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Total Synthesis of (+)-Azinothricin and (+)-Kettapeptin

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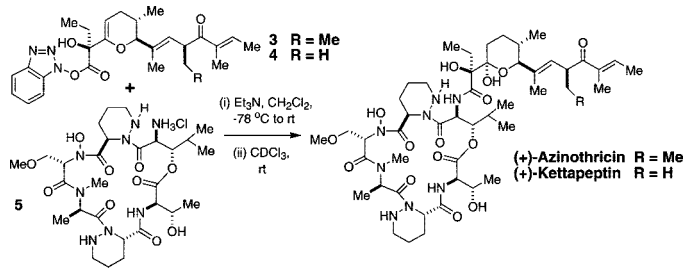
ABSTRACT



Asymmetric total syntheses of (+)-azinothricin and (+)-kettapeptin have been completed through a common new pathway that exploits a highly chemoselective coupling reaction between the fully elaborated cyclodepsipeptide 5 and the glycal activated esters 3 and 4 at the final stages of both respective syntheses.

(+)-Azinothricin[1] is the founding member of a potent and biologically intriguing family of antitumor antibiotics that now include A83586C,[2] citropeptin,[3] GE3,[4] and kettapeptin[5] among their number.

As part of a longstanding effort to understand how the A83586C/GE3/citropeptin and kettapeptin pyranylated cyclodepsipeptides function as antitumor agents,[6] we became interested in evaluating the anticancer properties of (+)-azinothricin and (+)-kettapeptin with the aid of cDNA microarray technology. However, due to the fact that natural samples of (+)-azinothricin no longer exist and because we also wished to biologically evaluate analogue structures, we elected to synthesize both natural products chemically, by a new and *considerably shortened* pathway to molecules of the A83586C/azinothricin/kettapeptin class (see Scheme 1 for all three structures).

Our approach to these targets would dispense with protecting groups at the final stages of each synthesis and would attempt the chemoselective coupling of fragments **3** and **4** with **5** to obtain glycals **1** and **2**, respectively. Regioselective hydration at C(30) would thereafter finalize both synthetic ventures (Scheme 1).

Regarding our tactics for constructing **5** and **6**, a fragment condensation between **7** and **8** would initiate proceedings. A union between the resulting Fmoc-deprotected tetrapeptide and acid chloride **9** would thereafter yield a suitably protected linear hexapeptide. Its two Boc-protecting groups would then

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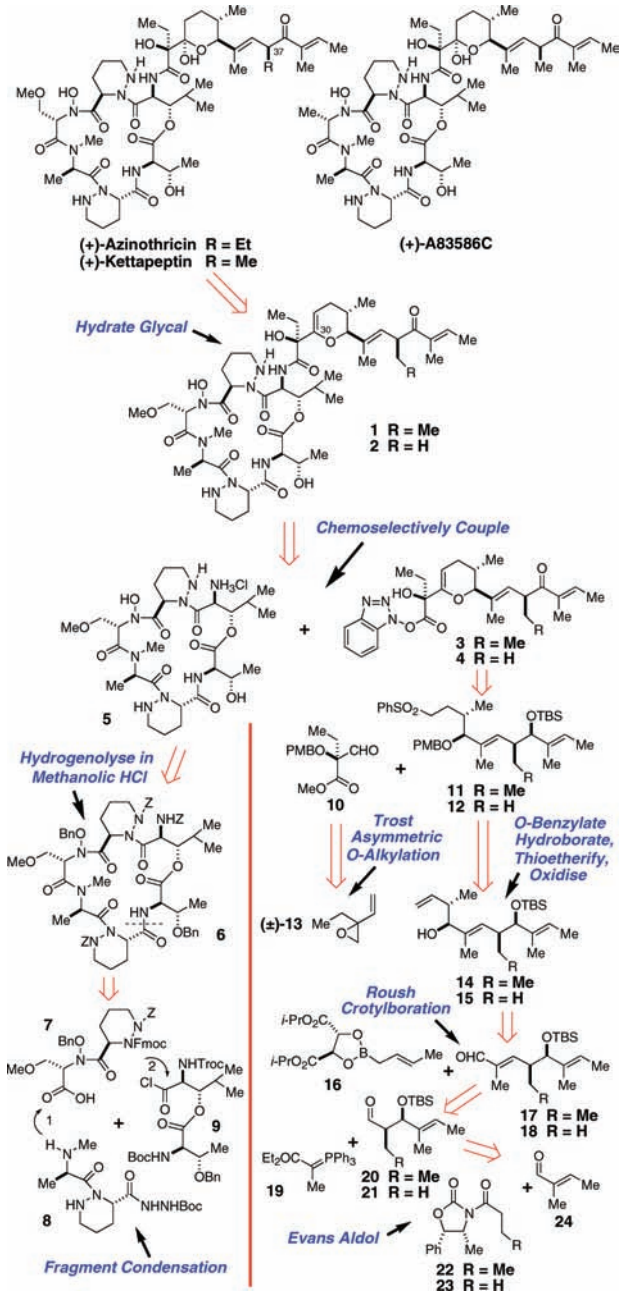
Scheme 1. Retrosynthetic Strategy for the Asymmetric Total Synthesis of (+)-Azinothricin and (+)-Kettapeptin



be removed, the resulting (3*S*)-piperazic acid acyl hydrazide oxidatively converted to an acid, and a macrolactamization effected between the D-threonine and (3*S*)-piperazic acid residues. Further protecting group adjustment would then provide **6** and **5**.

The activated esters **3** and **4** would derive from the respective unions of **11** and **12** with aldehyde **10**, following further synthetic manipulation. Our favored pathway to **10** would apply a Trost asymmetric alcoholysis reaction[7] to the racemic vinyl epoxide **13** to introduce the requisite OPMB stereocenter. Oxidative manipulation would thereafter complete the route. Phenylsulfones **11** and **12** would emanate from the alkenes **14** and **15** by O-*p*-methoxybenzylation, regioselective hydroboration/oxidation, thioetherification, and sulfide oxidation. Homoallylic alcohols **14** and **15** would themselves be obtainable from enals **17** and **18** by Roush asymmetric crotylboration[8] with **16**. An Evans asymmetric aldol reaction[9] and a Wittig olefination sequence would suffice to secure **20** and **21** from the precursors **22**/**23** and **24**.

Initial attention focused upon the preparation of aldehydes **20** and **21** via Evans asymmetric aldol chemistry[9] (Scheme 2). The synthesis of aldehyde **21** had previously been published by our group in 2005[10] in another context. The route to **20** proceeded analogously, setting off with a *syn* aldol reaction between **22** and **24** to access **25** as essentially a single diastereoisomer in 85% yield. It was then subjected to a Weinreb amidation[11] to obtain **26** which was O-silylated before being reduced with DIBAL-H to secure aldehyde **20**. Aldehydes **20** and **21** were individually converted to enals **17** and **18** by stereoselective Wittig olefination, DIBAL-H reduction, and MnO_2 oxidation. Roush crotylboration[9] of **17** and **18**, respectively, with **16** furnished **14** and **15** with a 2.3:1 level of selectivity in favor of the desired *anti*-configured products. The individual alcohols **14** and **15** were readily purified by SiO_2 flash chromatography.

Following O-benzylation of **14** or **15** with *p*-methoxybenzyl trichloroacetimidate and catalytic TfOH in Et_2O, regioselective hydroboration/oxidation of the two less hindered terminal alkenes in these products with 9-BBN and basic H_2O_2 provided the desired individual primary alcohols **27** and **28** in good overall yield (71% and 73% yield, respectively, over two steps). Sulfones **11** and **12** were each prepared by thioetherification with $Bu_3P/(PhS)_2$ in DMF and Oxone oxidation in THF/MeOH/H_2O.

Although chiral aldehyde **10** had previously featured in our original route to A83586C,[6] a major flaw in our first-generation synthesis of **10**[12] was the low regioselectivity (2:1 desired: undesired product) we had obtained in the introduction of the tertiary OPMB group by an O-*p*-methoxybenzylidene acetal reduction tactic.[12] Our new, second-generation pathway to **10** (Scheme 3) now overcomes all of these past difficulties by applying a Trost Pd(0)-catalyzed asymmetric O-alkylation/kinetic resolution reaction[7] to racemic vinyl epoxide **13**. With PMBOH as the nucleophile and (*R*,*R*)-phosphine ligand **37** as the key asymmetry-inducing additive, this process delivered the desired alcohol **38** in good yield (74%) and excellent ee (95%). Successive Swern and Pinnick[13] oxidations converted **38** into the acid **39** which was then O-methylated and ozonized to provide aldehyde **10**.

Sulfones **11** and **12** were now metallated with *n*-BuLi in THF, and the resulting anions individually condensed with aldehyde **10** at −78 °C (Scheme 2). Swern oxidation and

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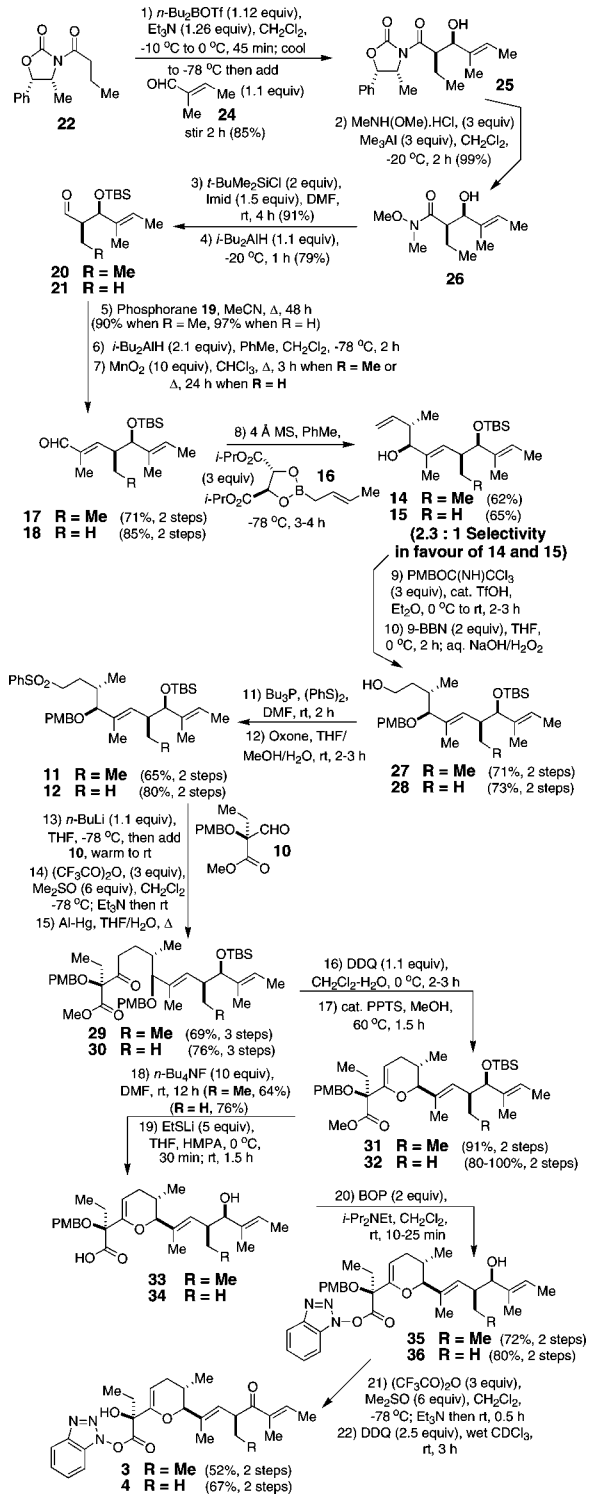
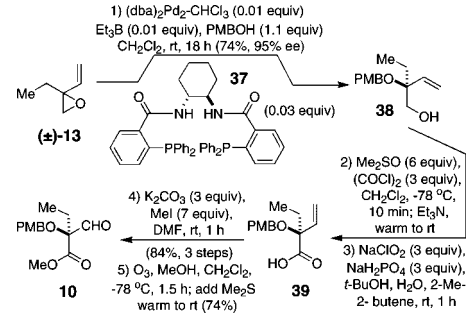
Scheme 2. Routes Developed to Pyran Activated Esters **3** and **4**



Al/Hg amalgam reduction thereafter procured the β-ketoesters **29** and **30**. The less hindered and more electron-rich secondary OPMB group was now selectively deprotected from **29** and **30** with DDQ in aqueous CH_2Cl_2, and the resulting hydroxyketones were dehydrated with PPTS in MeOH at 60 °C. Glycals **31** and **32** were then taken forward to the activated esters **3** and **4** by analogous reactions to those

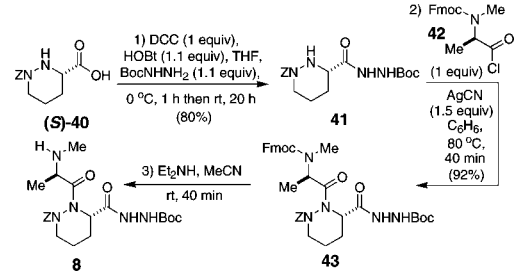
Scheme 3. Our New Asymmetric Route to Aldehyde **10**



deployed in our original A83586C synthesis.[6,12]

Our new abridged pathway to **8**[6] is shown in Scheme 4. Major new advances include the direct preparation of the acyl hydrazide **41**[6] from (3*S*)-*N*(1)-*Z*-piperazic acid **40**[14] without protection of N(2).

Scheme 4. New Improved Route to Dipeptide **8**

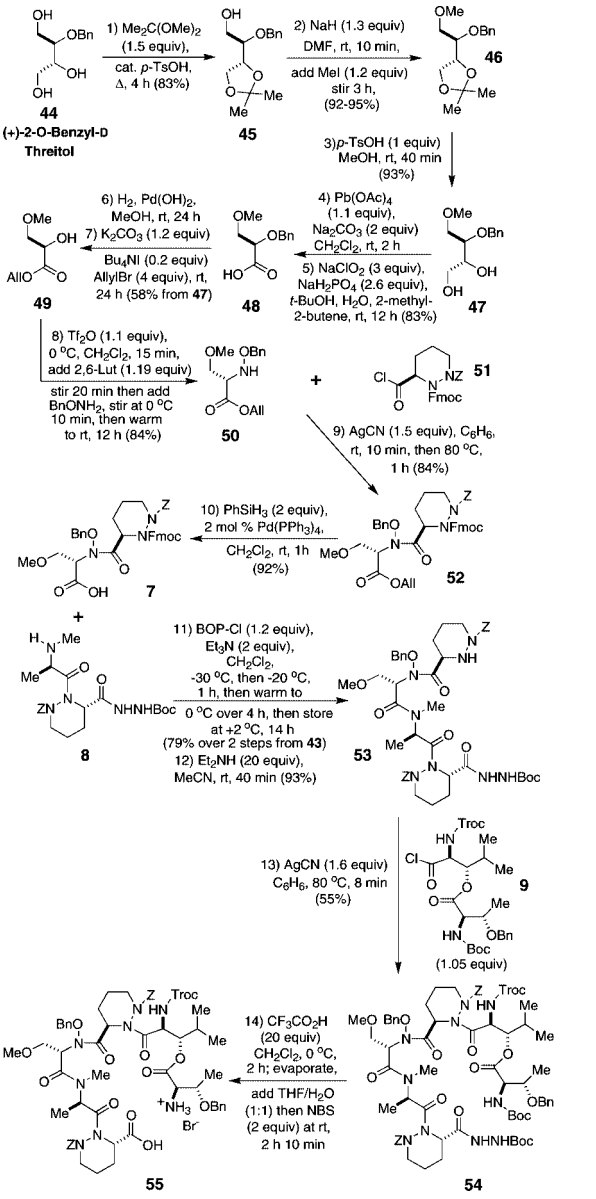


Our pathway to **50** (Scheme 5) began from Jager's 2-*O*-benzyl-D-threitol.[15] Following regioselective O-isopropylidenation with 1,1-dimethoxypropane and O-methylation with NaH/MeI in DMF to obtain **46**, the isopropylidene group was detached, and the resulting diol **47** was oxidatively cleaved. The intermediary aldehyde was then subjected to a Pinnick oxidation[13] to access acid **48**. Hydrogenolytic O-debenzylation of **48** with Pearlman's catalyst provided the chiral α-hydroxyacid needed for chemoselective O-allylation with K_2CO_3/AllylBr in DMF. The product alcohol **49** was subsequently converted to an *O*-triflate ester and this subjected to an Ottenheijm S_N2-type displacement[16] with $BnONH_2$ to obtain **50**.

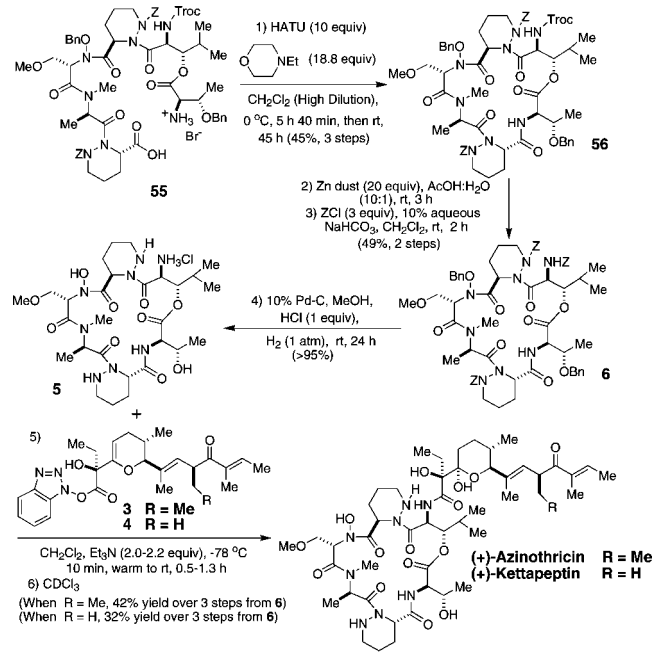
A silver cyanide assisted amidation[6] was now effected between alkoxyamine **50** and acid chloride **51** to procure dipeptide **52** in 84% yield. It underwent clean O-deallylation under neutral conditions with phenylsilane and catalytic $Pd(PPh_3)_4$[17] to produce the acid **7** needed for our BOP−Cl coupling with **8**. The latter proceeded in 79% yield from **43** and afforded the tetrapeptide **53** after Et_2NH-induced cleavage of the Fmoc group.

A third silver cyanide mediated amidation was now implemented, on this occasion, with **53** and acid chloride **9**;[6] it delivered **54** in 55% yield after purification. Both Boc

Scheme 5. Route Used to Secure **50** and Linear Hexadepsipeptide **55**



Scheme 6. Endgames for (+)-Azinothricin and (+)-Kettapeptin



groups were now removed from **54** with TFA, and the acyl hydrazide was oxidatively hydrolyzed with *N*-bromosuccinimide (NBS) in aqueous THF.[6] The hexapeptide salt **55** thereafter cyclized with HATU[18] under high dilution conditions over several days (Scheme 6). The latter reaction proceeded in 45% overall yield for these last three steps. The next phase of the synthesis was deprotection of the Troc group from **56** with Zn dust in acetic acid. N-Acylation with $PhCH_2OC(O)Cl$ thereafter furnished **6** in 49% yield for the last two steps, with SiO_2 flash chromatography allowing **6** to be purified to very high standards. The time had now come to deprotect **6** to secure **5**; the desired hydrogenolysis proceeded successfully in HCl/MeOH with 10% Pd on C.

The subsequent individual couplings of **5** with **3** and **4** took place cleanly to give **1** and **2**, respectively (Scheme 6). After individual chromatographic purification and dissolution in $CDCl_3$, compound **1** gave rise to (+)-azinothricin in 42% yield from **6**, while compound **2** produced (+)-kettapeptin in 32% yield from **6**.

In summary, the first total syntheses of (+)-azinothricin and (+)-kettapeptin have been achieved by a new unified synthetic strategy *that cuts 12 steps off the original route* to molecules of the A83586C class.[6]

Acknowledgment. We thank Novartis Pharma AG and Queen's University Belfast for financial support.

Supporting Information Available: Full experimental procedures, spectral data, and copies of 500 MHz ^1H and 125 MHz ^{13}C NMR spectra are provided along with IR spectra and HRMS data. This material is available free of charge via the Internet at http://pubs.acs.org.

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