Total synthesis of diazonamide A†

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Abstract

A total synthesis of the marine natural product diazonamide A (**1**) has been accomplished. This work features a highly stereoselective synthesis of the C(10) quaternary center and the central furanoindoline core enabled by an iminium-catalyzed alkylation–cyclization cascade. Additionally, a magnesium-mediated intramolecular macroaldolization and a palladium-catalyzed tandem borylation/annulation were developed to enable the closure of the two 12-membered macrocycles of diazonamide A. This synthesis involves 20 steps in its longest linear sequence and proceeds in 1.8% overall yield.

Introduction

The diazonamides are a structurally unique class of secondary metabolites first isolated by Fenical and coworkers from the colonial marine ascidian *Diazona angulata*.[1] Within this family, diazonamide A (**1**) was found to be a potent antimitotic agent, exhibiting low nanomolar GI_{50} values towards a diverse panel of human cancer cell lines.[1a, 2a] Cells treated with **1** fail to develop a mitotic spindle, a phenotype commonly associated with tubulin-binding agents such as taxol and vinblastine. However, the cellular receptor of **1** was identified by Harran and Wang to be ornithine δ-amino-transferase (OAT), a mitochondrial matrix protein previously unknown to play any role in spindle regulation.[2b] Given the documented viability of OAT-null organisms, it was subsequently proposed that OAT-dependence may be a differential characteristic of mitosis in cancerous and healthy cells. If correct, **1** would represent a cancer-selective therapeutic agent[2c] and a valuable molecular probe of the oncology associated with OAT-dependent mitosis.

As a consequence of this intriguing bioactivity and its remarkable molecular structure, diazonamide A has been the target of intense and sustained synthetic interest for nearly two decades.[3] The structure of **1** was misassigned in the original isolation report,[1] but was later corrected by Harran and coworkers in 2001 following a seminal synthesis of the nominal structure.[4] The correct structure of **1** is characterized by two 12-membered macrocycles that are conjoined through a triaryl-substituted quaternary carbon stereocenter embedded in an unusual furanoindoline core. Together with a large degree of unsaturation, these structural elements comprise an exceptionally compact and rigid framework whose inner atoms possess almost no rotational degrees of freedom. While many groups have reported partial syntheses of **1** over the past decade, Nicolaou[5a–d] and Haran[5e] have reported the only three completed total syntheses of **1** to date, while Magnus[6a] and Sammakia[6b] have recently outlined formal syntheses.
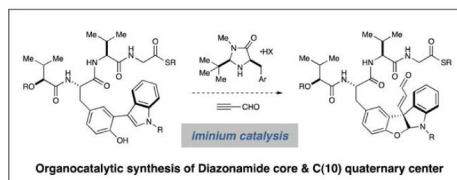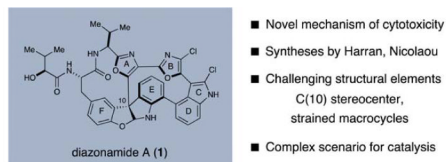
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Design plan

Retrosynthetically, the principal challenge associated with the synthesis of **1** is the stereoselective installation of the C(10) quaternary carbon stereocenter. Collective consideration of earlier synthetic efforts offer support for this view, as this aspect of the target structure has not been successfully addressed in any of the three completed total syntheses.[7] With the specific aim of developing catalytic asymmetric solutions to the C(10) problem, we initiated a program directed towards the total synthesis of diazonamide A. In this communication we describe the

diazonamide A (1)

- Novel mechanism of cytotoxicity
- Syntheses by Harran, Nicolaou
- Challenging structural elements
  C(10) stereocenter,
  strained macrocycles
- Complex scenario for catalysis

Organocatalytic synthesis of Diazonamide core & C(10) quaternary center

realization of these efforts, which features a highly stereoselective synthesis of the C(10) quaternary center with concomitant installation of the central furanoindoline enabled by an iminiumcatalyzed diastereoselective conjugate addition/phenol cyclization cascade (depicted above).[8] In addition, we present novel solutions to the syntheses of the two large ring systems of **1**, including a magnesium-mediated intramolecular macroaldolization in the construction of the left-hand twelve-membered ring, as well as a palladium-catalyzed tandem borylation/annulation to furnish the intact right-hand macrocycle. The details of our synthetic sequence are described herein.

Results and discussion

Our synthesis began with the Suzuki coupling of boronic ester **2** and iodophenol **3** under the action of catalytic Pd(dppf)Cl$_2$ to yield biaryl **4** in 82% yield (Scheme 1). The methyl ester of **4** was then hydrolyzed with aqueous lithium hydroxide and the resulting carboxylic acid was coupled to an *N*-TFA salt of valine·glycine dipeptide thioester, providing access to **5**, the substrate required for our proposed key organocatalytic transformation.

In accord with our design plan, treatment of **5** with 30 mol% of imidazolidinone catalyst **6**·TFA and excess propynal in dichloromethane and methanol at −70 °C resulted in full conversion to **7**, though as a modest 4.2 : 1 mixture of diastereomers at the critical C(10) position (Table 1, entry 1).

During subsequent optimization studies, it was found that the use of **6**·TCA and the replacement of dichloromethane with chloroform or toluene resulted in improved selectivity with no associated loss of reactivity (Table 1, entries 2–4). Interestingly, the use of a ternary solvent mixture comprised of toluene, chloroform and methanol ultimately proved superior, to deliver **7** in 86% isolated yield and >20 : 1 dr after 24 h at −50 °C (Table 1, entry 5). Notably, use of racemic imidazolidinone catalyst **6**·TCA results in a 1 : 1 mixture of diastereomers at C(10), demonstrating that the observed stereoselectivity is entirely amine catalyst-controlled (Table 1, entry 6). In addition to being well suited to address this specific synthetic problem, we believe this is the most complex and challenging setting in which organocatalysis has been employed to date.

With the diazonamide core in hand, the indoline protecting group was exchanged to ensure the stability of the nascent aminal towards a subsequent ozonoylsis, which cleanly furnished aldehyde **9** in 84% yield. Aldehyde **9** was specifically targeted as the substrate for a proposed intramolecular aldol reaction to furnish a 13-membered, ring-opened form of the left-hand macrocycle. This unconventional macroaldolization approach was targeted after prior experimental efforts suggested that closure of the intact 12-membered ring *via* a traditional macrolactamization would not proceed efficiently. More specifically, we reasoned that creating a larger, more conformationally flexible macrocycle that could then undergo ring contraction with concomitant formation of the central oxazole would allow ring strain to be offset by the net gain in aromaticity. While such aldol reactions are rare,[9] a careful evaluation of Lewis acids, amine bases and solvents led to the discovery that treatment of thioester **9** with $MgBr_2 \cdot Et_2O$, TMSCl and triethylamine in THF at room temperature readily effected soft enolization, allowing an efficient, intramolecular macroaldolization to deliver **10** as a single diastereomer in 67% yield (Scheme 1). Notably, the addition of TMSCl was necessary to circumvent the possibility of retroaldol pathways, a characteristic concern of magnesium aldol processes.[10]

While alcohol **10** could be readily oxidized with the Dess–Martin periodinane to its corresponding ketone, subsequent cyclodehydration to furnish the central oxazole ring proved unsuccessful using many standard protocols. However, we were pleased to discover that direct treatment of the β-ketothioester with an excess of DAST in benzene led to a highly efficient cyclodehydration, furnishing intact macrocycle **11** in 61% yield over two steps.[11] At this stage, the structure and relative stereochemistry of **11** were confirmed through X-ray crystallographic analysis of its corresponding carboxylic acid (supporting information†).

With the synthesis and stereochemistry of the left-hand macrocycle secured, we next turned our attention to the second and more challenging 12-membered ring of diazonamide A. With intermediates similar to **11**, Harran and Nicolaou both employed an elegant photochemical Witkop cyclization to furnish the D–E biaryl bond and close the right hand macrocycle.[5] With a goal of developing a distinctive solution to this challenging construction, we elected to explore an approach wherein the same biaryl bond could be formed utilizing a palladium-catalyzed cross-coupling protocol. In assessing this approach, we were wary of attempting to carry a sensitive aryl stannane or boronic ester through the synthetic steps prior to the proposed annulation. Rather, we elected to install the requisite coupling functionality immediately prior to ring closure *via* reaction conditions that would then facilitate subsequent annulation in a single, tandem operation, in analogy to the well-known Stille–Kelly protocol.[12]

Towards these ends, the thioester functionality of **11** was activated with AgTFA and displaced by amine **12** to yield ketoamide **13** in 88% yield.[13] Furanoindoline **13** was in turn subjected to the Wipf conditions[14] for oxazole cyclodehydration, furnishing bisoxazole **14** in 86% isolated yield (Scheme 2). Deprotection of the benzyloxy and trifluoroacetamide groups of **14** with BBr_3, followed by treatment of the crude product with excess PhNTf$_2$ provided bromo-bistriflate **15** in 80% yield over two steps. After extensive optimization, we were able to realize a successful tandem borylation/annulation, as treatment of **15** with $(Bpin)_2$, KF, and $Pd(PPh_3)_4$ in a 5% aqueous solution of dioxane under microwave heating at 120 °C yielded the desired biaryl bond of macrocycle **16** in 50% yield.[15] Mass spectrometric analysis of the progressing reaction suggests that this reaction proceeds

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†Electronic supplementary information (ESI) available: Experimental procedures, structural proofs, and spectral data for all new compounds are provided.

through rapid and selective borylation of the aryl bromide, followed by a slower coupling between the nascent boronate and the aryl triflate.[16]

With the carbon framework of diazonamide A fully installed, selective introduction of the aryl chlorides was accomplished by first brominating the activated indoline *E*-ring, followed by *in situ* hydrolysis of the indolyl triflate to yield **17** in 83% isolated yield. Subsequent chlorination of the desired oxazole and indole functionalities of **17** was achieved upon exposure to NCS, and the aryl bromide was selectively excised by hydrogenolysis over Pearlman's catalyst in a two-step, one-pot procedure. Finally, treatment with TASF removed the remaining silyl ether to furnish synthetic diazonamide A (**1**), whose spectral characteristics were identical to the natural product in all respects. The completed synthesis as it stands was accomplished in 20 steps in the longest linear sequence and in 1.8% overall yield.

Conclusions

In summary, we have completed a 20 step total synthesis of diazonamide A from commercial materials, wherein a series of synthetic solutions to many of the challenging structural features of **1** were realized. In particular, the use of asymmetric iminium catalysis provided an efficient and highly stereoselective synthesis of the C(10) center and the complete furanoindoline core. A complete account of our studies towards the synthesis of diazonamide A will be reported in due course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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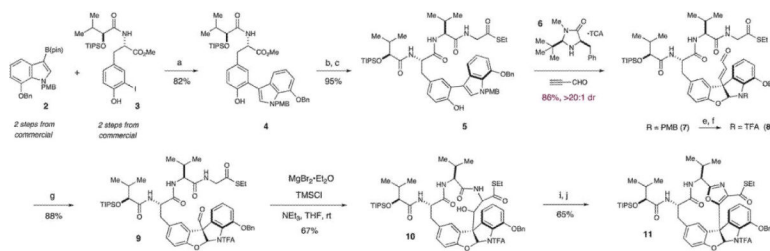
Scheme 1.
Organocatalytic synthesis of the furanoindoline core and Lewis acid mediated synthesis of left-hand macrocycle of diazonamide A. Reagents and conditions: (a) 5 mol% Pd(dppf)Cl$_2$, K$_3$PO$_4$, dioxane, 40 °C (b) LiOH, THF, MeOH, H$_2$O, rt (c) EDC, HOBt, (*S*)-S-ethyl 2-(2-amino-3-methyl-butanamido)ethanethioate·TFA, NaHCO$_3$, DMF, rt (d) Table 1, entry 5 (e) DDQ, CH$_2$Cl$_2$, pH 7 buffer, 0 °C (f) TFAA, DMAP, CH$_2$Cl$_2$, 0 °C (g) O$_3$, CH$_2$Cl$_2$, MeOH, −78 °C (h) MgBr$_2$·Et$_2$O, TMSCl, NEt$_3$, THF, rt (i) Dess–Martin, CH$_2$Cl$_2$, rt (j) DAST, C$_6$H$_6$, rt.
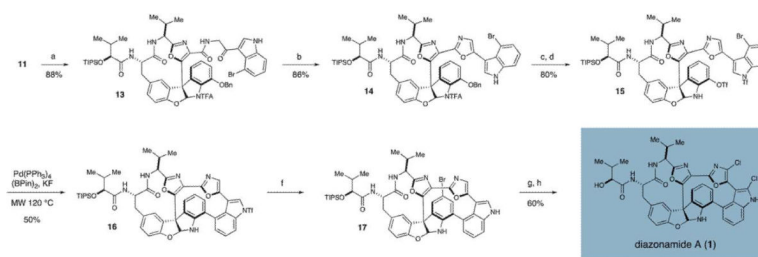
Scheme 2.
Construction of the second macrocyclic ring, dichloro installation and completion of the total synthesis of diazonamide A (**1**). Reagents and conditions: (a) AgTFA, NaHCO$_3$, 2-amino-1-(4-bromo-1H-indol-3-yl)ethanone·TFA, DMF, 40 °C (b) PPh$_3$, C$_2$Cl$_6$, NEt$_3$, CH$_2$Cl$_2$, 0 °C (c) BBr$_3$, CH$_2$Cl$_2$, −78 °C (d) PhNTf$_2$, NEt$_3$, CH$_2$Cl$_2$, rt (e) (Bpin)$_2$, KF, 70 mol% Pd(PPh$_3$)$_4$, dioxane:H$_2$O (20 : 1), MW 120 °C (f) NBS, THF; then LiOH, THF, MeOH, H$_2$O (g) NCS, THF, 40 °C; then H$_2$, Pd(OH)$_2$, THF, 40 °C (h) TASF, DMF, rt.

Table 1

Organocatalytic installation of the C(10) quaternary center[a]
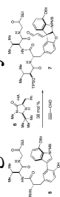
Entry	Catalyst·HA	$T/°C$	solvent: MeOH	% conv[b]	dr[b]
1	**6**·TFA	−70	CH_2Cl_2(20 : 1)	>95	4.2 : 1
2	**6**·TCA	−70	CH_2Cl_2(20 : 1)	>95	7.7 : 1
3	**6**·TCA	−70	$CHCl_3$(20 : 1)	>95	8.2 : 1
4	**6**·TCA	−70	PhMe (20 : 1)	>95	8.3 : 1
5	**6**·TCA	−50	$CHCl_3$:PhMe (10 : 10 : 1)	86[c]	>20 : 1
6	*rac*-**6**·TCA	−50	$CHCl_3$:PhMe (10 : 10 : 1)	80	1 : 1

[a]Optimizations performed on 0.05 mmol scale for 24 h.

[b]Determined by ^{1}H-NMR analysis of the crude reaction mixture.

[c]Isolated yield for reaction performed on 15 mmol scale.