## Formation of Highly Substituted Tetrahydropyranones: Application to the Total Synthesis of Cyanolide A

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ABSTRACT



A new tetrahydropyranone synthesis has been developed that leads to cis-2,6-disubstituted 3,3-dimethyltetrahydropyran-4-one rings by condensation of an aldehyde and a hydroxy silyl enol ether. The reaction works with a variety of aldehydes to produce the tetrahydropyranone products in moderate to high yields. This new method was applied to the enantioselective synthesis of cyanolide A and its aglycone.

Highly substituted tetrahydroyrans (THPs) are prevalent in the structure of many natural products, where they act as rigidifying scaffolds.<sup>1</sup> The natural products cyanolide A  $(1)^2$  and psymberin (irciniastatin A, 2)<sup>3</sup> have been the focus of considerable interest from synthetic chemists in part because both have THP rings containing quaternary centers (Figure 1).<sup>4</sup> Cyanolide A has been prepared a number of times,<sup>5</sup> including a particularly elegant synthesis from the Krische group.<sup>6</sup> Our interest in the synthesis of cyanolide A stimulated the development of a robust and convergent method for the synthesis of 3,3-disubstituted THPs. Herein we present this new method and its application to the synthesis of cyanolide A.



Figure 1. Tetrahydropyran rings containing quaternary centers are found in natural products such as cyanolide A and psymberin.

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Tetrahydropyrans are commonly prepared by hetero-Diels–Alder reactions and by Prins cyclizations, among other methods.<sup>7</sup> Synthesis of tetrahydropyran-4-ones followed by reduction also has been used to prepare complex 4-hydroxytetrahydropyran rings. Examples include the synthesis of phorboxazole and other natural products by the Smith lab<sup>8</sup> using the Petasis–Ferrier and related reactions.<sup>9</sup> Michael addition–cyclizations have also been used to prepare these rings.<sup>10</sup> Other synthetic methods that focus on the preparation of tetrahydropyran-4-ones include oxacarbenium ion cyclizations of enol ethers<sup>11,12</sup> or enamines.<sup>13</sup> Our method is designed around a new oxacarbenium ion cyclization.

The tetrahydropyranone synthesis is shown in Scheme 1. Silyl ketene acetal<sup>14</sup> **3** reacted with dimethylketene,<sup>15</sup> prepared by zinc reduction of the 2-bromo-2-methylpropionyl bromide,<sup>16</sup> to produce deconjugated silyl enol ether **4** in moderate yield. The ester was converted to Weinreb amide **5**,<sup>17</sup> and addition of an organometallic reagent produced the expected ketone. Reduction of the ketone led to the desired enol ether alcohol **6**. Cyclization to tetrahydropyranone **7** takes place upon treatment with an aldehyde and a Lewis acid. The many points of variation in this sequence ensure a wide scope for the method.

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**Scheme 1.** Tetrahydroyran-4-one Synthesis from Weinreb Amide **5**, an Organomatallic Reagent and an Aldehyde



Syntheses of a variety of enol ether alcohols 6a-e are presented in Table 1. Grignard and alkyllithium reagents were added to amide 5 to deliver the expected ketones 8 in good yields. Reduction to the alcohol generally yields racemic products, although enantioselective reductions are plausible for several substrates.<sup>18</sup> The  $\beta$ -oxy-alkyllithium reagent in entry 4 was optically pure,<sup>19</sup> and syn-selective reduction of the ketone produced 6d as a single diastereomer in good yield. Tertiary alcohol 6e was available by methylmagnesium bromide addition to ester 4. The intermediates 6a-e are poised to form tetrahydropyran-4-one rings.

Table 1.	Preparation	of the Sily	l Enol Eth	er Alcohols 6a-e
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Me \ N O		( <u>M]-R<sup>1</sup></u> R <sup>1</sup>	B OTBS	
entr	y [M]-R <sup>1</sup>	yield (%) step 1	yield (%) step 2	product
1	<i>॑</i> ∭MgBr	-	47% <sup>a</sup>	OH OTBS
2	PhMgBr	73%	85%	Ph OTBS 6b
3	<i>n-</i> BuLi	82%	92%	n-Bu 6C
4	OLi Li	82%	80%	OH OH OTBS
5 <sup>b</sup>	MeMgBr	66%	-	OH OTBS

<sup>*a*</sup>Crude ketone was directly reduced with DIBAL-H. <sup>*b*</sup>Double addition to ester 4 gave the observed product.

Optimization of the tetrahydropyranone synthesis was conducted using diol **6d**, and the results are displayed in Table 2. Initial studies were carried out with benzaldehyde. Formation of tetrahydropyranone **7** was best achieved with  $BF_3 \cdot OEt_2$  at low temperature (entry 1), although TESOTF was also effective. Saturated aldehydes proved to be more difficult substrates; dihydrocinnamaldehyde failed to form the desired product in significant quantities

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with a variety of Lewis acids, including  $BF_3 \cdot OEt_2$  and TESOTf (entries 4 and 5). After testing a range of Lewis acids, the highly reactive TMSOTf was identified as a reasonable promoter. The yield in this case is moderate, but the reaction does produce the desired tetrahydropyranone as a single diastereomer. The preferred Lewis acids for the cyclization step are  $BF_3 \cdot OEt_2$  for unsaturated aldehydes and TMSOTf for saturated aldehydes.

**Table 2.** Optimization of Tetrahydropyridin-4-one FormationUsing Diol Enol Ether 6d

	OH OH OTBS Et	$\begin{array}{c} O \\ H \\ Lewis acid \\ DCM, -78 \ ^{\circ}C \end{array}$ $\begin{array}{c} O \\ H \\ C \\ DCM, -78 \ ^{\circ}C \end{array}$ $\begin{array}{c} O \\ H \\ O \\ C \\ Ta \\ R = Ph \\ 7b \\ R = CH_2CH_2Ph \end{array}$		
$entry^a$	Lewis acid	R	yield of $7$ (%)	
1	$BF_3 \cdot OEt_2$	Ph	64	
2	TESOTf	Ph	54	
3	$TiCl_4$	Ph	<5	
4	$BF_3 \cdot OEt_2$	$CH_2CH_2Ph$	0	
5	TESOTf	$CH_2CH_2Ph$	10	
6	$TiCl_4$	$CH_2CH_2Ph$	<5	
7	$Sc(OTf)_3$	$CH_2CH_2Ph$	0	
8	$Et_2AlBr$	$CH_2CH_2Ph$	NR	
9	$TiBr_4$	$CH_2CH_2Ph$	decomposition	
10	TMSOTf	$\rm CH_2\rm CH_2\rm Ph$	55	

<sup>*a*</sup> The reactions were conducted with 1.0 equiv of **6d**, 3.0 equiv of aldehyde and Lewis acid, and run at 0.4 M in DCM at -78 °C for 4 h.

The scope of the tetrahydropyran-4-one synthesis was then explored (Table 3). The C2 substituent comes from the aldehyde, and the C6 substituent comes from the organometallic reagent (Table 1). Aside from the examples in Table 2, the reaction works well with a variety of aromatic aldehydes (entries 2-6). In general, electron-rich aromatic substrates (entries 2-3) appear to be more effective than electron-poor substrates (entry 6), probably due to the stability of the intermediate oxacarbenium ions. Unsaturated aldehydes appear to be particularly good substrates and lead to the highest yields (entries 7 and 8). The reaction is compatible with halides. Boc-protected amines, esters, and alcohols. It is worth noting that two quaternary centers were introduced in high yield using this cyclization reaction (entry 8). Tetrahydropyran 7i was produced with high optical purity (entry 7).<sup>20</sup> The aliphatic example leads to a modest yield of product using the preferred TMSOTf catalyst (entry 1). In all of these examples, the cyclizations were highly stereoselective and only the 2.6-cis diastereomer was isolated.

The tetrahydropyranone method was designed to facilitate the synthesis of cyanolide A and its aglycone (Figure 2).

## **Table 3.** Scope of the Tetrahydropyran-4-one Synthesis withDifferent Enol Ethers and Aldehydes<sup>a</sup>



<sup>*a*</sup> The reactions were run with 1.0 equiv **6**, 1.5 equiv of aldehyde and Lewis acid, and run at 1.0 M in DCM at -78 °C for 4 h. <sup>*b*</sup> TMSOTf was used as a Lewis acid instead of BF<sub>3</sub>·OEt<sub>2</sub>.

The key intermediate, THP **20**, would be assembled from the optically pure diol **6d** and the aliphatic aldehyde **21**.<sup>21</sup> There is precedent for the key dimerization and macrocyclization of acid **20** to generate the cyanolide core **19** based on work by Hong and other groups.<sup>5,6</sup> The versatility of the tetrahydropyranone synthesis as demonstrated in Table 3 suggests that this route would be amenable to the preparation of analogues of cyanolide A.

The synthesis of cyanolide A aglycone is presented in Scheme 2. The synthesis of **6d** was outlined in Table 1 and is shown in more detail below. Generation of the dianion from optically pure **22**,<sup>19</sup> followed by addition to Weinreb amide **5**, gave the  $\beta$ -hydroxy ketone **23** in good yield. Reduction under Narasaka's conditions<sup>22</sup> delivered the syn-1,3-diol **6d** as a single diastereomer. The THP ring was formed by reaction of the aldehyde **21** with diol **6d** and TMSOTf at low temperature. The reaction presumably occurs through formation and cyclization of an oxacarbenium ion intermediate and produces **24** as the 2,6-cis

<sup>(20)</sup> The enantiomeric ratio of alcohol **22**, the precursor to **6d** (Scheme 2), was 98.0:2.0, and the enantiomeric ratio of **7i** (entry 7) was 97.9:2.1, demonstrating that essentially no optical purity is lost in the cyclization reaction. Enantiomeric ratios for compounds **22** and **7i** were measured by HPLC on a Chiralpak AD column using 10% *i*-PrOH/*n*-hexane. Details are provided in the Supporting Information.

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**Figure 2.** Retrosynthetic analysis of cyanolide A aglycone (19) with the tetrahydropyran-4-one synthesis and an esterification – macrolactonization.

diastereomer. The TBS group was lost in the transformation. Selective oxidation of the primary alcohol to the acid with TEMPO and PhI(OAc)<sub>2</sub>, followed by direct macrocyclization using Shiina's conditions,<sup>23</sup> gave the  $C_2$  symmetric diolide **25** in a very modest yield. This sequence resisted optimization despite numerous attempts. The problem is attributed to the reactivity of the ketone; the cyclization reaction was messy, but no identifiable side products were isolated from the reaction. Reduction of the ketones with NaBH<sub>4</sub> delivered the desired cyanolide A aglycone in good yield, and in only six steps from alcohol **22**. The configuration of aglycone **19** arose from the enantiopure alcohol **22**.

The modest yield in the prior sequence led to the exploration of an alternative route to cyanolide A, which is presented in Scheme 3. The presence of a ketone imparted unexpected fragility to the cyclization precursor. and thus the revised sequence would remove the ketone and introduce the xylose derivative prior to cyclization. The diol 24 was protected as the bis-PMB ether.<sup>24</sup> Reduction of the ketone, followed by glycosidation with phenyl sulfide  $27^{25}$  using MeOTf activation, generated the desired  $\beta$ -anomer **28** as the major component of a 3.5:1 mixture. The anomers were separated, and the major isomer was taken on in the synthesis. Deprotection of the PMB ethers led to the diol 29, a cyclization precursor analogous to the diol 24 used in Scheme 2. In this case, selective oxidation with TEMPO and cyclization with Shiina's conditions<sup>23</sup> produced cyanolide A directly in 88% yield. The use of protecting groups adds two steps to the synthesis, but the overall process is more effective because it avoids the problematic cyclization of ketone 24.

Scheme 2. Synthesis of Cyanolide A Aglycone



Scheme 3. Synthesis of Cyanolide A



The new method provides ready access to a variety of substituted tetrahydropyran-4-ones in moderate to good yields. Syntheses of cyanolide A and its aglycone were accomplished easily by building upon the tetrahydropyran-4-one **24** prepared using the method. The flexibility of the THP formation makes it suitable for preparing analogues of cyanolide A for biological evaluation and for the synthesis of other natural products.

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**Supporting Information Available.** Experimental procedures, <sup>1</sup>H and <sup>13</sup>C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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