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Highly Functionalized Tricyclic Oxazinanones via Pairwise Oxidative Dearomatization and *N*-Hydroxycarbamate Dehydrogenation: Molecular Diversity Inspired by Tetrodotoxin

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Abstract

Benzenoids in principle represent attractive and abundant starting materials for the preparation of substituted cyclohexanes; however, the synthetic tools available for overcoming the considerable aromatic energies inherent to these building blocks limit the available product types. In this paper, we demonstrate access to heretofore unknown heterotricyclic structures by leveraging oxidative dearomatization of 2-hydroxymethyl phenols with concurrent *N*-hydroxycarbamate dehydrogenation using a common oxidant. The pairwise-generated, mutually reactive species then participate in a second stage acylnitroso Diels–Alder cycloaddition. The reaction chemistry of the derived [2.2.2]-oxazabicycles, bearing four orthogonal functional groups and three stereogenic centers, is shown to yield considerable diversity in downstream products. The methodology allows for the expeditious synthesis of a functionalized intermediate bearing structural and stereochemical features in common with the complex alkaloid tetrodotoxin.

The latent functionality embedded within the benzene nucleus offers opportunities to chemists seeking to deploy the parent aromatic core structure as a point of departure for synthesizing chiral, functionalized cyclohexanes. The key challenge thwarting the realization of this potential is the design not only of transformations that overcome the formidable aromatic stabilization energy associated with benzenoids^{1–7} but also a suitable second stage reaction that takes advantage of the functionality, often of tenuous stability, revealed in the first stage. The work described here uses the cyclohexane substructure of the complex natural product tetrodotoxin (TTX, **1**, Scheme 1a) as an inspiration to develop a new oxidative dearomatization cascade sequence for the *de novo* creation of heterotricyclic

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Notes

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Supporting Information

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Experimental procedures, characterization, spectral data (PDF)

Crystallographic data for **9** (CIF)

Crystallographic data for **14** (CIF)

Crystallographic data for **31** (CIF)

Crystallographic data for **34** (CIF)

Crystallographic data for **35** (CIF)

compounds presenting four orthogonal functional groups. We demonstrate that considerable product diversity is available from this new platform.

Tetrodotoxin (**1**), a potent neurotoxin first isolated from puffer fish, has garnered significant attention since its structure was first elucidated in 1964 due to its unique biological properties and densely functionalized structure (Scheme 1a).⁸ (–)-TTX inhibits voltage gated sodium ion channels and is consequently a leading molecular probe for further study in this area.⁹ Additionally, (–)-TTX has been under study as a treatment for chemotherapy-induced neuropathic pain.¹⁰ Since the first synthesis of (±)-TTX by Kishi in 1972, there have been five total syntheses, each enabled by the development of creative tactics to access the densely functionalized core.^{11–19} “Tetrodamine” (**2**, Scheme 1a) is a common conceptual target in tetrodotoxin syntheses.^{11–18} The C6–C7–C8–C8a stereotetrad comprises a challenging functional group constellation. The C7/C8 *syn* diol is suggestive of a *cis* alkene difunctionalization; direct dihydroxylation of a suitably substituted benzene has been suggested as a potential entry point for tetrodotoxin²⁰ and OsO₄-catalyzed alkene functionalization was realized en route to **1**.¹⁸ Perhaps more nettlesome is the C6/C8a *syn*-1,4-amino-cyclohexanol where both heteroatoms reside at fully substituted stereogenic centers (Scheme 1a).

In considering retrosynthetic approaches, the presence of a C7/C8 alkene and antithetic reconnection of the C6/C8a amino alcohol (red arrows) would create a retron for an acylnitroso Diels–Alder cycloaddition.²¹ We envisioned oxidative remodeling of an achiral benzenoid could be triggered by Adler oxidation of the corresponding salicyl alcohol **4**.²² Trapping the resulting spiroepoxydienone **6** with a concurrently generated dienophile **5** might trigger a second stage hetero-Diels–Alder cycloaddition (Scheme 1b). An enabling feature of the envisioned strategy is that acyl nitroso **5** and epoxydienone **6** could in principle be prepared by oxidation of *N*-hydroxycarbamate **3**²³ and salicyl alcohol **4**, respectively, with a common oxidant.²⁴ Development of this methodology would allow for the rapid preparation of rigid, bicyclic products with four orthogonal functional groups from simple, aromatic feedstock while potentially allowing for an expeditious, flexible synthesis of the tetrodamine substructure and ultimately (±)-TTX and its structural congeners.²⁵

We began by investigating the proposed acylnitroso Diels–Alder cycloaddition. The known dimerization of spiroepoxydienones was a concern;²⁶ therefore, spiroepoxydienone **7**, a compound we observed to be resistant to dimerization, was chosen as a model substrate. Moreover, dienone **7** bears an analogous substitution pattern to an idealized substrate for elaboration to TTX. Treating spiroepoxydienone **7** with *N*-hydroxycarbamate **8** under Cu(II)-catalyzed aerobic oxidation conditions²⁸ afforded a 1.5:1 mixture of the desired Diels–Alder cycloadduct **9** (5.4:1 dr) and salicyl alcohol **12** (Table 1a, entry 1). Formation of alcohol **12** only occurred in the presence of **8**, suggesting the *in situ* reduction of **7** could not be prevented under these reaction conditions. Stoichiometric quantities of tetra-*n*-butylammonium periodate (*n*Bu₄NIO₄) in CH₂Cl₂ afforded cycloadduct **9** (2.3:1 dr) in low conversion without any observable formation of **12** (entry 2). Repeating the reaction in CDCl₃ at 45 °C showed trace conversion to **9**, but full consumption of **8** after 1 h. On the basis of these observations, we speculated decomposition of the transient acylnitroso

species, which has a lifetime on the order of 1 ms at infinite dilution,²³ was likely the source of the poor reactivity.

Accordingly, we proposed the reactivity could be enhanced by maintaining an excess of spiroepoxydienone **7** relative to the acylnitroso species; therefore, an additional 2 equiv of *n*Bu₄NIO₄ was added followed by the dropwise addition of **8** (2 equiv) over 2 h, affording cycloadduct **9** (3.2:1 dr) in 57% conversion (entry 3). When the reaction was conducted in CHCl₃ (entry 5), phenol **12** was observed in similar quantities relative to the Cu(II)-catalyzed aerobic oxidation conditions (entry 1). The variance in reactivities observed between CHCl₃ and its deuterated counterpart are likely the result of reduction of **7** promoted by ethanol, typically present in CHCl₃ as a stabilizer. Indeed, a similar effect was observed when methanol was used as the solvent (entry 1). In light of these observations, we avoided these and similar reaction media in subsequent experiments. Further optimization showed increased conversion of **7** using Cbz analog **10**, but cycloadduct **11** was isolated in only 12% yield (entries 5, 6). Repeating the reaction at cooler temperatures resulted in increased conversions and isolated yields of **11** (entries 7, 8). The diminished yields at elevated temperatures indicated possible thermal instability of the cycloadducts. Specifically, retro Diels–Alder cycloaddition followed by incomplete recombination and decomposition of the acylnitroso species was hypothesized. This hypothesis was later confirmed via a crossover experiment (*vide infra*).

To explore the viability of a one-pot Adler oxidation/acylnitroso cycloaddition sequence, we added a solution of **10** over 2 h to a mixture of salicyl alcohol **13** and NaIO₄ in methanol/water (Table 1b, entry 1). Full conversion of phenol **13** to spiroepoxydienone **15** was observed after 15 min, but complete reduction of **15** back to **13** was observed after 1 h. Screening *n*Bu₄NIO₄ as the oxidant and removing methanol as a solvent returned identical results (entries 2–4). Excluding water from the reaction afforded cycloadduct **14** (>20:1 dr), albeit in low conversion (entry 5). These results indicated that excess water was promoting the Adler oxidation while simultaneously promoting the reduction of intermediate spiroepoxydienone in the presence of the acylnitroso species in water-miscible solvents. These results collectively suggested that biphasic reactions under phase-transfer catalysis conditions might be efficacious (entry 6, 7). Indeed, using CH₂Cl₂ as the cosolvent afforded **14** in excellent yield with complete consumption of **13** (entry 7).

We next probed the scope of the corresponding one-pot procedure (Table 2). Electron-rich and electron-poor salicyl alcohols^{29–31} were tolerated, affording the derived cycloadducts in good yield. For most substrates, the cycloadduct is initially formed with >20:1 dr; however, cycloadducts **11** and **19** were isolated as a mixture of equilibrating diastereomers (determined by chemical derivatization and selective 1D NOESY NMR analysis; see the Supporting Information (SI) for details).

An X-ray diffraction study of bicyclic dihydrooxazine **9** revealed a regiochemical preference for the illustrated isomer, which matched that needed for extrapolation to TTX,²⁷ and acylnitroso approach from the methylene face of the epoxide of **7**. The observed facial selectivity was surprising as C=C dienophile approach from the oxygen face of spiroepoxydienones is well documented.²⁶ By contrast, an X-ray diffraction study of

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Scheme 1.
Synthetic Strategy for Tetrodotoxin and Proposed Pairwise Oxidation/Cycloaddition Cascade

Scheme 2. Chemoselective Reactions of Heterocycloadducts*

*Conditions: ^aNaBH₄ (0.33 equiv), THF, 0 °C; ^bBr₂ (2.0 equiv), Me₂S (2.5 equiv), CH₂Cl₂, 0 °C to rt; ^cOsO₄ (1 mol %), NMO (6.0 equiv), THF/acetone/H₂O (5:5:1), 0 °C to rt; ^dHONH₂·HCl (1.5 equiv), NaOAc (2.0 equiv), THF, rt; ^emCPBA (1.5 equiv), NaHCO₃ (2.0 equiv) CH₂Cl₂, rt; ^fHCl in 1,4-dioxane (4 N, 25.0 equiv), rt; ^gNaBH₄ (2.0 equiv), anhydrous MeOH, 0 °C; ^hp-O₂NC₆H₄COCl (2.2 equiv), TEA (3 equiv), DMAP (10 mol %), anhydrous THF, rt; ⁱNaH (60 wt %, 1.1 equiv), Me₃SO·I (1.1 equiv), anhydrous THF, 0 °C.

Scheme 3. Application of the Oxidation/Cycloaddition Cascade Procedure towards the TTX Core Structure*

*Conditions: ^ai. NaIO₄, MeOH/H₂O (2:1), ii. BnO₂CNHOH (2 equiv, 2 h addition), BnEt₃NCl (20 mol %), NaIO₄ (2.1 equiv), CH₂Cl₂/H₂O (1.3:1), 0 °C; ^bNaIO₄ (5.1 equiv), BnEt₃NCl (20 mol %), CH₂Cl₂/H₂O (1.3:1), rt then BnO₂CNHOH (4 equiv, 3 h addition), 0 °C; ^cOsO₄ (1 mol %), NMO (5.0 equiv), THF/acetone/H₂O (5:5:1), rt; ^dH₂, Pd/C (10 wt %), AcOH (5 equiv), MeOH/THF (3:2).

Table 1

Optimization of the Sequential and One-Pot Adler Oxidation/Acyl Nitroso Cycloaddition Protocol

entry	R =	oxidant	solvent	T(°C)	conv. of 7	dr (yield)
1 ^{a,b}	^t Bu	CuCl ₂ L, O ₂	MeOH	rt	85% (1.5:1 9/12)	5.3:1
2 ^c	^t Bu	ⁿ Bu ₄ NIO ₄	CH ₂ Cl ₂	rt-35	30%	2.2:1
3 ^{c,d}	^t Bu	ⁿ Bu ₄ NIO ₄	CDCl ₃	45	57%	3.2:1
4 ^e	^t Bu	ⁿ Bu ₄ NIO ₄	CDCl ₃	45	58%	2.1:1
5 ^e	^t Bu	ⁿ Bu ₄ NIO ₄	CHCl ₃ ^f	45	100% (1.4:1 9/12)	2.3:1
6 ^g	Bn	ⁿ Bu ₄ NIO ₄	CDCl ₃	45	68%	2.7:1 (12%) ^h
7 ^g	Bn	ⁿ Bu ₄ NIO ₄	CDCl ₃	30	87%	4.0:1 (51%) ^h
8 ^g	Bn	ⁿ Bu ₄ NIO ₄	CDCl ₃	rt	91%	4.3:1 (74%) ^h

entry	oxidant	solvent	catalyst	conv. of 13	product
1	NaIO ₄	MeOH/water	—	100%	13 ⁱ
2	NaIO ₄	THF/water	—	100%	13 ⁱ
3	ⁿ Bu ₄ NIO ₄	MeOH/water	—	100%	13 ⁱ
4	ⁿ Bu ₄ NIO ₄	THF/water	—	100%	13 ⁱ
5	ⁿ Bu ₄ NIO ₄	THF	—	20%	14/15 (10:1)
6	NaIO ₄	CDCl ₃ /water	BnEt ₃ NCl ^j	100% (60%) ^k	14/15 (10:1)
7	NaIO ₄	CH ₂ Cl ₂ /water	BnEt ₃ NCl ^j	100% (76%) ^k	14/15 (20:1)

^a CuCl₂ (10 mol %), L = 2-ethyloxazoline (20 mol %).^b 1.5 equiv **8**.^c 1.5 equiv **8**, 1.5 equiv ⁿBu₄NIO₄.^d 2.0 additional equiv of ⁿBu₄NIO₄ and **8** (2 h addition) were added.^e 2.0 equiv **8**, 2.0 equiv ⁿBu₄NIO₄.^f 0.75% EtOH as stabilizer.

^g2.0 equiv **10**, 2.0 equiv *n*Bu₄NIO₄.

^hIsolated yields.

ⁱInitial full conversion to **15** was observed followed by reduction back to **13**.

^j10 mol %.

^kIsolated yields in parentheses.

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Table 2

Scope of the One-Pot Oxidative Dearomatization/Acyl Nitroso Cycloaddition Cascade

^aEquilibrated dr.^bThermal isomerization occurs > 40 °C.^cIsomerization is observed after standing at rt (see SI).