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Organometallic Enantiomeric Scaffolding. A Molybdenum-Mediated Intramolecular Nucleophilic Ketalization−Demetalation Cascade. Total Synthesis of (+)-(1*R*,2*S*,5*S*,7*R*)-2-Hydroxy-*exo*-brevicomin

Bo Cheng and Lanny S. Liebeskind*

Emory University, Department of Chemistry, 1515 Dickey Drive, Atlanta, Georgia 30322

chemLL1@emory.edu

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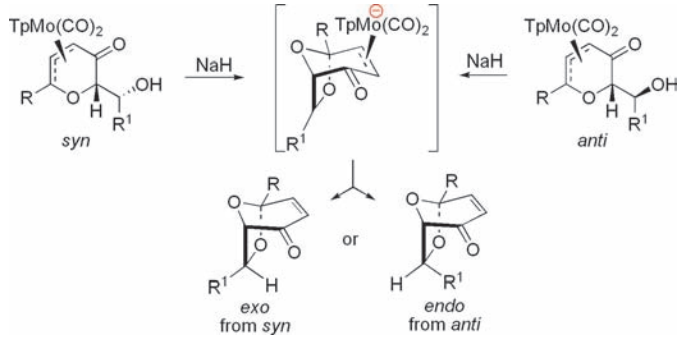
ABSTRACT



TpMo(CO)$_2$(5-oxo-η^3-pyranyl) scaffolds bearing an internal alkoxide undergo a novel intramolecular nucleophilic ketalization reaction. The anionic intermediate is easily demetalated, 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*-brevicomin was accomplished utilizing the reaction sequence.

Highly enantiopure air- and moisture-stable TpMo(CO)$_2$(η^3-pyranyl) and TpMo(CO)$_2$(η^3-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] 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 TpMo(CO)$_2$(η^3-pyranyl) and TpMo(CO)$_2$(η^3-pyridinyl) complexes was recently disclosed:[1j,o] 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 TpMo(CO)$_2$(5-oxo-η^3-pyranyl) complexes at the

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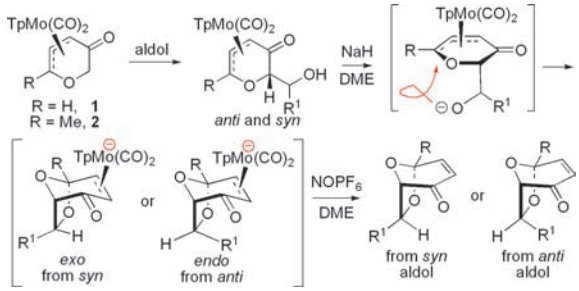
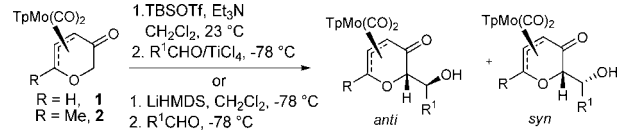
terminus of the η^3-allyl moiety by an internal alkoxide. This strategically new C−O bond formation establishes a bicyclic ketal stereospecifically and, after *in situ* oxidative decomplexation of the anionic bicyclic intermediate produced upon alkoxide addition, allows the rapid, one-pot enantiocontrolled construction of the 6,8-dioxabicyclo[3.2.1]octane framework[3] with complete regio- and stereocontrol (Scheme 1).

Scheme 1. Aldol-Nucleophilic Ketalization-Demetalation Cascade of $TpMo(CO)_2(\eta^3$-pyranyl) Complexes



Synthetic studies of this new regio- and stereocontrolled intramolecular nucleophilic ketalization reaction started with the transformation of (±)-5-oxopyranyl complex **1** and (±)-2-methyl-5-oxopyranyl **2** to the corresponding *anti*- and *syn*-alcohols **3**−**7** by a Mukaiyama-aldol reaction[4] 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, nonracemic (−)-**1** (98.7% ee)[1m] (Table 1, entry 1), high enantiopurity (98.7% ee) aldol adducts *syn*- and *anti*-(−)-**3** were prepared.

Table 1. Aldol Reactions of $TpMo(CO)_2(\eta^3$-pyranyl) Complexes

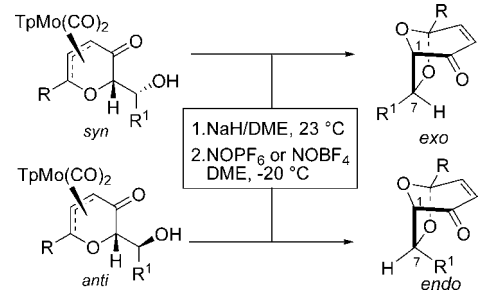


entry	R	R^1	*anti*:*syn*	% yield	% ee
1	H	Me	2:1	85,[a] (−)-**3**	98.7
2	H	Et	1:1	76,[a] **4**	
3	H	*E*-prop-1-enyl	2:1	41,[a] **5**	
4	H	Ph	9:1	90,[a] **6**	
5	Me	Et	4:1	80,[b] **7**	

[a] Through a Mukaiyama-aldol reaction. [b] Through a traditional aldol reaction.

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]

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	(−)-*syn*-**3**	H	Me	80, **8**	98.7[b]
2	(±)-*syn*-**5**	H	(*E*)-prop-1-enyl	56, **9**	
3	(±)-*syn*-**6**	H	phenyl	56, **10**	
4	(±)-*syn*-**7**	Me	Et	73, **11**	
5	(−)-*anti*-**3**	H	Me	70, **12**	98.7[b]
6	(±)-*anti*-**5**	H	(*E*)-prop-1-enyl	44, **13**	
7	(±)-*anti*-**6**	H	phenyl	61,[c] **14**	
8	(±)-*anti*-**7**	Me	Et	66, **15**	

[a] $NOPF_6$ and $NOBF_4$ 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**.

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

(1) (a) Yin, J.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1999**, *121*, 5811–5812. (b) Malinakova, H. C.; Liebeskind, L. S. *Org. Lett.* **2000**, *2*, 3909–3911. (c) Malinakova, H. C.; Liebeskind, L. S. *Org. Lett.* **2000**, *2*, 4083–4086. (d) Moretto, A. F.; Liebeskind, L. S. *J. Org. Chem.* **2000**, *65*, 7445–7455. (e) Yin, J.; Llorente, I.; Villanueva, L. A.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2000**, *122*, 10458–10459. (f) Arrayás, R. G.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2001**, *123*, 6185–6186. (g) Shu, C.; Alcudia, A.; Yin, J.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2001**, *123*, 12477–12487. (h) Arrayás, R. G.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2003**, *125*, 9026–9027. (i) Shu, C.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2003**, *125*, 2878–2879. (j) Zhang, Y.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2005**, *127*, 11258–11259. (k) Zhang, Y.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2006**, *128*, 465–472. (l) Arrayás, R. G.; Yin, J.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2007**, *129*, 1816–1825. (m) Coombs, T. C.; Lee IV, M. D.; Wong, H.; Armstrong, M.; Cheng, B.; Chen, W.; Moretto, A. F.; Liebeskind, L. S. *J. Org. Chem.* **2008**, *73*, 882–888. (n) Garnier, E. C.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2008**, *130*, 7449–7458. (o) Coombs, T. C.; Zhang, Y.; Garnier-Amblard, E. C.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2009**, *131*, 876–877.

(2) Ephritikhine, M.; Francis, B. R.; Green, M. L. H.; MacKenzie, R. E.; Smith, M. J. *J. Chem. Soc., Dalton Trans.* **1977**, 1131–1135.

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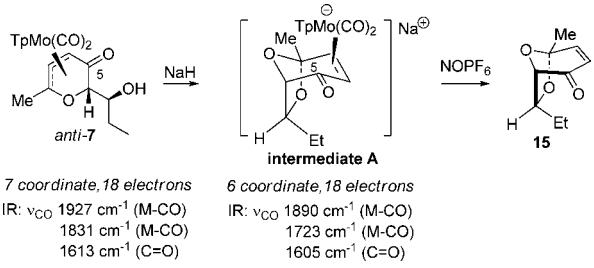
(4) Mahrwald, R. *Chem. Rev.* **1999**, *99*, 1095–1120.

(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 Supporting Information.

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−C_1-C_7−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, nonracemic 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** (and complexes **3**−**7**) is likely facilitated by the propensity of the $TpMo(CO)_2$ moiety to favor 6-coordinate over 7-coordinate structures.[7] This would generate the anionic $TpMo(CO)_2$ 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, $TpMo(CO)(NO)(\eta^2$-enone),[8] that spontaneously demetalates upon workup to afford the observed 6,8-dioxabicyclo[3.2.1]oct-3-en-2-ones.

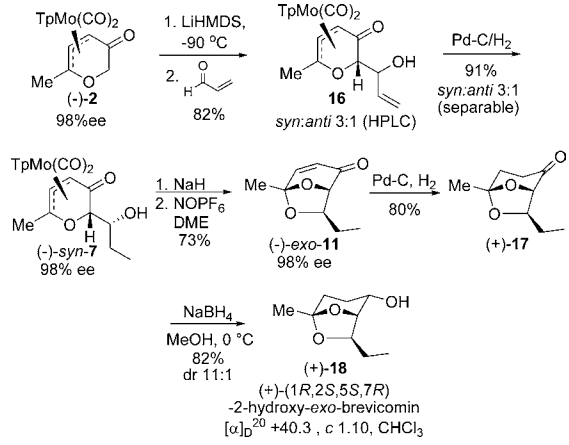
Scheme 2. In Situ Infrared Analysis of the Anionic η^2-Enone Complex



Infrared analysis of the anionic intermediate **A** derived from compound *anti*-**7** (Scheme 2) displays two metal carbonyl stretches at 1890 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*-brevicomin (Scheme 3).[9] Aldol reaction of 98% ee (−)-**2** (synthesis described in Supporting Information) with acrolein[10] 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** can be recycled to *syn*-**7** by a Mitsunobu reaction as described in Supporting Information. Upon treatment with NaH in DME followed by a decomplexative quench with $NOPF_6$, (−)-*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 $NaBH_4$ completed the synthesis of (+)-(1*R*,2*S*,5*S*,7*R*)-2-hydroxy-*exo*-brevicomin **18** in 82% yield:

Scheme 3. Enantiocontrolled Total Synthesis of (+)-(1*R*,2*S*,5*S*,7*R*)-2-Hydroxy-*exo*-brevicomin **18**



(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 $NOBF_4$ (121 mg, 0.98 mmol, 4.0 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 CH_2Cl_2 and H_2O. The aqueous layer was separated and back-extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, concentrated, and purified by column chromatography on silica gel (hexanes/EtOAc 3:1) to afford (−)-(1*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). ^{1}H NMR (400 MHz, $CDCl_3$): 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). ^{13}C NMR (100 MHz, $CDCl_3$): δ 194.7, 147.6, 126.6, 96.6, 85.0, 70.8, 19.9. HRMS (ESI) calcd for $C_7H_9O_3$ ($[M + H]^+$) 141.0546, found 141.0544. $[\alpha]^{20}_D$ −230.1 (*c* 1.35, CH_2Cl_2). HPLC: CHIRALPAK AS-RH column, CH_3CN: H_2O with 0.1% TFA = 10:90, 0.5 mL/min, λ = 254 nm, t_- = 22.33 min, 98.7% ee. Enantiomer: t_+ = 18.19 min.

(7) Curtis, M. D.; Shiu, K. B.; Butler, W. M. *Organometallics* **1983**, *2*, 1475–1477.

(8) The TpMo(CO)(NO)(enone) complex precursor to *exo*-6,8-dioxabicyclo[3.2.1]oct-3-en-2-one **8** was isolated and fully characterized. It is labelled compound **19** within Supporting Information .

(9) (a) Francke, W.; Schröder, F.; Philipp, P.; Meyer, H.; Sinnwell, V.; Gries, G. *Bioorg. Med. Chem.* **1996**, *4*, 363–374. (b) Francke, W.; Schröder, F. *Curr. Org. Chem.* **1999**, *3*, 407–443. (c) Francke, W.; Kitching, W. *Curr. Org. Chem.* **2001**, *5*, 233–251. (d) Takikawa, H.; Shimbo, K.-I.; Mori, K. *Liebigs Annalen/Recueil* **1997**, 821–824. (e) Kumar, D. N.; Rao, B. V.; Ramanjaneyulu, G. S. *Tetrahedron: Asymmetry* **2005**, *16*, 1611–1614. (f) Gautam, D.; Kumar, D. N.; Rao, B. V. *Tetrahedron: Asymmetry* **2006**, *17*, 819–821. (g) Prasad, K. R.; Anbarasan, P. *Tetrahedron: Asymmetry* **2006**, *17*, 850–853.

(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.

$[\alpha]^{20}_D$ +40.3 (*c* 1.10, $CHCl_3$), lit.[9d] $[\alpha]^{24}_D$ +33.3 (*c* 1.94, $CHCl_3$). 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*-brevicomin.

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Supporting Information Available: Experimental procedures, synthesis and characterization of all new compounds, and scanned spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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