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Catalytic Enantioselective Peroxidation of α,β-Unsaturated Aldehydes for the Asymmetric Synthesis of Biologically Important Chiral Endoperoxides

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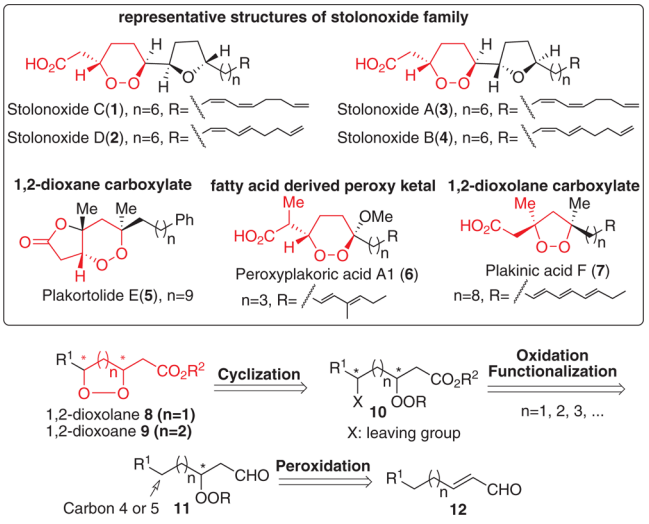
Supporting Information

ABSTRACT: We have developed an unprecedented highly enantioselective catalytic peroxidation of enals. Critical to this development is the discovery that varying the structure of the hydroperoxide has a significant impact on the enantioselectivity of the organocatalytic asymmetric peroxidation. This novel transformation enabled the development of an enantioselective route toward the core structure shared by all members of the stolonoxide family of anticancer natural products, a connected *trans*-3,6-disubstituted-1,2-dioxane and *trans*-2,5-disubstituted-tetrahydrofuran ring system. Our route also features an unprecedented cyclization cascade of a chiral bis(epoxy)-hydroperoxide. The new methodology and synthetic strategy established in this work should be applicable to the enantioselective synthesis of a broad range of chiral 1,2-dioxolanes and 1,2-dioxanes, thereby facilitating biological and medicinal chemistry studies of peroxy natural products.

A large number of biologically interesting peroxy natural products contain either a 1,2-dioxolane (**7**) or 1,2-dioxane (**1**–**6**) bearing an acetyl ester substituent and two or more stereocenters (Scheme 1).[1] It is particularly noteworthy that many of these peroxy natural products have been identified as highly potent anticancer agents.[1,2] A general enantioselective approach toward these structural motifs would greatly facilitate biological and medicinal chemistry studies of peroxy natural products. However, to our knowledge, such a synthetic approach has not yet been established.[3,4] The presence of nonadjacent stereocenters in these chiral 1,2-dioxolanes and 1,2-dioxanes and the general lack of asymmetric peroxidations of broad substrate scope render the efficient stereoselective constructions of such motifs an outstanding challenge in the development of not only synthetic strategy but also methodology.[3c,5]

We envisioned that asymmetric peroxidation of α,β-unsaturated aldehydes **12** followed by oxidation of the aldehydes to the acid derivatives would provide an attractive route toward β-peroxy acid derivatives **10** (Scheme 1). Asymmetric functionalization of **10** at either carbon 4 or 5 followed by cyclization via nucleophilic attack by the hydroperoxide would generate **8** or **9**.[6] This strategy could provide a general approach toward chiral 1,2-dioxolane and 1,2-dioxane motifs, thereby facilitating the total synthesis of a broad range of peroxy natural products. Critical to the implementation of this strategy is the development of a general and highly enantioselective nucleophilic peroxidation of enals **12** that is highly general with respect to the β-alkyl substituent. Here we report the realization of such an unprecedented asymmetric peroxidation and the application of this new reaction to the development of a stereocontrolled, concise, and flexible route for the construction of the connected *trans*-3,6-disubstituted-1,2-dioxane and *trans*-2,5-disubstituted-tetrahydrofuran ring system, the core structure shared by all members of the stolonoxide family of marine natural products.[7]

Scheme 1. Representative Peroxy Natural Products and Our General Synthetic Strategy



Our previous investigations with 9-amino cinchona alkaloid **18** led to the development of the first highly enantioselective catalytic peroxidation, namely, the peroxidation of α,β-unsaturated ketones with hydroperoxides.[8] We examined **18** for promotion of the peroxidation of enal **13A** with cumene peroxide (**14a**). Although the reaction with **14a** proceeded to completion to afford the desired peroxide **15** as the major product, the enantioselectivity afforded by **18** in this peroxidation was found to be very poor (Table 1, entry 4). Attempts to discover another active catalyst among cinchona alkaloid derivatives revealed that **18** is uniquely active (entries 1–4). Although we could improve the enantioselectivity

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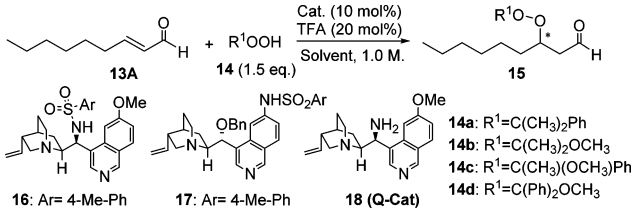
Table 1. Peroxidation of α,β-Unsaturated Aldehyde 13A with Hydroperoxides 14



entry	peroxide	cat.	solvent	T (°C)	t (h)	conv. (%)[a]	ee of 15 (%)[b]
1	**14a**	DABCO	CH_2Cl_2	25	24	0	NA
2	**14a**	**16**	CH_2Cl_2	25	24	0	NA
3	**14a**	**17**	CH_2Cl_2	25	24	0	NA
4	**14a**	**18**	CH_2Cl_2	25	6	100	43
5	**14a**	**18**	CH_2Cl_2	0	24	60	67
6	**14a**	**18**	toluene	0	24	70	72
7	**14b**	**18**	toluene	0	24	56	78
8	**14c**	**18**	toluene	0	24	60	71
9	**14d**	**18**	toluene	0	24	80	91
10[c]	**14d**	**18**	toluene	0	48	100	91

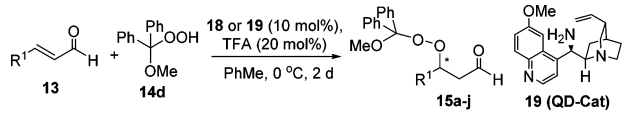
[a]Determined by ^{1}H NMR spectroscopy. [b]Determined by HPLC. [c]2.5 equiv of **14d** was used.

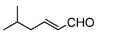
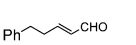
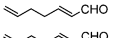
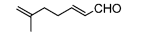
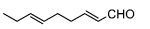
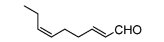
delivered by **18** through further optimizations of other reaction parameters such as the reaction temperature and solvent (entries 5 and 6), we were still not able to obtain β-peroxy aldehyde **15** with synthetically useful ee.

Since a wide variety of tertiary hydroperoxides can be easily prepared in one step from readily available tertiary alcohols or 1,1′-disubstituted olefins,[9] we next investigated the effect of varying the structure of the hydroperoxide on the **18**-catalyzed enantioselective peroxidation. We found that the structure of the hydroperoxide has a significant impact on the enantioselectivity (Table 1, entries 6−9). By exploring this effect, we established that a highly enantioselective peroxidation of enal **13A** could be achieved with α-methoxydiphenyl hydroperoxide (**14d**) (Table 1, entry 10). Importantly, we were able to extend this high enantioselectivity to the peroxidation of a considerable range of β-alkyl enals (Table 2). The ability to tolerate steric variations and the presence of olefins in the enals rendered this new reaction particularly valuable to facilitate the asymmetric synthesis of chiral 1,2-dioxolanes and 1,2-dioxanes as outlined in Scheme 1.

To demonstrate the synthetic consequences of this new asymmetric peroxidation, we next turned our attention to the enantioselective construction of the connected *trans*-3,6-disubstituted-1,2-dioxane and *trans*-2,5-disubstituted-tetrahydrofuran ring system, the core structure shared by all members of the stolonoxide family of natural products. These peroxy natural products were isolated from the metabolites of the marine ascidian *Stolonica socialis*.[7] To date no total synthesis of any stolonoxide has been reported, although preliminary bioassay studies have shown that stolonoxides C (**1**), D (**2**), A (**3**), and B (**4**) exhibit strong cytotoxicity against the mouse lymphoma P-388, human melanoma MEL-28, human prostate carcinoma DU-145, human lung carcinoma A-549, and human colon carcinoma HT-29 tumor cell lines with half-maximal inhibitory concentrations ranging from 0.01 to 0.1 μg/mL.[7b] In addition, **1** and **3** were also found to be inhibitors of the mitochondrial respiratory chain, affecting specifically the functionality of complex II (succinate:ubiquinone oxidoreductase) and complex III (ubiquinol:cytochrome *c* oxidoreductase) in mammalian cells.[7c] Notably, these bioactivities have been attributed to the presence of the common dioxane−tetrahydrofuran bicyclic core structure.[7b]

Table 2. Peroxidation of α,β-Unsaturated Aldehydes 13 with 14d[a]

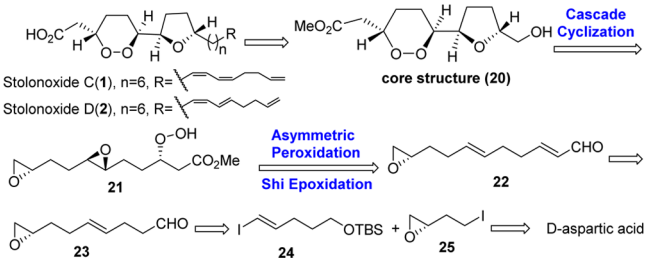


entry	enal		catalyst	yield (%) 15	ee (%) 15[b]
1		**13A**	**18**	60	91(R)[c]
2		**13B**	**18**	62	87(R)
3		**13C**	**18**	67	90(R)
4		**13D**	**18**	57	90(R)
5		**13E**	**18**	61	90(R)
6		**13F**	**19**	60	85(S)
7		**13G**	**19**	58	86(S)
8[d]		**13H**	**19**	54	87(S)
9		**13I**	**19**	55	87(S)
10		**13J**	**19**	58	85(S)

[a]Unless otherwise noted, reactions were run with 0.20 mmol of enal and 0.50 mmol of **14d** in 0.20 mL of toluene at 0 °C for 2 days. [b]See the Supporting Information (SI). [c]The absolute configuration of **15a** was determined to be *R* (see the SI). [d]The reaction was carried out with 3.0 mmol of **13H** and 6.25 mmol of **14d**.

As shown in our retrosynthetic analysis (Scheme 2), the stereochemically dense core **20** was to be constructed by an unprecedented acid-promoted, hydroperoxide-initiated epoxide-opening cascade from bis(epoxy)hydroperoxide **21**. Intermediate **21** would be prepared from epoxy enal **22** via the newly developed asymmetric peroxidation reaction followed by Shi epoxidation of the *trans*-olefin. **22** could be prepared from the known compounds epoxy iodide **25** and vinyl iodide **24**. Overall, the four stereocenters in **20** were to be created from the **19**-catalyzed asymmetric peroxidation, a Shi olefin epoxidation, and D-aspartic acid.

Scheme 2. Retrosynthesis of the Core Structure of (+)-Stolonoxides C and D



Our synthesis commenced from the coupling of epoxy iodide **25** (available from D-aspartic acid via four simple operations in 58% overall yield and 99% ee[10]) with *trans*-alkenyl iodide **24** (Scheme 3).[11] **24** was first allowed to react with isopropylmagnesium chloride to generate the *trans*-alkenylmagnesium chloride,[12] which then coupled with **25** to form **26** in THF. Through considerable optimization, we found that the use of a

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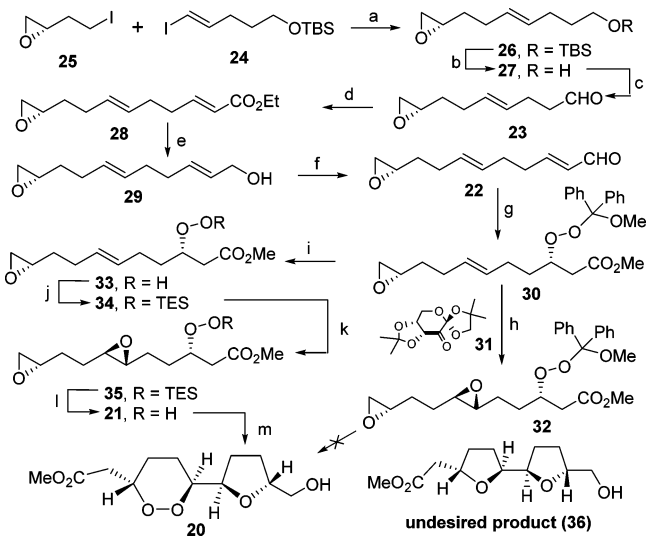
Scheme 3. Synthesis of the Core Structure of (+)-Stolonoxides C and D



Reagents and conditions: (a) **24** (1.67 equiv), ^{i}PrMgCl·LiCl, THF, −10 °C; then CuI, HMPA/THF, −30 °C, 66%. (b) TBAF, AcOH (1.2 equiv), THF, 92%. (c) Dess−Martin periodinane, DCM, 88%. (d) $Ph_3P{=}CHCO_2Et$, DCM, 94%. (e) DIBAL-H, THF, −78 °C, 89%. (f) MnO_2, DCM, rt, 87%. (g) (1) **19** (10 mol%), TFA (0.2 equiv), **14d** (2.0 equiv), toluene, 0 °C; (2) $NaClO_2$, NaH_2PO_4, *t*-BuOH/H_2O, rt; (3) $TMSCHN_2$, MeOH/benzene, rt, 57%, 82% d.e. (h) **31** (1.0 equiv), Oxone, K_2CO_3, BuN_4HSO_4, DMM/CH_3CN/buffer, 68%. (i) TFA, $CHCl_3$, −30 °C, 75%. (j) TESCl, TEA, DCM, 0 °C, 85%. (k) Same conditions as (h), 66%. (l) TBAF, buffer (pH 7), THF, 69%. (m) CsOH, $(CF_3)_2CHOH$/MeOH, rt, 52%.

stoichiometric amount of CuI and 4.0 equiv of HPMA was required for the reaction to proceed with high chemoselectivity in favor of the desired coupling reaction. Otherwise, nucleophilic ring opening of the terminal epoxide became the dominant reaction.[13] Deprotection of **26** was readily accomplished, and the resulting alcohol **27** was converted into α,β-unsaturated ester **28** via Dess−Martin oxidation followed by Wittig olefination. Reduction of unsaturated ester **28** with DIBAL followed by oxidation of the resulting allylic alcohol afforded the key enal intermediate **22**. Catalytic asymmetric peroxidation of **22** with **14d** under the optimal conditions described previously (Table 1) readily afforded the desired β-peroxy aldehyde, which was immediately subjected to sodium chlorite and then $TMSCHN_2$ to form ester **30** in 57% yield over three steps. Importantly, the key peroxidation was found to proceed with high stereoselectivity to furnish the desired chiral peroxide in a 10:1 diastereomeric ratio.

Following our original plan, we carried out a Shi epoxidation[14] to convert **30** to **32** in 68% yield and attempted a cascade of peroxyketal deprotection and epoxide opening to reach the dioxane−tetrahydrofuran bicyclic core structure **20** directly from **32**. However, these attempts were not successful in spite of our extensive efforts, as subjecting **32** to various acidic conditions to remove the α-methoxydiphenyl group led to decomposition of **32** resulting from ring opening of the bisepoxide motif. After considerable experimentation, we developed an alternative route to accomplish the synthesis of **20** from **30**. Specifically, we first converted **30** to hydroperoxide **33** in 75% yield by treatment with TFA at −30 °C. TES protection of **33** followed by Shi epoxidation transformed **34** into **35** in a highly diastereoselective fashion as determined by ^{13}C NMR analysis. Deprotection of **35** with TBAF under neutral conditions[15] generated bis(epoxy)hydroperoxide **21**, the precursor required for the key ring-opening cascade, in 69% yield.

The construction of the connected *trans*-3,6-disubstituted-1,2-dioxane and *trans*-2,5-disubstituted-tetrahydrofuran ring system from **21** via an unprecedented cyclization cascade turned out to be very challenging. We initially attempted the cyclization cascade in the presence of various acids such as camphorsulfonic acid, trifluoroacetic acid, trichloroacetic acid, and triflic acid. Unfortunately, all of these attempts were unsuccessful because of decomposition of **21** to form unidentifiable mixtures. A trace amount of the desired cyclization product **20** was detected when the cyclization cascade was promoted with a heterogeneous acid, Amberlyst 15.[6c] Upon further screening and optimization, we found that a catalytic amount of phosphomolybdic acid (PMA) supported on silica gel[6d] could promote the desired cyclization cascade to afford **20** in 15% isolated yield along with the tetrahydrofuran−tetrahydrofuran linked bicyclic compound **36** in 36% yield.[16] We next turned our attention to the promotion of the cyclization cascade under basic conditions. Treatment of **21** with common inorganic and organic bases such as KOH, LiOH, DAMP, and Et_3N led to the formation of complex mixtures. After extensive experimentation, we found that cesium hydroxide could promote the desired cyclization cascade in a mixed solvent of hexafluoroisopropanol and methanol (7:3) to afford **20** in 52% yield (Scheme 3).[6e]

In conclusion, we have developed the first highly enantioselective catalytic peroxidation of enals. It is noteworthy that we were able to achieve synthetically useful enantioselectivity only after the discovery that varying the structure of the hydroperoxide has a significant impact on the enantioselectivity of the organocatalytic asymmetric peroxidation. We have demonstrated the synthetic utility of this transformation in the development of an enantioselective route toward the core structure of stolonoxides C and D featuring an unprecedented cyclization cascade of a chiral bis(epoxy)hydroperoxide. Importantly, the new methodology and synthetic strategy established herein should be applicable to the enantioselective synthesis of a broad range of chiral 1,2-dioxolanes and 1,2-dioxanes, thereby facilitating biological and medicinal chemistry studies of peroxy natural products.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization of the products. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b05345.

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Notes

The authors declare no competing financial interest.

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