# Oxidative Carbocation Formation in Macrocycles: Synthesis of the Neopeltolide Macrocycle**

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Processes for the functionalization of carbon–hydrogen bonds are the focus of significant attention in organic synthesis[1] in response to the need to streamline molecular assembly. As a continuation of our efforts to generate carbocations through single-electron oxidation reactions,[2] we recently reported[3] DDQ-mediated cyclization reactions of benzylic and allylic ethers (Scheme 1; DDQ = 2,3-dichloro-4,5-dicyanoquinone).
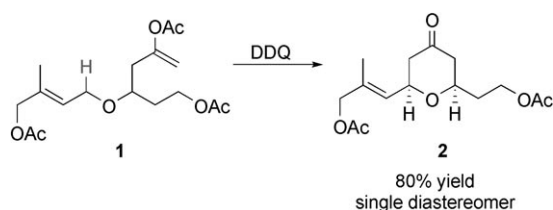

Scheme 1. Cyclization through oxidative C−H bond functionalization.

These reactions proceed through oxidative cleavage of a carbon–hydrogen bond to form oxocarbenium ions that react with appended nucleophiles.[4] The use of relatively inert ethers as precursors to reactive electrophiles is strategically attractive, because facile substrate preparation makes ether-ification a useful fragment-coupling process for convergent syntheses. Oxidative carbocation generation enables the inclusion of acid-sensitive functional groups in starting materials and products, and provides an opportunity to incorporate multiple precursors to electrophiles in a synthetic intermediate. These electrophiles can later be revealed through the use of chemically orthogonal conditions.[5]

Macrocyclic oxocarbenium ions are interesting synthetic intermediates as a result of their capacity to engage in transannular nucleophilic addition reactions. The viability of these intermediates was demonstrated by the Wender research group in the synthesis of bryostatin analogues.[6] Scheidt and co-workers recently reported[7] carbon–carbon

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bond formation via a macrocyclic oxocarbenium ion formed in a Lewis acid mediated condensation, and related examples followed.[8] However, the generality of this remarkable protocol is not clear: In the absence of conformational preorganization, the process requires the formation of highly reactive intermediates through kinetically unfavorable path-ways. A potentially more general approach to the formation of macrocyclic oxocarbenium ions for carbon–hydrogen-bond functionalization is the oxidation of preformed macrocyclic ethers with DDQ (Scheme 2). Herein, we report cyclization
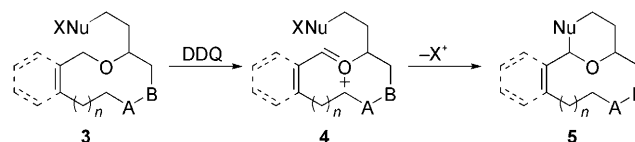
Scheme 2. Ring formation via an oxidatively generated macrocyclic oxocarbenium ion.

reactions that proceed through oxidatively generated macro-cyclic oxocarbenium ions (**3**→**4**→**5**) and demonstrate the applicability of the protocol to the construction of complex molecules through a brief formal synthesis of neopeltolide.

The concept was initially validated through the synthesis and cyclization of the macrocyclic ether **11**, which was prepared from aldehyde **6**[9] (Scheme 3). The exposure of **11** to DDQ under our previously reported conditions[3] resulted in a smooth reaction to form tetrahydropyrone **12** in 73% yield. The *cis* relationship between the substituents at the 2- and 6-positions of the tetrahydropyrone ring was confirmed by a strong cross-peak between the axial hydrogen atoms in the NOESY spectrum.
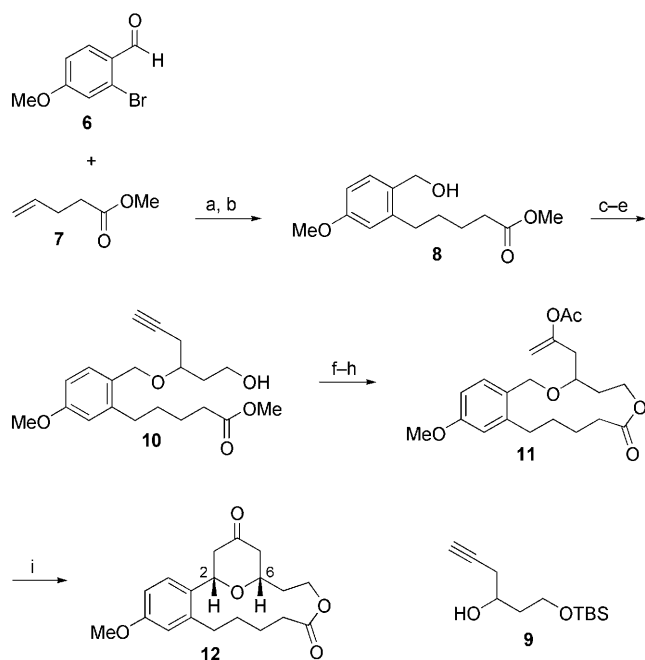
The scope of this protocol is indicated by the examples in Table 1. Stereogenic centers can be incorporated into the macrocycle without significantly impacting the efficiency of the transformation (Table 1, entries 1 and 2). Changes in the size of the macrocycle alter the rate of the reaction but not the yield (Table 1, entries 3 and 4). The *para*-methoxy group promotes faster reactions, though benzolactone substrates that do not contain an electron-donating group can be coerced to cyclize in acceptable yields with gentle heating (Table 1, entry 5). A decrease in the distance between the oxygen atom of the oxocarbenium ion and the lactone carbonyl group results in a rate reduction (compare entries 4 and 6 in Table 1) due to inductive destabilization of the cationic intermediate.

These cyclization reactions were uniformly slower than reactions that we had conducted previously with *p*-methoxy-benzyl ethers.[3] To determine whether the rate retardation

Scheme 3. Substrate synthesis and cyclization: a) 9-BBN, THF, [Pd-(dppf)Cl₂], K₂CO₃, DMF, 50°C;[10] b) NaBH₄, MeOH, 50% (two steps); c) Cl₃CCN, DBU, CH₂Cl₂, 90%; d) **9**, La(OTf)₃, toluene;[11] e) p-TsOH, MeOH, 60% (two steps); f) LiOH, THF, MeOH, H₂O; g) trichloroben-zoyl chloride, Et₃N, DMAP, toluene, 65°C, 75% (two steps);[12] h) HOAc, Na₂CO₃, [{Ru(p-cymene)Cl₂}₂], 1-decyne, toluene, 80°C, 75%;[13] i) DDQ, 2,6-dichloropyridine, DCE, 2 h, 73%. 9-BBN = 9-borabicyclo[3.3.1]nonane, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DCE = 1,2-dichloroethane, DMAP = 4-dimethylaminopyridine, DMF = N,N-dimethylformamide, dppf = 1,1'-bis(diphenylphosphanyl)-ferrocene, TBS = tert-butyldimethylsilyl, Tf = trifluoromethanesulfonyl, Ts = p-toluenesulfonyl.

Table 1: Reaction scope.[a]

Entry	Substrate	Product	t [h]	Yield [%][b]
1	**13**	**14**	4	74
2	**15**	**16**	4	69
3	**17**	**18**	3.25	76
4	**19**	**20**	6	73
5[c]	**21**	**22**	24	71
6	**23**	**24**	28	65

[a] General procedure: DDQ (1.5 equiv), 2,6-Cl₂Py, and 4 Å molecular sieves were added to a solution of the substrate in 1,2-dichloroethane at room temperature. The reaction mixture was stirred at room temperature for the indicated time. For specific details, see the Supporting Information. [b] Yield of the isolated, purified product. [c] The reaction was conducted at 50°C.
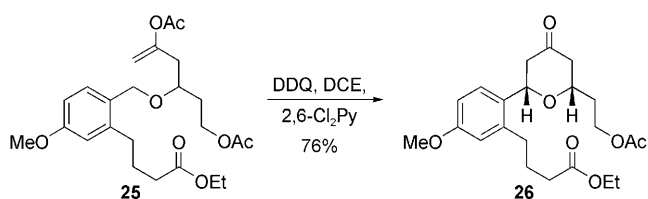
arises from the lactone structure or the presence of an *ortho*-alkyl group, we prepared substrate **25**, an analogue of **17** with respect to inductive effects, and subjected it to the cyclization conditions (Scheme 4). Tetrahydropyrone **26** was formed in 76% yield within 0.5 h, which indicates that constraining the ether in a macrocycle slows oxidative carbocation formation. This effect can most likely be attributed to conformational restrictions associated with cyclization, for which overlap is required between the cleaving bond and the π orbitals of the radical cation.[14]

Allylic ethers undergo oxidative carbocation formation with an efficiency that rivals or exceeds that of benzylic ethers.[3] We chose to establish the viability of forming macrocyclic α,β-unsaturated oxocarbenium ions and to val-idate the applicability of the method in the construction of natural products through a formal synthesis of neopeltolide (**27**; Scheme 5). Neopeltolide was isolated from sponges of the genus *Deadolapelta* off the Jamaican coast and was shown to exhibit potent cytotoxic activity (IC₅₀ values < 10 nm) against a number of cancer cell lines.[15] The Panek[16] and Scheidt[7] research groups independently established the correct stereostructure of neopeltolide through total syn-thesis, and several total and formal syntheses followed these initial reports.[8a, 17] The objective of our synthesis was to

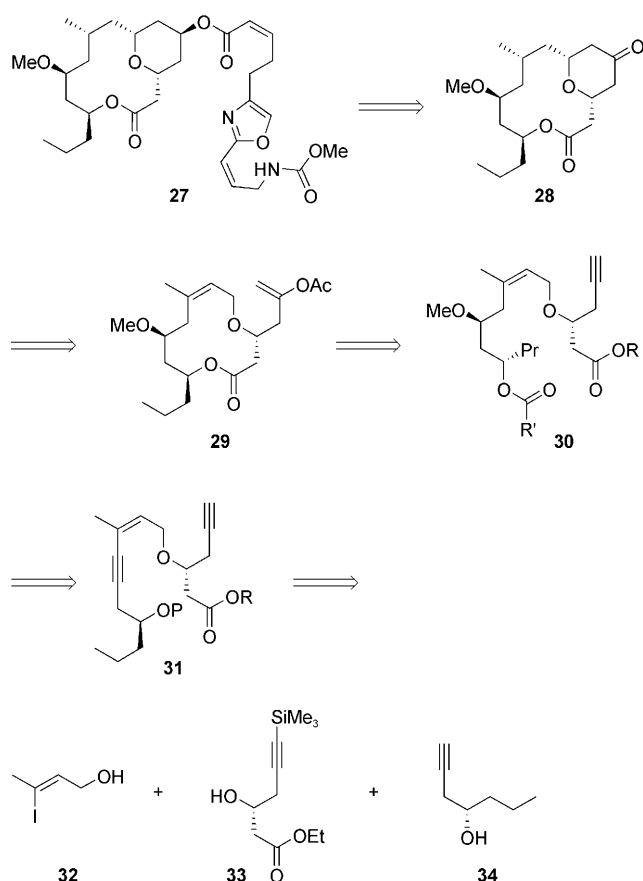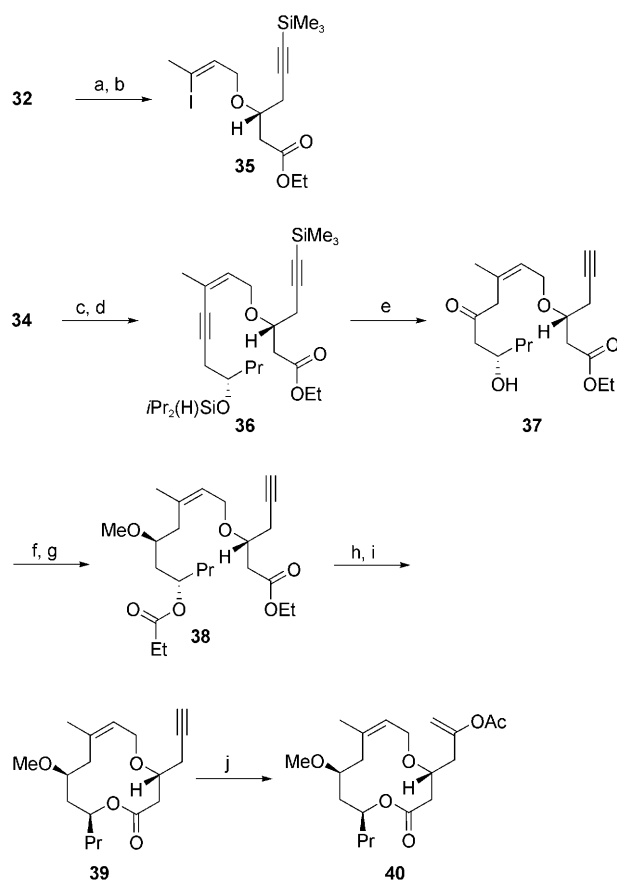**Scheme 4.** Cyclization of an acyclic analogue of **17**. 2,6-Cl₂Py = 2,6-dichloropyridine.

prepare tetrahydropyrone **28**, which was converted into **27** in two steps by Paterson and Miller.[17d] This structure can be accessed from **29** through an oxidative cyclization followed by a stereoselective alkene reduction. The lactone derives from diester **30**, which can be formed from enyne **31** through a regioselective alkyne-hydration reaction. Building blocks **32**, **33**, and **34** serve as the starting structures for the synthesis.

Scheme 5. Retrosynthesis of neopeltolide (**27**).

Scheme 6. Reagents and conditions: a) NaH, Cl₃CCN, Et₂O, 0 °C, 100%; b) **33**, TfOH, cyclohexane, 77%; c) iPr₂Si(H)Cl, imidazole, THF, 77%; d) **35**, [(Ph₃P)₂PdCl₂], CuI, iPr₂NH, 89%; e) [Pt(DVDS)], THF, then H₂O₂, KF, Bu₄NF, KHCO₃, DMF, 40 °C, 57% (67% based on starting-material purity); f) EtCHO, SmI₂, THF, −10 °C, 77%; g) Me₃OBF₄, proton sponge, CH₂Cl₂, 0 °C, 93%; h) LiOH, H₂O, MeOH, 45 °C; i) Et₃N, 2,4,6-Cl₃BzCl, THF, then DMAP, toluene, 65 °C, 72% (two steps); j) HOAc, Na₂CO₃, [{Ru(p-cymene)Cl₂}₂], (2-furyl)₃P, 1-decyne, toluene, 80 °C, 82%, 5:1 regioisomer mixture. Bz = benzoyl, DVDS = 1,3-divinyl-1,1,3,3-tetramethyldisiloxane.

The synthetic sequence commenced with the conversion of **32**[18] into its trichloroacetimidate, followed by etherification with **33**[19] in the presence of TfOH to give **35** as an inseparable 7.3:1 mixture of alkene stereoisomers (Scheme 6). Exploratory studies indicated that the Sonogashira coupling of **35** with derivatives of **34**[20] proceeded most effectively when the homopropargylic alcohol was protected as a silyl ether. In consideration of downstream transformations, **34** was converted into a diisopropylsilyl ether and coupled to **35**[21] to provide **36** in 69% overall yield as an inseparable 5.7:1 mixture of alkene stereoisomers. The diisopropylsilyl group was selected because it is stable during coupling and purification steps but is also sufficiently reactive to be useful in the impending alkyne-hydration step. Regioselective alkyne hydration through a sequence of [Pt(DVDS)]-mediated hydrosilylation[22] followed by oxidative cleavage of the intermediate vinylsilane and concomitant alkyne desilylation under conditions similar to those described by Tamao et al.[23] provided **37**.[24] A single alkene stereoisomer was isolated after the reaction, and, remarkably, minimal migration of the alkene into conjugation with the ketone was observed. A stereoselective reduction of **37** with EtCHO and SmI₂,[25] followed by methylation of the resulting hydroxy group, provided diester **38**. Cleavage of both esters and lactonization of the seco acid under Yamaguchi conditions[12] provided macrolactone **39** in 72% yield. The synthesis of cyclization substrate **40** was completed by a ruthenium-mediated addition of HOAc across the alkyne.[13] This reaction provided an inseparable 5:1 mixture of enol acetate regioisomers in 82% yield.

The exposure of **40** to DDQ in the presence of LiClO₄ (which has been shown to minimize side reactions of allylic ether substrates)[3] and 2,6-dichloropyridine resulted in the formation of tetrahydropyrone **41** as a single stereoisomer in 58% yield (Scheme 7). The yield of **41** from pure **40** can be extrapolated to 65%, since the cyclization substrate contained an unproductive regioisomer. The structure of **41** was confirmed by crystallographic analysis.[26] The conformation of **41** suggested that alkene hydrogenation should occur preferentially from the top face of the molecule to provide the correct stereochemical orientation at C9. Indeed, when **41** was treated with H₂ and Pd/C, **28** was obtained in 74% yield to complete the formal synthesis. A negligible amount (<10%) of the separable undesired C9 stereoisomer of **28** was formed. All spectral data matched those reported[17d] by Paterson and Miller. The capacity to functionalize the alkene

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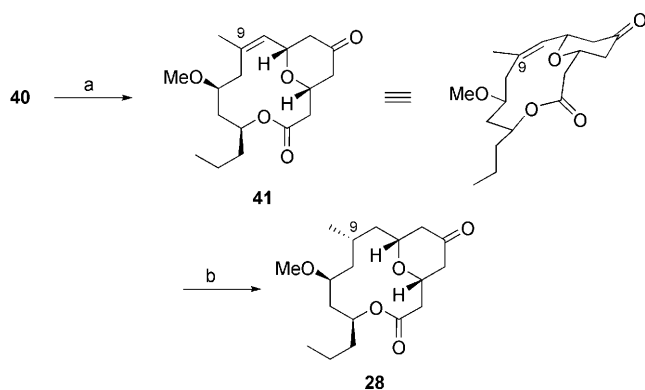
Scheme 7. Reagents and conditions: a) DDQ, 2,6-Cl$_2$Py, LiClO$_4$, DCE, 58% (65% based on starting-material purity); b) H$_2$, Pd/C, EtOH, 74%.

in **41** with predictable stereocontrol presents numerous options for the preparation of neopeltolide analogues.

We have demonstrated that oxocarbenium ions can be formed in macrocycles through oxidative carbon–hydrogen-bond functionalization, and that these intermediates react with appended nucleophiles to form bridged bicyclic structures. The reactions are somewhat slower than related cyclization reactions of noncyclic precursors as a result of conformational constraints, but the overall efficiency and stereocontrol are comparable. A formal synthesis of neopeltolide on the basis of this process enables access to the natural product in 13 steps from 2-butyn-1-ol. In addition to the oxidative cyclization reaction, key steps in the synthesis include the use of etherification and Sonogashira reactions as fragment-coupling processes, the application of an intramolecular hydrosilylation reaction to effect a regioselective alkyne hydration, and the use of a stereoselective alkene hydrogenation to establish the C9 stereocenter. Early formation of the ether group as an oxocarbenium ion precursor enables minimal reliance upon protecting groups in the sequence. This feature is a significant benefit of selective carbon–hydrogen-bond activation in complex-molecule synthesis.

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