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.

(+)-Azinothricin¹ is the founding member of a potent and biologically intriguing family of antitumor antibiotics that now include A83586C,² citropeptin,³ GE3,⁴ and kettapeptin⁵ 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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be removed, the resulting (3S)-piperazic acid acyl hydrazide oxidatively converted to an acid, and a macrolactamization effected between the D-threonine and (3S)-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 reaction⁷ 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,

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regioselective hydroboration/oxidation, thioetherification, and sulfide oxidation. Homoallylic alcohols **14** and **15** would themselves be obtainable from enals **17** and **18** by Roush asymmetric crotylboration⁸ with **16**. An Evans asymmetric aldol reaction⁹ 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 chemistry⁹ (Scheme 2). The synthesis of aldehyde 21 had previously been published by our group in 2005¹⁰ 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 amidation¹¹ 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 MnO₂ oxidation. Roush crotylboration⁹ of 17 and 18, respectively, with 16 furnished 14 and 15 with a 2.3:1 level of selectivity in favor of the desired anticonfigured products. The individual alcohols 14 and 15 were readily purified by SiO₂ flash chromatography.

Following O-benzylation of 14 or 15 with *p*-methoxybenzyl trichloroacetimidate and catalytic TfOH in Et₂O, 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/H₂O.

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 reaction⁷ 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 Pinnick¹³ 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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Al/Hg amalgam reduction thereafter procured the β -ketoesters **29** and **30**. The less hindered and more electronrich secondary OPMB group was now selectively deprotected from **29** and **30** with DDQ in aqueous CH₂Cl₂, 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 $\mathbf{8}^6$ is shown in Scheme 4. Major new advances include the direct preparation of the acyl hydrazide $\mathbf{41}^6$ from (3*S*)-*N*(1)-*Z*-piperazic acid $\mathbf{40}^{14}$ without protection of N(2).



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 oxidation¹³ to access acid **48**. Hydrogenolytic O-debenzylation of **48** with Pearlman's catalyst provided the chiral α -hydroxyacid needed for chemoselective O-allylation with K₂CO₃/AllylBr in DMF. The product alcohol **49** was subsequently converted to an *O*-triflate ester and this subjected to an Ottenheijm S_N2-type displacement¹⁶ with BnONH₂ to obtain **50**.

A silver cyanide assisted amidation⁶ 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 Et₂NH-induced cleavage of the Fmoc group.

A third silver cyanide mediated amidation was now implemented, on this occasion, with **53** and acid chloride 9_{5}^{6} it delivered **54** in 55% yield after purification. Both Boc



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

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 HATU¹⁸ 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 PhCH₂OC(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. Scheme 6. Endgames for (+)-Azinothricin and (+)-Kettapeptin



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 CDCl₃, 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

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Supporting Information Available: Full experimental procedures, spectral data, and copies of 500 MHz ¹H and 125 MHz ¹³C 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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