Enantioselective Synthesis of the Cyclopiazonic Acid Family Using Sulfur Ylides

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In memory of Gilbert Stork

Abstract: A convergent, nine-step (LLS), enantioselective synthesis of α-cyclopiazonic acid and related natural products is reported. The route features a) an enantioselective aziridination of an imine with a chiral sulfur ylide; b) a bioinspired (3+2)-cycloaddition of the aziridine onto an alkene; and c) installation of the acetyltetramic acid by an unprecedented tandem carboxylative lactamization/N–O cleavage of a bromoisoxazole.

Indole alkaloids have long been a source of inspiration for the development of new synthetic methods and strategies. α-Cyclopiazonic acid (α-CPA, 1) is a prenylated indole alkaloid produced by a number of Penicillium species including P. commune, P. griseofulvum, and P. camemberti.[1] It is a potent inhibitor of Ca2+-dependent ATPase (SERCA) which prevents calcium reuptake in muscle.[2] In addition to its significant biological activity, α-CPA-producing fungi are found in cheese, meat, and other dietary products, making it important to the food industry.

Several structurally related natural products have been identified (Figure 1): iso-α-cyclopiazonic acid (2),[3] α-CPA imine (3),[3b] speradines A–D,[4] and aspergillines A–E,[5] all sharing a 3-acetyltetramic acid unit.

Biosynthetically, α-CPA is derived from L-tryptophan (Figure 1B).[1a,k,6] The tetramic acid is assembled at an early stage followed by several alkylations to give β-cyclopiazonic acid (β-CPA, 4), a direct biosynthetic precursor of α-CPA. Flavin-mediated oxidation of β-CPA and subsequent cyclization give α-CPA.[6d]

Four total syntheses of α-CPA have been published (Figure 2A).[7] They all share the same end-game strategy, in which the tetramic acid unit is installed by a Dieckmann condensation, forming the C6–C7 bond. Kozikowski[7a] and Natsume[7b] constructed the C–D rings in a stepwise manner, but with low diastereoselectivity. Knight developed an elegant cationic cascade, in which acyclic precursor 9 was converted into indole 6 with high stereocontrol,[7c,d] although Scherenbeck found that the same substrate cyclized to give a 1:1 mixture of diastereomers across the CD ring junction under slightly different conditions.[7e,f]

In our retrosynthetic approach to α-CPA we considered a different, bioinspired strategy (Figure 2B). We were attracted by the possibility of using an aziridine 13 as a precursor to the zwitterionic intermediate 12 that would participate in a (3+2)-cycloaddition to construct the C–D ring system. Whilst this type of (3+2)-cycloaddition has been reported for the construction of pyrrolidines,[8] its application in total synthesis is much rarer.[9] Aziridine 13 could be assembled from simple building blocks 14 and 15 using our asymmetric sulfur ylide methodology.[10] We envisaged using an isoxazole as a masked 1,3-dicarboxyl group[11] attached to the sulfur ylide. A further attractive feature of this approach is that the ylide could carry all the carbons and functionality required for making rings C and D. We would then have to build ring E by N–C8 bond formation, rather than the C6–C7 bond, which is commonly used to construct tetramic acids.

We began our synthesis by targeting the imine building block 14 which was obtained in 4 steps from commercially...
available indole 16 (Scheme 1A). Suzuki cross-coupling of aryl bromide 16 with allyl boronic ester followed by N-tosylation gave indole 17. Cross-metathesis of the terminal alkene 17 in neat 2-methyl-2-butene [12] delivered 18 in good yield. Initial attempts to affect one-step prenylation of 16 under various conditions led to substantial prenylboration of the aldehyde giving alcohol 19. The aldehyde 18 was converted into the N-nosyl [13] imine 14, thus completing the synthesis of the indole fragment.

Sulfonium salts 15a,b were prepared from known alcohol 21 [14] by a two-step sequence via triflate 22 (Scheme 1B). The use of the triflate instead of the corresponding bromide resulted in 1) much faster alkylations, and 2) the sulfonium salts precipitating directly from the ethereal solvent, permitting straightforward isolation by simple filtration. [15]

Our initial synthetic campaign was performed with an achiral sulfonium salt 15a to evaluate the viability of the route (Scheme 2). Reaction of imine 14 with an ylide derived from 15a proceeded smoothly and delivered aziridine 24 in good yield (72%) and diastereoselectivity (trans/cis 9:1). Trans-24 was prone to rapid isomerization into cis-24 in CDCl₃ or on silica, and so was used crude. Notably, compound 24 already contains all the carbon atoms present in α-CPA.

We then explored the bioinspired cycloaddition of 24 and tested a range of Lewis and Brønsted acids (see the Supporting Information, SI), and found that treatment of CH₂Cl₂ solutions of 24 with 2 equiv of In(OTf)₃ or 0.1–1 equiv of TIOH triggered the desired reaction. This gave pyrrolidine 25 as a mixture of diastereomers at C-11 (d.r. 3:1, in favor of the desired cis-isomer), from which the desired cis-product was isolated as a single isomer in 24% yield by crystallization from MeCN–H₂O. Then nosyl group was removed with PhSNa and the ester was hydrolyzed with LiOH yielding amino acid 26. Subjecting 26 to a standard amide coupling conditions (HATU, DIPEA, DMF) resulted in formation of lactam 27. Subsequent hydrogenolysis of the N–O bond under Pd catalysis gave N-Ts α-CPA imine 28 in 80% yield, which was then hydrolyzed [7b] to give (+)-α-CPA (1) in 60% yield (dr 3.8:1). The racemic synthesis of 1 was thus achieved in 11 steps (longest linear sequence).

Unexpectedly, the attempted enantioselective campaign met with failure. The use of the chiral sulfonium salt 15b gave the desired aziridine 24 but with poor diastereo- and enantioselectivity (dr 1.9:9, er 40:60). We believe that the ylide derived from sulfonium salt 15b behaves as a stabilized rather than a semi-stabilized ylide and so reacts reversibly with the imine 14, resulting in low stereosecontrol [10a,c]. We therefore considered alternative isoxazole substrates 31a–c (Scheme 3) bearing a less anion-stabilizing group (bromide in

Figure 2. A) Previous syntheses of α-CPA. B) Our retrosynthetic analysis.
First-Generation (Racemic) Synthesis

Scheme 2. Reagents and conditions: 1) Cs$_2$CO$_3$, CH$_3$Cl, $-40^\circ$C, 72%; 2) ln(OTf)$_2$, CH$_3$Cl, $-78$ to $23^\circ$C, 24%; 3) PhSNa, DMF, $23^\circ$C, 73%; 4) LiOH, THF-MeOH-H$_2$O, $23^\circ$C, 83%; 5) HATU, DIPEA, DMF, $23^\circ$C, 81%; 6) H$_2$ (1 atm), Pd(OH)$_2$/C, MeOH, 80%; 7) KOH, EtOH, $65^\circ$C. HATU = N-[(dimethylamino)-1H-1,2,3-triazolo-[4,5-b]pyridin-1-ylmethylene]-N-methylmethanaminium hexafluorophosphate N-oxide, DIPEA = N,N-disopropylethylamine.

Synthesis of Bromoisoxazole Building Blocks 31a-c

Scheme 3. Reagents and conditions 1) acetaldoxime, NaClO, CH$_2$Cl$_2$-H$_2$O, 0 to $23^\circ$C, 65%; 2) NBS, AcOH, then NaOH workup, 85%; 3) TF$_2$O, CH$_2$Cl$_2$, 0°C, 93% for 31a, 77% for 31b, 47% for 31c. NBS = N-bromosuccinimide.

Second Generation (Enantioselective) Synthesis

Scheme 4. Reagents and conditions: 1) K$_2$CO$_3$, MeCN, $-20^\circ$C, 56% (trans/cis 9:1, er 98:2 [trans], 89:11 [cis]); 2) TFOH, CH$_3$Cl, $-55$ to $10^\circ$C, 50% (dr 3.5:1, er 98:2); 3) PhSH, K$_2$CO$_3$, 18-crown-6, MeCN, $23^\circ$C, 63%; 4) CO (1 atm), Pd(OAc)$_2$, n-BuPAd$_2$, DABCO, DMSO, $120^\circ$C, 80%; 5) Cs$_2$CO$_3$, MeOH-THF-H$_2$O, $65^\circ$C, 70%. Ad = adamantyl, DABCO = 1,4-diazabicyclo[2.2.2]octane.
Conflict of interest

The authors declare no conflict of interest.

Keywords: \((3+2)\)-cycloaddition · aziridination · sulfur ylide · total synthesis · \(\alpha\)-cyclopiazonic acid

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1. provided validation of our hypothesis: the ylide with the less electron-withdrawing bromine atom is now behaving as a semi-stabilized ylide, rendering betaine formation the enantiodetermining step.

As with aziridine 24, trans-aziridine 32 was prone to isomerization into cis-32, and thus was used without purification. Treatment of crude 32 with TIOH gave pyrrolidine 33 as a 3.5:1 mixture of diastereomers[18] at C-11 in favor of the desired cis-isomer, in 50% yield with complete enantiospecificity (er 98:2).[18] Deprotection of the diastereomeric mixture with PhSH/K₂CO₃ gave amine 34, at which point the diastereomers were separated. We were initially concerned about the next Pd-catalyzed carbylonylation-amide formation due to the severe angle strain inherent in the fused bicyclic isoxazole 27.[19] However, we were delighted to find that treatment of 34 with Pd(OAc)₂, under an atmosphere of CO in the presence of DABCO and \(\alpha\)-BuPAd[20] triggered a reaction cascade leading directly to the formation of \(N\)-Ts \(\alpha\)-CPA imine 28 in 80% yield. The cascade involves palladium-catalyzed carbylonylation, acylation, followed by reduction of the \(N\)-O bond in situ,[21] facilitated by the inherent angle strain of the fused unsaturated ring system 27. Presumably, the facility of the cyclization stems from ready formation of the undistorted amino-acyl palladium intermediate, before ring strain is introduced through the subsequent reductive elimination. Hydrolysis of \(N\)-Ts species 28 under basic conditions[24] in MeOH-TFA-H₂O (10:10:1) provided a mixture of \((-\alpha\)-CPA (1) and \((+\)-iso-\(\alpha\)-CPA (2) (dr 2.5:1) which was separated by reverse-phase prep-HPLC.

Synthetic \(-\alpha\)-CPA was identical in all respects to the natural material, including TLC, LCMS, HRMS, NMR and optical rotation[3] data (see SI). When the reaction was performed under strictly anhydrous conditions, \(\alpha\)-CPA imine 3 was the major product. This constitutes the first direct synthesis of \(\alpha\)-CPA imine: the previous method relied on the amination of \(\alpha\)-CPA itself.[25] This completed our synthesis of the \(\alpha\)-CPA family.

In summary, we have achieved an enantioselective total synthesis of \(-\alpha\)-CPA and \((+\)-iso-\(\alpha\)-CPA in 9 steps (LLS) from commercially available materials (13 total steps). The route is convergent with the key asymmetric aziridination bringing together the two halves of the molecule with high stereoselectivity and with all the functionality required to complete the target. Additional features of the sequence include 1) a bio-inspired intramolecular alkeno-aziridine (3+2)-cycloaddition to assemble a polysubstituted pyrroli- dine; and 2) a one-pot carbylonylation/cleavages/isoxazole cleavage to give an acetyltetramic acid. The latter represents a novel route to tetramic acids which could have broader applications in synthesis.


[17] Although the diastereoselectivity might appear moderate, it should be noted that the use of an ester group (32, \( R = \text{CO}_2\text{Et} \)) in place of the isoxazole resulted a 10:1 product ratio in favor of the undesired trans-isomer highlighting the sensitivity of the diastereomeric ratio to the substituent.

[18] cis- and trans-aziridines 32 converted into pyrrolidine 33 with the same diastereoselectivity and enantiospecificity but reacted at different rates. The reaction of trans-32 was cleaner, faster and higher yielding (50–60%) than that of cis-32 (30%).

[19] Molecular modelling (B3LYP 6-311G(d)) shows that the \( \psi_1/\psi_2 \) angles in 27 should be close to 146° and 135°, respectively, which deviates substantially from the 124° and 117° in the strain-free system:

![strain model](image1)

![strain-free model](image2)


[21] The source of the two hydrogen atoms is intriguing. Exclusion experiments showed that either CO or DABCO could independently reduce the N–O bond of 27 under the reaction conditions (see SI, Table 7) but the reduction with CO was much cleaner. It is possible that adventitious H\(_2\)O participates in a water-gas shift with CO generating CO\(_2\) and H\(_2\) which then reduces the N–O bond.

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