ORGANIC LETTERS

2013
Vol. 15, No. 17
4536–4539

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

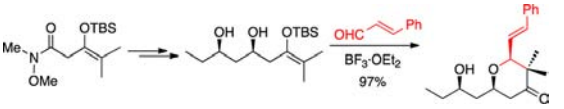
Gidget C. Tay, Michael R. Gesinski, and Scott D. Rychnovsky*

Department of Chemistry, 1102 Natural Sciences II, University of California—Irvine, Irvine, California 92697, United States

srychnov@uci.edu

Received July 24, 2013

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 tetrahydropyrans (THPs) are prevalent in the structure of many natural products, where they act as rigidifying scaffolds.[1] The natural products cyanolide A (**1**)[2] and psymberin (irciniastatin A, **2**)[3] have been the focus of considerable interest from synthetic chemists in part because both have THP rings containing quaternary centers (Figure 1).[4] Cyanolide A has been prepared a number of times,[5] including a particularly elegant synthesis from the Krische group.[6] 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.

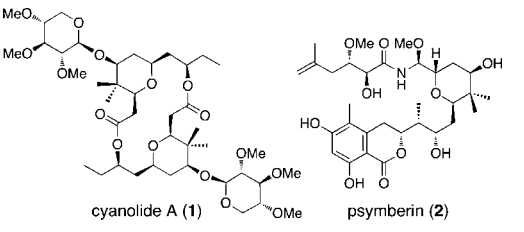


Figure 1. Tetrahydropyran rings containing quaternary centers are found in natural products such as cyanolide A and psymberin.

(1) (a) Wender, P. A.; Loy, B. A.; Schrier, A. J. *Isr. J. Chem.* **2011**, *51*, 453–472. (b) Smith, A. B.; Fox, R. J.; Razler, T. M. *Acc. Chem. Res.* **2008**, *41*, 675–687. (c) Clarke, P. A.; Santos, S. *Eur. J. Org. Chem.* **2006**, 2045–2053.

(2) Pereira, A. R.; McCue, C. F.; Gerwick, W. H. *J. Nat. Prod.* **2010**, *73*, 217–220.

(3) (a) Pettit, G. R.; Xu, J.-P.; Chapuis, J.-C.; Pettit, R. K.; Tackett, L. P.; Doubek, D. L.; Hooper, J. N. A.; Schmidt, J. M. *J. Med. Chem.* **2004**, *47*, 1149–1152. (b) Cichewicz, R. H.; Valeriote, F. A.; Crews, P. *Org. Lett.* **2004**, *6*, 1951–1954.

(4) Formal and total syntheses of psymberin: (a) An, C.; Jurica, J. A.; Walsh, S. P.; Hoye, A. T.; Smith, A. B., III. *J. Org. Chem.* **2013**, *78*, 4278–4296. (b) Feng, Y.; Jiang, X.; Brabander, J. K. D. *J. Am. Chem. Soc.* **2012**, *134*, 17083–17093. (c) An, C.; Hoye, A. T.; Smith, A. B., III. *Org. Lett.* **2012**, *14*, 4350–4353. (d) Byeon, S. R.; Park, H.; Kim, H.; Hong, J. *Org. Lett.* **2011**, *13*, 5816–5819. (e) Wan, S.; Wu, F.; Rech, J. C.; Green, M. E.; Balachandran, R.; Horne, W. S.; Day, B. W.; Floreancig, P. E. *J. Am. Chem. Soc.* **2011**, *133*, 16668–16679. (f) Watanabe, T.; Imaizumi, T.; Chinen, T.; Nagumo, Y.; Shibuya, M.; Usui, T.; Kanoh, N.; Iwabuchi, Y. *Org. Lett.* **2010**, *12*, 1040–1043. (g) Shao, N.; Huang, X.; Palani, A.; Aslanian, R.; Buevich, A.; Piwinski, J.; Huryk, R.; Seidel-Dugan, C. *Synthesis* **2009**, *17*, 2855–2872. (h) Crimmins, M. T.; Stevens, J. M.; Schaaf, G. M. *Org. Lett.* **2009**, *11*, 3990–3993. (i) Smith, A. B., III; Jurica, J. A.; Walsh, S. P. *Org. Lett.* **2008**, *10*, 5625–5628. (j) Huang, X.; Shao, N.; Palani, A.; Aslanian, R.; Buevich, A. *Org. Lett.* **2007**, *9*, 2597–2600. (k) Shangguan, N.; Kiren, S.; Williams, L. J. *Org. Lett.* **2007**, *9*, 1093–1096. (l) Jiang, X.; Garcia-Fortanet, J.; De Brabander, J. K. *J. Am. Chem. Soc.* **2005**, *127*, 11254–11255.

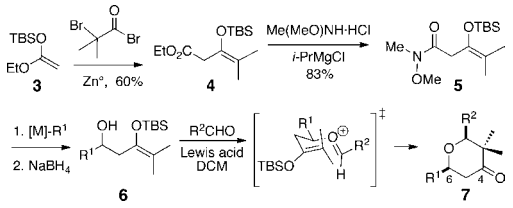
(5) Formal and total syntheses of cyanolide A: (a) Kim, H.; Hong, J. *Org. Lett.* **2010**, *12*, 2880–2883. (b) Hajare, A. K.; Ravikumar, V.; Khaleel, S.; Bhuniya, D.; Reddy, D. S. *J. Org. Chem.* **2011**, *76*, 963–966. (c) Yang, Z.; Xie, X.; Jing, P.; Zhao, G.; Zheng, J.; Zhao, C.; She, X. *Org. Biomol. Chem.* **2011**, *9*, 984–986. (d) Pabbaraja, S.; Satyanarayana, K.; Ganganna, B.; Yadav, J. S. *J. Org. Chem.* **2011**, *76*, 1922–1925. (e) Gesinski, M. R.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2011**, *133*, 9727–9729. (f) Sharpe, R. J.; Jennings, M. P. *J. Org. Chem.* **2011**, *76*, 8027–8032.

10.1021/ol402095g
Published on Web 08/20/2013

Tetrahydropyrans are commonly prepared by hetero-Diels–Alder reactions and by Prins cyclizations, among other methods.[7] 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[8] using the Petasis–Ferrier and related reactions.[9] Michael addition–cyclizations have also been used to prepare these rings.[10] Other synthetic methods that focus on the preparation of tetrahydropyran-4-ones include oxacarbenium ion cyclizations of enol ethers[11,12] or enamines.[13] Our method is designed around a new oxacarbenium ion cyclization.

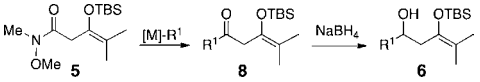
The tetrahydropyranone synthesis is shown in Scheme 1. Silyl ketene acetal[14] **3** reacted with dimethylketene,[15] prepared by zinc reduction of the 2-bromo-2-methylpropionyl bromide,[16] to produce deconjugated silyl enol ether **4** in moderate yield. The ester was converted to Weinreb amide **5**,[17] 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.

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.[18] The β-oxy-alkyllithium reagent in entry 4 was optically pure,[19] 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 Silyl Enol Ether Alcohols **6a–e**



entry	[M]-R^1	yield (%) step 1	yield (%) step 2	product
1	MgBr	–	47%[a]	**6a**
2	PhMgBr	73%	85%	**6b**
3	*n*-BuLi	82%	92%	**6c**
4	OLi, Li	82%	80%	**6d**
5[b]	MeMgBr	66%	–	**6e**

[a] Crude ketone was directly reduced with DIBAL-H. [b] 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

(6) Waldeck, A. R.; Krische, M. J. *Angew. Chem., Int. Ed.* **2013**, *52*, 4470–4473.

(7) Perry, M. A.; Rychnovsky, S. D.; Sizemore, N. Synthesis of Saturated Tetrahydropyrans. In *Synthesis of Saturated Oxygenated Heterocycles*; Cossy, J., Ed.; Topics in Heterocyclic Chemistry Series; Springer-Verlag: Berlin, 2014.

(8) (a) Smith, A. B.; Verhoest, P. R.; Minbiole, K. P.; Lim, J. J. *Org. Lett.* **1999**, *1*, 909–912. (b) Smith, A. B.; Minbiole, K. P.; Verhoest, P. R.; Beauchamp, T. J. *Org. Lett.* **1999**, *1*, 913–916. (c) Smith, A. B., III; Minbiole, K. P.; Verhoest, P. R.; Schelhaas, M. *J. Am. Chem. Soc.* **2001**, *123*, 10942–10953. (d) Smith, A. B., III; Sfouggatakis, C.; Gotchev, D. B.; Shirakami, S.; Bauer, D.; Zhu, W.; Doughty, V. A. *Org. Lett.* **2004**, *6*, 3637–3640. (e) Smith, A. B.; Mesaros, E. F.; Meyer, E. A. *J. Am. Chem. Soc.* **2005**, *127*, 6948–6949. (f) Smith, A. B., III; Simov, V. *Org. Lett.* **2006**, *8*, 3315–3318.

(9) (a) Petasis, N. A.; Lu, S. P. *Tetrahedron Lett.* **1996**, *37*, 141–144. (b) Ferrier, R. J.; Middleton, S. *Chem. Rev.* **1993**, *93*, 2779–2831. (c) Bae, H. J.; Jeong, W.; Lee, J. H.; Rhee, Y. H. *Chem.—Eur. J.* **2011**, *17*, 1433–1436.

(10) (a) Clarke, P. A.; Martin, W. H. C.; Hargreaves, J. M.; Wilson, C.; Blake, A. J. *Chem. Commun.* **2005**, 1061–1063. (b) Reiter, M.; Turner, H.; Gouverneur, V. *Chem.—Eur. J.* **2006**, *12*, 7190–7203. (c) Kim, H.; Park, Y.; Hong, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 7577–7581. (d) Clarke, P. A.; Santos, S.; Mistry, N.; Burroughs, L.; Humphries, A. C. *Org. Lett.* **2011**, *13*, 624–627. (e) Yao, H.; Ren, J.; Tong, R. *Chem. Commun.* **2012**, *49*, 193–195.

(11) (a) Dalgard, J. E.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2004**, *126*, 15662–15663. (b) Dalgard, J. E.; Rychnovsky, S. D. *Org. Lett.* **2005**, *7*, 1589–1591.

(12) (a) Cockerill, G. S.; Kocienski, P. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2093–2100. (b) Morris, W. J.; Custar, D. W.; Scheidt, K. A. *Org. Lett.* **2005**, *7*, 1113–1116. (c) Tu, W.; Floreancig, P. E. *Angew. Chem., Int. Ed.* **2009**, *48*, 4567–4571.

(13) Cossey, K. N.; Funk, R. L. *J. Am. Chem. Soc.* **2004**, *126*, 12216–12217.

(14) Wenzel, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 12964–12965.

(15) Rathke, M. W.; Sullivan, D. F. *Tetrahedron Lett.* **1973**, 1297–1300.

(16) (a) Smith, W. C.; Norton, D. G.; *Organic Syntheses*; Wiley: New York, 1963; Collect. Vol. IV, pp 348–350. (b) Baigrei, L. M.; Lenoir, D.; Seikaly, H. R.; Tidwell, T. T. *J. Org. Chem.* **1985**, *50*, 2105–2109.

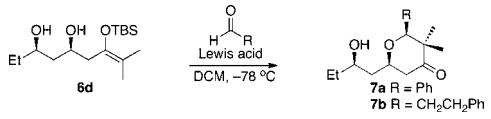
(17) Williams, J. M.; Jobsen, R. B.; Yasuda, N.; Marchesini, G.; Dolling, U.-H.; Grabowski, E. J. J. *Tetrahedron Lett.* **1995**, *36*, 5461–5464.

(18) (a) Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1986–2012. (b) Noyori, R.; Hashiguchi, S. *Acc. Chem. Res.* **1997**, *30*, 97–102.

(19) Malathong, V.; Rychnovsky, S. D. *Org. Lett.* **2009**, *11*, 4220–4223.

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 Formation Using Diol Enol Ether **6d**



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	CH_2CH_2Ph	55

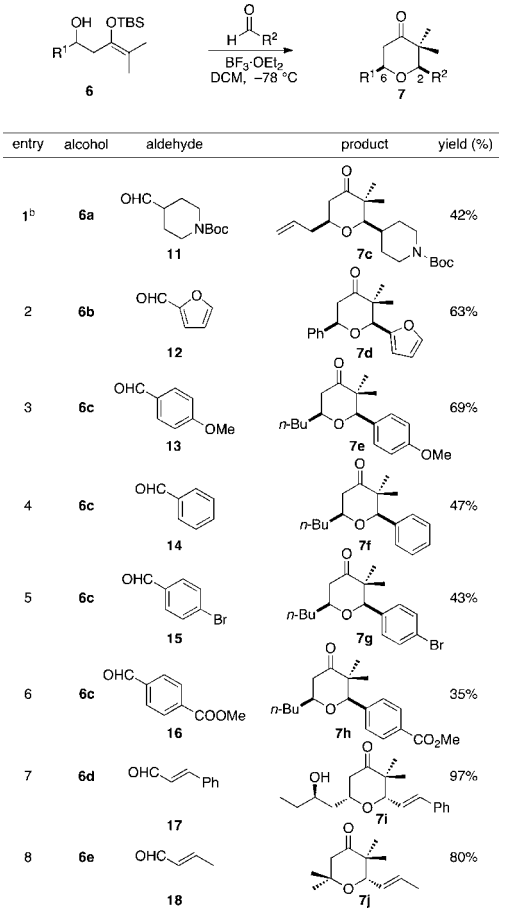
[a] The reactions were conducted with 1.0 equiv of **6d**, 3.0 equiv of aldehyde and Lewis acid, and run at 0.4 M in DCM at −78 °C for 4 h.

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).[20] 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).

(20) 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.

Table 3. Scope of the Tetrahydropyran-4-one Synthesis with Different Enol Ethers and Aldehydes[a]



[a] 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. [b] TMSOTf was used as a Lewis acid instead of $BF_3 \cdot OEt_2$.

The key intermediate, THP **20**, would be assembled from the optically pure diol **6d** and the aliphatic aldehyde **21**.[21] 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.[5,6] 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**,[19] followed by addition to Weinreb amide **5**, gave the β-hydroxy ketone **23** in good yield. Reduction under Narasaka's conditions[22] 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

(21) Wang, J.; Chen, J.; Kee, C. W.; Tan, C.-H. *Angew. Chem., Int. Ed.* **2012**, *51*, 2382–2386.

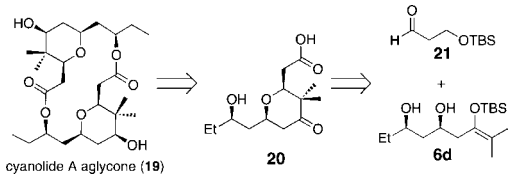


Figure 2. Retrosynthetic analysis of cyanolide A aglycone (**19**) with the tetrahydropyran-4-one synthesis and an esterification–macrolactonization.

diastereomer. The TBS group was lost in the transformation. Selective oxidation of the primary alcohol to the acid with TEMPO and $PhI(OAc)_2$, followed by direct macrocyclization using Shiina's conditions,[23] 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 $NaBH_4$ 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.[24] Reduction of the ketone, followed by glycosidation with phenyl sulfide **27**[25] using MeOTf activation, generated the desired β-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[23] 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**.

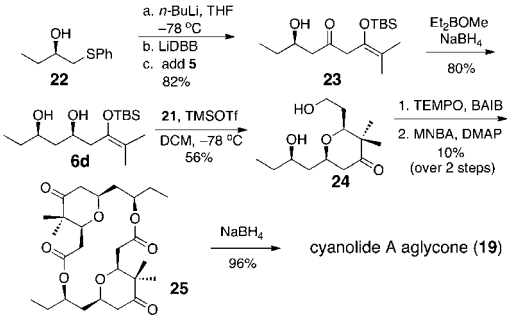
(22) (a) Chen, K.-M.; Hardtman, G. E.; Prasad, K.; Repic, O.; Shapiro, M. J. *Tetrahedron Lett.* **1987**, *28*, 155–158. (b) Narasaka, K.; Pai, F. C. *Tetrahedron* **1984**, *40*, 2233–2238.

(23) (a) Shiina, I.; Fukui, H.; Sasaki, A. *Nat. Protoc.* **2007**, *2*, 2312–2317. (b) Shiina, I.; Kubota, M.; Oshiumi, H.; Hashizume, M. *J. Org. Chem.* **2004**, *69*, 1822–1830. (c) Wu, Y.; Yang, Y.-Q. *J. Org. Chem.* **2006**, *71*, 4296–4301.

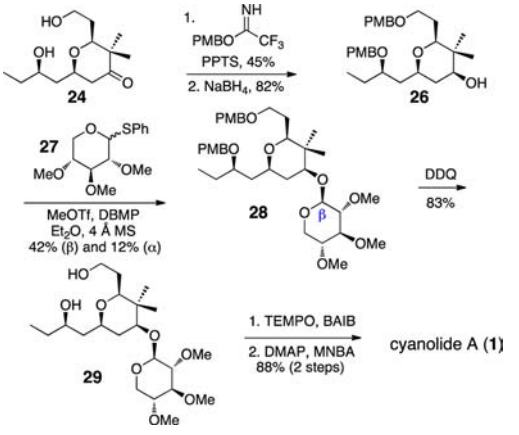
(24) In addition to the bis-PMB ether, the mono-PMB ether was isolated in 31% yield and resubjected to the protection conditions to deliver more bis-PMB material.

(25) (a) Lopez, R.; Fernandez-Mayoralas, A. *J. Org. Chem.* **1994**, *59*, 737–745. (b) Barry, C. S.; Bushby, N.; Charmant, J. P. H.; Elsworth, J. D.; Harding, J. R.; Willis, C. L. *Chem. Commun.* **2005**, 5097–5099.

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.

Acknowledgment. Support was provided by the National Institute of General Medicine (GM-43854). M.R. G. was supported by a Lilly Graduate Research Fellowship. We acknowledge Yu Yi (Chloe) Huang at UC Irvine for her assistance in substrate preparation.

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

The authors declare no competing financial interest.