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Oxazolone Cycloadducts as Heterocyclic Scaffolds for Alkaloid Construction – Synthesis of (±)-2-*epi*-Pumiliotoxin C

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Abstract

Intramolecular Diels-Alder cycloaddition of *N*-substituted oxazolone triene **I** allows direct entry to the functionalized octahydroquinoline **II**. Further manipulation of this framework by stereo- and regioselective introduction of the 5-methyl substituent, followed by excision of the carbamate, yields (±)-2-*epi*-pumiliotoxin C.

The skin secretions of neotropical frogs have long proven a rich and varied source of alkaloid natural products, many of which possess powerful yet specific bioactivity allied to their complex structure. A case in point is provided by the decahydroquinolines, with over 50 examples reported to date.¹ Several of these mild toxins display intriguing neurological activity as reversible antagonists of the nicotinic acetylcholine receptor channel.² As many of the proposed structures are based solely on MS and IR studies, confirmation by synthesis provides further compelling reason for development of a general approach to targets of this type. The parent member of this class, *cis*-195A³ (the alkaloid formerly known as pumiliotoxin C, **1**) is typical of their general 2,5-disubstituted *cis*-fused decahydroquinoline pattern, Figure 1. Altogether rarer is the 2-*epi*-*cis* motif, represented by 2β,5β-diallyl congener *cis*-219A, **2**, and the related 5β-Z-ene-yne variant *cis*-243A, **3**.⁴ This framework is also found embedded within the tricyclic core of gephyrotoxin 287C, **4**, another related neuroactive alkaloid.⁵ Whereas *cis*-195A has been synthesized on numerous occasions,⁶ we were intrigued by the potential offered by the 2-*epi*-series and sought to develop a general route to compounds of this ilk. In this Note we describe one such route, culminating in a preliminary synthesis of 2-*epi*-pumiliotoxin C, **5**.

As part of an ongoing program of research at the interface of heterocyclic and natural products chemistry, we recently reported the first intramolecular Diels-Alder reaction of *N*-alkylated oxazolones.⁷ This thermally activated cycloaddition allows rapid entry into a number of important heterocyclic frameworks, chiefly, densely functionalized hexahydroindoles and

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Supporting Information Available. Full experimental procedures and data for all remaining new compounds; ¹H & ¹³C NMR spectra for compounds **8**, **6** & **14**, **15** to **19**, & **5**; solved X-ray structures for **6** & **17**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

octahydroquinolines. As we continued our studies of oxazolone chemistry,⁸ it was clear that the latter appeared ideally suited to construction of decahydroquinoline alkaloids *via* direct incorporation of the initial cycloadduct framework. We therefore selected 2-*epi*-pumiliotoxin C, **5**, by way of example. Although previously synthesized on a number of occasions,⁹ most often as a minor byproduct *en route* to pumiliotoxin C itself, this compound has remained an important benchmark for the testing of new synthetic methodologies and is thus a fitting initial target.

In keeping with the overall theme of our methodology, our proposed synthesis is based on a key intramolecular Diels-Alder cycloaddition – the reaction of an oxazolone dienophile with a substituted diene fragment, tethered *via* nitrogen. This first generation approach involves trienic system **8**, as shown in our initial retrosynthetic analysis (Scheme 1). Our earlier studies with the heptadienyl parent system had shown the *cis*-cycloadduct to predominate [3.8:1, *cis* to *trans*], *via* an *endo* mode of cycloaddition.⁷ Assuming a similar transition state, the precise aspect of the propyl substituent would now be the critical issue. From early examination of models, we surmised that a pseudo-axial arrangement would minimize unfavorable allylic-type strain¹⁰ with the oxazolone carbonyl. Cycloaddition in this fashion would thus establish 3 of the 4 required stereocenters in a single step. It would only remain to introduce the 5-methyl group in regio- and stereoselective fashion, then excise the carbamate functionality, most probably by a hydrolysis-deoxygenation protocol.

Construction of the required triene system proceeded from commercially available divinyl carbinol **9** (Scheme 2). Saucy-type rearrangement¹¹ afforded heptadienal **10**, which underwent simple Grignard reaction to yield alcohol **11**. A three-step protocol as developed by Shibuya¹² was utilized to introduce the 2° oxazolone moiety: Mitsunobu reaction with oxazolidine-2,4-dione **12**, followed by reduction and elimination to generate the dienophilic olefin.

Investigation of the key cycloaddition ensued (Scheme 3). Simple thermal activation proceeded smoothly to furnish two main cycloadducts, **6** and **14**, in 3.7:1 ratio and 81% overall yield. Ring junction stereochemistry was readily assigned as *cis*- and *trans*- for each, in accordance with our previous findings. However, the signal at C2 was initially occluded, and extensive decoupling studies were required.¹³ These indeed confirmed the C2-propyl substituent as axial in both cycloadducts, with added proof for **6** from X-ray crystallography. Considerable effort was spent on optimization of conditions; a brief survey is presented in Table 1 for comparison. In all cases C2-*epi-cis*-cycloadduct **6** predominated, even to the extent that under thermal Lewis acid-promoted conditions¹⁴ it was the sole product isolated.

With the structure of the major cycloadduct confirmed as **6**, we proceeded with the next phase of our approach. This centered on successful installation of the 5-methyl substituent in regio- and stereocontrolled fashion. In order to address both these concerns simultaneously, we chose to pursue a two-step protocol – cyclopropanation followed by reductive cleavage. Given the inherent topology of the cycloadduct, we reasoned that simple cyclopropanation would favor the convex β -face. Subsequent hydrogenolysis of the most sterically-accessible edge would locate the 5-methyl as required. If successful, this would offer a fairly novel solution for stereocontrolled installation of an isolated methyl substituent, though precedent does arise from a seminal study on bicyclo[4.1.0]heptane.¹⁵

In the event, cyclopropanation under modified Denmark conditions¹⁶ proceeded with a high degree of β -facial control to yield the expected tetracycle **15**,¹³ (Scheme 4). Subsequent rupture at the 6-position was best achieved by simple hydrogenation over Adams' catalyst,¹⁷ with reasonable selectivity in favor of the desired isomer **16** (5.5:1, 5-Me to 6-Me). However, for reasons yet unclear to us this transformation required superstoichiometric quantities of PtO₂

to effect completion. The intermediacy of a discrete platinocyclic species has not been discounted.¹⁸

As this initial 5.5:1 mix proved inseparable, it was employed directly in studies of oxazolidinone cleavage. We found methyl lithium¹⁹ to be doubly effective in this regard, as not only did this afford the amine conveniently protected as acetamide, but also enabled separation of the required regioisomer **17**, in 79% overall yield from **15**. Once again X-ray crystallography provided unequivocal confirmation of our ongoing structural assignments. Deoxygenation at C8 proceeded smoothly *via* a modified Barton-McCombie protocol²⁰ to afford the *N*-acetylated target, **19**.

In these latter stages of the synthesis (**17** through **19**), both ¹H and ¹³C spectra were complicated by the presence of broadened and/or doubled signals. This observation was also noted by Meyers,^{9e} and studied in detail by Polniaszek^{9f} and Daly,²¹ all of whom concluded this arose from rapid equilibration of the *cis*-fused bicyclic systems, in itself a well-established property of *cis*-decahydroquinolines.^{22,23} A final deprotection of the *N*-acetamide group under Pearson's dissolving metal conditions²⁴ yielded (±)-2-*epi*-pumiliotoxin C, **5**, identical in all respects to that previously reported.^{9a,c,e}

In summary, this study has demonstrated the utility of oxazolone IMDA cycloadducts as valuable scaffolds for alkaloid construction, culminating in the synthesis of (±)-2-*epi*-pumiliotoxin C by a direct incorporation approach.

Experimental Section

Diels-Alder cycloaddition of triene **8**

To a stirred solution of triene **8** (698 mg; 3.16 mmol; 1.0 equiv), in *o*-dichlorobenzene (63.1 mL; ~0.05 M), was added a trace of hydroquinone (14 mg; 2% by wt). The colorless solution was freeze-thaw degassed (3 ×), placed under an atmosphere of argon, and brought rapidly to reflux. After 72 h, heat was removed and the brown solution partially reduced *in vacuo* (hi-vac; 85 °C) to yield 878 mg of the crude cycloadducts as a dark brown solid. Further purification by flash chromatography (silica ratio 100:1; hexane/EtOAc, 4:1 to 3:1 to 2:1 to 1:1) yielded each cycloadduct as a colorless solid.

First, the minor *trans*-cycloadduct, (±)-(3¹*S*,4*R*,6*aR*,9*aR*)-4-propyl-4,5,6,6*a*,9,9*a*-hexahydrooxazolo[5,4,3-*ij*]quinolin-2(3¹*H*)-one, **14**: 120 mg; 0.54 mmol; 17%. *R*_f 0.36 (hexane/EtOAc 2:1); ¹H NMR: (400 MHz; CDCl₃) δ 5.77 (m, 2H), 4.58 (td, *J* = 2 × 8.1, 5.9 Hz, 1H), 3.96 (dt, *J* = 10.1, 2 × 5.1 Hz, 1H), 2.99 (dd, *J* = 10.0, 8.0 Hz, 1H), 2.89 (m, 1H), 2.20 (ddm, *J* = 14.2, 5.8 Hz, 1H), 1.94 (dq, *J* = 12.9, 3 × 3.3 Hz, 1H), 1.81 (m, 1H), 1.75 (ddd, *J* = 13.4, 5.8, 4.2 Hz, 1H), 1.61-1.71 (m, 2H), 1.58 (qd, *J* = 3 × 12.8, 3.2 Hz, 1H), 1.29-1.43 (m, 3H), 0.92 (t, *J* = 7.2 Hz, 3H); ¹³C NMR (DEPT): (100.6 MHz; CDCl₃) δ 157.6 (C), 132.0 (CH), 125.4 (CH), 71.6 (CH), 57.2 (CH), 49.8 (CH), 37.0 (CH), 33.2 (CH₂), 28.7 (CH₂), 28.4 (CH₂), 23.4 (CH₂), 19.5 (CH₂), 13.7 (CH₃); IR: (thin film) *v*_{max} 2958, 2932, 1744, 1020 cm⁻¹; HRMS: *m/z* [M+H]⁺ Calcd for C₁₃H₂₀NO₂: 222.1494. Found: 222.1489.

Next, the major *cis*-cycloadduct, (±)-(3¹*S*,4*R*,6*aS*,9*aR*)-4-propyl-4,5,6,6*a*,9,9*a*-hexahydrooxazolo[5,4,3-*ij*]quinolin-2(3¹*H*)-one, **6**: 444.4 mg; 2.01 mmol; 64%. *R*_f 0.22 (hexane/EtOAc 2:1); ¹H NMR: (400 MHz; CDCl₃) δ 5.91 (ddt, *J* = 9.5, 6.4, 2 × 3.1 Hz, 1H), 5.67 (dm, *J* = 9.5 Hz, 1H), 4.88 (dddd, *J* = 9.3, 4.0, 1.9, 1.2 Hz, 1H), 4.04 (ddd, *J* = 9.3, 4.6, 1.4 Hz, 1H), 3.88 (dt, *J* = 9.6, 2 × 4.8 Hz, 1H), 2.59 (ddd, *J* = 16.3, 7.0, 2.0 Hz, 1H), 2.13 (m, 1H), 2.02 (ddq, *J* = 16.4, 3.9 Hz, 3 × 2.9 Hz, 1H), 1.90 (tt, *J* = 2 × 13.9, 2 × 3.8 Hz, 1H), 1.64-1.80 (m, 3H), 1.43 (dm, *J* = 13.9 Hz, 1H), 1.26-1.39 (m, 3H), 0.92 (t, *J* = 7.2 Hz, 3H); ¹³C NMR (DEPT): (100.6 MHz; CDCl₃) δ 157.2 (C), 131.4 (CH), 126.7 (CH), 72.4 (CH),

51.9 (CH), 48.5 (CH), 31.8 (CH₂), 30.9 (CH), 27.6 (CH₂), 23.3 (CH₂), 22.6 (CH₂), 19.4 (CH₂), 13.8 (CH₃); IR: (thin film) $\nu_{\max}$ 3024, 2943, 2867, 1731, 1047 cm⁻¹; HRMS: m/z [M + H]⁺ Calcd for C₁₃H₂₀NO₂: 222.1494. Found: 222.1487; Anal. Calcd for C₁₃H₁₉NO₂: C, 70.56; H, 8.65; N, 6.33. Found: C, 70.51; H, 8.64; N, 6.24.

Direct cyclopropanation of major cycloadduct – (±)-(3*R*,4¹*S*,6*aR*,7*aR*,8*aR*,8*bS*)-3-propyloctahydro-1*H*-cyclopropa[*f*]oxazolo[5,4,3-*ij*]quinolin-5(4¹*H*)-one, 15

A 75-mL heavy-walled sealed tube, fitted with septum and stir-bar, was flame dried under vacuum, flushed with Ar and allowed to cool to r.t. CH₂Cl₂ (2 mL) was added, followed by diethyl zinc (Aldrich, 1.0M in heptane; 2.65 mL; 2.65 mmol; 5.0 equiv) and the solution cooled to 0 °C. Neat chloriodomethane (0.39 mL; 5.36 mmol; 10.1 equiv) was added dropwise with caution over a period of 2 min, in order to prevent exotherm. During addition, a heavy colorless gum was precipitated; this was broken up by addition of further CH₂Cl₂ (5 mL), followed by vigorous stirring, to yield a milky suspension. The mixture was allowed to warm to r.t. After 10 min, a solution of cis-cycloadduct **6** (117 mg; 0.53 mmol; 1.0 equiv) in CH₂Cl₂ (2 mL + 2 mL rinse) was added dropwise. The tube was sealed and heated immediately to 120 °C with vigorous stirring. After 5 h, heat was removed and the reaction allowed to cool to r.t. The tube was opened, the contents poured onto 1 M HCl (25 mL), and the residue broken up with further 1 M HCl (25 mL) and CH₂Cl₂ (25 mL). The resulting mixture was partitioned and the aqueous phase extracted with further CH₂Cl₂ (2 × 25 mL). The combined organic phases were dried (MgSO₄), filtered and reduced *in vacuo* to yield 161 mg of crude cyclopropanes as a yellow oil. Further purification by flash chromatography (silica ratio 300:1; hexane/EtOAc 4:1 to 3:1) yielded the title β-cyclopropane **15** as a colorless oil: 107 mg; 0.46 mmol; 86%. *R*_f 0.25 (hexane/EtOAc 2:1); ¹H NMR: (400 MHz; CDCl₃) δ 4.72 (dt, *J* = 9.2, 2 × 2.6 Hz, 1H), 3.98 (dt, *J* = 10.3, 2 × 5.2 Hz, 1H), 3.72 (dd, *J* = 9.4, 3.8 Hz, 1H), 2.51 (ddd, *J* = 15.3, 6.7, 2.9 Hz, 1H), 1.95 (m, 1H), 1.86 (m, 2H), 1.71 (m, 1H), 1.43 (dm, *J* = 12.8 Hz, 1H), 1.29-1.40 (m, 3H), 1.09 (app sextet, *J* = 3.6 Hz, 1H), 0.94 (t, *J* = 7.0 Hz, 3H), 0.91-0.97 (occluded m, 1H), 0.87 (td, *J* = 2 × 8.2, 4.4 Hz, 1H), 0.82 (ddd, *J* = 15.5, 8.4, 2.3 Hz, 1H), 0.73 (qd, *J* = 3 × 8.2, 4.3 Hz, 1H), -0.03 (q, 4.3 Hz, 1H); ¹³C NMR (DEPT): (100.6 MHz; CDCl₃) δ 156.6 (C), 73.1 (CH), 51.5 (CH), 48.4 (CH), 32.4 (CH), 32.2 (CH₂), 27.5 (CH₂), 22.6 (CH₂), 22.1 (CH₂), 19.5 (CH₂), 15.4 (CH₂), 13.8 (CH₃), 6.7 (CH), 4.4 (CH); IR: (thin film) $\nu_{\max}$ 2933, 2868, 1739, 1051 cm⁻¹; HRMS: m/z [M+H]⁺ Calcd for C₁₄H₂₂NO₂: 236.1651. Found: 236.1641.

Regioselective hydrogenolysis of cyclopropane ring – (±)-(3¹*S*,4*R*,6*aS*,7*R*,9*aR*)-7-methyl-4-propyloctahydrooxazolo[5,4,3-*ij*]quinolin-2(3¹*H*)-one, 16

To a stirred solution of β-cyclopropane **15** (123 mg; 0.52 mmol; 1.0 equiv) in EtOAc (15 mL), cooled to 0 °C, was added platinum oxide (95 mg; 0.42 mmol; 0.8 equiv) and the dark brown suspension evacuated-flushed with H₂ (3 ×). Cooling was removed and stirring maintained under an atmosphere of H₂ (1 atm) at r.t. After 8 h, additional PtO₂ (48 mg; 0.21 mmol; 0.4 equiv) was added, and stirring maintained under H₂. Further PtO₂ (2 × 0.4 equiv) was added at 24 h, and again at 33 h, for a total of 2.0 equivalents. At each addition, the suspension would darken from brown to black, then precipitate a fine metallic solid, which could be re-suspended upon vigorous stirring. After 48 h total, the suspension was filtered through Celite (1 cm × 3 cm plug), flushing with EtOAc (3 × 10 mL). The combined organic phases were reduced *in vacuo* to yield an inseparable mixture of the desired 5-methyl isomer **16**, along with the minor 6-isomer (5.5 to 1 by NMR): 120 mg. This was used directly in the ensuing step without further purification. *R*_f 0.37 (hexane/EtOAc 2:1); ¹H NMR: (400 MHz; CDCl₃) (major isomer) δ 4.52 (dt, *J* = 7.6, 2 × 7.2 Hz, 1H), 3.84 (qm, *J* = 7.2 Hz, 1H), 3.80 (dd, *J* = 7.2, 4.4 Hz, 1H), 1.98 (m, 1H), 1.78 (dq, *J* = 13.6, 3 × 2.9 Hz, 1H), 1.25-1.72 (m, 12H total), 0.92 (t, *J* = 7.4 Hz, 3H), 0.91 (d, *J* = 6.4 Hz, 3H).

Final deprotection to (±)-2-*epi*-pumiliotoxin C – (2*R*,4*aS*,5*R*,8*aR*)-5-methyl-2-propyldecahydroquinoline, 5

A 2-necked 25 mL flask, equipped with septum, stir bar, dry-ice cold-finger condenser and bubbler, was flushed with liq. NH₃ (~9 mL) and allowed to reflux (–33 °C). To this was added, dropwise, a co-solution of acetamide **19** (26.7 mg; 0.112 mmol; 1.0 equiv) and anhydrous EtOH (18.5 mL; 0.317 mmol; 2.82 equiv) in DME (1.03 mL), followed by calcium (32.5 mg; 0.812 mmol; 7.22 equiv), resulting in a dark blue solution. After 3.5 h under reflux, excess calcium was quenched by addition of EtOH (2 mL) and the ammonia allowed to evaporate. The resulting white slurry was taken up in CHCl₃ (10 mL) and water (10 mL), and the pH of the aqueous layer adjusted from pH 14 to 1 using 6 M HCl. Sat. aq. K₂CO₃ (10 mL) was added, resulting in a flocculent colorless precipitate. The biphasic mixture was filtered, rinsing with additional CHCl₃ (5 mL), partitioned, and the aqueous phase extracted with further CHCl₃ (2 × 10 mL). The combined organic phases were dried (K₂CO₃), filtered and reduced *in vacuo* to yield 2-*epi*-pumiliotoxin C **5** as a colorless oil: 14.3 mg; 0.073 mmol; 65%. *R*_f 0.05 (hexane/EtOAc 1:2); ¹H NMR: (400 MHz; CDCl₃) δ 3.06 (dt, *J* = 10.5, 2 × 4.3 Hz, 1H), 2.75 (dm, *J* = 6.0 Hz, 1H), 1.61–1.84 (m, 4H total), 1.21–1.56 (m, 11H total), 0.99–1.13 (m, 2H total), 0.95 (d, *J* = 7.2 Hz, 3H), 0.86 (t, *J* = 6.8 Hz, 3H); ¹³C NMR: (100.6 MHz; CDCl₃) δ 50.0, 49.7, 42.2, 38.4 (br), 32.5 (br), 31.4 (br), 28.8 (v. br – 2 signals), 25.3 (br), 20.6, 19.4, 19.3, 14.1; IR: (thin film) *v*_{max} 2926, 2868, 1461, 1376 cm^{–1}; HRMS: *m/z* [M+H]⁺ Calcd for C₁₃H₂₆N: 196.2065. Found: 196.2058.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.
Representative decahydroquinoline targets

Scheme 1.
Oxazolone IMDA approach to 2-*epi*-pumiliotoxin C

Scheme 2.
Synthesis of triene precursor

Scheme 3.
Initial cycloaddition studies

Scheme 4.
Synthesis of (±)-2-*epi*-pumiliotoxin C

Table 1

Reaction conditions vs. selectivity

Conditions (in <i>o</i> -dichlorobenzene)	Yield	6 : 14
sealed tube, 210 °C, 72 h	78%	3.1 : 1
μ -wave, 225 °C, 5 h	59%	2.5 : 1
1.3 eq EtAlCl ₂ , reflux, 72 h	57%	1 : 0