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An Asymmetric Synthesis of 1,2,4-Trioxane Anticancer Agents via Desymmetrization of Peroxyquinols through a Brønsted Acid Catalysis Cascade

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Abstract

The desymmetrization of *p*-peroxyquinols using a Brønsted acid catalyzed acetalization/oxa-Michael cascade was achieved in high yields and selectivities for a variety of aliphatic and aryl aldehydes. Mechanistic studies suggest that the reaction proceeds through a dynamic kinetic resolution of the peroxy hemiacetal intermediate. The resulting 1,2,4-trioxane products were derivatized and show potent cancer cytotoxicity.

Trioxanes are important scaffolds, which appear in molecules that exhibit antimalarial, anticancer and antibacterial activities.[1] In particular, artemisinin, administered as a part of a combination therapy for the frontline treatment of malaria, contains a 1,2,4-trioxane as the key pharmacophore. The recent emergence of an artemisinin resistant malaria strain[2] combined with the fact that artemisinin's mode of action remains under debate[3] increases the difficulty of treating malaria and makes the pursuit of novel therapeutic agents more urgent. One potential solution has been the development of new synthetic endoperoxides.[4] Enantiomers of a few synthetic trioxanes have shown similar anti-malarial activities[5] but stereochemistry has a demonstrated impact on anti-cancer activity.[6] Current methods for the enantioselective synthesis of trioxanes are lengthy and use chiral starting materials or reagents.[5,6,7,8]

We envisioned that enantioenriched trioxanes could be accessed quickly and enantioselectively through a desymmetrization of *p*-peroxyquinols via an acetalization/oxa-Michael cascade first reported by Jefford.[9,10] Cascade catalysis[11,12,13] and desymmetrizations[14] are powerful methods utilized by our group and others to construct complex molecules containing multiple stereocenters in a rapid and efficient manner. Both enantioselective acetalization[15] and oxa-Michael[16] reactions are relatively unsolved problems. We were cognizant of the potential difficulties in this approach due to the inherent reversibility of both transformations particularly under acidic conditions. Nevertheless, we were emboldened by recent successes in this area.[17]

We began our investigation by studying the desymmetrization of *p*-peroxyquinol **2a**, trivially accessed from cresol, using chiral Brønsted acid catalyst **5** (TRIP) which afforded

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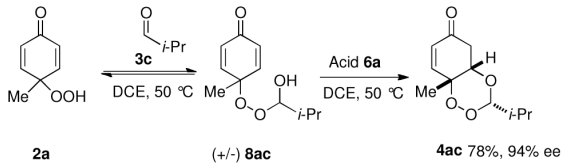
Experimental procedures, crystallographic data, and characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

the desired trioxane in good yield as a single diastereomer in 86% ee (entry 5, Table 1). Switching to the bis(2,4,6-triisopropylphenyl)spirobiindane phosphoric acid **6a** developed by List[15e,18] improved the enantioselectivity to 96%. Other biindane Brønsted acids were screened but the parent acid **6a** gave the best results. Lowering the catalyst loading from 10 mol % gave decreased reactivity, which could be restored through the use of thiourea **7** as a co-catalyst. Catalyst loadings as low as 2 mol% may be used at the expense of a longer reaction time (entry 7, Table 1). The use of thiourea **7** alone leads to no product.

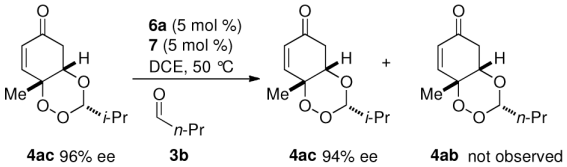
With our optimized reaction conditions in hand, we explored the aldehyde scope of the reaction (Figure 1). Paraformaldehyde and a variety of sterically hindered aliphatic aldehydes work well. Aldehydes containing alkyl halides, protected alcohols and protected amines are tolerated affording trioxanes in excellent selectivities. Aromatic aldehydes also participate in the reaction with high enantioselectivity but slightly decreased yields (Figure 1).

The reaction also proved tolerant of substitution on the *p*-peroxyquinol. Products with esters, ethers, and multiple tetrasubstituted stereocenters are all isolated in good yields and selectivities (Figure 2).

The enantiodetermining step is likely the oxa-Michael event based on the high enantioselectivity of the product formed from paraformaldehyde.[19] We propose that the reaction proceeds via a dynamic kinetic resolution of peroxy hemiacetal (+/−)**8a** (Equation 1). To further test this hypothesis, racemic peroxy-hemiacetal **8ac** was formed by heating *p*-peroxyquinol **2a** with isobutyraldehyde. After excess aldehyde was removed, unpurified (+/−) **8ac** was subjected to chiral acid **6a**. To our delight, trioxane **4ac** was formed in good yield as a single diastereomer in 94% ee. This suggests that peroxyhemiacetal **8ac** is resolved through a dynamic kinetic resolution (Equation 1). Additionally, monitoring the reaction under standard conditions with catalyst **6a** by HPLC, we note that the peroxyhemiacetal remains as a racemate throughout the course of the reaction. A crossover experiment subjecting **4ac** to *n*-butyraldehyde showed that the oxa-Michael is not reversible under the reaction conditions (Equation 2).[20]



(1)



(2)

The 1,2,4 trioxane products of the desymmetrization have a variety of synthetic handles for subsequent derivatization. A Luche reduction of **4ac** forms the allylic alcohol in 4:1 dr and subsequent directed epoxidation delivers highly oxygenated cyclohexane **9** (Figure 3).

Bromination of **4ac** followed by elimination forms vinyl bromide **10** which allows for the incorporation of a variety of functional groups though cross coupling. Chemoselective reduction of the olefin in the presence of the peroxide may be achieved under the aegis of Rh/Al_2O_3 and Adams' catalyst. This product can be further reduced under acidic conditions to reveal previously unreported diol **12**.

In addition to serving as the frontline antimalarial agent, artemisinin is cytotoxic toward cancer cells and the 1,2,4-trioxane is believed to play an important role.[1] Our products and their derivatives were screened for cytotoxicity against a variety of cancer cell lines. Compounds **4ac, 4an,** and **11** show promising activity toward bone and lung cancer cell lines with *in vitro* IC_{50}'s from 3-25 μM (Figure 4). Importantly, the significant cytotoxicity of the semi-reduced trioxane **12** demonstrates that their activity is not due solely to the presence of the Michael acceptor.

In conclusion we report the first catalytic enantioselective synthesis of trioxanes using a desymmetrization of *p*-peroxyquinols via an acetalization/oxa-Michael cascade. We propose that the reaction proceeds via a dynamic kinetic resolution of a peroxy-hemiacetal intermediate. The 1,2,4-trioxane products are easily derivatized and show promising cancer cytotoxicity. Further development of this reaction, antimalarial testing of these trioxanes and investigation of the cytotoxicity mode of action are currently underway.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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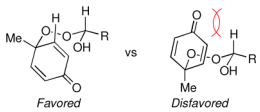
(19). The high diastereoselectivity of the desymmetrizations can be explained by the reduced 1,3-diaxial interactions in the transition state leading to the favored product.



(20). While yields are universally improved, enantioselectivities are not appreciably impacted by the presence of the thiourea co-catalyst suggesting that it is not involved in the enantioselectivity determining event. Its exact role in this transformation is the subject of further investigations.

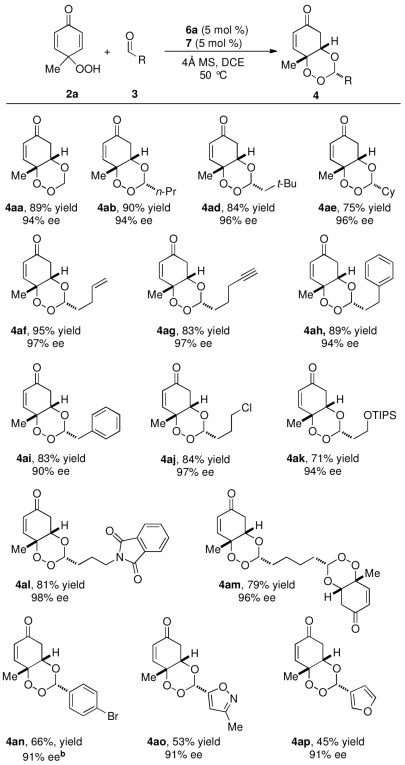


Figure 1.

Aldehyde substrate scope[a]

[a]Conditions: **2a** (0.3 mmol), **3** (1.25 equiv). All products formed as single diastereomers (>20:1). Enantiomeric excess determined by HPLC using a chiral stationary phase. [b]Absolute configuration established by X-ray analysis. The rest were assigned by analogy. [c]*ent*-**6a** used as catalyst.

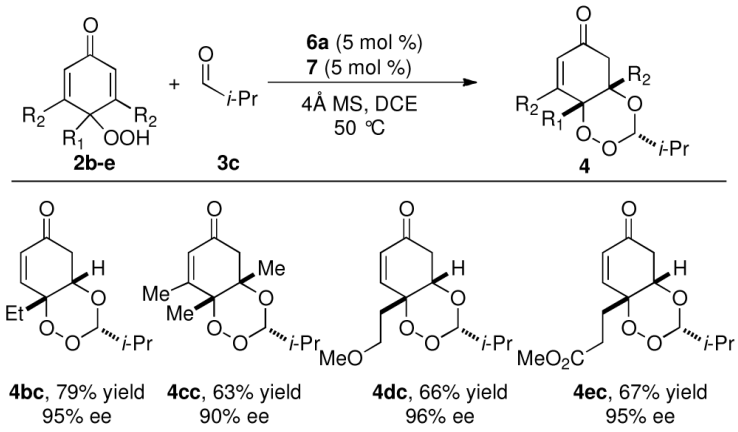


Figure 2.
Peroxyquinol substrate scope[a]
[a]See footnote a, Figure 1.

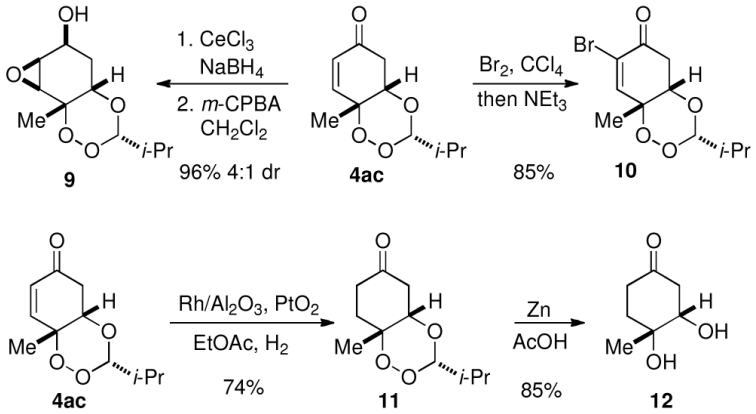
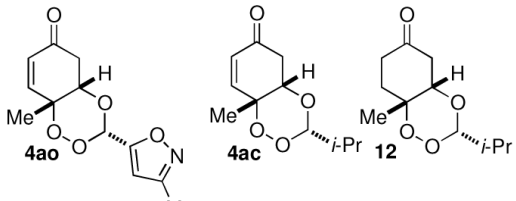


Figure 3.
Trioxane derivatizations.

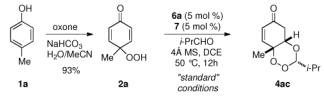


	4ao	4ac	12
D17 Canine osteosarcoma	10.0 μM	3.4 μM	43.1 μM
M21 Human melanoma	-	26.3 μM	~100 μM
MDA human breast carcinoma	-	> 100 μM	> 100 μM
A549 Human lung carcinoma	-	5.7 μM	25 μM
PC3 Human prostate carcinoma	-	11.1 μM	~100 μM

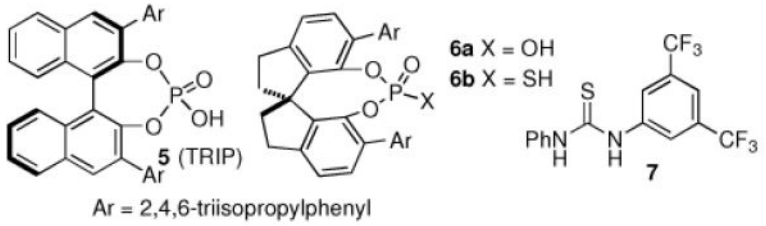
Figure 4.
Anticancer activity of 1,2,4-trioxane products.

Table 1

Reaction optimization.



entry	variation from "standard" conditions	yield (%)[b]	ee (%)[c]
1	none	92	96
2	no 4Å MS	90	88
3	no **7**	46	95
4	no **6a**	<5	-
5	**5**, instead of **6a**	93	86
6	no **7**, **6a** (10 mol%)	93	96
7	**6a** (2 mol%), 72h	88	98
8	**6b**, instead of **6a**	65	95
9	23 °C, 48h, instead of 50 °C, 24	85	96



[a] Reactions were performed on 0.1 mmol scale (0.25 M solution).

[b] Isolated yields of analytically pure material.

[c] Enantiomeric excess determined by HPLC using a chiral stationary phase.