Synthesis of Cyclic Peroxides *via* Enyne-RCM/Diels-Alder Reaction Sequence

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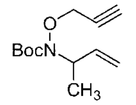
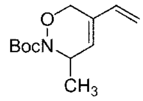
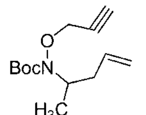
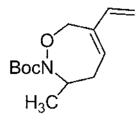
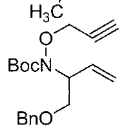
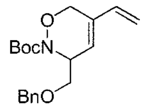
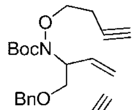
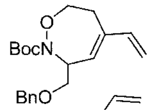
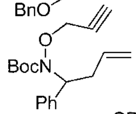
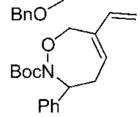
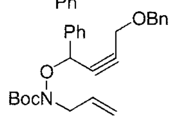
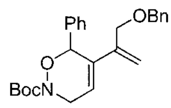
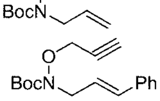
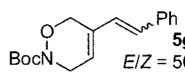
The sequence of an enyne ring-closing metathesis (enyne-RCM)[1,2] followed by a Diels-Alder reaction has been applied widely in organic synthesis for the expeditious generation of molecular complexity. Although several dienophiles have been employed to date in Diels-Alder reactions of the cyclic conjugated dienes generated from enyne-RCM, singlet oxygen has not been one of them. The conjugated dienes **5**, which are readily obtained by enyne-RCM, could be reacted with singlet oxygen[3] to generate the corresponding cyclic peroxides **6**, as shown in Scheme 1. The cyclic peroxide unit is a component of many biologically important structures; furthermore, it can be transformed into several other valuable skeletons. For example, reductive cleavage of the O–O bond could generate allylic diols.[4] Base- or transition metal-catalyzed O–O bond cleavage, followed by dehydration, is a well-known reaction strategy to synthesize furans.[4b,5] We have recently reported the synthesis of 1,2-oxaza and 1,2-diaza heterocycles, having a diverse range of scaffolds, by ring-closing metathesis.[6,7] Herein, we report our recent results on the synthesis of cyclic peroxides by Diels-Alder reactions between singlet oxygen and enyne-RCM adducts.

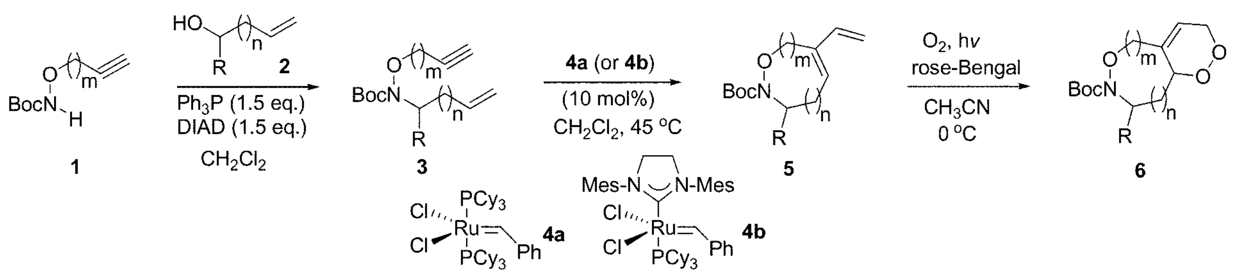
The substituted enyne substrates **3** were prepared from the secondary alcohols **2** and *N*-Boc-protected alkynyl hydroxylamines **1** under the Mitsunobu conditions (Scheme 1). The enynes **3** were treated with Grubbs' catalyst **4a** according to our previously reported procedure[6b] to give the enyne-RCM adducts **5** in moderate to good yields (Table 1). For substrates **3e** and **3g**, more reactive second generation Grubbs' catalyst **4b** was used for the metathesis reactions (Table 1, entries 5 and 7).

The substituted conjugated dienes **5** and previously synthesized ones[6b] were utilized in the cycloaddition reaction with singlet oxygen. Acetonitrile solutions of the dienes and a catalytic amount of rose Bengal sensitizer were irradiated using a 400-W tungsten lamp while a steady flow of oxygen was passed though the solution. The reaction flask was cooled in an ice-bath during this procedure. Table 2 summarizes the results of these cycloaddition reactions. The formation of **6a** from the corresponding enyne-RCM adduct was complete after 7 h; this product was isolated in 73% yield (Table 2, entry 1). The analogous peroxide **6b** was obtained in 82% yield (Table 2, entry 2). The homologues with adjacent 7- and 8-membered 1,2-oxaza rings were also

Table 1. Synthesis of Conjugated Dienes by Enyne-RCM

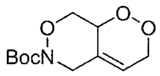
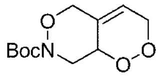
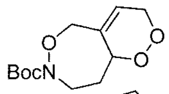
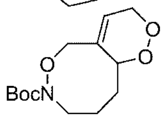
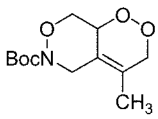
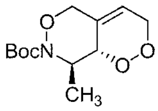
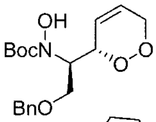
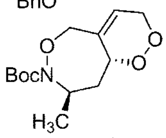
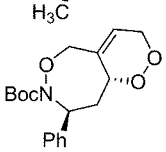
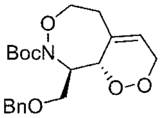
Entry	3	Conditions[a]	5 (% yields)[b]
1	 3a	28 h 0.02 M	 5a (75)
2	 3b	15 h 0.02 M	 5b (82)
3	 3c	29 h 0.02 M	 5c (72)
4	 3d	21 h 0.02 M	 5d (77)
5[c]	 3e	15 h 0.02 M	 5e (80)
6	 3f	4 h 0.03 M	 5f (83)
7[c]	 3g	16 h 0.02 M	 5g (79) *E/Z* = 50 : 29

[a]Reaction time and concentrations. [b]Isolated yields. [c]Used 10 mol% of **4b**, toluene, reflux.



Scheme 1

Table 2. Diels-Alder Reactions of Conjugated Dienes with Singlet Oxygen[a]

Entry	Time[b]	Product		Yield (%)
1	7 h		**6a**	73
2	7 h		**6b**	82
3	6 h		**6c**	75
4	6 h		**6d**	80
5	8 h		**6e**	69
6	11 h		**6f**	66 (*trans* only)[d]
7	12 h		**6g**	70 (*trans/cis* = 80 : 20)[d]
8	7 h		**6h**	78 (*trans/cis* = 51 : 49)[d]
9	11 h		**6i**	71 (*trans/cis* = 58 : 42)[d]
10	16 h		**6h**	54 (89)[c] (*trans* only)[d]

[a]Reaction conditions: O_2, cat. rose Bengal, 400-W tungsten lamp, CH_3CN, 0 °C. [b]Reaction time. [c]The yield in parenthesis is based on the recovered starting material. [d]The relative stereochemistries were determined by nOe experiments.

prepared in good yields (Table 2, entries 3 and 4).

Next, we examined dienes featuring greater degrees of substitution on either their 1,2-oxaza or 1,2-dioxine ring. Trisubstituted peroxide **6e** was synthesized in 69% yield (Table 2, entry 5). Additional substituents on the 1,2-oxaza rings results in the generation of two diastereoisomeric products. In general, substituents on the carbon atom adjacent to the ring-forming sites produced the higher diastereoisomeric ratios. The peroxides **6f** and **6j** were obtained as single diastereoisomers and **6g** was obtained as the major product in a 4 : 1 ratio (Table 2, entries 6, 10, and 7, respectively). On the other hand, compounds having substituents positioned one extra carbon atom away from the ring-forming sites exhibited poor diastereoselectivity – they yielded nearly equal amounts of their two diastereoisomers – but the yields of their products are comparable to those of the other reactions (Table 2, entries 8 and 9).

In conclusion, we have shown that the reaction sequence of an enyne-RCM followed by a [4+2] cycloaddition with singlet oxygen is synthetically valuable method for the synthesis of cyclic peroxides. By this reaction sequence, we have synthesized several cyclic peroxides fused with a cyclic hydroxylamine ring.

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8. *Representative procedure for the singlet oxygen Diels-Alder reaction*: An acetonitrile solution (5 mL) of the RCM adduct (100 mg, 0.444 mmol) and a catalytic amount of rose Bengal bengal sensitizer (2 mg) was irradiated using a 400-W tungsten lamp while a steady flow of oxygen was passed though the solution. The reaction flask was cooled in an ice-bath during this procedure. After 6 h, the solvent was removed under reduced pressure and the residue mixture was column chromatographed on silica gel (elution with 5% ethyl acetate in hexanes) to give 86 mg (75%) of **6c**. Spectral data for **6c**: colorless oil; R_f = 0.2 (silica gel, hexane/EtOAc = 2 : 1); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 5.79 (s, 1H), 4.68-4.61 (m, 3H), 4.56-4.48 (m, 2H), 3.99 (d, *J* = 13.4 Hz, 1H), 3.34-3.28 (m, 1H), 2.26-2.24 (m, 1H), 2.14-2.11 (m, 1H), 1.49 (s, 9H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ = 155.7, 137.2, 120.7, 81.9, 79.0, 75.1, 69.8, 46.3, 32.6, 28.7; IR (film, cm^{-1}) 2976, 2930, 1706, 1404, 1368, 1251, 1168, 1117; HRMS: *m/z* calcd. for $C_{12}H_{19}NO_5$ $(M+H)^+$: 258.1341; found: 258.1343.