Halocarbocyclization Entry into the Oxabicyclo[4.3.1]decyl Exomethylene-δ-Lactone Cores of Linearifolin and Zaluzanin A - Exploiting Combinatorial Catalysis

Sandeep K. Ginotra
University of Nebraska - Lincoln

Jacob A. Friest
University of Nebraska - Lincoln

David B. Berkowitz
University of Nebraska - Lincoln, dberkowitz1@unl.edu

Follow this and additional works at: http://digitalcommons.unl.edu/chemistryberkowitz
Part of the Chemistry Commons

http://digitalcommons.unl.edu/chemistryberkowitz/8

This Article is brought to you for free and open access by the Published Research - Department of Chemistry at DigitalCommons@University of Nebraska - Lincoln. It has been accepted for inclusion in David Berkowitz Publications by an authorized administrator of DigitalCommons@University of Nebraska - Lincoln.
Halocarbocyclization Entry into the Oxabicyclo[4.3.1]decy1 Exomethylene-δ-Lactone Cores of Linearifolin and Zaluzanin A - Exploiting Combinatorial Catalysis

Sandeep K. Ginotra, Jacob A. Friest, and David B. Berkowitz*
Department of Chemistry, University of Nebraska, Lincoln, NE 68588-0304

Abstract

A streamlined entry into the sesquiterpene lactones (SQL) cores of linearifolin and zaluzanin A is described. Stereochemistry is controlled through transformations uncovered by ISES (In-Situ-Enzymatic-Screening). Absolute stereochemistry derives from kinetic resolution of 5-benzyloxypentene-1,2-oxide, utilizing a β-pinene-derived-Co(III)-salen. Relative stereochemistry (1,3-cis-fusion) is set via formal halometalation/carbocyclization, mediated by [Rh(O2CC3F7)2]2/LiBr. Subsequent ring-closing metathesis (RCM-Grubbs II) yields the title exomethylene-δ-lactone SQL-cores. In complementary fashion, RCM with Grubbs-I catalyst provides the oxabicyclo[3.3.1]nonyl-core of xerophilusin R and zinagrandinolide.

ISES (In Situ Enzymatic Screening)-assisted catalyst development has led to the (i) discovery of the first asymmetric Ni(0)-mediated allylic amination chemistry,1 (ii) new halometalation/carbocyclization transformations2 and (iii) the identification of novel chiral salen ligands for asymmetric catalysis.3 This Letter describes the deployment of the latter two methods for stereocontrolled entry into bicyclic terpenoid natural product (NP) cores bearing a reactive exomethylene δ-lactone functionality.

This functional group has been linked to NFKB-inhibition via active site cysteine capture, leading Merfort to propose a QSAR model for NFKB inhibition/anti-cancer activity in such sesquiterpene lactones (SQLs).4 Against this medicinal chemistry backdrop there has been vigorous synthetic activity in the exomethylene SQL area,5 including approaches that permit core synthesis6 and chain extension.7 While a number of routes focus on end game methyleneation,8 we favored a convergent strategy in which a formal halometalation/carbocyclization would at once close the lactone, control ring fusion geometry, and set in place the reactive, conjugated exomethylene moiety.2 This approach has an added benefit for chemical biology: as the resultant β-bromo-α,β-unsaturated carbonyl system should be advantageous for library generation.9

dbb@unlserve.unl.edu.

Supporting Information Available Experimental details, characterization, NMR spectra and HPLC traces.

Targeted herein are the cores of SQLs carrying this functionality within a bridged oxabicyclo[4.3.1]decyl framework, as in linearifolin angelate\textsuperscript{10} (Fig. 1; from \textit{H. linearifolium}, related to fastigilin A, a potent anti-neoplastic agent)\textsuperscript{11} and zaluzanin A (muscle relaxant).\textsuperscript{12}

Interestingly, these two terpenoid lactone cores have opposite handedness, therefore efficient hydrolytic kinetic resolution (HKR)\textsuperscript{3,13} should allow for assembly of both cores from a common racemic epoxide building block precursor (Fig. 2), one from the diol product (as the cyclic sulfate), the other from the remaining epoxide. Such a convergent sequence would both allow for the efficient assembly of the exomethylene δ-lactone and set the cis-1,3-fusion stereochemistry in the key halometalation-carbocyclization step, a transformation for which both Rh-perfluorocarboxylate and Pd(II) catalysts have been uncovered recently in our lab.\textsuperscript{2,14}

Toward this end, an improved ISES screen [Fig. 3-new KRED (ketoreductase) enzymes\textsuperscript{15}] identified salen \textit{4a} catalyst, assembled from the β-pinene-derived diamine and α-hydroxy-β-naphthaldehyde, in its Co(III)-OAc form as a generally (S)-selective catalyst for terminal epoxides. This KRED assay has advantages over the previously reported hexene oxide screen,\textsuperscript{3a} as the two reporting enzymes show opposite enantioselectivities (see Supporting Information) and both are readily available. For the synthesis at hand, efficient HKR of an O-protected 5-hydroxy-1,2-pentene oxide was desired. Accordingly, a series of such potential building blocks were screened for HKR with Co(III)-\textit{4a}-OAc. As can be seen (Table 1), this catalyst is generally (S)-selective for substrates bearing arylmethyl ether protecting groups.

In the event, when racemic \textit{9} was treated with Co(III)-\textit{4a}-OAc, on a 13 g scale, both antipodal building blocks, (R)-epoxide \textit{9b} and (S)-diol \textit{12} were obtained in high ee (Scheme 1) attesting to the potential\textsuperscript{3a} of this new chiral salen in asymmetric catalysis. The diol was easily converted to the corresponding cyclic sulfate \textit{13}.

As is illustrated in Scheme 2, the requisite 3-carbon allylic carbonate “acceptor” functionality for the carbocyclization could be installed via cyclic sulfate opening with a lithiated propargyl ether. Lindlar semi-hydrogenation and unveiling of the masked terminal olefin, was followed by selective carbonylation of the primary alcohol. The propiolate moiety then enters with Mitsunobu inversion at the HKR-derived stereocenter.

The title bromorhodiation/carbocyclization was carried out on \textit{18a,2} crafting both the Z-configured C-Br bond and the ring-forming C-C bond, thereby setting in place the requisite cis-1,3-ring fusion in \textit{19a}. Moreover, a detailed study (50 mg scale) showed that yields could be increased to >90\%, with 5 mol % catalyst, by reducing temperature and increasing reaction time (Supporting Information). Note that this formal halometalation/carbocyclization bears some resemblance, particularly in the product structure, to Rh(I)-mediated carbocyclizations reported by Zhang, that involve formal Alderene alkyne/allyl C-H cycloisomerization\textsuperscript{16} or alkyne/allylic C-Cl condensation, with an accompanying halide shift.\textsuperscript{17} The vinyl halide geometry obtained here is opposite that found in the Zhang chemistry, and both the Rh catalyst (Rh(II)-perfluorocarboxylate/LiBr) and educts (allylic carbones) employed here also differ.

Subsequent RCM (Grubbs II catalyst)\textsuperscript{18} closes the bicyclo[4.3.1]decenyl linearifolin core. The 3D-structure of the core was solved by x-ray crystallography which also served to confirm absolute stereochemistry (Scheme 3). The antipodal series follows from the (R)-epoxide obtained in the initial HKR of 5-benzyloxy-pentene oxide mediated by Co(III)-\textit{4a}-OAc (Scheme 1). The sequence mirrors that described for entry into the linearifolin core with the exception that epoxide \textit{9b}, rather than a cyclic sulfate is opened by the lithiated...
propargyl ether, a reaction found to proceed optimally in the presence of F3B-OEt2 (Scheme 4). Here too, x-ray crystallography established 3D structure and absolute stereochemistry.

In the course of this investigation, it was also discovered that one could gain access to ring contracted cores by RCM modification. Olefin isomerization is known to occasionally accompany metathesis, presumably via the intermediacy of Ru-H species, as studied by Schmidt,19 Grubbs20 and Snapper.21 This serves as an added benefit of this synthetic route, with the Grubbs I catalyst22 giving ring contraction, and thereby access to the oxabicyclo[3.3.1]nonyl core in zinagrandinolide23 and xerophilusin R24 (Scheme 5), both antineoplastic natural products.23–24 Future studies will be directed at the further exploration of this promising β-pinene-based salen scaffold in asymmetric catalysis, and this versatile halocarbocyclization transformation, and at the deployment of these NP cores in chemical biology.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The NSF (CHE-0911732) is acknowledged for support. Xiang Fei and Robert A. Swyka are thanked for assistance. Douglas Powell (U. of Oklahoma) is acknowledged for X-ray structures. Thanks to the NIH (SIG-1-510-RR-06307)/NSF (CHE-0091975; MRI-0079750) (NMR,) & NIH (RR016544) (facilities).

References


Org Lett. Author manuscript; available in PMC 2013 February 17.
Figure 1.
Targeted Oxabicyclo[4.3.1]decal SQL Cores
Figure 2.
Retrosynthetic Analysis
Figures 3.
ISES Readout on Salen-Set/New Reporting Enzymes
ISES screens for sense (+ $S$; $-R$) and magnitude of enantiopreference for Co(III)-salen-mediated HKR with hexene oxide (purple) and propylene oxide (green) and $3\alpha$ 1,2-Diamines: 4 ($\beta$-pinene-derived); 5 (L-$\beta$-naphthyl-Ala-derived); 6 (L-Phe-derived); 7 (L-phenyl-Gly-derived). Hydroxybenzaldehydes: a ($\alpha$-hydroxy-$\beta$-naphthaldehyde); b (3,5-diodosalicylaldehyde); c (3-$t$-Bu-salicylaldehyde); d (3,5-di-$t$-Bu-salicylaldehyde). Note:
For entries 4c, 5b,c, 6a–d & 7a–d new reporting enzymes (KRED (Ketoreductase) 107 – $S$-selective; KRED 119 $R$-selective for the HKR of hexene oxide were employed.

Org Lett. Author manuscript; available in PMC 2013 February 17.
Scheme 1.
HKR (salen 4a) Provides both SQL Building Blocks
Scheme 2.
Convergent Assembly of the Halometalation/Carbocyclization Substrate
Scheme 3.
Halometalation/Carbocyclization-RCM Sequence into the Linearifolin Core
Scheme 4.
(R)-Epoxide Leads into the Zaluzanin A Core
Scheme 5.
Isomerization-RCM: Oxabicyclo[3.3.1]nonyl Cores of Zinagrandinolide/Xerophilusin R
### Table 1

**HKR of AcO-Co(III)-4a Across Potential Synthons**

<table>
<thead>
<tr>
<th>epoxide</th>
<th>conv</th>
<th>% ee; E-value (epoxide)</th>
<th>% ee; E-Value (diol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>![Image](83x640 to 154x655)</td>
<td>44%</td>
<td>52% (12)</td>
<td>80% (17)</td>
</tr>
<tr>
<td>![Image](83x593 to 199x626)</td>
<td>47%</td>
<td>92% (182)</td>
<td>97% (183)</td>
</tr>
<tr>
<td>![Image](83x548 to 198x579)</td>
<td>51%</td>
<td>93% (60)</td>
<td>90% (66)</td>
</tr>
<tr>
<td>![Image](24x684 to 197x533)</td>
<td>44%</td>
<td>75% (97)</td>
<td>96%</td>
</tr>
</tbody>
</table>

*Conditions:* 1.3 mmol epoxide; 0.67 mmol H₂O in 100 μL THF, with 2.5 mol % Co(III)-salen derived from 4a. Conversion estimated by NMR and ee by HPLC-chiral stationery phase (Supporting Information).