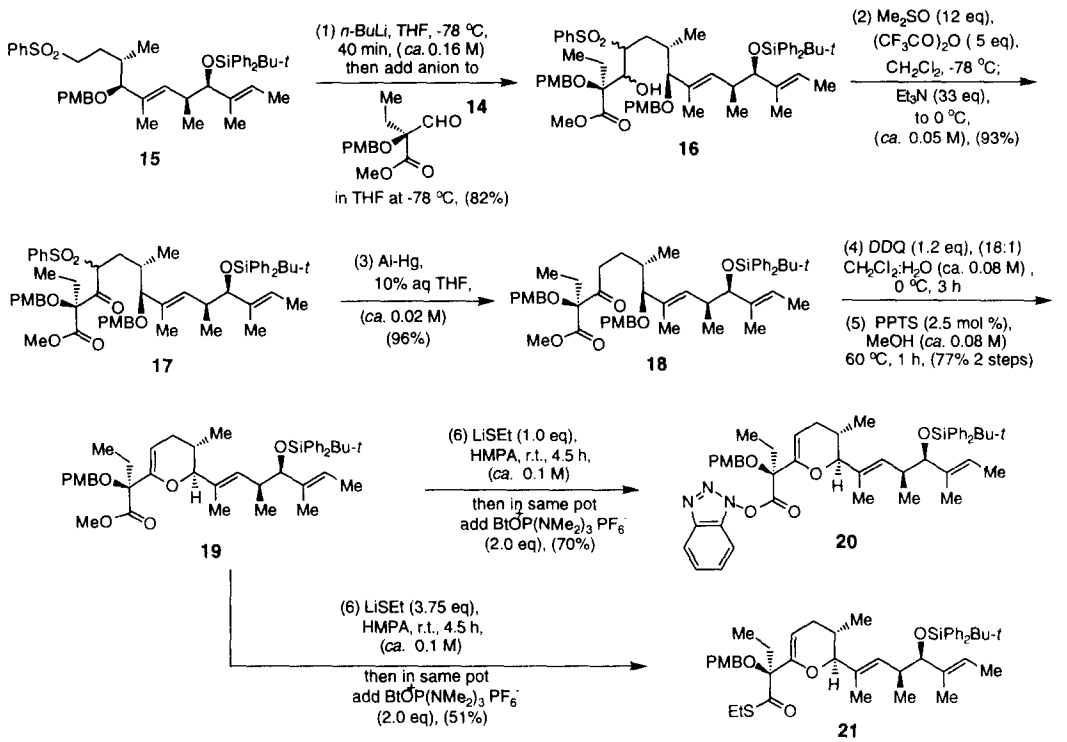
The starting compound for our synthesis of **20** and **21** was alkene **6**. It was subjected to Sharpless asymmetric dihydroxylation[5] with AD-mix-β under the standard conditions to give diol **7** in 70-99% yield and 91% ee.[6] Treatment of **7** with PPTS (2.5 mol%) and *p*-anisaldehyde dimethylacetal (1.2 eq) in dry DMF at 55 °C at 25 mm Hg for 2 h furnished **8** as a mixture of diastereoisomers in 98% yield. The latter were then reduced with *i*-Bu_2AlH[7] at low temperature to give a 1:2 mixture of **9** and **10** in which the latter regioisomer predominated. Both alcohols were readily separated by flash chromatography. While it proved relatively straightforward to oxidise the primary alcohol in **10** to the corresponding carboxylic acid **11** with pyridinium dichromate in DMF,[8] the reaction did prove rather slow, taking 4 days to reach completion. Acid **11** was then

Scheme 2



transformed into ester **12** by treatment with ethereal diazomethane in $CHCl_3$; the overall yield for the two steps was 64%. Esterification was followed by *O*-desilylation to obtain alcohol **13** and subsequent oxidation[9] to aldehyde **14**. The latter condensed readily with the α-phenylsulfonyl anion derived from **15**[3b] to give a mixture of β-hydroxy sulfones **16** that underwent Swern oxidation[10,3b] to afford the β-keto sulfones **17** in 76% combined yield (Scheme 3). Desulfonylation of **17** proceeded efficiently with aluminium amalgam in aqueous THF[11] to produce ketone **18** in 96% yield. Treatment of **18** with 1.2 equiv. of DDQ[12] in aq. CH_2Cl_2 at 0 °C for 3 h brought about a remarkably regioselective *O*-debenzylation at C(34) to furnish an α/β mixture of ring-closed hemiketals in addition to hydroxy ketone. Exposure of this mixture to catalytic PPTS and methanol at 60 °C furnished glycal **19** in excellent yield. Unfortunately, all our attempts to directly hydrolyse the methyl ester in **19** with base to obtain the carboxylic acid were unsuccessful. Eventually, it was discovered that compound **19** could be converted directly into the activated *N*-hydroxybenzotriazolyl ester **20** by sequential dealkylative cleavage with LiSEt (1.0 eq) in HMPA[13] for 4.5 h and addition of excess BOP reagent [benzotriazol-1-yloxy-tris(dimethyl-

Scheme 3



amino)phosphonium hexafluorophosphate][14] to the reaction mixture. It also proved possible to convert **19** directly into the activated thioester **21** by reaction of the methyl ester with excess LiSEt in HMPA[13] followed by addition of the BOP reagent. In our view, this new one-pot method for converting methyl esters directly into activated esters merits further attention since it operates under very mild conditions and should be applicable to other molecules in which conventional ester hydrolysis presents difficulties.

In summary, we have completed an asymmetric synthesis of the activated esters **20** and **21**;[15] both molecules have structures that are functionally equivalent to the C(28)-C(47) sector of A83586C. Further elaboration of **20** and **21** into A83586C and its analogues should now prove possible.

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15. All new compounds gave satisfactory IR, 400 MHz ^{1}H and 100 MHz ^{13}C NMR spectra as well as HRMS and/or microanalyses within 0.4%. Selected physical data now follow (N.B. All ^{1}H and ^{13}C NMR δ values are quoted in $CDCl_3$ as solvent and are relative to the residual $CHCl_3$ peak at 7.24 or 77.0 ppm respectively).
Compound **18**: 400 MHz ^{1}H NMR δ 7.68-7.56 (m, 4H), 7.43-7.24 (m, 8H), 7.10 (m, 2H), 6.84 (m, 2H), 6.77 (m, 2H), 4.96 (m, 1H), 4.84 (d, *J* = 9.9 Hz, 1H), 4.37 (1/2 AB q, *J* = 10.7 Hz, 1H), 4.28 (1/2 AB q, *J* = 10.7 Hz, 1H), 4.14 (1/2 AB q, *J* = 11.3 Hz, 1H), 3.84 (1/2 AB q, *J* = 11.3 Hz, 1H), 3.78 (d, *J* = 8.7 Hz, 1H), 3.77 (s, 3H), 3.74 (s, 3H), 3.66 (s, 3H), 3.00 (d, *J* = 9.6 Hz, 1H), 2.74-2.53 (m, 3H), 2.17 (m, 1H), 2.06 (m, 1H), 1.95 (m, 1H), 1.57 (m, 1H), 1.50 (m, 3H), 1.46 (s, 3H), 1.23 (d, *J* = 6.7 Hz, 3H), 1.21 (m, 1H), 1.04 (s, 9H), 0.91 (d, *J* = 6.7 Hz, 3H), 0.80 (t, *J* = 7.5 Hz, 3H), 0.54 (d, *J* = 6.7 Hz, 3H); 100 MHz ^{13}C NMR δ 208.2, 169.9, 159.2, 158.9, 136.8, 136.3, 136.1, 134.5, 134.2, 133.6, 131.7, 131.0, 129.8, 129.5, 129.3, 129.9, 127.3, 127.0, 122.5, 113.7, 113.6, 89.8, 84.5, 69.0, 66.5, 55.3, 55.21, 55.19, 52.4, 37.6, 36.5, 34.4, 27.2, 26.9, 24.5, 19.6, 18.3, 15.9, 12.8, 11.1, 10.5, 7.3.
Compound **19**: $[\alpha]_D$ +29.5 ° (*c* 3.0 CH_2Cl_2); 100 MHz ^{13}C NMR δ 172.3, 158.9, 150.7, 136.2, 136.1, 134.6, 134.3, 132.4, 131.6, 131.0, 129.3, 129.0, 127.2, 127.1, 122.1, 113.5, 97.9, 87.6, 83.9, 83.8, 66.1, 55.3, 51.9, 37.5, 29.1, 28.7, 27.2, 25.7, 19.6, 17.7, 17.4, 12.6, 11.7, 11.2, 7.7.
Compound **20**: $[\alpha]_D$ +35.0 ° (*c* 1.0 CH_2Cl_2); 400 MHz ^{1}H NMR δ 8.04 (d, *J* = 8.3 Hz, 1H), 7.65-7.56 (m, 4H), 7.43-7.24 (m, 11H), 6.84 (m, 2H), 5.23 (m, 1H), 5.04 (d, *J* = 9.0 Hz, 1H), 4.97 (m, 1H), 4.64 (1/2 AB q, *J* = 10.5 Hz, 1H), 4.50 (1/2 AB q, *J* = 10.5 Hz, 1H), 3.82 (d, *J* = 7.6 Hz, 1H), 3.77 (s, 3H), 3.63 (d, *J* = 9.5 Hz, 1H), 2.64 (m, 1H), 2.20 (m, 3H), 1.84 (m, 2H), 1.61 (s, 3H), 1.41 (s, 3H), 1.23 (d, *J* = 6.8 Hz, 3H), 1.03 (s, 9H superimposed on t, 3H), 0.92 (d, *J* = 6.7 Hz, 3H), 0.76 (d, *J* = 6.4 Hz, 3H); HRMS Calcd. for $C_{50}H_{61}N_3O_6SiNa$ *m/e* 850.4227 $(M+Na)^{+\cdot}$. Found: 850.4222.
Compound **21**: 400 MHz ^{1}H NMR δ 7.68-7.57 (m, 4H), 7.42-7.25 (m, 8H), 6.85 (d, *J* = 8.7 Hz, 2H), 4.96 (m, 2 H), 4.89 (d, *J* = 10.0 Hz, 1H), 4.43 (1/2 AB q, *J* = 10.7 Hz, 1H), 4.29 (1/2 AB q, *J* = 10.7 Hz, 1H), 3.78 (s, 3H superimposed on d, 1H), 3.51 (d, *J* = 9.0 Hz, 1H), 2.76 (m, 2H), 2.61 (m, 1H), 2.05 (m, 1H), 1.96 (m, 2H), 1.70 (m, 2H), 1.48 (s, 3H), 1.40 (s, 3H), 1.28 (d, *J* = 6.6 Hz, 3H), 1.18 (t, *J* = 7.4 Hz, 3H), 1.04 (s, 9H), 0.87 (d, *J* = 6.7 Hz, 3H), 0.80 (t, *J* = 7.3 Hz, 3H), 0.67 (d, *J* = 6.1 Hz, 3H); HRMS Calcd. for $C_{46}H_{62}O_5SSiNa$ *m/e* 777.3985 $(M+Na)^{+\cdot}$. Found: 777.3980.

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