Published in final edited form as:
J Org Chem. 2010 February 5; 75(3): 933–936. doi:10.1021/jo902172r.

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

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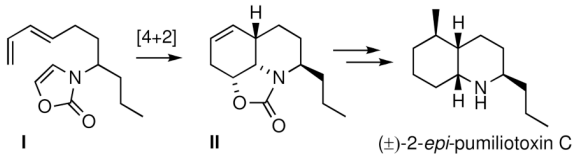
Abstract



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*-195A[3] (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*-eneyne 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; ^{1}H & ^{13}C 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 strain[10] 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 rearrangement[11] afforded heptadienal **10**, which underwent simple Grignard reaction to yield alcohol **11**. A three-step protocol as developed by Shibuya[12] 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 conditions[14] 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 conditions[16] 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 PtO_2

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 lithium[19] 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 protocol[20] to afford the *N*-acetylated target, **19**.

In these latter stages of the synthesis (**17** through **19**), both ^{1}H and ^{13}C 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 conditions[24] 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, (±)-**(3^{1}*S*,4*R*,6a*R*,9a*R*)-4-propyl-4,5,6,6a,9,9a-hexahydrooxazolo[5,4,3-*ij*]quinolin-2(3^{1}*H*)-one, 14:** 120 mg; 0.54 mmol; 17%. R_f 0.36 (hexane/EtOAc 2:1); ^{1}H NMR: (400 MHz; $CDCl_3$) 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); ^{13}C NMR (DEPT): (100.6 MHz; $CDCl_3$) δ 157.6 (C), 132.0 (CH), 125.4 (CH), 71.6 (CH), 57.2 (CH), 49.8 (CH), 37.0 (CH), 33.2 (CH_2), 28.7 (CH_2), 28.4 (CH_2), 23.4 (CH_2), 19.5 (CH_2), 13.7 (CH_3); IR: (thin film) ν_{max} 2958, 2932, 1744, 1020 cm^{-1}; HRMS: *m/z* $[M+H]^+$ Calcd for $C_{13}H_{20}NO_2$: 222.1494. Found: 222.1489.

Next, the major *cis*-cycloadduct, (±)-**(3^{1}*S*,4*R*,6a*S*,9a*R*)-4-propyl-4,5,6,6a,9,9a-hexahydrooxazolo[5,4,3-*ij*]quinolin-2(3^{1}*H*)-one, 6:** 444.4 mg; 2.01 mmol; 64%. R_f 0.22 (hexane/EtOAc 2:1); ^{1}H NMR: (400 MHz; $CDCl_3$) 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); ^{13}C NMR (DEPT): (100.6 MHz; $CDCl_3$) δ 157.2 (C), 131.4 (CH), 126.7 (CH), 72.4 (CH),

51.9 (CH), 48.5 (CH), 31.8 (CH_2), 30.9 (CH), 27.6 (CH_2), 23.3 (CH_2), 22.6 (CH_2), 19.4 (CH_2), 13.8 (CH_3); IR: (thin film) ν_{max} 3024, 2943, 2867, 1731, 1047 cm^{-1}; HRMS: *m/z* $[M+H]^+$ Calcd for $C_{13}H_{20}NO_2$: 222.1494. Found: 222.1487; Anal. Calcd for $C_{13}H_{19}NO_2$: 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*,4[1]*S*,6a*R*,7a*R*,8a*R*,8b*S*)-3-propyloctahydro-1*H*-cyclopropa[*f*]oxazolo[5,4,3-*ij*]quinolin-5(4[1]*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. CH_2Cl_2 (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 chloroiodomethane (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 CH_2Cl_2 (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 CH_2Cl_2 (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 CH_2Cl_2 (25 mL). The resulting mixture was partitioned and the aqueous phase extracted with further CH_2Cl_2 (2 × 25 mL). The combined organic phases were dried ($MgSO_4$), 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; $CDCl_3$) 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); ^{13}C NMR (DEPT): (100.6 MHz; $CDCl_3$) δ 156.6 (C), 73.1 (CH), 51.5 (CH), 48.4 (CH), 32.4 (CH), 32.2 (CH_2), 27.5 (CH_2), 22.6 (CH_2), 22.1 (CH_2), 19.5 (CH_2), 15.4 (CH_2), 13.8 (CH_3), 6.7 (CH), 4.4 (CH); IR: (thin film) ν_{max} 2933, 2868, 1739, 1051 cm^{-1}; HRMS: *m/z* $[M+H]^+$ Calcd for $C_{14}H_{22}NO_2$: 236.1651. Found: 236.1641.

Regioselective hydrogenolysis of cyclopropane ring – (±)-(3[1]*S*,4*R*,6a*S*,7*R*,9a*R*)-7-methyl-4-propyloctahydrooxazolo[5,4,3-*ij*]quinolin-2(3[1]*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 H_2 (3 ×). Cooling was removed and stirring maintained under an atmosphere of H_2 (1 atm) at r.t. After 8 h, additional PtO_2 (48 mg; 0.21 mmol; 0.4 equiv) was added, and stirring maintained under H_2. Further PtO_2 (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; $CDCl_3$) (major isomer) δ4.52 (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*,4a*S*,5*R*,8a*R*)-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. NH_3 (~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 $CHCl_3$ (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. K_2CO_3 (10 mL) was added, resulting in a flocculent colorless precipitate. The biphasic mixture was filtered, rinsing with additional $CHCl_3$ (5 mL), partitioned, and the aqueous phase extracted with further $CHCl_3$ (2 × 10 mL). The combined organic phases were dried (K_2CO_3), 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); ^{1}H NMR: (400 MHz; $CDCl_3$) 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); ^{13}C NMR: (100.6 MHz; $CDCl_3$) 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) ν_{max} 2926, 2868, 1461, 1376 cm^{-1}; HRMS: *m/z* $[M+H]^+$ Calcd for $C_{13}H_{26}N$: 196.2065. Found: 196.2058.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We are grateful to the National Institutes of Health (GM08153-30) for generous support of this research. Acknowledgment is also made to the Donors of the American Chemical Society Petroleum Research Fund for partial support. We thank Dr. Cliff Sol of the CUNY Mass Spectrometry Facility, and Dr. Louis Todaro of the CUNY X-Ray Facility, both at Hunter College, for mass spectral and X-ray crystallographic analysis, respectively. These facilities are supported by a "Research Centres in Minority Institutions" award, RR-03037, from NCRR/NIH. Funding for MS instrumentation was provided by an NIH Shared Instrumentation Grant (1S10RR022649-01), and the CUNY Instrumentation Fund.

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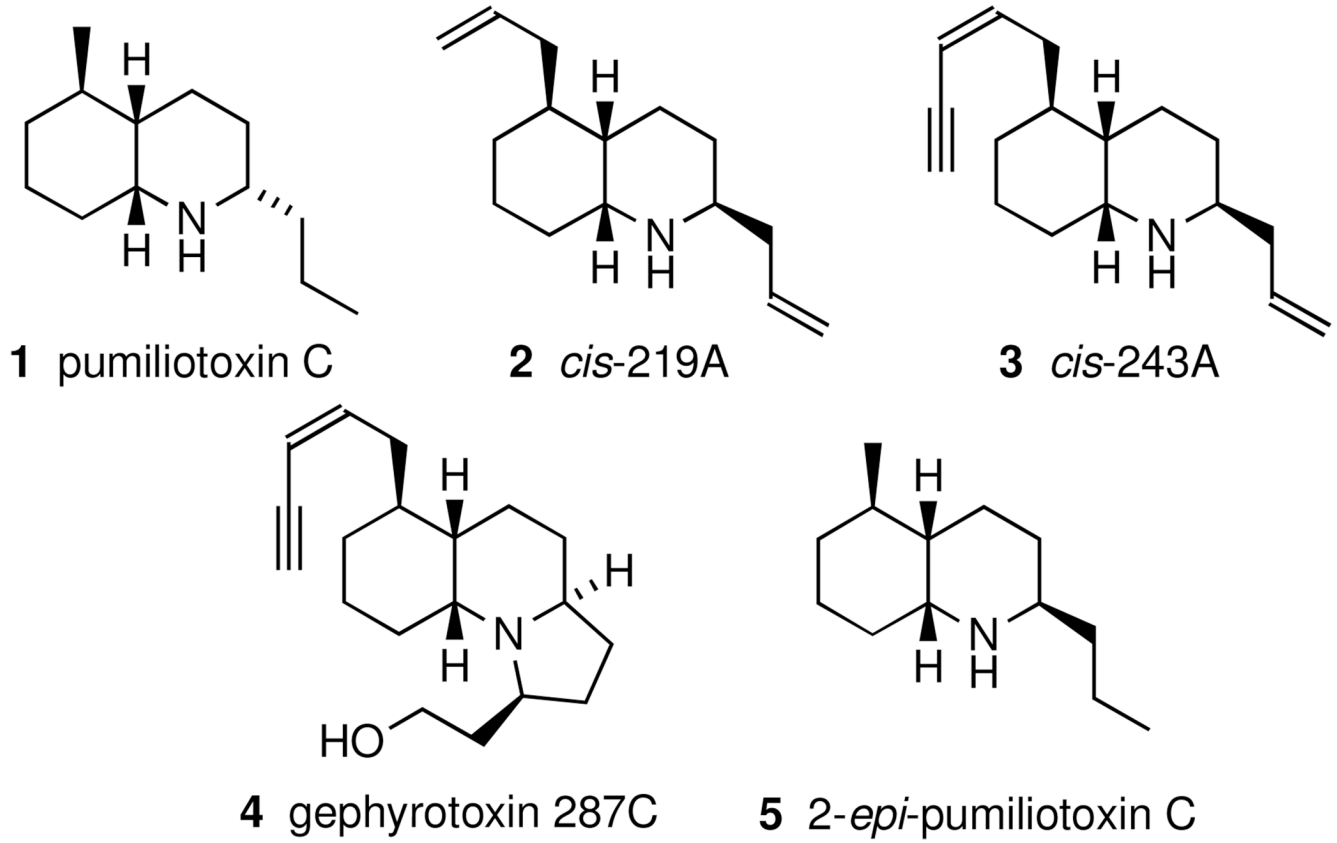
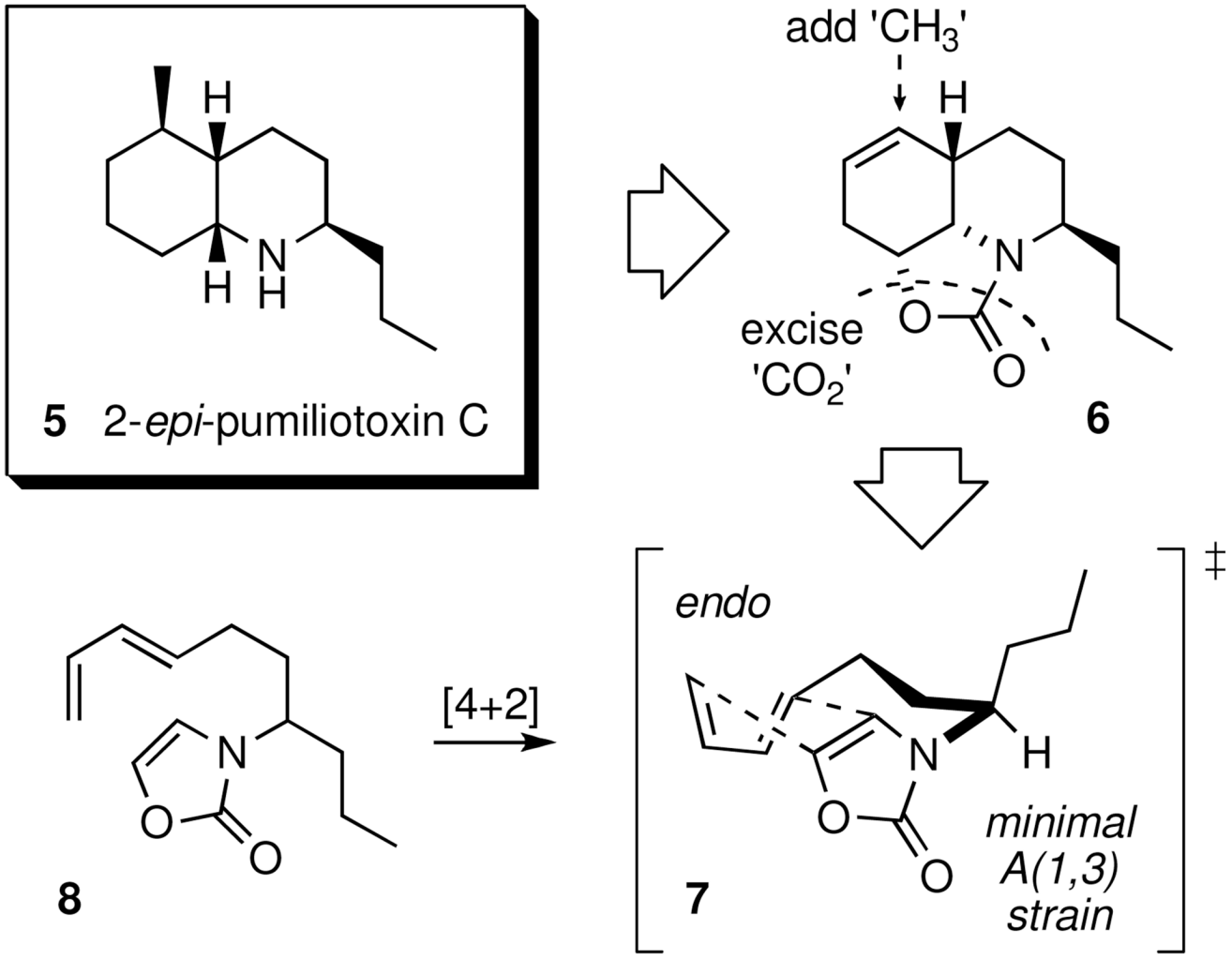
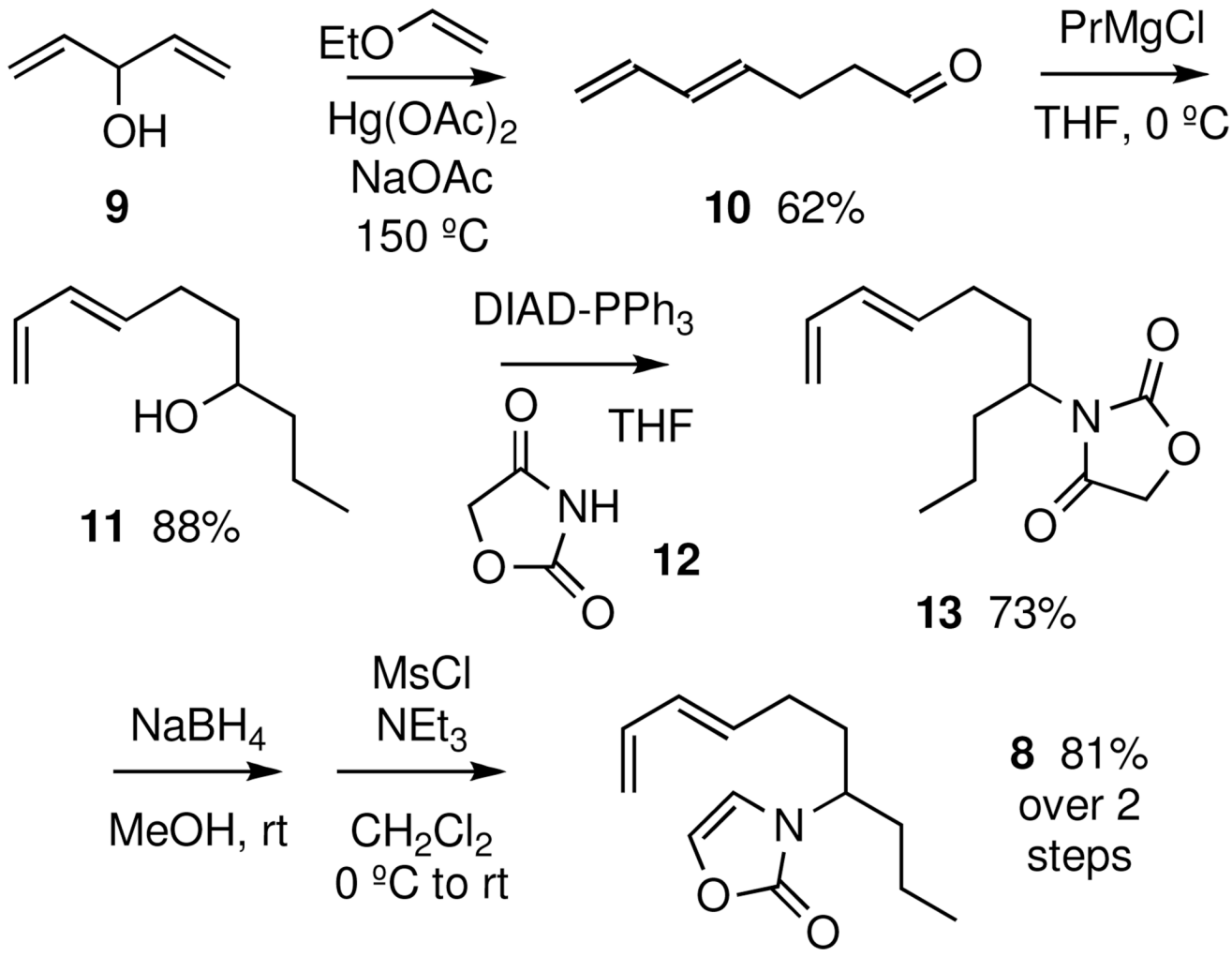


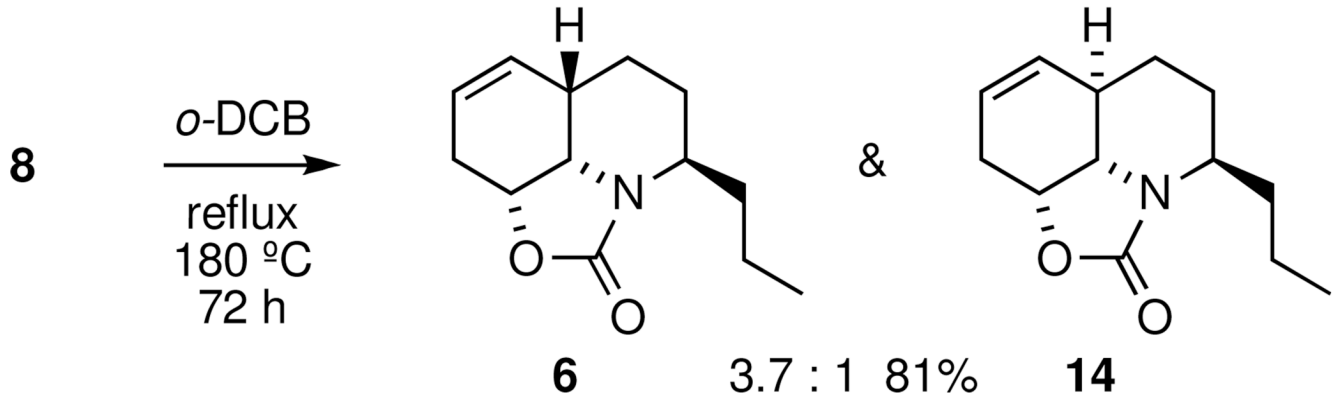
Figure 1.
Representative decahydroquinoline targets



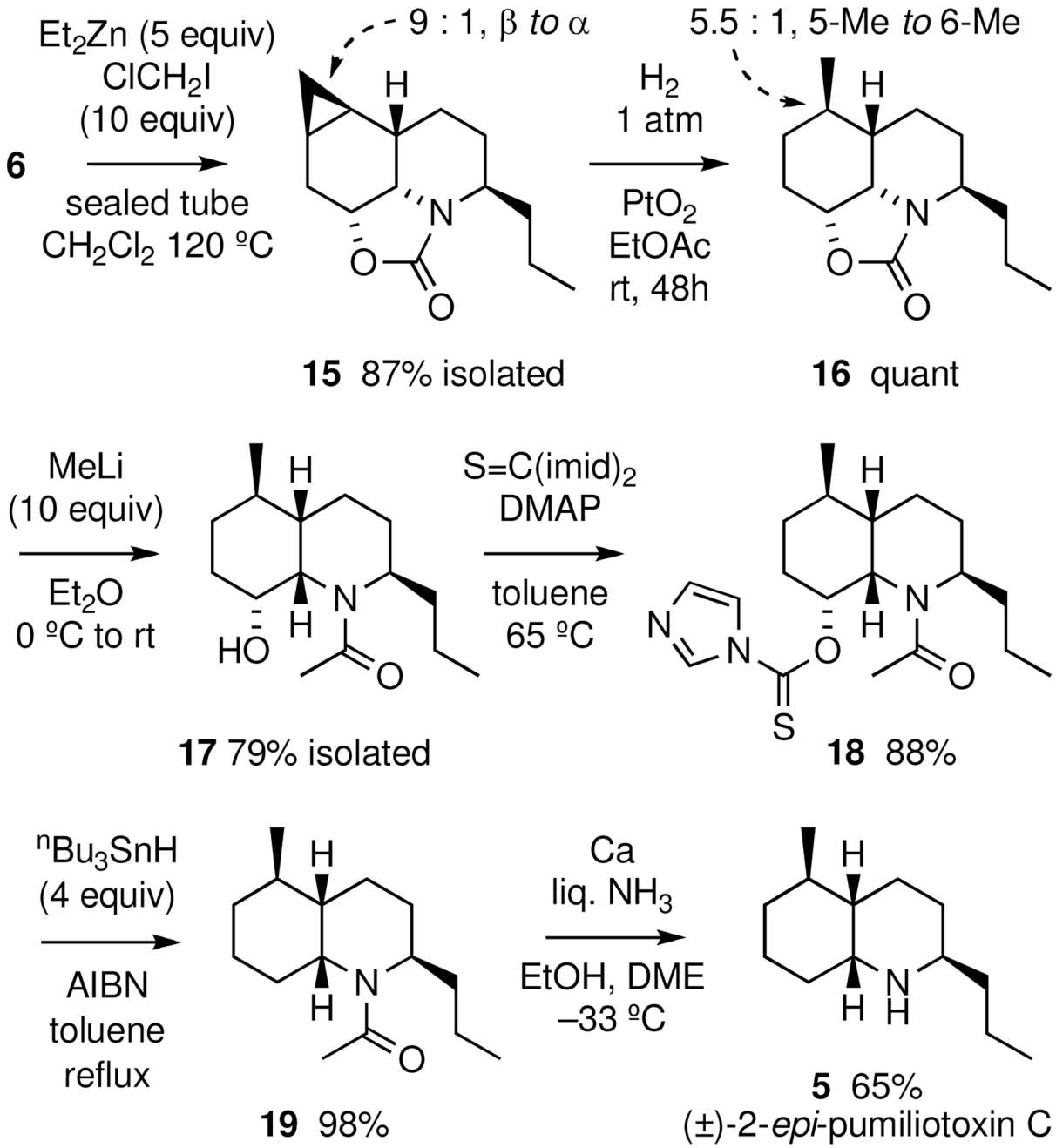
Scheme 1.
Oxazolone IMDA approach to 2-*epi*-pumiliotoxin C



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 *o*-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