Published in final edited form as:

Org Lett. 2009 August 20; 11(16): 3682–3685. doi:10.1021/ol901523g.

Organometallic Enantiomeric Scaffolding. A Molybdenum-mediated Intramolecular Nucleophilic Ketalization-Demetallation Cascade. Total Synthesis of (+)-(1*R*,2*S*,5*S*,7*R*)-2-Hydroxy-*exo*-brevicommin

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Abstract

$\text{TpMo}(\text{CO})_2(5\text{-oxo-}\eta^3\text{-pyranyl})$ scaffolds bearing an internal alkoxide undergo a novel intramolecular nucleophilic ketalization reaction. The anionic intermediate is easily demetallated, rapidly providing the 6,8-dioxabicyclo[3.2.1]oct-3-en-2-one framework in moderate to good yields with high enantiopurity. An enantiocontrolled total synthesis of (+)-(1*R*,2*S*,5*S*,7*R*)-2-hydroxy-*exo*-brevicommin was accomplished utilizing the reaction sequence.

High enantiopurity air and moisture-stable $\text{TpMo}(\text{CO})_2(\eta^3\text{-pyranyl})$ and $\text{TpMo}(\text{CO})_2(\eta^3\text{-pyridinyl})$ complexes have been utilized in the asymmetric construction of structurally diverse heterocyclic systems.¹ Readily available in multigram quantities,^{1m} these complexes function as versatile *organometallic enantiomeric scaffolds*. Synthetic bond construction strategies that have evolved from these novel scaffolds have relied almost solely on processes that proceed through molybdenum-stabilized cationic intermediates because, with very few exceptions,²

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Supporting Information **Available** Experimental procedures, synthesis and characterization of all new compounds (27 pages) and-scanned spectra (50 pages). This material is available free of charge via the internet at <http://pubs.acs.org>

coordinatively saturated, charge-neutral η^3 -allylmolybdenum complexes are typically unreactive toward direct nucleophilic functionalization at the allyl moiety. Complementing these traditional cationic pathways, an unprecedented reactivity profile for coordinatively saturated, charge neutral $\text{TpMo}(\text{CO})_2(\eta^3\text{-pyranyl})$ and $\text{TpMo}(\text{CO})_2(\eta^3\text{-pyridinyl})$ complexes was recently disclosed:^{1j,10} the direct nucleophilic addition of an internal enolate to a terminal π -carbon of the η^3 -allyl moiety. This new mode of reactivity allows one to amplify the use of organometallic enantiomeric scaffolds for conceptually novel strategies of synthesis. Herein we report the direct nucleophilic functionalization of $\text{TpMo}(\text{CO})_2(5\text{-oxo-}\eta^3\text{-pyranyl})$ complexes at the terminus of the η^3 -allyl moiety by an internal alkoxide. This strategically new C—O bond formation establishes a bicyclic ketal, stereospecifically, and, after *in situ* oxidative decomplexation of the anionic bicyclic intermediate produced upon alkoxide addition, allows the rapid, one-pot enantiocontrolled construction of the 6,8-dioxabicyclo[3.2.1]octane framework³ with complete regio- and stereocontrol (Scheme 1).

Synthetic studies of this new regio- and stereocontrolled intramolecular nucleophilic ketalization reaction started with the transformation of ($\pm$)-5-oxopyranyl complex **1** and ($\pm$)-2-methyl-5-oxopyranyl **2** to the corresponding *anti* and *syn* alcohols **3–7** by a Mukaiyama-aldol reaction⁴ for complex **1** or a traditional aldol reaction for complex **2**.⁵ Four different aldehydes were studied in each case (Table 1). The aldol reactions took place in moderate to excellent yields with a slight preference for *anti* selectivity. The *anti* and *syn* relationships of these keto alcohols were determined by comparing the coupling constant between the hydrogen adjacent to the hydroxyl group and the vicinal hydrogen on the pyran ring. For the *anti* isomers, the vicinal coupling constants are approximately 5–6 Hz, while the vicinal coupling constants for the *syn* isomers are approximately 2–3 Hz. Using chiral, non-racemic (–)-**1** (98.7% ee)^{1m} (Table 1, entry 1), high enantiopurity (98.7% ee) aldol adducts *syn* and *anti* (–)-**3** were prepared.

Treatment of *syn*- and *anti*-**3–7** with NaH followed by *in situ* quenching with either NOPF_6 or NOBF_4 directly afforded the *exo* and *endo* 6,8-dioxabicyclo[3.2.1]oct-3-en-2-ones in moderate to good yields as depicted in Table 2.⁶

This one-pot transformation proceeds with complete facial diastereoselectivity. The *exo* and *endo* relationships of the C-7 substituent of 6,8-dioxabicyclo[3.2.1]oct-3-ene-2-one products are controlled by the stereochemistry of the hydroxyl groups: *syn*-alcohols afford the *exo* stereoisomers whereas the *anti*-alcohols afford the *endo* stereoisomers. The H-C₆-C₇-H vicinal coupling constants of the *exo* isomers are typically around 1–1.5 Hz, whereas the analogous coupling constants of *endo* isomers are relatively larger, around 6.0 Hz. It was also demonstrated that this sequence proceeded with no detectable loss of enantiopurity when carried out with chiral, non-racemic molybdenum complexes. Both the *exo* and *endo* demetalation products (**8** and **12**) can be prepared in 98.7% ee (Table 2, entries 1, 5) from (–)-*syn*-**3** and (–)-*anti*-**3**, respectively.

Direct nucleophilic addition to the 5-oxo- η^3 -pyranyl complexes **1** and **2** is likely facilitated by the propensity of the $\text{TpMo}(\text{CO})_2$ moiety to favor 6-coordinate over 7-coordinate structures.⁷ This would generate the anionic $\text{TpMo}(\text{CO})_2$ intermediate **A** shown in brackets in Scheme 2, which possesses three good π -back-bonding ligands to delocalize the charge: 2 terminal CO's and the η^2 -enone ligand. *In situ* quenching of the bracketed anionic intermediate **A** with NOPF_6 or NOBF_4 generates in most cases an unstable complex, $\text{TpMo}(\text{CO})(\text{NO})(\eta^2\text{-enone})$,⁸ that spontaneously demetalates upon workup to afford the observed 6,8-dioxabicyclo[3.2.1]oct-3-en-2-ones.

Infrared analysis of the anionic intermediate **A** derived from compound *anti*-**7** (Scheme 2) displays two metal carbonyl stretches at 1890 cm^{-1} and 1723 cm^{-1} ; these are shifted to lower energy from those of the starting material (*anti*-**7**: 1927 and 1831 cm^{-1}). The C-5 ketonic

carbonyl stretch of the anionic intermediate also shifted from 1613 cm⁻¹ for *anti*-**7** to 1605 cm⁻¹. These data support the presence of a reaction intermediate bearing an anionic TpMo (CO)₂ moiety.

The synthetic potential of this new nucleophilic ketalization methodology was demonstrated by an enantiocontrolled synthesis of (+)-(1*R*,2*S*,5*S*,7*R*)-2-hydroxy-*exo*-brevicomine (Scheme 3).⁹ Aldol reaction of 98% ee (-)-**2** (synthesis described in the Supporting Information) with acrolein¹⁰ furnished *syn* and *anti*-**16** in 82% yield (*syn* : *anti* = 3:1, HPLC). Since *syn* and *anti*-**16** are inseparable by column chromatography on silica gel, the mixture of *syn* and *anti*-**16** was converted to the chromatographically separable *syn* and *anti*-**7** in 91% yield and 98% ee by Pd catalyzed hydrogenation. *Anti*-**7** be recycled to *syn*-**7** by a Mitsunobu reaction as described in the Supporting Information. Upon treatment with NaH in DME followed by a decomplexative quench with NOPF₆, (-)-*syn*-**7** was transformed to bicyclic acetal (-)-*exo*-**11** in 73% yield (98% ee). Hydrogenation then afforded ketone (+)-**17** in 80% yield. Finally, reduction of the carbonyl with NaBH₄ completed the synthesis of (+)-(1*R*,2*S*,5*S*,7*R*)-2-hydroxy-*exo*-brevicomine **18** in 82% yield: [α]_D²⁰ +40.3 (*c* 1.10, CHCl₃), Lit.^{9d} [α]_D²⁴ +33.3 (*c* 1.10, CHCl₃). The spectroscopic properties of compound (+)-**18** are in full accordance with those of the natural product.^{9d,11}

In conclusion, this study discloses the use of a new organometallic enantiomeric scaffold-based aldol reaction-nucleophilic ketalization-demetalation sequence to rapidly generate the 6,8-dioxabicyclo[3.2.1]oct-3-en-2-one framework in moderate to good yields with high enantiopurity. The method was showcased with an effective enantioselective total synthesis of (+)-(1*R*,2*S*,5*S*,7*R*)-2-hydroxy-*exo*-brevicomine.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgment

The National Institute of General Medical Sciences, DHHS, supported this work through Grant GM043107. The contributions of Drs. Ethel Garnier-Amblard (Emory) and Yongqiang Zhang (Displaytech) are gratefully acknowledged.

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5. Complex **1** underwent reaction through its corresponding silyl enol ether using Mukaiyama-aldol conditions, whereas complex **2** necessitated the use of traditional lithium enolate aldol conditions because of the unexpected formation of an isomeric η^3 -siloxyallylmolybdenum complex under Mukaiyama-aldol conditions. Details are provided in the Supporting Information.
6. **Representative Procedure.** To a Schlenk flask charged with (–)-**syn-3** (125 mg, 0.25 mmol, 1 equiv) dissolved in dry dimethoxyethane (8 mL) was added NaH (60% dispersed in mineral oil, 20 mg, 0.5 mmol, 2 equiv) under argon. After being stirred for 2 h at room temperature, the reaction mixture was cooled to –20 °C and NOBF₄ (121 mg, 0.98 mmol, 4 equiv) or (4.0 equiv) was added as a solid. The orange solution immediately turned brown and vigorous bubbling was noted. After 5 min at –20 °C, the reaction was opened to air and the cold bath was removed. The reaction was allowed to slowly warm to room temperature and then stirred for an additional 30 min. The reaction mixture was partitioned between CH₂Cl₂ and H₂O. The aqueous layer was separated and back extracted with CH₂Cl₂. The combined organic layers were washed with brine, dried over MgSO₄, filtered, concentrated, and purified by column chromatography on silica gel (hexanes-EtOAc 3:1) to afford (–)-(1*S*,2*S*,5*S*,7*R*)-7-methyl-6,8-dioxabicyclo[3.2.1]oct-3-en-2-one, (–)-**8** (28 mg, 98.7% ee, 81%) as a colorless oil: TLC (*R*_f = 0.59, hexanes-EtOAc 2:1). IR (cm^{–1}): 2926 (w), 1695 (s), 1046 (w), 934 (m). ¹H NMR (400 MHz, CDCl₃): δ 7.10 (dd, *J* = 9.6, 3.2 Hz, 1H), 6.05 (dt, *J* = 9.6, 1.2 Hz, 1H), 5.82 (d, *J* = 2.8 Hz, 1H), 4.32 (t, *J* = 1.4 Hz, 1H), 4.03 (qd, *J* = 6.4, 1.2 Hz, 1H), 1.39 (d, *J* = 6.0 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 194.7, 147.6, 126.6, 96.6, 85.0, 70.8, 19.9. HRMS (ESI) Calcd for C₇H₉O₃ ([M+H]⁺): 141.0546. Found: 141.0544. (–)-**8**: [α]_D²⁰ –230.1 (*c* = 1.35, CH₂Cl₂). HPLC: CHIRALPAK AS-RH column, CH₃CN : H₂O with 0.1% TFA = 10 : 90, 0.5 mL/min, λ = 254 nm, *t*_R = 22.33 min, 98.7% ee. Enantiomer: *t*_S = 18.19 min.
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10. Acrolein was chosen due to its relatively good *syn*-selectivity (*syn:anti* = 3:1) compared to propionaldehyde (*syn:anti* = 1:4) in the traditional aldol reaction.
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Scheme 1. Aldol-Nucleophilic Ketalization-emetalation Cascade of $\text{TpMo(CO)}_2(\eta^3\text{-pyranyl})$ Complexes

Scheme 2.
In Situ Infrared Analysis of the Anionic η^2 -Enone Complex

Scheme 3.

Enantiocontrolled Total Synthesis of (+)-(1R,2S,5S,7R)-2-Hydroxy-exo-brevicomin 18.

Table 1

Aldol Reactions of $\text{TpMo}(\text{CO})_2(\eta^3\text{-pyranyl})$ Complexes

<div> <div> $\text{TpMo}(\text{CO})_2$ </div> <div> <p>1. TBSOTf, Et_3N CH_2Cl_2, 23 °C 2. $\text{R}^1\text{CHO}/\text{TiCl}_4$, -78 °C</p> <p>or</p> <p>1. LiHMDS, CH_2Cl_2, -78 °C 2. R^1CHO, -78 °C</p> </div> </div>				
entry	R	R ¹	anti:syn	% yield
1	H	Me	2:1	85, ^[a] (-)- 3
2	H	Et	1:1	76, ^[a] 4
3	H	<i>E</i> -prop-1-enyl	2:1	41, ^[a] 5
4	H	Ph	9:1	90, ^[a] 6
5	Me	Et	4:1	80, ^[b] 7

^[a]Through a Mukaiyama-aldol reaction.

^[b]Through a traditional aldol reaction.

Table 2
One-Pot Synthesis of 6,8-Dioxabicyclo[3.2.1]oct-3-en-2-ones^[a]

entry	reactant	R	R ¹	% yield	% ee
1	(-)- <i>syn</i> -3	H	Me	80, 8	98, 7 ^[b]
2	(±)- <i>syn</i> -5	H	<i>E</i> -prop-1-enyl	56, 9	-
3	(±)- <i>syn</i> -6	H	phenyl	56, 10	-
4	(±)- <i>syn</i> -7	Me	Et	73, 11	-
5	(-)- <i>anti</i> -3	H	Me	70, 12	98, 7 ^[b]
6	(±)- <i>anti</i> -5	H	<i>E</i> -prop-1-enyl	44, 13	-
7	(±)- <i>anti</i> -6	H	phenyl	61, 14	-

1. NaH/DME, 23 °C
2. NOPF₆ or NOBF₄
DME, -20 °C

exo *endo*

entry	reactant	R	R ¹	% yield	% ee
8	(±)- <i>anti</i> -7	Me	Et	66, 15	-

[a] NOPF₆ and NOBF₄ were equally effective.

[b] Starting from 98.7% ee (–)-*syn*-3 and (–)-*anti*-3.

[c] Epimerization was observed at C7 (*exo:endo* 3:10) which is likely the result of a retro-aldol reaction of *anti*-6.