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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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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 hydroperoxides has a significant impact on the enantioselectivity of the organocatalytic asymmetric peroxidation. This novel transformation enabled the development of the enantioselective route toward the core structure shared by all members of the stolonoxides 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 from the current studies should be applicable to the enantioselective synthesis of a broad range of chiral 1,2-dioxolanes and 1,2-dioxanes, thereby facilitating the 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 acylester substituent and two or more stereocenters (Scheme 1).¹ It is particularly noteworthy that many of these peroxy natural products have been identified to be highly potent anticancer agents.^{1, 2} A general enantioselective approach toward these structural motifs would greatly facilitate the 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 non-adjacent 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 not only in synthetic strategy development but also in methodology development.^{3c, 5}

We envision that an asymmetric peroxidation of α , β -unsaturated aldehydes **12** followed by an oxidation of the aldehyde to the acid derivatives would provide an attractive route toward

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ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization of the products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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β -peroxy acid derivatives **10** (Scheme 1). Asymmetric functionalization of **10** at either carbon 4 or 5 followed by a cyclization with a nucleophilic attack by the hydroperoxide would generate **8** or **9**.⁶ This strategy could provide a general approach toward chiral 1,2-dioxolanes and 1,2-dioxanes 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 enal **12** that is highly general with respect to the β -alkyl substituent. In this manuscript, we wish to 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 stolonoxides family of marine natural products.⁷

Our previous investigations with the 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. We examined **18** for the promotion of a peroxidation of enal **13A** with cumene peroxide. Although the reaction with **14a** proceeded to completion to afford the desired peroxide **15** as the major product, the enantioselectivity afforded by **18** for this peroxidation was found to be very poor (entry 4, Table 1). Attempts to discover another active catalyst among cinchona alkaloid derivatives revealed that **18** is uniquely active (entries 1–4, Table 1). Although we could improve the enantioselectivity by **18** through further optimizations of other reaction parameters such as reaction temperature and solvent, we were still not able to obtain the β -peroxy aldehyde **15** in synthetically useful ee (entries 5–6, Table 1).

Since a wide variety of tertiary hydroperoxides could be easily prepared in one step from readily available tertiary alcohols or 1,1'-disubstituted olefins,⁹ we turned our attention to investigate the effect of varying the structure of the hydroperoxides on the **18**-catalyzed enantioselective peroxidation. We found the structure of the hydroperoxides has a significant impact on the enantioselectivity (entries 6–9, Table 1). By exploring this effect, we established a highly enantioselective peroxidation of enal **13A** could be achieved with α -methoxydiphenyl hydroperoxide **14d** (entry 10, Table 1). Importantly, we were able to extend this high enantioselectivity to the peroxidation of a considerable range of β -alkyl enals was quite general for all kinds of aliphatic enals (Table 2). The ability to tolerate steric variations of 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 consequence 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 stolonoxides 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 A-D (**1–4**) exhibited strong cytotoxicity against the tumor cell lines of mouse lymphoma P-388, human melanoma

MEL-28, human prostate carcinoma DU-145, human lung carcinoma A-549, and human colon carcinoma HT-29 with IC₅₀ values ranging from 0.01 to 0.1 µg/mL.^{7b} In addition, stolonoxides C (**1**) and A (**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 common dioxane-tetrahydrofuran bicyclic core structure.^{7b}

As shown in our retrosynthetic analysis (Scheme 2), the stereochemically dense core **20** was to be constructed by an acid-promoted unprecedented hydroperoxide-initiated epoxide-opening cascade from the bis(epoxy)hydroperoxide **21**. Intermediate **21** would be prepared from intermediate **22** via the newly developed asymmetric peroxidation of the epoxyenal **22** followed by a Shi epoxidation of the *trans*-olefin. The epoxyenal **22** could be prepared from known compounds epoxyiodide **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.

Our synthesis commenced from the coupling of epoxyiodide **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 epoxyiodide **25** to form **26** in THF. Through considerable optimizations, we found the use of a stoichiometric amount of CuI and 4.0 equivalents of HPMA was required for the reaction to proceed with high chemoselectivity in favor of the desired coupling reaction. Otherwise, the 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 the α, β-unsaturated ester **28** when subjected to a Dess-Martin oxidation followed by a Wittig olefination. Reduction of unsaturated ester **28** by DIBAL followed by an oxidation the allylic alcohol thus afforded the key enal intermediate **22**. Catalytic asymmetric peroxidation of **22** with α-methoxydiphenyl hydroperoxide **14d** applying the optimal condition described previously (Table 1) readily afforded the desired β-peroxyaldehyde, which was immediately subjected to sodium chlorite and then TMSCHN2 to form ester **30** in 57% yield over three steps. Importantly, the key peroxidation was found to proceed in high stereoselectivity to furnish chiral peroxide in 10:1 diastereomer ratio.

Following our original plan we carried out a Shi epoxidation¹⁴ to convert **30** to **32** in 68% yield and attempted a cascade of deprotection of peroxyketal and epoxide-opening to reach dioxane-tetrahydrofuran bicyclic core structure **20** directly from **32**. However, these attempts were not successful in spite of our extensive efforts, as subjectings of **32** to various acidic conditions applied to the removal of α-methoxydiphenyl group led to decompositions of **32** resulted from the ring-opening of the bisepoxide motif. After considerable experimentations, we developed an alternative route to accomplish the synthesis of **20** from **30**. Specifically, we first converted **30** to hydroperoxide **33** in 75% yield upon treatment of **30** 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 ¹³C NMR analysis.

Deprotection of **35** with TBAF under neutral condition¹⁵ generated the bis(epoxy)hydroperoxide **21**, the required precursor 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 due to the 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 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. Treatments of **21** with common inorganic and organic bases such as KOH, LiOH, DMAP and Et₃N led to the formations of complex mixtures. After extensive experimentations, 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 are able to achieve synthetically useful enantioselectivity only after the discovery that varying the structure of the hydroperoxides 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 from the current studies should be applicable to the enantioselective synthesis of a broad range of chiral 1,2-dioxolanes and 1,2-dioxanes, thereby facilitating the biological and medicinal chemistry studies of peroxy natural products.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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representative structures of stolonoxide family

1,2-dioxane carboxylate

fatty acid derived peroxy ketal

1,2-dioxolane carboxylate

Scheme 1.

Representative Peroxy Natural Products and Our General Strategy to Synthesize These Molecules

Scheme 2.

Retrosynthesis for the Core Structure of (+)- Stolonoxides C and D

Scheme 3.

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

Reagents and Conditions: (a) 24 (1.67 equiv.), $i\text{PrMgCl}\cdot\text{LiCl}$, THF, $-10\text{ }^{\circ}\text{C}$; then CuI , HMPA/THF, $-30\text{ }^{\circ}\text{C}$, 66%. (b) TBAF, AcOH (1.2 equiv.), THF, 92%. (c) Dess-Martin periodinane, DCM, 88%. (d) $\text{Ph}_3\text{Ph}=\text{CHCO}_2\text{Et}$, DCM, 94%. (e) DIBAL-H, THF, $-78\text{ }^{\circ}\text{C}$, 89%. (f) MnO_2 , DCM, rt, 87%. (g) (1) **19** (10 mol%), TFA (0.2 equiv.), **14d** (2.0 equiv.), toluene, $0\text{ }^{\circ}\text{C}$; (2) NaClO_2 , NaH_2PO_4 , $t\text{-BuOH}/\text{H}_2\text{O}$, rt; (3) TMSCHN_2 , MeOH/benzene, rt, 57%, 82% d.e. (h) **31** (1.0 equiv.), Oxzone, k_2CO_3 , BuN_4HSO_4 , DMM/ CH_3CN /Buffer, 68%. (i) TFA, CHCl_3 , $-30\text{ }^{\circ}\text{C}$, 75%. (j) TESCI, TEA, DCM, $0\text{ }^{\circ}\text{C}$, 85%. (k) same condition as (h), 66%. (l) TBAF, buffer (pH=7), THF, 69%. (m) CsOH, $(\text{CF}_3)_2\text{CHOH}/\text{MeOH}$, rt, 52%.

Table 1

Peroxidation of α, β -Unsaturated Aldehyde 13a with Hydroperoxides 14

entry	peroxide	Cat.	solvent	temp (°C)	time (h)	conv. (%) ^a	ee (%) 15^b
1	14a	DABCO	CH ₂ Cl ₂	25	24	0	NA
2	14a	16	CH ₂ Cl ₂	25	24	0	NA
3	14a	17	CH ₂ Cl ₂	25	24	0	NA
4	14a	18	CH ₂ Cl ₂	25	6	100	43
5	14a	18	CH ₂ Cl 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 ¹H NMR.^b Determined by HPLC.^c 2.5 eq. of **14d** was used.

Table 2

Peroxidation of α , β -Unsaturated Aldehydes 13 with 14d^a

entry	enal	catalyst	yield (%) 15	ee (%) 15^b
1		18	60	91(R) ^c
2		18	62	87(R)
3		18	67	90(R)
4		18	57	90(R)
5		18	61	90(R)
6		19	60	85(S)
7		19	58	86(S)
8 ^d		19	54	87(S)
9		19	55	87(S)
10		19	58	85(S)

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