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Synthesis of 1,2-Dioxolanes by Annulation Reactions of Peroxycarbenium Ions with Alkenes

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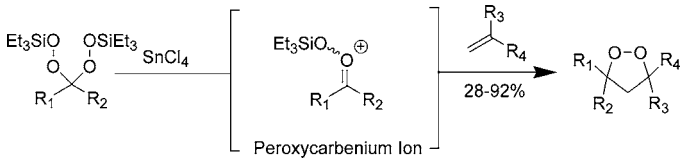
ABSTRACT



The annulation reactions of alkenes with peroxycarbenium ions enable the synthesis of a variety of functionalizable 1,2-dioxolanes. Triethysilyl-protected peroxycarbenium ions proved to be optimal for the annulation reaction. Using this method, plakinic acid analogues can be synthesized in three steps from the corresponding ketone and alkene.

The peroxide moiety is present in over 200 marine and terrestrial natural products, many of which possess potent biological activity.[1−8] For example, plakinic acid E and four of its isomers have been isolated from *Plakortis* sp., and they are cytotoxic against a range of cancer cell lines (Figure 1).[9]

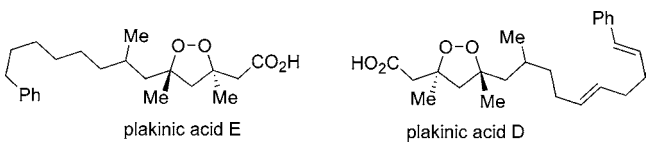


Figure 1. Natural products.

The weak oxygen−oxygen bond arises as the most challenging synthetic feature of these natural products.[10−12] To introduce the peroxide moiety, current methodology relies on reactions of ozone, singlet oxygen, and radical transformations involving molecular oxygen.[13−20]

Peroxycarbenium ions have emerged as useful reactive intermediates for the synthesis of peroxides.[21−25] For ex-

(1) Casteel, D. A. *Nat. Prod. Rep.* **1992**, *9*, 289−312.
(2) Casteel, D. A. *Nat. Prod. Rep.* **1999**, *16*, 55−73.
(3) McCullough, K. J.; Nojima, M. *Curr. Org. Chem.* **2001**, *5*, 601−636.
(4) Jung, M.; Kim, H.; Lee, K.; Park, M. *Mini-Rev. Med. Chem.* **2003**, *3*, 159−165.
(5) Fattorusso, E.; Parapini, S.; Campagnuolo, C.; Basilico, N.; Taglialatela-Scafati, O.; Taramelli, D. *J. Antimicrob. Chemother.* **2002**, *50*, 883−888.
(6) McCullough, K. J. *Contemp. Org. Synth.* **1995**, *4*, 225−249.
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(8) Chen, Y.; McCarthy, P. J.; Harmony, D. K.; Schimoler-O'Rourke, R.; Chilson, K.; Selitrennikoff, C.; Pomponi, S. A.; Wright, A. E. *J. Nat. Prod.* **2002**, *65*, 1509−1512.
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(10) Bach, R. D.; Dmitrenko, O. *J. Org. Chem.* **2002**, *67*, 2588−2599.
(11) Bach, R. D.; Dmitrenko, O. *J. Org. Chem.* **2002**, *67*, 3884−3896.
(12) Adam, W. In *Peroxide Chemistry*; Wiley: Weinheim, Germany, 2000; pp 1−25.
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(14) Creary, X.; Wolf, A.; Miller, K. *Org. Lett.* **1999**, *1*, 1615−1618.
(15) Dussault, P. H.; Zope, U. R. *Tetrahedron Lett.* **1995**, *36*, 2187−2190.
(16) Feldman, K. S.; Simpson, R. E. *J. Am. Chem. Soc.* **1989**, *111*, 4878−4886.
(17) Wimalasena, K.; Wickman, H. B.; Mahindaratne, M. P. D. *Eur. J. Org. Chem.* **2001**, 3811−3817.
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(19) Tokuyaso, T.; Kunikawa, S.; Masuyama, A.; Nojima, M. *Org. Lett.* **2002**, *4*, 3595−3598.
(20) Tokuyaso, T.; Kunikawa, S.; McCullough, K. J.; Masuyama, A.; Nojima, M. *J. Org. Chem.* **2005**, *70*, 251−260.
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ample, Dussault and Zope reported that reactions of peroxycarbenium ions **1** with allyltrimethylsilane provide 1,2-dioxolanes (Figure 2).[26] In this paper, we demonstrate an

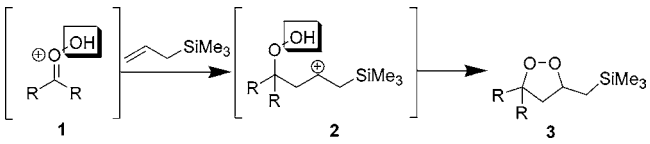


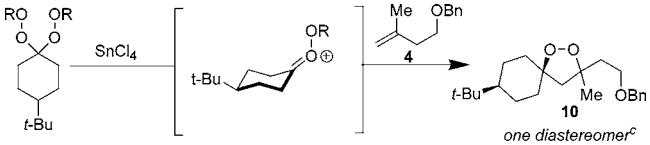
Figure 2. Synthesis of cyclic peroxides.

efficient generation of peroxycarbenium ions and their reactions with alkenes that permit the rapid synthesis of plakinic acid analogues.

We considered that some of the difficulties in the generation and reactivity of peroxycarbenium ions centered on the terminal oxygen atom. The success of the reaction shown in Figure 2 requires the terminal oxygen to be protected, but upon reaching intermediate **2**, the oxygen must be nucleophilic. Angle, in the course of developing annulations for the synthesis of tetrahydrofurans and tetrahydropyrans, encountered a similar challenge. He satisfied these requirements by protection of hydroxy aldehydes as their silyl ethers.[27−29]

The use of silyl-protected peroxyketals provided an ideal balance between stability and reactivity. Various peroxyketals were investigated in the annulation reaction with 1,1-disubstituted alkene **4** (Table 1). No annulation products were

Table 1. Investigation of Silyl Protecting Groups in Peroxycarbenium Ion Formation



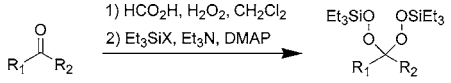
R	H	$SiMe_3$	$SiEt_3$	$SiMe_2$*t*-Bu	Si*i*-Pr_3
substrate[a]	**5**	**6**	**7**	**8**	**9**
yield (%)[b]	0	60	80	30	0

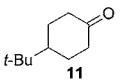
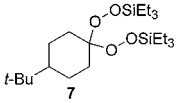
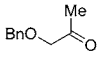
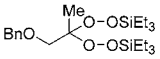
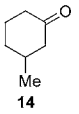
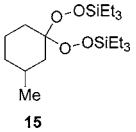
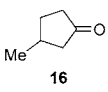
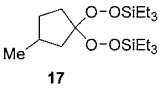
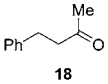
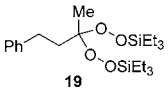
[a] Typical reaction conditions: $SnCl_4$ (2.0 equiv) and olefin (3.0 equiv) in CH_2Cl_2, −78 to −3 °C, 4−24 h. [b] Yields based on purified products. [c] Determined by ^1H NMR spectroscopy.

obtained with unprotected peroxyketal **5**. Silyl-protected peroxyketals, however, engaged in annulation reactions. The larger the silyl group, the greater the stability of the peroxyketal, but the increased size resulted in lower product yields. In general, the smaller the silyl group, the better the annulation yield. Protection with the triethylsilyl group was found to be optimal for peroxycarbenium ion generation and trapping.[30] In this case, cyclic peroxide **10** was obtained in 80% yield as a single diastereomer,[31] arising from equatorial attack to the peroxycarbenium ion intermediate.[32]

The utility of silyl peroxyketals was expanded by synthesizing several substrates from the corresponding ketones (Table 2). Attempting to synthesize peroxyketals according

Table 2. Synthesis of Silyl Peroxyketals



entry	substrate[a]	product	yield (%)[c]
(1)	 **11**	 **7**	75
(2)[b]	 **12**	 **13**	53
(3)	 **14**	 **15**	54
(4)	 **16**	 **17**	54
(5)	 **18**	 **19**	48

[a] Typical reaction conditions: (1) HCO_2H (30 equiv), H_2O_2 (30 equiv, 50 wt % in H_2O), 25 °C, 10 min; (2) Et_3SiCl or Et_3SiOTf (2.5−4.5 equiv), Et_3N (2.5−4.5 equiv), 0−25 °C, 4−18 h. [b] Typical reaction conditions: (1) CF_3CO_2H (12 equiv), H_2O_2 (9 equiv, 50 wt % in H_2O), 25 °C, 5 min; (2) Et_3SiOTf (3.2 equiv), Et_3N (3.0 equiv), 25 °C, 16 h. [c] Yields based on purified products.

to literature procedures resulted primarily in the formation of dimers and trimers.[33−36] The formation of oligomers was

(22) Dussault, P. H.; Lee, H.-J.; Niu, Q. J. *J. Org. Chem.* **1995**, *60*, 784−785.
(23) Dussault, P. H.; Lee, R. J.; Schultz, J. A.; Suh, Y. S. *Tetrahedron Lett.* **2000**, *41*, 5457−5460.
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(27) Angle, S. R.; El-Said, N. A. *J. Am. Chem. Soc.* **1999**, *121*, 10211−10212.
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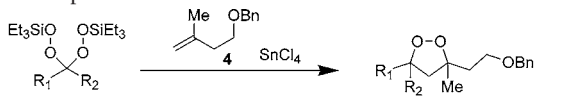
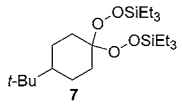
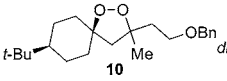
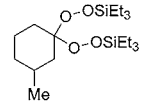
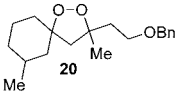
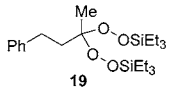
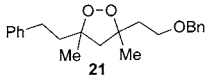
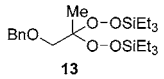
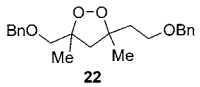
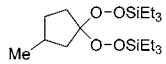
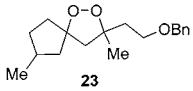
(29) Angle, S. R.; Belanger, D. S.; El-Said, N. A. *J. Org. Chem.* **2002**, *67*, 7699−7705.
(30) Our results are consistent with the relative rate of hydrolysis of silyl protecting groups: Schelhaas, M.; Waldmann, H. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2056−2083.
(31) The stereochemistry was proven by X-ray crystallographic analysis of a colorless crystal of 1,2-dioxolanol **40**.
(32) Laemmle, J.; Ashby, E. C.; Roling, P. V. *J. Org. Chem.* **1973**, *38*, 2526−2534.
(33) Tsuchiya, K.; Hamada, Y.; Masuyama, A.; Nojima, M.; McCullough, K. J.; Kim, H.-S.; Shibata, Y.; Wataya, Y. *Tetrahedron Lett.* **1999**, *40*, 4077−4080.
(34) Nonami, Y.; Tokuyasu, T.; Masuyama, A.; Nojima, M.; McCullough, K. J.; Kim, H.-S.; Wataya, Y. *Tetrahedron Lett.* **2000**, *41*, 4681−4684.

minimized using chlorinated solvents and strongly acidic conditions. Treatment of ketone **11** under the optimized reaction conditions followed by silyl protection resulted in 74% yield of the stable and easily handled silyl peroxyketal **7**, requiring only one purification.

The success of the annulation reaction is sensitive to the structure of the silyl peroxyketal (Table 3). Cyclohexanone-derived structures are favorable for the annulation reaction (entries 1 and 2). Annulation of silyl peroxyketal **19** provided 1,2-dioxolane **21**, which posseses the core structure of the *Plakortis* natural products (entry 3).[9] Entries 4 and 5 represent examples in which the driving force for Baeyer−Villiger oxidation[37−42] is greater than that of annulation, even under optimized conditions.

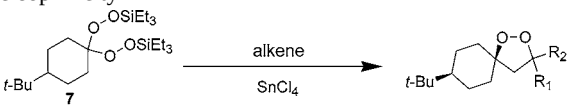
Table 3. Synthesis of 1,2-Dioxolanes from Silyl Peroxyketals: Substrate Scope

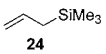
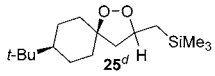
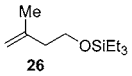
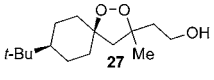
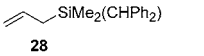
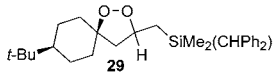
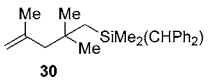
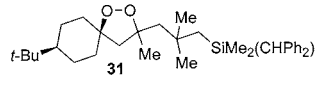
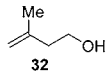
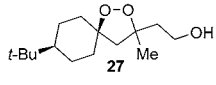
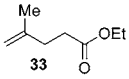
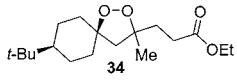
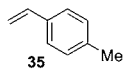
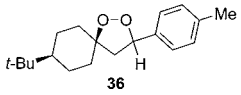


entry	substrate[a]	product	d.r.[b]	yield (%)[c]
(1)	 **7**	 **10**	*one diastereomer*	80
(2)	 **15**	 **20**	1:1	72
(3)	 **19**	 **21**	1:1	57
(4)	 **13**	 **22**	N/A	0
(5)	 **17**	 **23**	N/A	0

[a] Typical reaction conditions: $SnCl_4$ (2.0 equiv) and alkene (3.0 equiv) in CH_2Cl_2, −78 to −3 °C, 2−4.5 h. [b] Determined by ^1H NMR spectroscopy. [c] Yields based on purified products.

Table 4. Alkene Scope: Investigating the Effect of Alkene Nucleophilicity



entry	alkene[a]	product	yield (%)[e]
(1)[b]	 **24**	 **25**[d]	92
(2)	 **26**	 **27**	77
(3)[c]	 **28**	 **29**	72
(4)	 **30**	 **31**	48
(5)	 **32**	 **27**	47
(6)	 **33**	 **34**	34
(7)	 **35**	 **36**	28

[a] Typical reaction conditions: $SnCl_4$ (2.0 equiv), alkene (3.0 equiv), −78 to −3 °C, 3−24 h. [b] Typical reaction conditions: $SnCl_4$ (10 equiv), alkene (4.0 equiv), −78 to +25 °C, 24 h. [c] Typical reaction conditions: $SnCl_4$ (1.0 equiv), alkene (3.0 equiv), −78 to −5 °C, 22 h. [d] Stereochemistry determined by analysis of DPFGSE-NOE data. [e] Yields based on purified products.

Various alkenes can be employed as nucleophiles in the annulation reaction with silyl peroxyketal **7** (Table 4). Optimum results were obtained by employing 1,1-disubstituted alkenes as nucleophiles. Allylsilanes, which are comparably nucleophilic to 1,1-disubstituted alkenes,[43] also serve as potent nucleophiles to trap peroxycarbenium ions. Although *p*-methylstyrene **35** is as nucleophilic as allyltrimethylsilane,[43] an annulation using this alkene provided 1,2-dioxolane **36** and polymeric material.

A variety of monocyclic peroxides can be obtained employing silyl peroxyketal **19** (Table 5). Entry 1 shows the ideal system for establishing not only the cyclic peroxide moiety but also installating the acetic acid side chain common to peroxide natural products (vide infra).[1,2]

The use of a readily oxidized silyl group for the annulation reaction allowed us to obtain synthetically useful peroxides. Silyl groups can require forcing conditions to be oxidized,[44−46] but the labile benzhydryldimethylsilyl group proved to be useful for the synthesis of 1,2-dioxolanols.[47] Under relatively

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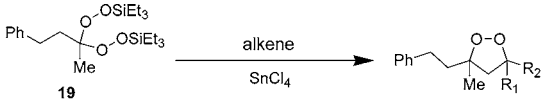
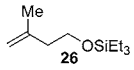
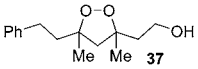
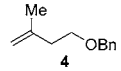
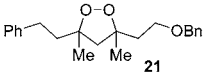
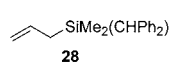
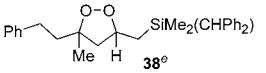
Table 5. Synthesis of Monocyclic 1,2-Dioxolanes

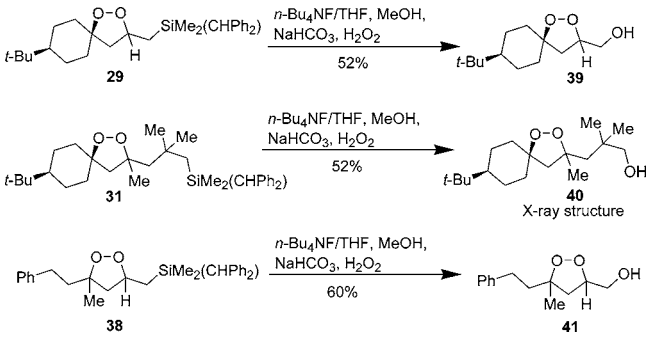


entry	alkene[a]	product	dr[b]	yield (%)[c]
(1)			1:1	67
(2)			1:1	57
(3)			2:1[d]	57

[a] Typical reaction conditions: $SnCl_4$ (1.0−2.0 equiv), alkene (1.0−3.0 equiv), −78 to −3 °C, 2−3 h. [b] Determined by ^1H NMR spectroscopy. [c] Yields based on purified products. [d] Measured by HPLC analysis of the unpurified reaction mixture. [e] The major diastereomer was isolated, and its stereochemistry was determined by analysis of DPFGSE-NOE data.

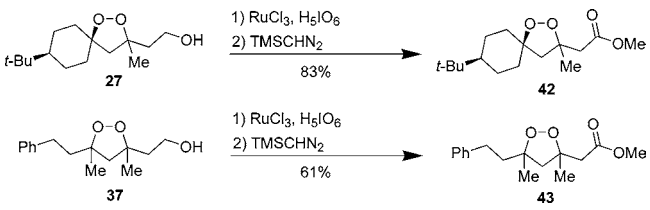
mild conditions, oxidation of the carbon−silicon bond occurred without significant destruction of the peroxide linkage (Scheme 1).

Scheme 1



The reactions of peroxycarbenium ions with protected butenol **26** allows for the rapid synthesis of plakinic acid analogues. This alkene incorporates all of the carbons required to introduce the acetic acid side chain common to many peroxide natual products (Scheme 2).[1,2] Dioxolanes

Scheme 2



27 and **37**, prepared in one step from the corresponding silyl peroxyketals, were converted to structures resembling the plakinic acids by oxidation of the primary alcohol.[48] Subsequent methylation of the carboxylic acid afforded 1,2-dioxolane methyl carboxylates **42** and **43** in good yield.[49]

In conclusion, the annulation reactions of alkenes with peroxycarbenium ions enables the synthesis of a variety of functionalizable 1,2-dioxolanes. The silyl protecting group used in the generation of peroxycarbenium ions governs the success of the annulation reaction. With the appropriate choice of ketones and alkenes, plakinic acid analogues can be synthesized in three steps.

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Supporting Information Available: Complete experimental procedures and product characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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