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Stereoselective Synthesis of Substituted Oxocene Cores by Lewis Acid Promoted Cyclization

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Abstract

Substituted oxocene derivatives have been synthesized by Lewis acid catalyzed reactions of ϵ -hydroxy-alkene and substituted aromatic aldehydes. The $\text{Cu}(\text{OTf})_2$ -bis-phosphine catalyzed reaction typically provides substituted dihydropyran derivatives through an olefin-migration, followed by a Prins cyclization. The corresponding reaction catalyzed by TMSOTf or $\text{BF}_3 \cdot \text{OEt}_2$ provided eight-membered cyclic ethers, oxocenes, selectively. This methodology provides convenient access to a variety of 2,4,8-trisubstituted oxocenes in good yields and excellent diastereoselectivities.

Graphical Abstract

Substituted medium-sized cyclic ethers, particularly eight-membered oxocane and oxocene derivatives, are structural features in a variety of bioactive natural products.^{1,2} This includes, lauthisan (**1**, Figure 1), helianane (**2**), laurencin (**3**), and others.^{3–6} As a result, stereoselective synthesis of these medium-sized oxocyclic rings have been the subject of much interest over the years.⁷ Unlike six-membered ring compounds, construction of eight-membered rings from acyclic precursors is problematic due to factors related to entropy, as well as developing transannular and torsional strains.^{8,9} A number of methods including cycloadditions,¹⁰ ring expansions,^{11,12} ring-closing metathesis^{13,14} and intramolecular acetal-alkene cyclizations^{15,16} have been developed. A number of these methods were utilized in the synthesis of bioactive molecules.⁷ A majority of these synthetic approaches, however, involve intramolecular reactions, especially in the case of the synthesis of oxocene core structures.

An intermolecular reductive cyclization leading to oxocene cores was reported by Solladie and coworkers.¹⁷ We recently reported that the reaction of substituted alkenol **4** with

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Supporting Information

Experimental procedures and ¹H- and ¹³C-NMR spectra are available for all new compounds.

benzyloxyacetaldehyde in the presence of a catalytic amount of $\text{Cu}(\text{OTf})_2$ and bis-phosphine complex provided the olefin migration and Prins cyclization product **5** (55% yield) along with a small amount of eight-membered cyclic ether **6** (11% yield, Scheme 1).^{18,19} Presumably, the 2,8-substituents in **6** are in a *cis*-relationship, as depicted and the oxocene product was formed by a nucleophilic attack of the olefin onto the oxocarbenium ion **7**, followed by elimination.

In an effort to access substituted oxocene derivatives, we investigated this reaction with a variety of Lewis acids and reaction conditions. Herein, we report the results of our investigations leading to the synthesis of 2,4,8-trisubstituted oxocenes in a highly diastereoselective manner. We initially investigated the Lewis acid catalyzed cyclization using 6-methylhept-6-en-2-ol (**4**) and *p*-nitrobenzaldehyde as the model substrates, as shown in Scheme 2. The use of 10 mol % $\text{Sc}(\text{OTf})_3$ as the Lewis acid in CH_2Cl_2 , in the presence of 4A molecular sieves at 23 °C, resulted in tetrahydropyran derivative **8** as the major product and oxocene derivative **9a** as the minor product in 36% combined yield. The ratios of products (**9a**:**8**) were 9:91 by ^1H -NMR analysis.

With the aim of forming oxocene **9a** as the major product directly, we explored a number of oxophilic Lewis acids for this cyclization. Overman and co-workers reported efficient construction of medium sized ring ethers by an intramolecular Prins-type reaction of mixed acetals using $\text{BF}_3\cdot\text{OEt}_2$ as the Lewis acid in *t*-BuOMe.²⁰ We first examined the reaction of alkenol **4** with *p*-nitrobenzaldehyde using catalytic amount of $\text{BF}_3\cdot\text{OEt}_2$ in CH_2Cl_2 . As it turns out, $\text{BF}_3\cdot\text{OEt}_2$ catalyzed cyclization provided mainly oxocene product **9a**. We have not been able to identify any 6-membered Prins product **8** by ^1H NMR analysis of the crude products. The trace amount of minor product appeared to be the exo-olefin product. As shown in Table 1, catalytic amount (20 mol %) of $\text{BF}_3\cdot\text{OEt}_2$ in CH_2Cl_2 provided 38% yield of oxocene product **9a** as the major product (entry 2). The use of 40 mol % $\text{BF}_3\cdot\text{OEt}_2$ resulted in a lower yield of oxocene cyclization product **9a** (entry 3). The use of $\text{BF}_3\cdot\text{OEt}_2$ (3 equiv) in *t*-BuOMe provided 33 % yield of oxocene product **9a** (entry 4). To further improve yields, we then explored TMSOTf in a number of solvent systems.²¹ As it turns out, one equivalent of TMSOTf in a variety of solvents afforded cyclization product, oxocene **9a** as the major product. The choice of diethyl ether in the presence of molecular sieves at 0 °C for 15 min provided oxocene **9a** in 60% yield (entry 6). The presence of 4A molecular sieves did not improve the yield of oxocene product, but it did improve the endo/exo ratio (entries 5 and 6). The use of toluene resulted in a lower endo/exo ratio. The reaction in DME provided a comparable yield, however, cyclization products were obtained in an 81:19 ratio (entry 8). These ratios were determined based upon ^1H -NMR analysis of the benzylic protons, as the products could not be separated by silica gel chromatography. This Prins-type cyclization provided the best result when THF was used as the solvent in the presence of 4A molecular sieves. As shown, oxocene product **9a** was obtained essentially as a single product (mixture ratio 98:2) in 73% isolated yield (entry 9). The reaction in a mixture of CH_2Cl_2 and THF also provided comparable yields and mixture ratios (entries 10 and 11). The use of TMSOTf in *t*-BuOMe provided 46 % yield (88:12) of oxocene product **9a** (entry 12).

We then examined the substrate scope of this intermolecular process. As shown in Table 2, a variety of alkyl substituents on the alkyl group of the alkenol substrate were accommodated

(entries 1–4). The structures of the major endo-products are shown in Figure 2. The electron withdrawing nitro group on the ortho, meta or para-position of the benzene ring of the benzaldehyde provided good yield of oxocene product and excellent endo/exo ratios (entries 5–7). Incorporation of *p*-F, *p*-CF₃ or *p*-Cl groups provided moderate yields of oxocene derivatives and the endo/exo ratio decreased at the same time (entries 8–10). The reaction with dihydrocinnamaldehyde afforded 35% yield of oxocene derivative **9k** and endo/exo olefin ratio was 94:6 (entry 11). Also, reaction with benzyloxyacetaldehyde provided oxocene derivative **6** in 24% yield (entry 12). However, 3-(4-methoxybenzyloxy)propanal and 3-(*tert*-butyldimethylsilyloxy) propanal failed to provide any oxocene product. The reaction with *m*-methyl or 2-naphthaldehyde provided only 8% and 16% yields of the corresponding oxocene derivatives, respectively (entries 13 and 14). The reaction with 4-fluoro-3-nitrobenzaldehyde resulted in reduction of yield over the 3-nitrobenzaldehyde (entry 15). This condition was also utilized in the preparation of nearly half a gram quantity of oxocene derivative **9f**.²²

Separation of endo and exo isomers proved difficult by silica gel chromatography or via HPLC methods. In order to confirm the identity of the exo-derivative, we exposed the mixture of products from entry 6 (Table 2) to ozonolytic cleavage at –78 °C in a mixture (1:1) of methanol and CH₂Cl₂ (Scheme 3). The resulting products were separated by silica gel chromatography. Ketone **12** was then subjected to Wittig olefination with methylene triphenylphosphorane to provide pure exo-olefin derivative **10f**. The ¹H-NMR and ¹³C-NMR of **10f** obtained in this manner matched completely with the minor product in the spectra containing the mixtures.

To determine the X-ray crystal structure, the main product **9a** (entry 6) was subjected to reduction with Zn dust in acetic acid as shown in Scheme 4.²³ The resulting aromatic amine was reacted with *p*-bromobenzenesulfonyl chloride in the presence of aqueous sodium bicarbonate solution to provide sulfonamide derivative **13**. This was recrystallized from ether/pentane at 23 °C for 48 h. The single crystal X-ray analysis (Scheme 4) further supports the assignment of *cis*-stereochemistry.^{24,25}

As shown in Table 2, the endo-olefin product was typically the major isomer observed by ¹H- and ¹³C-NMR-analysis. The stereochemical assignment of these compounds was carried out by ¹H NMR NOESY experiments of compound **9a** (Figure 3). The depicted conformation is chosen based upon the X-ray crystal structure. The observed strong NOESY correlation between H_E and H_D provided evidence of the assigned *cis*-relationship between the alkyl and aromatic ring in **9a**. Additional NOESY correlations between H_E-H_C, H_C-H_L, H_D-H_J, H_J-H_H and H_F-H_G are due to a preferred conformation of the eight-membered oxocene ring.²⁶

The stereochemical outcome of the current Prins-type cyclization, which provided *cis*-oxocene derivatives, can be rationalized based upon the transition-state models in Figure 4. The TMSOTf-catalyzed reactions of alkenol **4** and an aromatic aldehyde would lead to the formation of oxocarbenium ion intermediates **14a** and **14b**.

Subsequent cyclization followed by proton elimination is unlikely to proceed through transition-state **14b** as it shows unfavorable steric interactions. The cyclization is likely to proceed through transition-state **14a** leading to *cis*-product **15a**. The formation of *trans*-product **15b** was not observed.

In summary, we have developed an unprecedented TMSOTf-catalyzed intermolecular Prins-type cyclization for the synthesis of a variety of oxocene derivatives. The use of various 1-alkyl-5-methylhex-5-en-1-ol and an appropriate aromatic aldehyde afforded a range of oxocene endo olefin derivatives. A stereochemical model also provided explanation for the selective formation of 2,8-*cis*-oxocene derivatives in up to 87% yields and excellent diastereoselectivity for disubstituted derivatives. Mechanistic studies and application of these substituted oxocene derivatives are in the progress in our laboratory.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Structures of oxacyclic natural products

Figure 2.
Structure of major isomer

Figure 3.
¹H-NMR NOESY of compound **9a**

Figure 4.
Stereochemical analysis for *cis*-oxocene products

Scheme 1.
Formation of THP and oxocene products

Scheme 2.
Formation of oxocene products

Scheme 3.
Preparation of exo-oxocene isomer **10f**

Table 1

BF₃·OEt₂ and TMSOTf catalyzed reactions^a

entry	solvent	Lewis acid	equiv ^b	yield (%)	Ratio 9a:10a
1 ^c	CH ₂ Cl ₂	BF ₃ ·OEt ₂	0.1	14	98:2
2 ^c	CH ₂ Cl ₂	BF ₃ ·OEt ₂	0.2	38	98:2
3 ^c	CH ₂ Cl ₂	BF ₃ ·OEt ₂	0.4	21	98:2
4 ^c	<i>i</i> -BuOMe	BF ₃ ·OEt ₂	3.0	33	76:24
5 ^c	Et ₂ O	TMSOTf	1.0	60	95:5
6	Et ₂ O	TMSOTf	1.0	60	98:2
7	toluene	TMSOTf	1.0	---	68:32 ^d
8	DME	TMSOTf	1.0	58	81:19
9	THF	TMSOTf	1.0	73	98:2
10	CH ₂ Cl ₂ -THF (1:1)	TMSOTf	1.0	68	98:2
11	CH ₂ Cl ₂ -THF (3:1)	TMSOTf	1.0	68	98:2
12	<i>i</i> -BuOMe	TMSOTf	1.0	46	88:12

^a Conditions: 1 equivalent 6-methylhept-6-en-2-ol, 1.2 equivalent *p*-nitrobenzaldehyde, 0.1 M solution, 0 °C, 60 mg molecular sieves, ratio is endo:exo.^b equiv = equivalent of Lewis acid.^c No molecular sieves were used.^d No purification was conducted because the crude ratio was low.

Table 2

TMSOTf catalyzed synthesis of oxocenes^a

Entry	R	R ₁	compd	Ratio (9:10) ^b	Yield (%) ^c
1	H	<i>p</i> -NO ₂ Ph	9b	90:10	70
2	Et	<i>p</i> -NO ₂ Ph	9c	90:10	87
3	<i>i</i> -Pr	<i>p</i> -NO ₂ Ph	9d	91:9	62
4	Ph	<i>p</i> -NO ₂ Ph	9e	91:9	39
5	Me	<i>p</i> -NO ₂ Ph	9a	98:2	73
6	Me	<i>m</i> -NO ₂ Ph	9f	91:9	65
7	Me	<i>o</i> -NO ₂ Ph	9g	97:3	58
8	Me	<i>p</i> -F-Ph	9h	90:10	20
9	Me	<i>p</i> -CF ₃ Ph	9i	92:8	37
10	Me	<i>p</i> -Cl-Ph	9j	93:7	18
11	Me	Ph(CH ₂) ₂	9k	94:6	35
12	Me	CH ₂ OBn	6	98:2	24
13	Me	<i>m</i> -MePh	9l	92:8	8
14	Me	2-naphth	9m	94:6	16
15	Me	<i>p</i> -F, <i>m</i> -NO ₂ Ph	9n	91:9	41

^aReaction conditions are from entry 8, Table 1.^bThe endo:exo ratio was determined by ¹H NMR.^cIsolated yield of combined products.