

8-29-2014

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Citation of this paper:

Phillips, Geoffrey A.; Wright, Timothy B.; Stevens, Andrew C.; and Pagenkopf, Brian, "Synthesis of (+)-Bovidic Acid" (2014).
Chemistry Publications. 33.

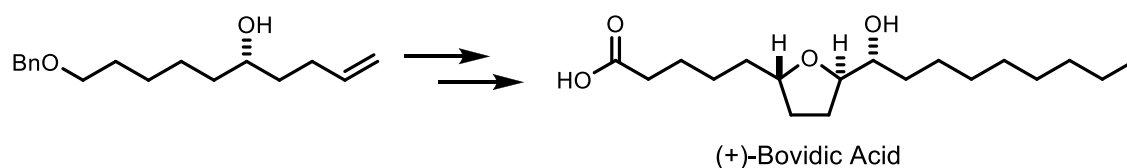
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Synthesis of (+)-Bovidic Acid

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Abstract: (+)-Bovidic acid is an 18-carbon hydroxyfuranoid acid isolated from the pelage of the guar (*B. frontalis*), and displays potential as an insect repellent. Both a formal and total synthesis of (+)-bovidic acid was carried out with the core of the natural product being synthesized through Mukaiyama aerobic oxidative cyclization employing the second generation $\text{Co}(\text{nmp})_2$ catalyst.

Keywords: tetrahydrofurans, natural products, synthesis, catalysis, green chemistry

The tetrahydrofuran (THF) ring is found in numerous natural products including many highly biologically active examples.¹ Stereoselective methods for the synthesis of THFs are critical within the area of natural products chemistry given the prevalence of the THF moiety. The Mukaiyama aerobic oxidative cyclization selectively forms 2,5-*trans*-THFs from simple bishomoallylic alcohols using a cobalt catalyst and atmospheric oxygen as the stoichiometric oxidant.² Recently, our group reported the development of an improved cobalt catalyst for use in

a modified Mukaiyama cyclization procedure.³ Our recently developed Co(nmp)₂ catalyst allows for simplified workup procedures and higher overall activity than previous catalysts, and has recently been employed in our work towards the total synthesis of amphidinolide C⁴ and in Fürstner's total synthesis of amphidinolide F.⁵

(+)-(6*S*,9*R*,10*R*)-Bovodic acid (Figure 1) is a natural product isolated from the pelage (fur) of the *Guar* (*B. Frontalis*).⁶ This hydroxy furanoid fatty acid has been shown to act as a repellent towards mosquitos and may circumvent the volatility and health risks associated with DEET based repellants.⁷

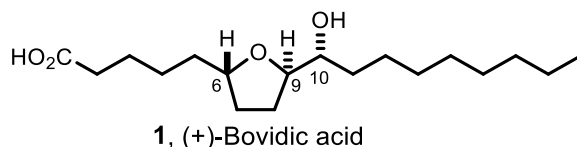


Figure 1. (+)-Bovodic Acid

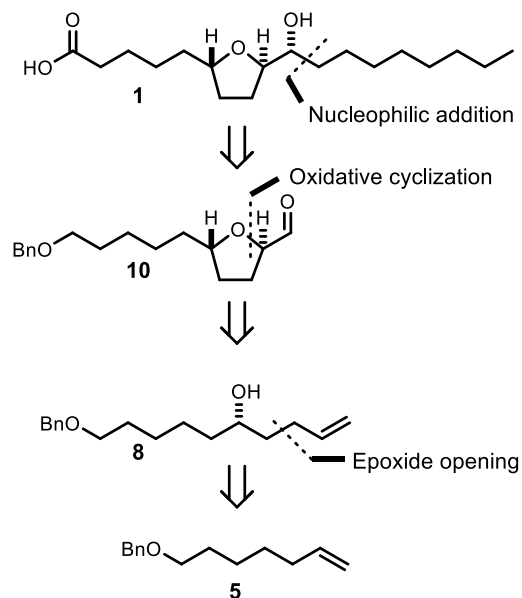
The 2,5-*trans*-THF core of bovidic acid presents a straight forward target for oxidative cyclizations employing Co(nmp)₂. As part of our ongoing interest in the synthesis of THF containing natural products,^{4,8} herein we report the formal and total synthesis of (+)-bovidic acid. One previous total synthesis of the natural product was completed by Yadav et al,⁹ and the enantiomer of bovidic acid, known as guar acid, was completed by Evans.¹⁰

Results and Discussion

It was believed that (+)-bovidic acid could be accessed through a diastereoselective addition of an appropriate organometallic nucleophile to protected tetrahydrofurfural **10** followed by deprotection and oxidation (Scheme 1). The aldehyde **10** would arise from a cobalt catalyzed oxidative cyclization of pentenol **8**, followed by oxidation of the resulting THF methanol. Key

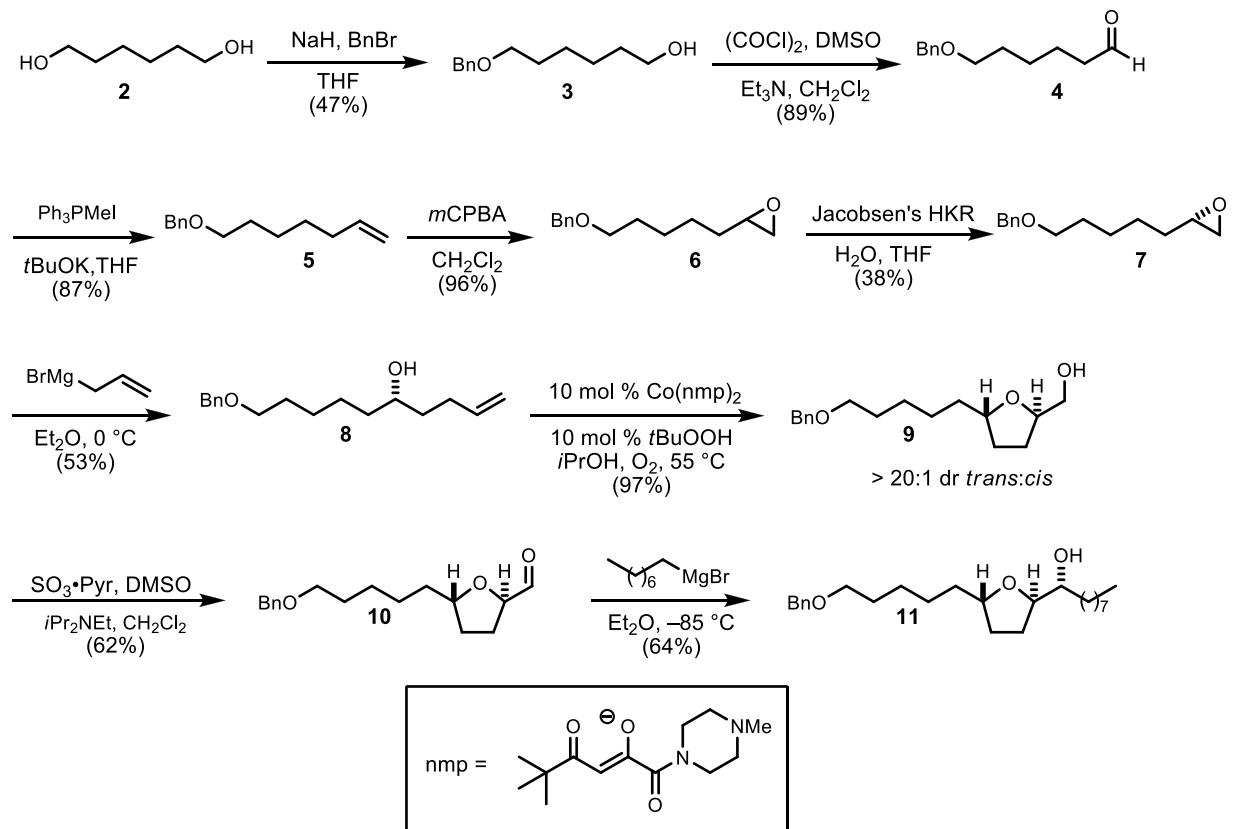
precyclization intermediate **8** would be arrived at through epoxidation and Jacobsen's hydrolytic kinetic resolution of alkene **5**.

Scheme 1. Retrosynthetic analysis of (+)-Bovidic Acid



The synthesis of (+)-bovidic acid began with desymmetrization of 1,6-hexandiol by by mono-benylation to afford **3** (Scheme 2).¹¹ Oxidation of the remaining primary alcohol under Swern conditions provided aldehyde **4** which was then subjected to Wittig homologation yielding olefin **5**.^{12,13} The protected hydroxy olefin was readily epoxidized with *m*CPBA giving racemic epoxide **6**. Resolution of the epoxide through Jacobsen's hydrolytic kinetic resolution (HKR) yielded enantioenriched epoxide **7** in 38% yield and 79% ee.¹⁴ Nucleophilic addition of allyl magnesium bromide to the epoxide furnished key oxidative cyclization substrate **8**.

Scheme 2. Synthesis of THF Aldehyde



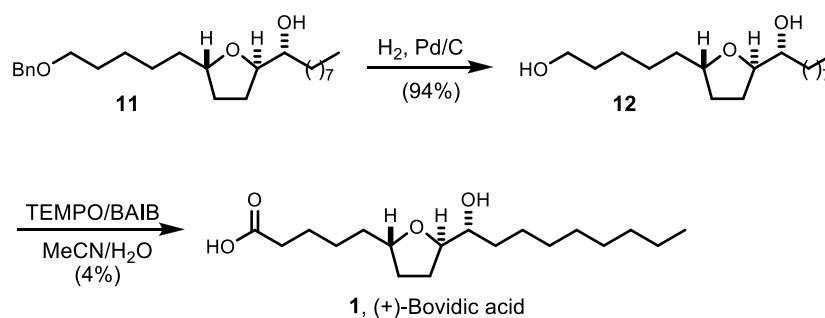
Formation of the THF core of the natural product was accomplished in 97% yield as a single diastereomer with 10 mol % Co(nmp)_2 under an atmosphere of oxygen, conditions that were previously established for the cyclization of pentenols.³ The hydroxymethyl tetrahydrofuran was then oxidized under Parikh-Doering conditions affording the sensitive tetrahydrofurfural **10**.¹⁵

Multiple conditions were probed in an effort to install the C(11)-C(18) side chain of the natural product. Initial attempts at lithium acetylide additions proved ineffective. The failure of this nucleophilic addition demonstrates the high compound-specificity of protocols of this nature, as previously this method has been successful with similar THF aldehydes.^{4c} Fortunately, the addition of octyl magnesium bromide at -85°C provided product **11** in 68% yield and a 3:1 dr

favoring the desired diastereomer.¹⁶ Compound **11** converges with an intermediate in Yadav's synthesis and thus constitutes a formal synthesis of (+)-bovidic acid.⁹

With the addition product in hand, completion of the synthesis required only two additional synthetic steps (Scheme 3). Reductive removal of the benzyl protecting group proceeded well (H_2 , Pd/C, 94%) and all that remained for the completion of the synthesis was the selective oxidation of the primary alcohol of **12** to the corresponding carboxylic acid. The procedure reported by Yadav for this exact transformation employed a TEMPO/BAIB oxidation of the primary alcohol.⁹ However, in our hands the reported conditions yielded only limited quantities of product by performing the reported procedure along with an unidentified but nearly inseparable impurity. Modification of the solvent system reported by Yadav (CH_2Cl_2/H_2O) to MeCN/ H_2O successfully provided access to limited amounts of product but inseparable impurities persisted. Attempts to purify the crude material by repeated flash chromatography gave bovidic acid of modest purity in a low yield of 4%.

Scheme 3. Synthesis of (+)-Bovodic Acid



Conclusions

In summation the total synthesis of (+)-bovidic acid was carried out in 11 steps from inexpensive 1,6-hexane diol. The synthesis of the THF core of the product was realized through a Mukaiyama oxidative cyclization employing our second generation $\text{Co}(\text{nmp})_2$ catalyst.

Acknowledgements

We thank the University of Western Ontario (UWO) for undergraduate research support (GAP and TBW) and the Natural Sciences and Engineering Research Council of Canada for financial assistance. We also thank Mr. Doug Hairsine (UWO) for obtaining high-resolution mass spectra and Dr. Mathew Willans (UWO) for NMR assistance.

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