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Geoffrey A. Phillips

Cory Palmer

Andrew C. Stevens

Mattew L. Piotrowski

Daryyl SR Dekruyf

See next page for additional authors

Authors
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Oxidative Cyclization of Tertiary Pentenol Derivatives Forming 2,5,5-trisubstituted THF Rings and the Total Synthesis of Cyclocapitelline

Geoffrey A. Phillips, Cory Palmer, Andrew C. Stevens, Mathew L. Piotrowski, Daryl S. R. Dekruyf, and Brian L. Pagenkopf *

[a] *The University of Western Ontario, Department of Chemistry, London, Ontario, N6G 5B7, Canada*

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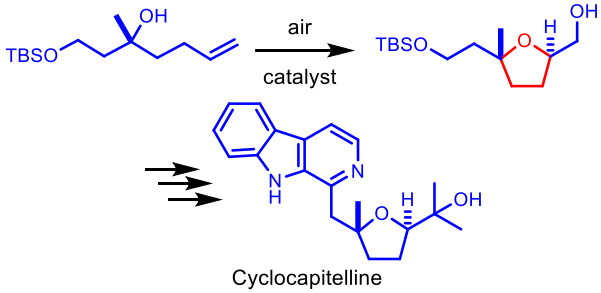
ABSTRACT

The synthesis of 2,5,5-trisubstituted tetrahydrofuran rings was accomplished via the Mukaiyama aerobic oxidative cyclization of tertiary 5-pentenols employing the $Co(nmp)_2$ catalyst. A variety of THFs were formed in moderate to good yield and diastereoselectivity. The method developed herein was successfully applied to an enantioselective total synthesis of cyclocapetalline.



* Corresponding author. Tel.: +1-519-661-2111; fax: +1-519-661-3022; e-mail: bpagenko@uwo.ca

1. Introduction

The tetrahydrofuran (THF) ring system is a common motif found in a wide variety of natural products with potent and varied biological activity.[1] Their prevalence has led to numerous methods for the efficient and selective synthesis of THFs with varying levels of substitution about the ring. Of the possible substitution patterns, 2,5-disubstituted THFs have received the most synthetic attention.[2] The synthesis of the 2,5,5-trisubstituted-THFs has seen considerably less attention, yet this structure is found in a number of notable biologically active compounds including boivinianin B, the ionophore ionomycin, and the kalihinols, a large family of triterpenoids.[3–5]

The Mukaiyama aerobic oxidative cyclization stands apart as an effective synthetic tool for the synthesis of 2,5-*trans*-THFs and has been successfully employed in synthetic studies and total synthesis of natural products including asimilobin[6], bullatacin[7], aplysiallene[8], bovidic acid[9], and amphidinolides C[10] and F[11]. The catalytic Mukaiyama oxidative cyclization facilitates the synthesis of THFs under mild reaction conditions, using oxygen as the stoichiometric oxidant.[12] The method produces the desired THFs with excellent *trans* diastereoselectivity and cyclization substrates can generally be accessed easily through simple additions to aldehydes, ketones, and epoxides. The primary alcohol formed in the cyclization also serves as a useful handle for further synthetic transformations.

Previous work from our laboratory has explored the synthesis of 2,5-*trans*-THF rings through the oxidative cyclization of secondary pentenol derivatives[7–10], with the best results obtained utilizing our $Co(nmp)_2$ catalyst.[13] The expanded substrate scope, improved yields, enhanced reactivity and simplified workup procedure with the nmp catalyst prompted us to explore the feasibility of extending the scope of the oxidative cyclization to the synthesis of 2,5,5-trisubstituted THF rings.

2. Results and Discussion

Our initial investigations began with exploration of the cyclization of tertiary pentenol **1** (Table 1), prepared by addition of homoallylmagnesium bromide to acetophenone. Conditions successfully employed for the cyclization of various secondary pentenols proved ineffective when applied to tertiary pentenols (entry 1).[13] With elevation of the temperature only traces of product were observed (entry 2). Previously we reported that pre-oxidizing the catalyst prior to substrate introduction successfully increased catalyst activity as well as reduced over oxidation by-product.[10b] Mechanistic studies by Hartung have suggested that substrates can interfere with oxidation of the Co(II) precatalyst to the active Co(III) catalyst.[14] Therefore, conditions were established for the cyclization of tertiary pentenols using pre-oxidized catalyst.

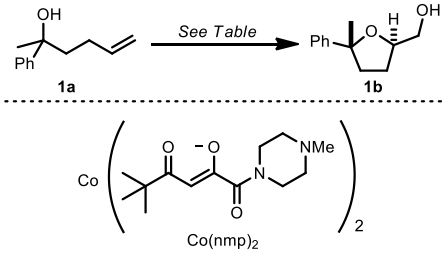


Table 1. Optimization of Cyclization Conditions

Entry	Catalyst loading[a] (mol %)	Time (Temp) h (˚C)	Concentration [M]	SM/pdt, % Mass Recovery
1	10[b]	16 (55)	0.13 *i*-PrOH	Only S.M.
2	10[b]	16 (80)	0.13 *i*-PrOH	2.5/1.0, 72%
3	15	16 (80)	0.13 *i*-PrOH	1.9/1.0, 76%
4	20	16 (80)	0.13 *i*-PrOH	1.3/1.0, 69%
5	10	16 (80)	0.25 *i*-PrOH	1.0/1.0, 77%
6	20	16 (80)	0.25 *i*-PrOH	0.27/1.0, 81%
7	10	16 (80)	2.0 *i*-PrOH	0.27/1.0, 79%
8	20	16 (80)	2.0 *i*-PrOH	0.19/1.0, 80%
9	20	16 (80)	1.0 *i*-PrOH	0.38/1.0, 75%
10	20	16 (80)	0.5 *s*-BuOH	0.12/1.0, quant.
11	20	24 (70)	0.5 *s*-BuOH	0.14/1.0, 88%
12	20	16 (70)	0.5 C_6H_6	0.38/1.0, quant.
13	20	16 (70)	0.5 $C_2H_4Cl_2$	0.71/1.0, quant.
14	30	16 (80)	0.5 *s*-BuOH	0.09/1.0, quant.
15	15	16 (80)	0.5 *s*-BuOH	0.22/1.0, quant.
16	17.5	16 (80)	0.5 *s*-BuOH	0.20/1.0, 84%
17	15[b]	16 (80)	0.5 *i*-PrOH	0.29/1.0, quant.

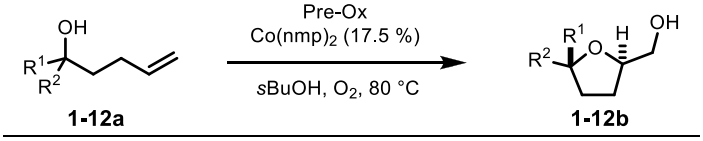
[a] Pre-activated catalyst was employed (see text).

[b] *in-situ* catalyst activation.

Pre-oxidation of the catalyst with tBuOOH under an atmosphere of oxygen followed by solvent removal gave a green solid. The cyclization substrate was then introduced and subjected to the reaction conditions (entries 3-16). An increase in the catalyst loading allowed for the isolation of product **1b** (entries 3-8) in modest yield with a high degree of mass recovery. Lowering the concentration (entries 9-11) improved overall ratios of product to starting material. An increase of the catalyst loading to 30% gave excellent levels of conversion; however, we felt such a loading to be impractical (entry 14). Overall, a catalyst loading of 17.5% was found to provide good levels of conversion to products along with an acceptable level of mass recovery (entry 16). In comparison to the optimized conditions, *in-situ* oxidation of the catalyst (entry 17) was less effective overall with lower levels of conversion.

With optimized conditions at hand the substrate scope of the reaction was explored (Table 2). The synthesis of the cyclization substrates was carried out simply by Grignard additions to ketones, aldehydes, or epoxides. The cyclization proved to be tolerant of a wide range of tertiary pentenols providing products in poor to moderate yields. The effect of sterics appears to be of consequence in the cyclizations as substrates with less steric bulk at the tertiary alcohol generally gave higher yields and better diastereomeric ratios (entries 1-2 and 5-6). Greater steric bulk in the proximity of the alcohol resulted in poorer levels of conversion and lower yields, possibly due to interference in catalyst coordination. THFs with differing electronics were also synthesized with both electron rich and electron deficient pentenols (entries 9-11) cyclizing with similar yields and levels of diastereoselectivity. Elucidating the fate of unaccounted material and the correspondingly poor mass recovery proved elusive, and we have no supposition as to its whereabouts.

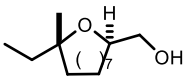
Table 2. Reaction Scope[a]



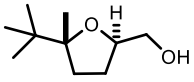
1-12a **1-12b**

1b 63 (72)%, 7:1 *dr*

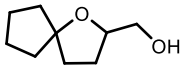
2b 56 (73)%, 5:1 *dr*



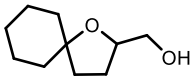
3b 36 (69)%, 3:1 *dr*



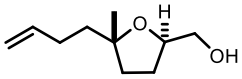
4b 25 (32)%, 2:1 *dr*



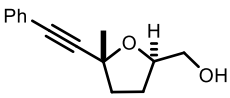
5b 41 (51)%



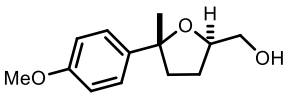
6b 39 (73)%



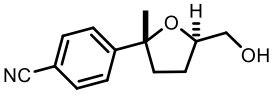
7b 55 (72)%, 2.5:1 *dr*



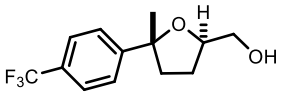
8b 19 (20)%, 5:1 *dr*



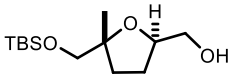
9b 44 (50)%, 2:1 *dr*



10b 35 (38)%, 4:1 *dr*



11b 49 (63)%, 4:1 *dr*



12b 45 (57)%, 2:1 *dr*

[a]Yield in brackets based on recovered starting material

Confirmation of the relative orientation of the substituents at the 2 and 5 positions of the THF products proved difficult, with NOE analysis being inconclusive. We surmised that the major diastereomeric component of the product mixtures corresponded to a *trans* orientation of the substituents at the 2 and 5 positions (*vide infra*).[15]

Having extended the use of the $Co(nmp)_2$ catalyst to the synthesis of 2,5,5-trisubstituted THFs we chose to apply the method to the synthesis of cyclocapitelline (Figure 1.0) which would affirm the predicted stereochemical assignments.[16,17]

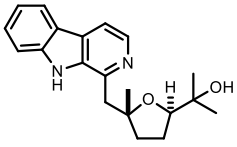
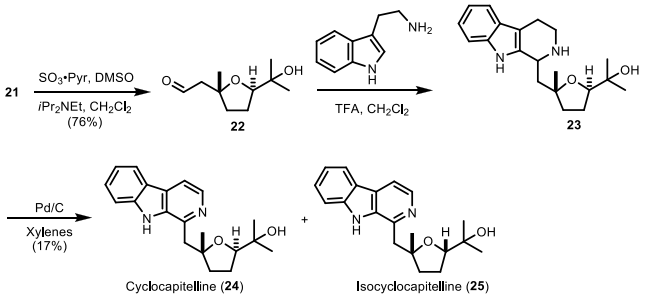


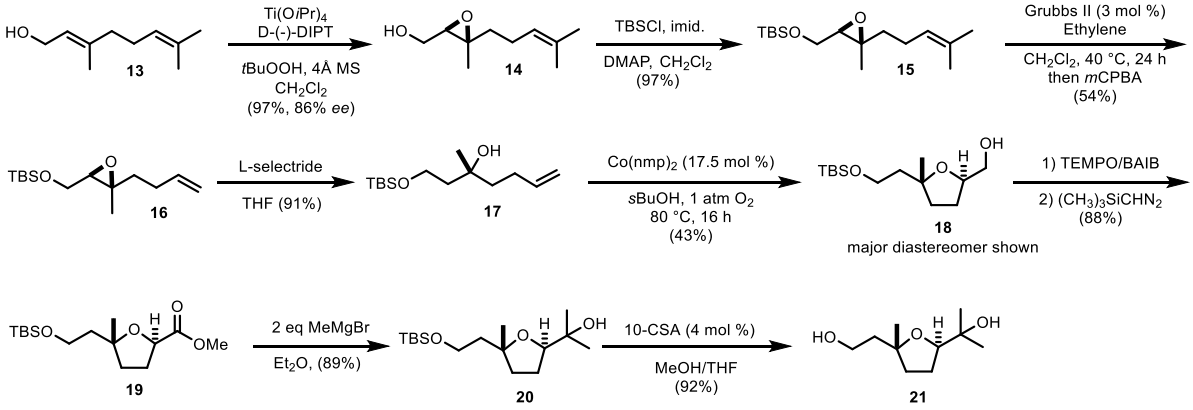
Figure 1. Cyclocapitelline

The synthetic effort began with the Sharpless epoxidation of commercially available geraniol (**13**) providing access to epoxide **14** (Scheme 1).[18] After protection as a TBS ether, cross metathesis reaction of **15** with ethylene gas gave epoxy alkene **16** in 54% yield.[19] An oxidative workup facilitated easy removal of unreacted olefin **15**. Epoxide opening was then accomplished with L-Selectride providing access to oxidative cyclization substrate **17**. Oxidative cyclization was then carried with $Co(nmp)_2$ under the optimized conditions to yield THF product **18** in 43% yield (52% BRSM) as a 3:1 mixture of diastereomers, that were carried through the synthesis. Oxidation of the primary alcohol of **18** with a TEMPO/BAIB oxidation system followed by methylation of the resulting carboxylic acid provided THF ester **19**.[20] The addition of two equivalents of methylmagnesium bromide furnished the tertiary alcohol of the natural product **20**, a mild deprotection of the primary alcohol with 10-CSA then afforded THF alcohol **21**.



Scheme 1. Completion of Cyclocapitelline.

Following comparison of the reported literature spectral data for cyclocapitelline and its diastereomer, isocyclocapitelline, the major diastereomer was found to correspond with cyclocapitelline (**24**) with trans orientation at the 2 and 5 positions of the THF ring,[15] whereas the minor diastereomer corresponded to isocyclocapitelline. Confirmation of the relative stereochemistry of the diastereomeric THFs confirmed our previous hypothesis that the oxidative cyclization of tertiary pentenols proceeds with a preference for relative *trans* stereochemistry of the larger substituents at the 2 and 5 positions.



Scheme 1. Synthesis of the Cyclocapitelline Core.

To complete the synthesis, the primary alcohol **21** was oxidized under Parikh-Doering conditions to afford THF aldehyde **22** (Scheme 2).[21] The Pictet-Spengler reaction between **22** and tryptamine provided access to **23** as a complex mixture of diastereomers. After careful purification, oxidation of the tetrahydro-β-carboline **23** with Pd/C provided cyclocapitelline (**24**) and isocyclocapitelline (**25**) in 17% yield over two steps as a 1.5:1 mixture of diastereomers.

3. Conclusion

2,5,5-Trisubstituted tetrahydrofurans were synthesized using the modified Mukaiyama aerobic oxidative cyclization in combination with our second generation nmp catalyst. The method provides access to the desired trisubstituted THFs in moderate to good yields over a broad range of substrates. The methodology was also applied to the total synthesis of the natural product cyclocapitelline and isocyclocapitelline.

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