AD_____

Award Number: DAMD17-01-1-0109

TITLE: Synthesis of Aceogenin Analogs as Potential Therapeutics for Treating Prostate Cancer

PRINCIPAL INVESTIGATOR: Brian L. Pagenkopf, Ph.D.

CONTRACTING ORGANIZATION: University of Texas at Austin
Austin, Texas 78713-7726

REPORT DATE: July 2003

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 074-0188

1. AGENCY USE ONLY (Leave blank)	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	July 2003	Annual (1 Jul 2002 - 30 Jun 2003)

4. TITLE AND SUBTITLE
Synthesis of Acetogenin Analogs as Potential Therapeutics for Treating Prostate Cancer

5. FUNDING NUMBERS
DAMD17-01-1-0109

6. AUTHOR(S)
Brian L. Pagenkopf, Ph.D.

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
University of Texas at Austin
Austin, Texas 78713-7726

E-Mail: pagenkopf@mail.utexas.edu

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSORING / MONITORING AGENCY REPORT NUMBER

11. SUPPLEMENTARY NOTES

12a. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

12b. DISTRIBUTION CODE

13. ABSTRACT (Maximum 200 Words)

New synthetic routes for preparing both the bis-THF and butenolide protions of the targeted acetogenin analogs have been established that avoid the pitfalls of previous strategies. These routes provide practical solutions to the problems associated with securing late-stage advanced intermediates in guantities sufficient for analog preparation. Current research efforts are focusing on optimizing the final aceogenin assembly. A brief investigation into alternative ways to connect the bis-THF with the butenolide led to development of a new Horner-Wadsworth-Emmons type coupling reaction between alkenes and aldehydes that involves rhodium catalyzed olefin hydrophosphorylation and a novel phosphonate elimination as key steps.

14. SUBJECT TERMS
Synthesis, analog design, chemotherapy, biological screening

15. NUMBER OF PAGES
25

16. PRICE CODE

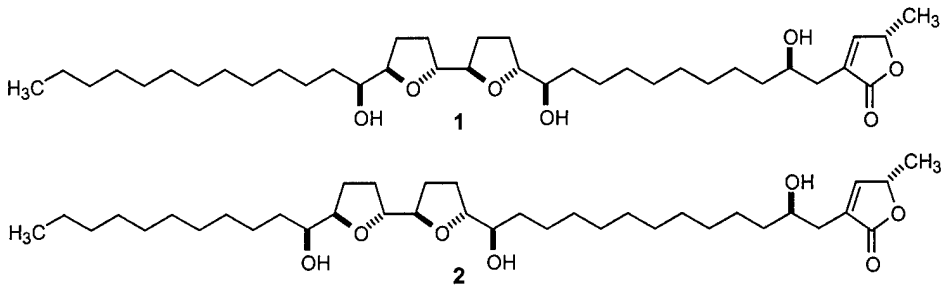
17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
Unclassified	Unclassified	Unclassified	Unlimited

Table of Contents

INTRODUCTION

The objective of this project described in the statement of work is to prepare synthetic analogs based on the natural acetogenins squamotacin **1** and bullatacin **2** so that structure-activity relationships concerning the location of the bis-THF part of the molecule relative to the rest of the structure can be investigated.[1] During this past year we encountered several serious synthetic challenges concerning reaction efficiency and scalability that required a reworking of the synthetic plan in several places. If the objective of this project were to make a small amount of one natural product then a synthetic sequence that contained several problematic and low yielding steps could have been tolerated. However, to ensure success in preparing a set of analogs we were determined to overcome the low yielding and unworkable synthetic steps.

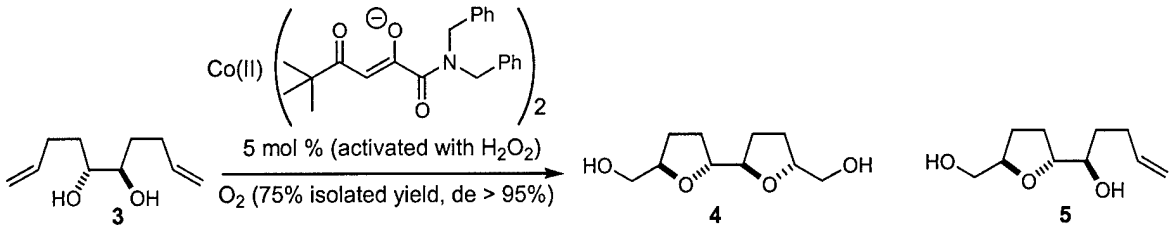
Figure 1



BODY

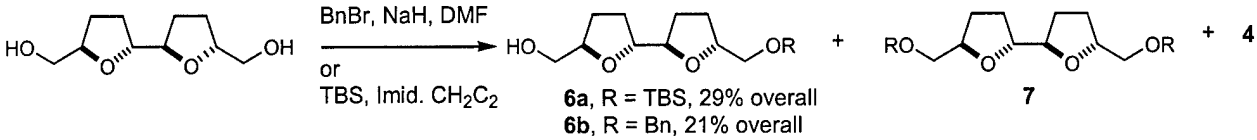
Part I of IV. Synthesis of Desymmetrized Bis-THF. The first goal in the approved statement of work was to develop an efficient route to the central bis tetrahydrofuran core **4** that was capable of providing sufficient quantities for analog production (Scheme 2). We partially met this goal by developing an efficient synthesis of **4** using new Mukaiyama-type cobalt oxidation catalysts.[2] The details of this oxidation were described in the previous annual report and we are preparing a full paper that will describe these oxidations. However, when scaled to 10 grams or more, separation of **4** from the mono-cyclization product **5** (less than 10%) and unreacted starting material **3** proved to be impossible. (The thin layer chromatography retardation factor between **3**, **4** and **5** is less than 0.4).

Scheme 2



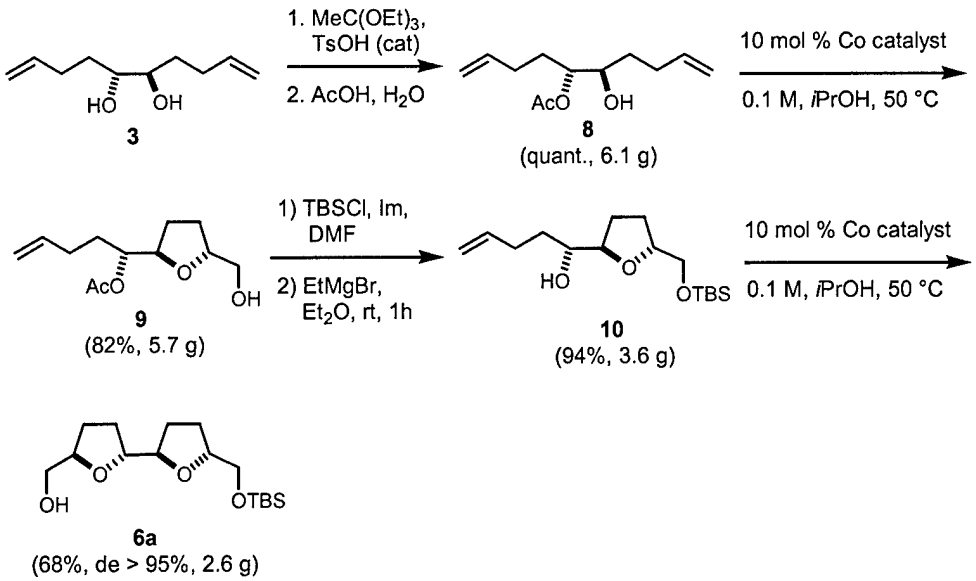
Furthermore, the mono-protection of **4** to ether **6** was problematic, despite claims of 71% for this procedure by Wang and Shi.[3] Even after optimization the efficiency of the desymmetrization remained below 30% (Scheme 3).

Scheme 3



Faced with a serious constriction in the synthetic pipeline we decided to address the mono-protection of the C2 symmetric diol at an earlier point in the synthesis. The solution that we have settled upon is shown in Scheme 4. The diol **3** was treated with $(EtO)_3CMe$ in the presence of catalytic tosic acid to form an intermediate ortho ester *in situ* and hydrolysis afforded the acetate **8** in quantitative yield.[4] Aerobic oxidation using our cobalt catalyst system gave the mono-THF **8** in 82% isolated yield. Protection of the free hydroxyl (TBSCl, imidazole) and removal of the acyl group with EtMgBr gave the alcohol **9** in 94% for the two steps. Final oxidation gave the desymmetrized bis-THF core in 68% yield. This sequence is lengthier than direct mono-protection of the bis-THF diol **4** that is presented in Scheme 4, but the overall yield has increased to about 53% and steps requiring difficult chromatographic purification are avoided. The yields indicated were averaged over several runs, and the amounts listed after the yields are the largest scale at which we have performed the reaction. We are uncertain why oxidation of the second THF (i.e., **10** to **6a**) is less efficient than the first oxidative cyclization, and attention will be given to optimizing this step. Currently we have 24 g of **3** and 2.9 g of **6a** at hand.

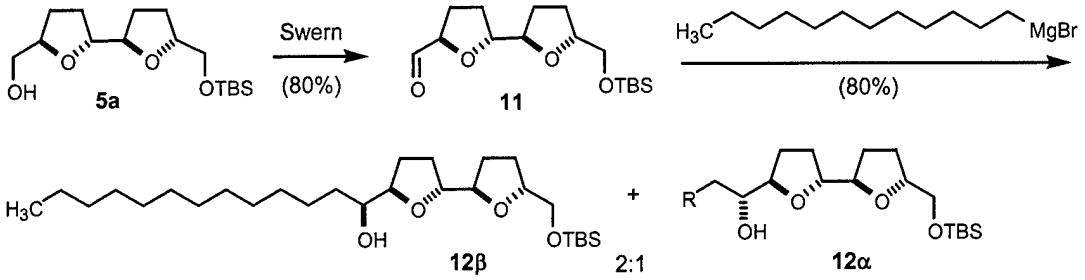
Scheme 4



Part II of IV. Functionalizing the Bis-THF. We are in the process of finding a scalable route for attaching the aliphatic groups to the bis-THF core, and none of the reactions presented in this section have been optimized. Swern oxidation of alcohol **6a** followed by Grignard

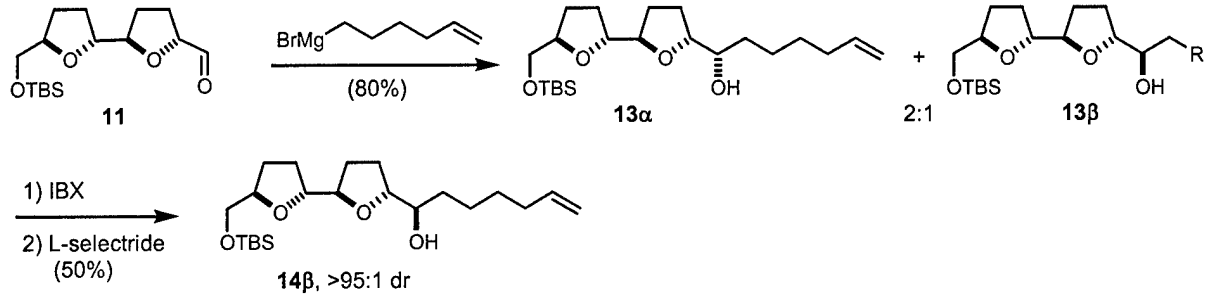
addition to aldehyde **11** gave a 2:1 ratio of the desired beta and alpha diastereomers **12β** and **12α** in 80% yield (Scheme 5). Alcohols **12** proved to be inseparable by flash chromatography, so we turned to installing the right hand side first.

Scheme 5



Work on the right hand side commenced with Grignard addition to aldehyde **10** (Scheme 6). Oxidation of the mixture of epimers **12α** and **12β** to the ketone with IBX followed by reduction with L-selectride gave **13β** with the required beta hydroxyl in greater than 95:1 selectivity.

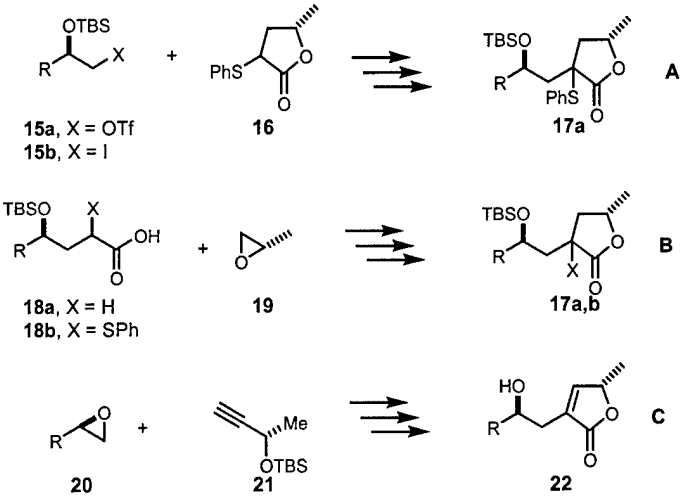
Scheme 6



We are currently evaluating how different hydroxyl protective groups will influence both subsequent chromatographic separations and the stereochemistry of the product resulting from addition of the left hand side. We plan to optimize the addition sequence to avoid as much as possible the need to invert the stereochemistry of the left hand hydroxyl. However, if necessary, the stereochemistry can be corrected by oxidation to the ketone and reduction with DIBAL.

Part III of IV. Butenolide Preparation. There have been many successful syntheses of acetogenins, and three strategies have primarily been employed to prepare the butenolide portion: a) alkylation of White's lactone **16** with an iodide or triflate (Scheme 7, A);[5,6] b) ring opening of propylene oxide by the dilithiated free acid (Scheme 7, B);[7] and c) condensation of a propargylic alcohol and an epoxide (Scheme 7, C).[8]

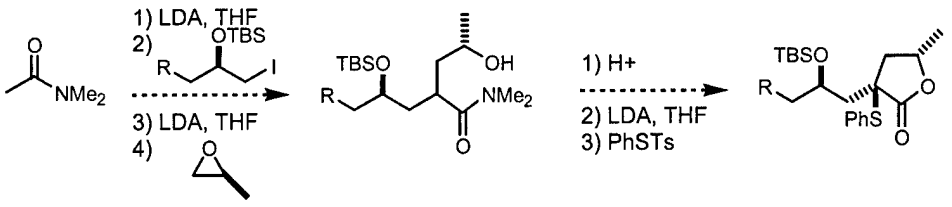
Scheme 7



No detailed procedures were published for the preparation of White's lactone, and at the end of the first year we had completed a modified lactone synthesis that reliably gave multi-gram quantities with high efficiency.[9] Unfortunately, alkylation with the enolate of **16** proved not to be a practical approach because alkylation with the requisite iodide gave less than 10% of the desired product. The unstable triflate worked only marginally better (40%) when toxic HMPA was used as co-solvent. A recent report by Marshall on another series of acetogenin analogs used this reaction sequence to prepare the butenolide, and he reported similarly poor yields for the reaction on only 50 mg scale. To the best of our knowledge only milligram quantities of acetogenins were prepared using the White lactone intermediate. The other two routes shown in Scheme 7 are also hampered by modest yields, use large quantities of HMPA, or require chiral precursors that are difficult to obtain.[10] Therefore, despite the many total syntheses of acetogenins, we sought to develop a practical synthetic route to the right hand butenolide.

Our synthetic strategy for the butenolide (Scheme 8) was inspired by Stork and coworkers[11] who circumvented a troublesome lactone alkylation by converting the lactone to an acyclic amide, alkylating the amide enolate and then hydrolysis back to the lactone. We suspected that the superior nucleophilicity of an amide enolate would be beneficial with the hindered alkyl iodide **14b**, and introducing the sulfur moiety last made sense given the many highly electrophilic sulfur reagents available.

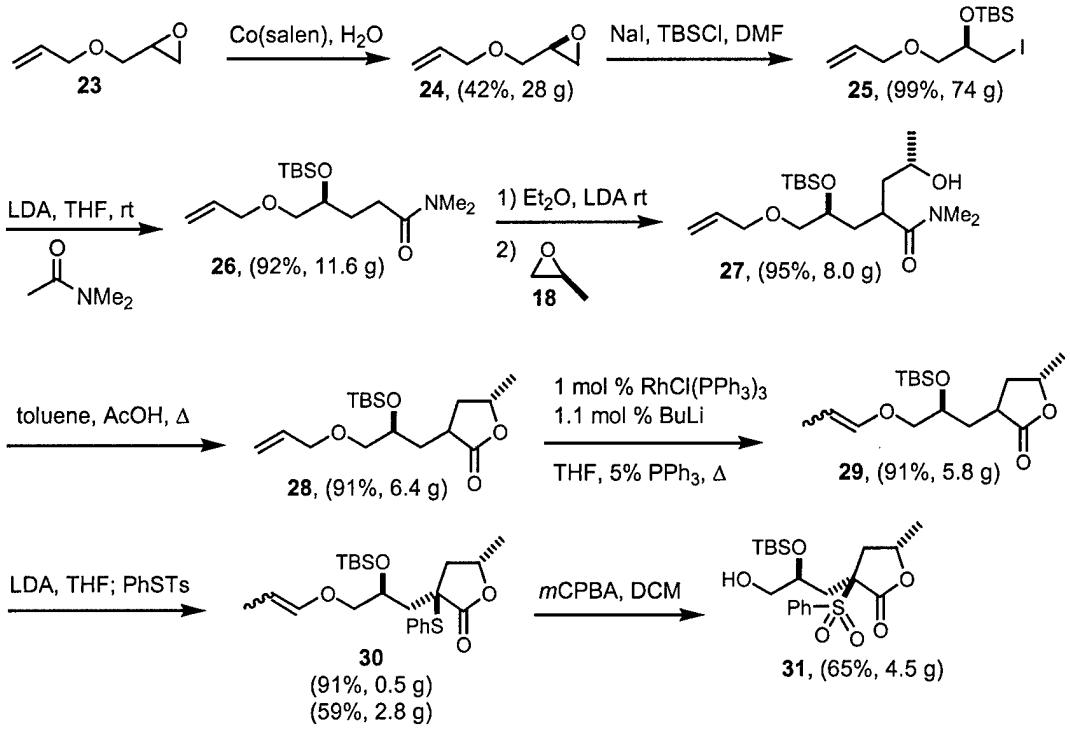
Scheme 8



Our successful realization of this strategy is shown in Scheme 9. Allyl glycidyl ether was resolved with the Jacobsen cobalt salen catalyst and subsequently transformed into the iodide without any difficulty.[12] We have successfully prepared 74 g of resolved iodide **25** in a single run. Alkylation of the iodide with dimethyl acetamide proved to be much more satisfying than

alkylation of the lactone, and a 92% yield of **26** was obtained on 12 gram scale without the use of HMPA. A second alkylation with propylene oxide gave **27** in excellent 95% yield on 8 gram scale. Heating amide **28** gave the lactone in 91% yield on 6 gram scale. We had investigated several hydroxyl protective groups for this sequence, and the allyl group has turned out to be ideal, both in terms of reaction efficiency, practicality and cost. Rhodium catalyzed isomerization of the allyl ether gave the vinyl ether **30** in 91% yield as a mix of E and Z isomers. Alkylation of the lactone with PhSTs is still under optimization, and oxidation with mCPBA gave the sulfone in 65% yield with concomitant hydrolysis of the vinyl ether.

Scheme 9



That we have obtained the correct relative stereochemistry in the joining of the two chiral fragments was confirmed by X-ray crystallography (Scheme 10). Treatment of the vinyl ether **30** with 0.1 M HCl in hot aqueous MeOH led to cleavage of both the vinyl ether and the TBS group. The resulting two lactones equilibrated under the reaction conditions, and lactone **33** formed crystals suitable for crystallographic X-ray analysis (Figure 2).

Scheme 10

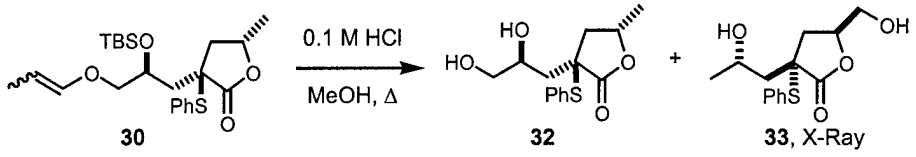
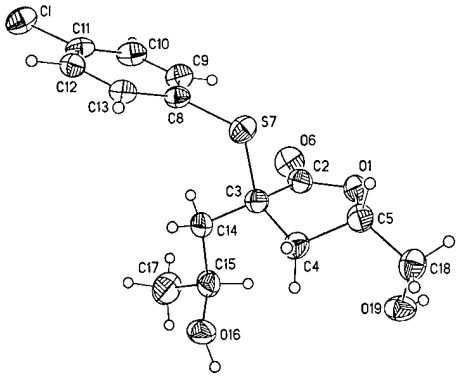


Figure 2



Part IV of IV. Phosphonate Chemistry. The statement of work describes installation of a variable length "spacer" between the butenolide and the bis-THF as a key synthetic strategy in the analog design. We had considered that a phosphonate coupling reaction might simplify the coupling sequence. Last year we published a highly selective rhodium catalyzed olefin hydrophosphorylation reaction in prelude to exploring phosphonate coupling.[13] This year the results of the phosphonate couplings were published in *The Journal of the American Chemical Society* and *The Journal of Organic Chemistry*, and copies of these manuscripts are in the appendix.

The funds from this Army medical research project have unquestionably had a very positive effect on the overall well being of the PI's research group. We felt it was appropriate to acknowledge the Army funds in a paper which appeared in *The Journal of the American Chemical Society* that described a new formal [3+2] cycloaddition between donor-acceptor cyclopropanes and nitriles, even though this work was unrelated.

KEY RESEARCH ACCOMPLISHMENTS

- Developed an efficient second-generation synthesis of the mono-protected bis-THF acetogenin domain
- Developed a scalable and efficient synthesis of the key butenolide precursor
- Discovered a new Horner-Wadsworth-Emmons type phosphonate coupling reaction

REPORTABLE OUTCOMES

Manuscripts

New Mixed Phosphonate Esters by Transesterification of Pinacol-phosphonates and their use in Aldehyde and Ketone Coupling Reactions with Non-stabilized Phosphonates. John F. Reichwein and Brian L. Pagenkopf, *J. Org. Chem.* **2003**, *68*, 1459-14630.

A New Horner-Wadsworth-Emmons Type Coupling Reaction Between Non-stabilized β-Hydroxy Phosphonates and Aldehydes or Ketones. John F. Reichwein and Brian L. Pagenkopf, *J. Am. Chem. Soc.* **2003**, *125*, 1821-1824.

Formal [3+2] Cycloadditions of Donor-acceptor Cyclopropanes and Nitriles. Ming Yu and Brian L. Pagenkopf, *J. Am. Chem. Soc.* **2003**, *125*, 8122-8123.

Presentations

March, 24-28, 2003, "Mono-Deprotection of Di-tert-butyl Silylene Ethers: A New Protocol for Selective Protection of Secondary Alcohols." Ming Yu and Brian L. Pagenkopf, presented at The Annual Meeting of the American Chemical Society, New Orleans, LA.

March, 24-28, 2003, "Synthesis and Chemistry of New Donor-acceptor Cyclopropane-derived Glucals." Ming Yu and Brian L. Pagenkopf, presented at The Annual Meeting of the American Chemical Society, New Orleans, LA.

November, 11-14, 2002, "Intramolecular Cyclopropanation of Glycals." Ming Yu and Brian L. Pagenkopf, presented at Annual Southern west Regional Meeting of American Chemical Society, Austin, TX.

Funding Applied For

A revised version of a previously reviewed NIH will be submitted. That proposal focuses on developing other applications for the cobalt catalyzed oxidation chemistry. A similar proposal will be submitted to NSF.

Funding Received

A grant from the Petroleum Research Fund has been awarded to explore the oxidative cyclization that was discovered while working on this project. "Stereoselective THF Synthesis by Cobalt Catalyzed Air Oxidation of Hydroxy Olefins" $80,000 total over two years starting September, 2003.

Employment

One postdoctoral fellow who worked on this project is now seeking permanent employment. He has presented this work to various representatives from Merck, Pfizer, BMS, Lilly, Albany and other pharmaceutical companies.

CONCLUSIONS

The critique of our last annual reported noted that we had fallen behind our original timeline. However, that timeline was based on a budget three times of that actually received. Given the difference in funding, we hope our progress this past year is viewed favorably.

It was frustrating to find that several literature steps and procedures for the butenolide and the bis-THF portions proved to be unreliable or unscaleable. Difficulties encountered forced us to develop new routes to key acetogenin precursors, and our efforts have been rewarded with a workable synthetic plan that employs efficient, scalable and practical steps. The final push toward completing assembly of the first set of acetogenin analogs is underway. We are optimistic that the most challenging synthetic steps are behind us, and that with a reliable pipe-line for key intermediates progress toward the final targets can continue without interruption.

So what? Steady progress toward the primary goal of generating a library of acetogenin analogs continues. Given our progress a year ago we could have decided to push forward with the existing route through several low yielding steps, and perhaps we would have made one acetogenin by now. However, no serious collection of analogs could be prepared by such a frenzied approach, at least not by a few students, and project continuity would be jeopardized. Instead, by focusing on ensuring that forward progress proceeds though efficient and reproducible synthetic pathways the eventual realization of project objectives is more assured. Moreover, the synthetic routes that we have developed for both the bis-THF and butenolide portions of the acetogenins are superior to all previously reported methods, and when reported these protocols will have a positive effect on acetogenin cancer research.

REFERENCES

[1] (a) Rupprecht, J. K.; Hui, Y.-H.; McLaughlin, J. L. Annonaceous Acetogenins: A Review. *J. Nat. Prod.* **1990**, *53*, 237-278. (b) Cavé, A.; Cortes, D.; Figadere, B.; Hocquemiller, R.; Laprévote, O.; Laurens, A.; Leboefu, M. Recent Advances in the Acetogenins of Annonaceae. In *Recent Advances in Phytochemistry. Pytochemical Potential of Tropical Plants*; Downum, K. R.; Romeo, J. T.; Stafford, H. A.; Eds.; Plenum: New York; 1993; Vol 27; 167-202. (c) Gu, Z.-M.; Zhao, G. X.; Oberlies, N. H.; Zeng, L.; McLaughlin, J. L. Annonaceous Ancetogenins: Potent Mitochondrial Inhibitors with Diverse Applications. In *Recent Advances in Phytochemistry. Phytochemistry of Medicinal Plants*; Arnason, J. T.; Mata, R.; Romeo, J. T., Eds.; Plenum: New York; 1995; Vol 29; 249-310. (d) Figadere, B. Synthesis of Acetogenins of Annonaceae: A New Class of Bioactive Polyketides. *Acc. Chem. Res.* **1995**, 28, 259-365. (e) Feras, Q.A.; Liu, X.-X.; McLaughlin, J. L. Annonaceous Acetogenins: Recent Progress. *J. Nat. Prod.* **1999**, *62*, 504-540.

[2] Inoki, S.; Mukaiyama, T. A convenient Method for the stereoselective Preparation of trans-2-hydroxymethyltetrahydrofurans by the Oxidative Cyclization of 5-hydroxy-1-alkenes with Molecular Oxygen Catalyzed by Cobalt(II) Complex. *Chem. Lett.* **1990**, 67-70.

[3] Wang, Z.-M.; Tian, S.-K.; Shi, M. The Synthesis of Asimilobin and the Correction of its Tetrahydrofuran Segement's Configuration. *Tetrahedron Lett.* **1999**, *40*, 977-980.

[4] Udodong, U. E.; Rao, C. S.; Fraser-Reid, B. Normal-pentenyl glycosides in the efficient assembly of the blood-group substance-b tetrasaccharide. *Tetrahedron* **1992**, *48*, 4713-4724.
[5] White, J. D.; Somers, T. C.; Reddy, G. N. Degradation and absolute configurational assignment to c-34-botryococcene. *J. Org. Chem.* **1992**, *57*, 4991-4998.
[6] Marshall, J. A.; Piettre, A.; Paige, M. A.; Valeriote, F. *J. Org. Chem.* **2003**, *68*, 1780-1785; Marshall, J. A.; Piettre, A.; Paige, M. A.; Valeriote, F. *J. Org. Chem.* **2003**, *68*, 1771-1779.
[7] Emde, U.; Koert, U. *Eur. J. Org. Chem.* **2000**, 1889-1904; Emde, U. Koert, U. *Tetrahedron Lett.* **1999**, *40*, 5979-5982.
[8] Hoye, T. R.; Humpal, P. E.; Jimenez, J. I.; Mayer, M. J.; Tan, L.; Ye, Z. *Tetrahedron Lett.* **1994** *35*, 7517-7520; Marshall, J. A.; Hinkle, K. W. *J. Org. Chem.* **1997**, *62*, 5989-5995.
[9] White, J. D.; Somers, T. C.; Reddy, G. N. Degradation And Absolute Configurational Assignment To C-34-Botryococcene. *J. Org. Chem.* **1992**, *57*, 4991-4998; Schaus, S. E.; Branalt, J.; Jacobsen, E. N. Total synthesis of muconin by efficient assembly of chiral building blocks. *J. Org. Chem.* **1998**, *63*, 4876-4877.
[10] Hoye, T. R.; Humpal, P. E.; Jimenez, J. I.; Mayer, M. J.; Tan, L.; Zhixiong, Y. An efficient and versatile synthesis of the butenolide subunit of 4-hydroxyylated annonaceous acetogenins. *Tetrahedron Lett.* **1994**, 7517-7519.
[11] Stork, G.; Niu, D.; Fujimoto, A.; Koft, E. R.; Balkovec, J. M.; Tata, J. R.; Dake, G. R. The first stereoselective total synthesis of quinine. *J. Am. Chem. Soc.* **2001**, *123*, 3239-3242.
[12] Tokunaga, M.; Larrow, J. F.; Kakiuchi, F.; Jacobsen, E. N. Asymmetric catalysis with water: Efficient kinetic resolution of terminal epoxides by means of catalytic hydrolysis. *Science* **1997**, *277*, 936-938.
[13] John F. Reichwein, Mittun C. Patel and Brian L. Pagenkopf, Rhodium Catalyzed Regioselective Olefin Hydrophosphorylation. *Org. Lett.* **2001**, *3*, 4303-4306.

J|A|C|S
ARTICLES
Published on Web 01/25/2003

A New Horner–Wadsworth–Emmons Type Coupling Reaction between Nonstabilized β-Hydroxy Phosphonates and Aldehydes or Ketones

John F. Reichwein and Brian L. Pagenkopf*

Contribution from the Department of Chemistry and Biochemistry, The University of Texas at Austin, Austin, Texas 78712

Received July 11, 2002; E-mail: pagenkopf@mail.utexas.edu

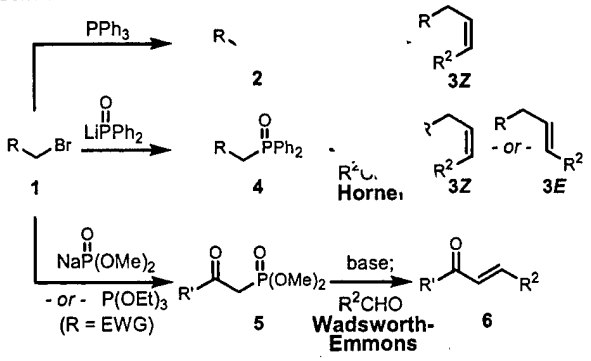
Abstract: Treatment of nonstabilized β-hydroxy phosphonic acid mono methyl esters with diisopropyl carbodiimide at ambient temperature leads to clean stereospecific elimination. The phosphonic acid mono alkyl esters are accessible by the selective partial saponification of dimethyl or diethyl alkyl phosphonates with NaOH or $MgBr_2$. Isolated yields over both hydrolysis and elimination steps average 55–75%.

Introduction

The Wittig,[1,2] Horner,[3,4] and Wadsworth–Emmons[5,6] reactions are classic methods for joining two complex molecular fragments through relatively simple functional groups, and these reliable olefin-forming reactions are well-accepted transformations in both academia and industry (Scheme 1).[7] The synthetic power inherent with these kinds of coupling and homologation reactions has spurred research into optimizing, modifying, or supplanting[8] these methods with others that operate under different reaction conditions,[9] can be prepared from alternative starting materials,[10] or that enhance stereochemical control.[11,12]

The dialkyl phosphonates of the Wadsworth–Emmons reaction can be prepared by Arbuzov, Michaelis–Becker,[13,14] or other methods,[14] and the alkylation of α-lithio phosphonates with aldehydes is well known. However, a carbanion-stabilizing

Scheme 1

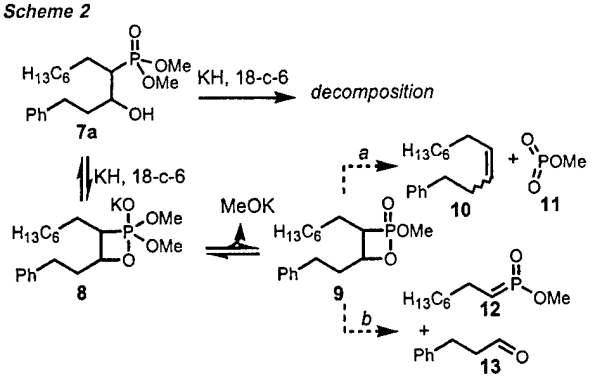


group in the β-position is necessary for elimination and olefin formation, without which addition to aldehydes gives stable β-hydroxyphosphonates.[6,7,15] The elimination of nonstabilized β-hydroxy phosphonates to olefins has long been recognized as a difficult transformation. In pioneering studies on the formation of olefins from nonstabilized β-hydroxy phosphonates derived from benzophenone, Corey and Kwiatkowski reported that the optimal yield of 1,1-diphenylethylene was at best 30%, and benzophenone, unsaturated phosphonate, and acidic materials were also formed.[16] To overcome these difficulties, Corey et al. ingeniously developed phosphonic bisamides[17] and thiophosphonates[16] as alternative coupling reagents.[18] During the intervening decades, a general protocol for the elimination of nonstabilized β-hydroxyphosphonates has not been advanced. In this paper, we describe a novel method for the utilization of nonstabilized β-hydroxyphosphonates in Horner–Wadsworth–

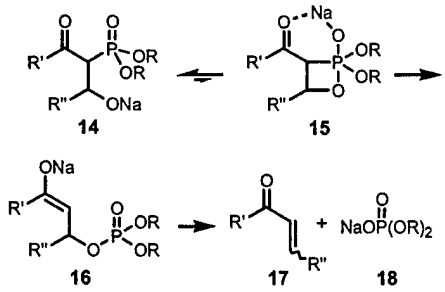
(1) Wittig, G.; Geissler, G. *Justus Liebigs Ann. Chem.* **1953**, *580*, 44–68.
(2) For reviews, see: (a) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863–927. (b) Maercker, A. *Org. React.* **1965**, *14*, 270–490.
(3) Horner, L.; Hoffmann, H.; Wipel, H. C.; Klahre, G. *Chem. Ber.* **1959**, *92*, 2499–2505.
(4) For reviews, see: (a) Clayden, J.; Warren, S. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 241–270. (b) Buss, A. D.; Warren, S. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2307–2325.
(5) Wadsworth, W. S., Jr.; Emmons, W. D. *J. Am. Chem. Soc.* **1961**, *83*, 1733–1738.
(6) Boutagy, J.; Thomas, R. *Chem. Rev.* **1974**, *74*, 87–99. Wadsworth, W. A., Jr. *Org. React.* **1977**, *25*, 73–253.
(7) Nicalaou, K. C.; Harter, M. W.; Gunzner, J. L.; Nadin, A. *Liebigs Ann. Recl.* **1997**, 1283–1301.
(8) (a) Chatterjee, A. K.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **2002**, *41*, 3171–3174. (b) Pederson, R. L.; Fellows, I. M.; Ung, T. A.; Ishihara, H.; Hajela, S. P. *Adv. Synth. Catal.* **2002**, *344*, 728–735.
(9) Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1994**, *25*, 2183–2186.
(10) For examples with diazoesters, see: (a) Lu, X.; Fang, H.; Ni, Z. *J. Organomet. Chem.* **1989**, *373*, 77–84. (b) Herrmann, W. A.; Wang, M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1641–1643. (c) Zhou, Z.; Huang, Y.; Shi, L. *Tetrahedron* **1993**, *49*, 6821–6830. (d) Herrmann, W. A.; Roesky, P. W.; Wang, M.; Scherer, W. *Organometallics* **1994**, *13*, 4531–4535. (e) Ledford, B. E.; Carreira, E. M. *Tetrahedron Lett.* **1997**, *38*, 8125–8128. (f) Lebel, H.; Paquet, V.; Proulx, C. *Angew. Chem., Int. Ed.* **2001**, *40*, 2887–2890.
(11) Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1993**, *24*, 4405–4408.
(12) For examples with phosphonates, see: Chemler, S. R.; Coffey, D. S.; Roush, W. R. *Tetrahedron Lett.* **1999**, *40*, 1269–1272.
(13) Bhattacharya, A. K.; Thyagarajan, G. *Chem. Rev.* **1981**, *81*, 415–430.
(14) Kosolapoff, G. M. *Org. React.* **1951**, *6*, 273–338.
(15) Kelly, S. E. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 1, Chapter 3.1, pp 729–817.
(16) Corey, E. J.; Kwiatkowski, G. T. *J. Am. Chem. Soc.* **1966**, *88*, 5654–5656.
(17) (a) Corey, E. J.; Kwiatkowski, G. T. *J. Am. Chem. Soc.* **1966**, *88*, 5652–5653. (b) Corey, E. J.; Kwiatkowski, G. T. *J. Am. Chem. Soc.* **1966**, *88*, 5653–5654. (c) Corey, E. J.; Kwiatkowski, G. T. *J. Am. Chem. Soc.* **1968**, *90*, 6816–6821. (d) Corey, E. J.; Cane, D. E. *J. Org. Chem.* **1969**, *34*, 3053–3057.
(18) Rein, T.; Reiser, O. *Acta Chem. Scand.* **1996**, *50*, 369–379.

10.1021/ja027658s CCC: $25.00

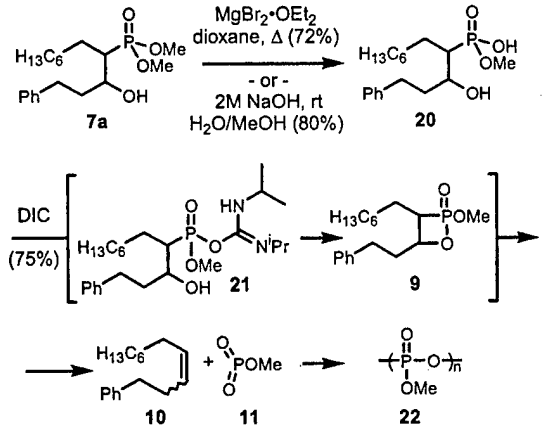
Scheme 2



Scheme 3



Scheme 4



Emmons type reactions under ambient conditions using mild dehydrating reagents.

With the advent of convenient olefin hydrophosphorylation reactions,[19,20] we decided to reinvestigate the conversion of β-hydroxy phosphonates to olefins despite the discouraging heritage for their elimination. Initially we speculated that the use of crown ethers, which were not commercially available three decades ago, would result in a more nucleophilic alkoxide for generating the oxaphosphetane **9**, which could then convert to the desired olefin by a retro [2 + 2] fragmentation pathway (Scheme 2). The more exothermic *pathway a* leads to the desired olefin and meta phosphate **11**,[21] whereas *pathway b* leads to release of aldehyde **13** and the reactive intermediate **12**. However, the alkali salts (NaH, *n*-BuLi, *t*-BuOK) of β-hydroxy phosphonates **7** in the presence of crown ethers[22] showed no reaction at low temperatures, and the substrates underwent decomposition to various dehydrated vinylic and β,γ-unsaturated phosphonates as the reactions warmed to room temperature.[23] Weaker bases (PhONa, wet K_2CO_3) have been reported to result in olefin formation with tertiary β-hydroxy phosphonates,[24] but these methods were ineffective here, even at elevated temperatures (100 °C in DMF).[25] Partial ester hydrolysis occurred in the presence of Lewis acids, and only CsF in hot DMF provided some olefin **10** (8% after 16 h).[26]

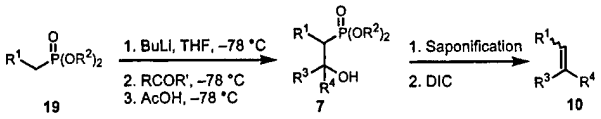
In the Wadsworth–Emmons reaction,[6] the reversible formation of the pentavalent phosphorus species **15** is thought to precede collapse to the stabilized anion **16**, and E1cb elimination leads to release of phosphate and the coupled enone product **17** (Scheme 3). The β-hydroxy phosphonates investigated in this paper also likely form equilibrating pentavalent phosphorus intermediates, but because they lack the β-electron-withdrawing or -stabilizing group, there is no low energy pathway for collapse leading to olefin formation.

It was clear from NMR data that no discernible amounts of the oxephosphetane **9** were formed by treatment of **7a** with alkali metals.[27–29] We postulated that a leaving group superior to methoxide (or methanol) was required for oxephosphetane formation. Dehydration of the free phosphonic acid appeared to be an attractive strategy, and the ideal dehydrating reagent for this task proved to be the peptide coupling reagent diisopropylcarbodiimide (DIC). In this regard, the addition of DIC to a $CHCl_3$[30] solution of the free phosphonic acid **20** resulted in clean formation of olefin **10**.[31] Subsequent NMR investigations revealed that the formation of oxaphosphetane **9** was nearly instantaneous after the addition of DIC to a solution of **20**, whereas the intermediate urea phosphonate **21** could not be detected.[32] The oxaphosphetane **9** slowly converted over 24 h to olefin **10** in 75% yield. The partial saponification of dimethylphosphonate **7a** to **20** was achieved with $MgBr_2 \cdot OEt_2$ at 100 °C in dioxane or, more conveniently, by saponification with NaOH in H_2O/MeOH at room temperature (Scheme 4).

A variety of β-hydroxy phosphonates prepared from aldehydes and ketones were made for exploring the generality of the elimination protocol (Table 1). An important consideration when evaluating the alkylation yields in Table 1 is that the ratio of phosphonate anion to carbonyl electrophile was maintained at 1:1, and the reaction stoichiometry was not adjusted to increase efficiency. The alkylation of octyl dimethyl phosphonate **19a** with aliphatic or aromatic aldehydes provided the β-hydroxy phosphonates **7a,b** in 81 and 84% isolated yields,

(19) Han, L.-B.; Mirzaei, F.; Zhao, C.-Q.; Tanaka, M. *J. Am. Chem. Soc.* **2000**, *122*, 5407–5408.
(20) Reichwein, J. F.; Patel, M. C.; Pagenkopf, B. L. *Org. Lett.* **2001**, *3*, 4303–4306.
(21) Westheimer, F. H. *Chem. Rev.* **1981**, *81*, 313–326.
(22) These conditions are commonly used in Wadsworth–Emmons reactions, see: Clayden, J.; Warren, S. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 241–270.
(23) Based on ^1H and ^{31}P NMR.
(24) Dimethyl 2-hydroxy-2,2-dibenzylethylphosphonate, K_2CO_3 (8 equiv) and H_2O (8 equiv) in DMF at 95 °C for 48 h gave 80% olefin: Kawashima, T.; Ichii, T.; Inamoto, N. *Chem. Lett.* **1984**, 1097–1100; ref 35.
(25) Abbreviations used: BHT = 2,6-di-*tert*-butyl-1-hydroxy toluene, DMF = *N*,*N*-dimethylformamide, DIC = 1,3-diisopropylcarbodiimide.
(26) Dimethyl 2-hydroxy-2,2-diphenylethylphosphonate, CsF (3.5 equiv) and H_2O (3.5 equiv) in DMF at 55 °C for 16 h gave 83% olefin: Kawashima, T.; Ichii, T.; Inamoto, N. *Chem. Lett.* **1983**, 1375–1378; ref 35.
(27) Oxaphosphetane structures analogous to **9** have been isolated, some even by distillation. See refs 28 and 29.
(28) Kawashima, T.; Takami, H.; Okazaki, R. *Chem. Lett.* **1994**, 1487–1490.
(29) Henning, H.-G.; Morr, M. *Chem. Ber.* **1968**, *101*, 3963–3968.
(30) Chloroform was found to be the ideal solvent, see Supporting Information.
(31) A similar observation was reported for DCC: Kawashima, T.; Nakamura, M.; Nakajo, A.; Inamoto, N. *Chem. Lett.* **1994**, 1843–1486.
(32) Mitsunobu conditions were equally effective, whereas other dehydration reagents were not: P_2O_5, PPh_3BrBr, and 2-chloro-*N*-methylpyridine iodide in the presence of Et_3N or 2,6-di-*tert*-butyl-4-methyl-pyridine.

Table 1. Phosphonate Alkylation, Saponification, and Elimination



entry	19	R^1	R^2	R^3COR^4	yield 7[a]		saponification[b]	yield 10[c]	
1	**19a**	C_7H_{15}	Me	$PhCH_2CH_2CHO$	81%[b]	**7a**	A	55%	**10a**
2	**19a**	C_7H_{15}	Me	PhCHO	84%[b]	**7b**	A	59%	**10b**
3	**19a**	C_7H_{15}	Me	cHexCHO	42%	**7c**	B	54%	**10c**
4	**19a**	C_7H_{15}	Me	Et_2CO	60%	**7d**	A or B		**10d**
5	**19b**	H	Me	$PhCH_2CH_2CHO$	79%	**7e**	B	55%	**10e**
6	**19c**	H	Et	PhCHO	83%[b]	**7f**	B		**10f**
7	**19c**	H	Et	$PhCH_2CH_2CHO$	86%[b]	**7g**	B	75%	**10e**

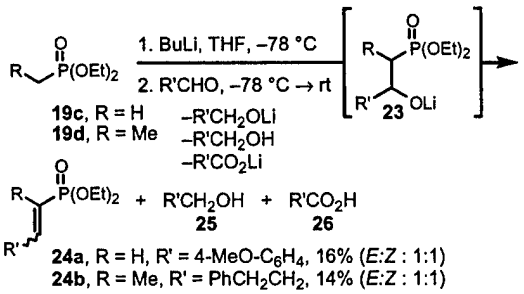
[a] Isolated yields. [b] Saponification methods: A, $MgBr_2$; B, NaOH. [c] Isolated yields for two steps.

but the alkylation was less efficient when β-branching was present (entry 3). Both the aromatic and the aliphatic β-hydroxy phosphonates underwent saponification and elimination equally well (entries 1−3). In contrast, ketone alkylation tended to be less efficient, and the reaction with 3-pentanone afforded the β-hydroxy phosphonate **7d** in 42% yield (entry 4). Moreover, the saponification of **7d** caused disconcerting substrate decomposition.[33] The alkylation of commercially available methyl dimethyl phosphonate **19b** or ethyl diethyl phosphonate **19c** with aliphatic or aromatic aldehydes gave >79% yield in each case (entries 5−7), but the user must be cautioned that the use of low molecular weight phosphonates can be complicated by poor solubility of the anion at low temperature. The reaction of ethyl diethylphosphonate **19c** (entries 6 and 7) illustrates that phosphonates easily accessible by Arbuzov[13] reaction can also be saponified for use in the coupling reaction. While alkylation of the lower molecular weight phosphonates proceeded without incident, the subsequent saponification proved problematic with benzylic β-hydroxy phosphonates (entry 6). From the table, it appears that in the absence of steric bulk or enolizable ketones, high reaction efficiency is observed in the alkylation step. However, these test substrates revealed that to avoid substrate decomposition with certain benzylic β-hydroxy phosphonates, milder saponification methods are required.[33]

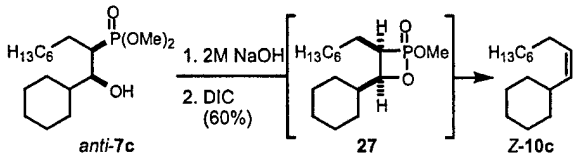
For efficient yields in the aldehyde or ketone alkylation reactions, it was necessary to perform the entire sequence at −78 °C, including the final addition of a proton source to neutralize the lithium alkoxide. At higher temperatures, Tischenko type products[34] were formed, along with vinylic phosphonates **24**,[16,35] especially with electron-rich aldehydes (Scheme 5). For example, with anisaldehyde, the redox products *p*-$MeOC_6H_4CH_2OH$ (**25**) and *p*-MeO $C_6H_4CO_2H$ (**26**) were isolated from reaction mixtures that were allowed to warm to room temperature prior to a protic workup.

In most instances, the β-hydroxy phosphonates were obtained as nearly 1:1 mixtures of syn and anti diastereomers. However, when the stereochemically pure anti diastereomer of **7c** was saponified and eliminated under the standard reaction conditions, the *Z* stereoisomer **10c** was formed exclusively (Scheme 6). This observation is consistent with formation of the oxaphosphetane

Scheme 5



Scheme 6



intermediated **27** followed by a stereospecific collapse to the olefin. Moreover, this method resembles the powerful Horner reaction in that the stereochemical purity of the olefin directly correlates with that of the intermediate β-hydroxy phosphonate that precedes the elimination. No detectable racemization occurred during the saponification, and the more easily handled diesters **7** can be separated instead of the highly hydrophilic phosphonic acids.

In summary, the first general method for the stereospecific dehydrative elimination of secondary, tertiary, and benzylic β-hydroxy phosphonates has been developed. The intermediate β-hydroxy phosphonates are fairly robust under neutral reaction conditions, which may allow them to be carried intact through a synthetic sequence before revealing the olefin. Alkyl dimethyl or diethyl phosphonates, accessible from Arbuzov or Michaelis–Becker reactions, can participate in the coupling reaction, and no special functionality on the β-hydroxy phosphonate is required for olefin formation.

Experimental Section[36]

Compound **19c** was obtained from commercial sources and distilled prior to use. Compounds **19a**,[37] **19b**,[37] and **19d**[37] were prepared according to literature procedures. Compounds **7** and **10** were prepared by one of the following general methods.

β-Hydroxy-phosphonic Acid Dialkyl Esters 7 from 19. To a cooled (−78 °C) solution of **19** (0.80 mmol) in THF (2.5 mL) was added *n*-BuLi in hexanes (0.80 mmol). After being stirred at −78 °C for 15 min, the aldehyde (0.80 mmol) in THF (1 mL) was added. After 60 min at −78 °C, aqueous NH_4Cl was added, and the mixture was extracted with EtOAc. The organic layer was washed with brine and dried over $MgSO_4$. Purification by flash chromatography afforded **7** as a colorless oil.

Olefins 10 from 7. To a solution of **7** (1.1 mmol) in MeOH (5 mL) was added 4 M NaOH (5 mL). After being stirred at room temperature for 16 h, the reaction mixture was acidified to pH < 2 with 1 M HCl, extracted with CH_2Cl_2, dried ($MgSO_4$), and concentrated in vacuo. The reaction residue containing crude **20** was dissolved in $CHCl_3$ (5 mL) and treated with DIC (2.2 mmol), and after being stirred at room temperature for 4 h, the reaction mixture was concentrated in vacuo.

(33) The mild saponification of orthogonal protective groups will be reported elsewhere. See: Reichwein, J. F.; Pagenkopf, B. L. *J. Org. Chem.* **2003**, *68*, in press.
(34) Ogata, Y.; Kawasaki, A. *Tetrahedron* **1969**, *25*, 929−935.
(35) Kawashima, T.; Ishii, T.; Inamoto, N.; Tokitoh, N.; Okazaki, R. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 209−219.
(36) For general experimental details, see: Reichwein, J. F.; Iacono, S. T.; Pagenkopf, B. L. *Tetrahedron* **2002**, *58*, 3813−3822.
(37) Prepared via Arbuzov reaction analogously to: Ford-Moore, A. H.; Perry, B. J. *Org. Synth. Coll. Vol. 4* **1963**, 325−327.

Purification of the residue by flash chromatography afforded **10** as a colorless oil.

Acknowledgment. We thank the DOD Prostate Cancer Research Program DAMD17-01-1-0109, the Robert A. Welch Foundation, and the Texas Advanced Research Program 003658-0455-2001 for financial support.

Supporting Information Available: Table of solvents tested for the elimination. Preparation and characterization data for **7**, **10**, and **19** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA027658S

JOC Article

New Mixed Phosphonate Esters by Transesterification of Pinacol Phosphonates and Their Use in Aldehyde and Ketone Coupling Reactions with Nonstabilized Phosphonates

John F. Reichwein and Brian L. Pagenkopf*

Department of Chemistry and Biochemistry, The University of Texas at Austin,Austin, Texas 78712

pagenkopf@mail.utexas.edu

Received December 10, 2002

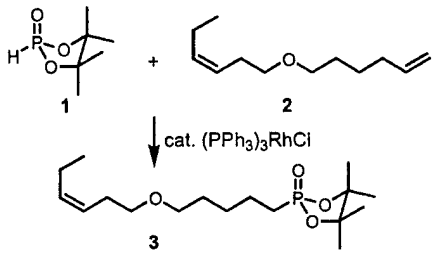
Alkylpinacol phosphonates were prepared by rhodium-catalyzed olefin hydrophosphorylation, and attempted α-deprotonation of the pinacol derived alkyl phosphonates resulted in ring cleavage. The propensity of the alkylpinacol phosphonates to undergo ring opening was exploited to prepare phosphonic acid monomethyl esters in high yield by transesterification in acidulated methanol. Esterification and alkylation with aldehydes or ketones gave β-hydroxy mixed phosphonate esters. *tert*-Butyl and benzylic phosphonate ester protective groups were introduced to improve the efficiency and functional group compatibility of β-hydroxy phosphonate saponification. The β-hydroxy phosphonic acid monomethyl esters were dehydrated with diisopropylcarbodiimide, which gave oxaphosphetane intermediates that collapse to an olefin. The overall reaction sequence complements the arsenal of Horner–Wadsworth–Emmons-type coupling reactions.

Recently, we described a novel method for the utilization of nonstabilized β-hydroxy phosphonates in Horner–Wadsworth–Emmons-type coupling reactions by a mild diisopropylcarbodiimide-mediated dehydration.[1] However, an intermediate step requiring phosphonate ester saponification led to decomposition in a number of β-aryl and low molecular weight phosphonates. One avenue for avoiding the decomposition during the saponification step would be to utilize more labile phosphonate esters.

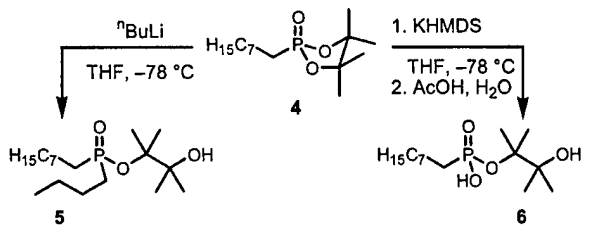
In this regard, we also reported that Wilkinson's complex efficiently catalyzed the hydrophosphorylation of terminal olefins with Tanaka's[2] pinacol hydrogen phosphite **1** (Scheme 1).[3] Under these conditions, the hydrophosphorylation was remarkably selective for a terminal olefin in the presence of other sites of unsaturation. Cyclic phosphonates are generally more reactive and prone to polymerization than their acyclic counterparts,[4] but whether the pinacol phosphonates would prove useful in phosphonate coupling reactions was uncertain given that the chemistry of alkylpinacol phosphonates was virtually unexplored. In this paper, the alkylation and transesterification chemistry of pinacol phosphonates is discussed and a set of orthogonal phosphonate ester protective groups are introduced that extend the scope of the nonstabilized β-hydroxy phosphonate olefination reaction.

α-Carbanions of nonactivated phosphonates are readily generated in situ by deprotonation with *n*-BuLi or LDA, and their reaction with aldehydes, ketones, and esters

SCHEME 1



SCHEME 2



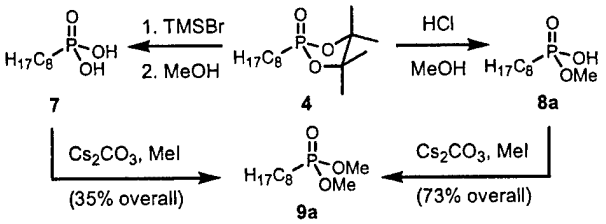
is well documented.[5,6] However, ring-cleavage reactions were found to dominate the alkylation chemistry of pinacol phosphonates (Scheme 2), and the attempted deprotonation by treatment with alkyllithiums (e.g., *n*-BuLi, *t*-BuLi, PhLi) or sterically hindered amine bases (e.g., LDA, LiHMDS, NaHMDS, KHMDS, LiTMP) at −78 °C universally resulted in rapid cleavage of the pinacol ester. Evidence for nucleophilic attack at phosphorus by

(1) Reichwein, J. F.; Pagenkopf, B. L. *J. Am. Chem. Soc.*, in press.
(2) Han, L.-B.; Mirzaei, F.; Zhao, C.-Q.; Tanaka, M. *J. Am. Chem. Soc.* **2000**, *122*, 5407–5408.
(3) Reichwein, J. F.; Patel, M. C.; Pagenkopf, B. L. *Org. Lett.* **2001**, *3*, 4303–4306.
(4) Nifant'ev, E. E.; Nasonovskii, I. S.; Miklashevskii, A. V.; Zavalishina, A. I.; Smirnova, E. I. *Zh. Org. Khim.* **1975**, *11*, 2206–2210.

(5) See, e.g.: (a) Collado, I.; Ezquerra, J.; Mazon, A.; Pedregal, C.; Yruretagoyena, B.; Kingston, A. E.; Tomlinson, R.; Wright, R. A.; Johnson, B. G.; Schoepp, D. D. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2849–2854.
(6) Takahashi, H.; Fujiwara, K.; Ohta, M. *Bull. Chem. Soc. Jpn.* **1962**, *35*, 1498–1500.

10.1021/jo026834c CCC: $25.00
Published on Web 01/24/2003

SCHEME 3

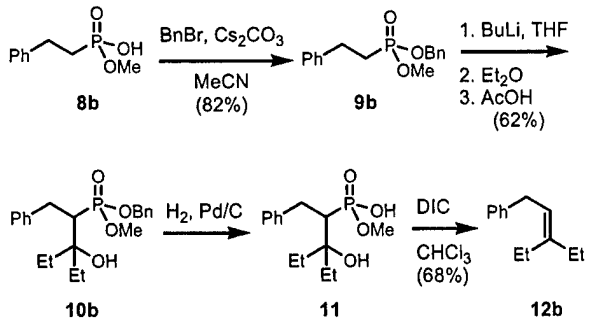


n-BuLi was obtained by isolation of phosphinic ester **5**, and the formation of phosphoramidates was implicated in the reaction with bulky amine bases by the isolation of the phosphonic acid **6** after mild hydrolysis.

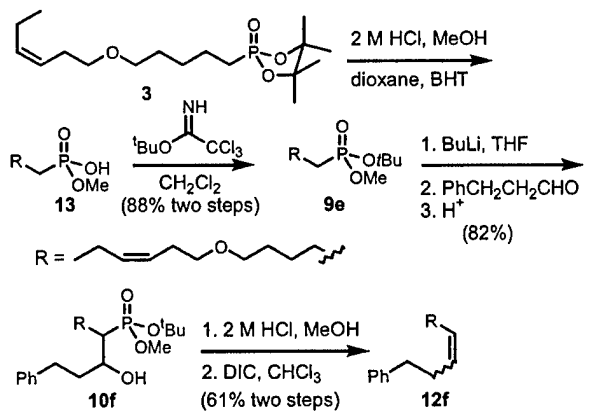
At its current state of development, hydrogen phosphonate **1** unfortunately remains the sole reagent yet identified for transition-metal-catalyzed olefin hydrophosphorylation; therefore, any further progress in the phosphonate alkylation reaction by an α-deprotonation strategy necessitates circumventing reactive intermediate pinacol phosphonates, such as by transesterification to a less reactive phosphonate.[7] Treatment of **4** with Me_3SiBr, which is known to cleave alkyl dimethylphosphonate esters,[8] gave diacid **7** after hydrolysis with dry methanol (Scheme 3). The reaction of **4** with excess HCl in anhydrous methanol hydrolyzed the pinacol ester with greater efficiency, giving the phosphonic acid mono methyl ester **8a**.[9] None of the dimethyl ester **9a** was observed from the transesterification in methanol, but methylation of the crude phosphonic acids **7** and **8a** (Cs_2CO_3, MeI, MeCN) gave the dimethyl octyl phosphonate **9a** in 35% and 75% yield, respectively.[10] Replacing the MeOH in the esterification reaction with ethanol or allyl alcohol was equally effective, but trifluoroethanol resulted in phosphonate decomposition.[11] Curiously, no saponification of phosphonate **4** was observed in NaOH/MeOH.[1] The preparation of dimethyl phosphonate **9a** from the pinacol ester **4** bridges olefin hydrophosphorylation chemistry to the previously established aldehyde and ketone coupling reactions.[1]

In our reported procedure,[1] the strongly basic (2 M NaOH, 16 h) reaction conditions required for the saponification of the dimethyl phosphonate esters caused extensive substrate decomposition in several cases, and it was evident that alternative protective groups were required. A search for complementary phosphonate ester protective groups was greatly simplified by efficient access to phosphonic acid monomethyl esters **8** now possible from the selective transesterification of pinacol phosphonates. Both benzyl and *tert*-butyl esters emerged as the most useful ester protective groups that can be removed under mild conditions yet are compatible with the phosphonate alkylation conditions (Schemes 4 and 5). The monobenzyl phosphonate **9b** was prepared by

SCHEME 4



SCHEME 5



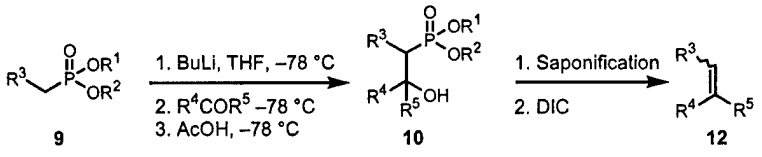
conditions (BnBr, Cs_2CO_3, MeCN, 82%) that were similar to those used to install the methyl ether, and alkylation with 3-pentanone afforded β-hydroxy phosphonate **11** in 62% yield. The benzyl ester was removed by hydrogenation (H_2, Pd/C), and without further purification the resulting phosphonic acid was dehydrated with DIC in $CHCl_3$ to give olefin **12b** (68%).

Aldehyde and ketone condensation reactions with the mixed benzyl phosphonate esters are summarized in Table 1. Note that the harsher alkaline conditions required for the saponification of the analogous dimethyl ester **10a** lead to substrate decomposition (Table 1, entry 1). Alkylation of phosphonate **9c** with benzaldehyde (entry 3) provided the benzylic alcohol **10c**, and subsequent deprotection of the benzyl ester (H_2, Pd/C) occurred selectively without over-reduction of the benzylic β-alcohol. A slightly reduced yield of 62% was observed with the elimination of adducts from aliphatic aldehydes. The yields for the hydrogenation and elimination steps generally exceed those utilizing the NaOH-mediated saponification, and hydrogenation avoids a difficult aqueous workup altogether.

While hydrogenation is by far the easiest and most common method for removal of a benzyl protecting group, it is usually unsuitable if other sites of unsaturation in the molecule need to remain intact. An alternative protecting group with orthogonal reactivity was desired, and the *tert*-butyl group met this requirement. The olefinic pinacol phosphonate **3** was selected as a model substrate to illustrate the overall coupling sequence and to verify compatibility of the various reactions with a substrate bearing simple functional groups (Scheme 5). Reaction of the phosphonic acid mono methyl ester **13**

(7) See the Supporting Information.
(8) (a) McKenna, C. E.; Higa, M. T.; Cheung, N. H.; McKenna, M.-C. *Tetrahedron Lett.* **1977**, *2*, 155–158. (b) McKenna, C. E.; Schmidhauser, J. *J. Chem. Soc., Chem. Commun.* **1979**, *16*, 739.
(9) See, e.g.: Huber, R.; Knierzinger, A.; Obrecht, J.-P.; Vasella, A. *Helv. Chim. Acta* **1985**, *68*, 1730–1747.
(10) Modification of: Mauger, C.; Masson, S.; Vazeux, M.; Saint-Clair, J.-F.; Midura, W. H.; Drabowicz, J.; Mikolajczyk, M. *Tetrahedron: Asymmetry* **2001**, *12*, 167–174.
(11) A similar observation has been reported by: Fortin, S.; Dupont, F.; Deslongchamps, P. *J. Org. Chem.* **2002**, *67*, 5437–5439.

TABLE 1. Phosphonate Alkylation, Saponification, and Elimination



9 10 12

entry	9	R^1	R^2	R^3	R^4COR^5	yield of 10[a] (%)		saponification[b]	yield of 12[c] (%)	
1	**9a**	Me	Me	C_7H_{15}	Et_2CO	60	**10a**	A or B		**12a**
2	**9b**	Me	Bn	$PhCH_2$	Et_2CO	62	**10b**	C	68	**12b**
3	**9c**	Me	Bn	C_7H_{15}	PhCHO	80	**10c**	C	59	**12c**
4	**9c**	Me	Bn	C_7H_{15}	$PhCH_2CH_2CHO$	57	**10d**	C	55	**12d**
5	**9d**	Me	*t*Bu	$PhCH_2$	$PhCH_2CH_2$ CHO	53	**10e**	D	42	**12e**

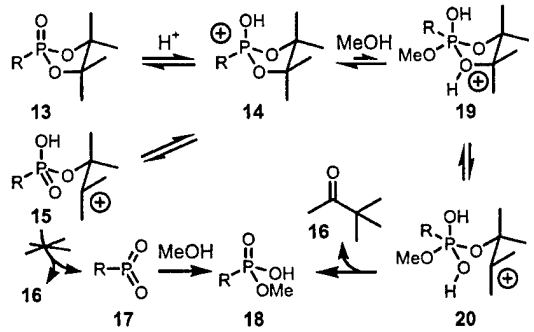
[a] Isolated yields. [b] Saponification methods: A, $MgBr_2$; B, NaOH; C, H_2, Pd/C; D, HCl. [c] Isolated yields for two steps.

with trichloro-*tert*-butyl imidate[12] provided ester **9e** (88%, two steps), and it was interesting to note that the phosphonic acid mono ester was sufficiently acidic to self-catalyze the reaction without additional acid. Alkylation as described above afforded the β-hydroxy phosphonate **10f**. Removal of the *tert*-butyl group with HCl in methanol followed by dehydration of the unpurified acid afforded olefin **12f** as a 1:1 mixture of *E* and *Z* stereoisomers in 44% overall yield from **3**. Similar yields were observed with **9d** (Table 1, entry 5).

In some instances, e.g., **3** → **13**, the standard 2 M HCl in MeOH/dioxane combination for cleavage of the pinacol esters surprisingly resulted in extensive decomposition. The mildly acidic conditions used to deprotect the phosphonate ester would not be expected to interfere with unactivated 1,2-disubsituted olefins or aliphatic ethers, and this result (along with several incongruent reactions) suggested a more complicated mode of decomposition was occurring. Addition of the radical scavenger 2,6-di-*tert*-butyl-1-hydroxy toluene (BHT) to the reaction suppressed the decomposition, and to ensure consistent results it is now routinely added to the phosphonate esterification and deprotection reactions described here.

The success of this coupling process was aided by the accessibility of pinacol phosphonates and their unique acid-catalyzed transesterification. Efficient methods for the preparation of phosphonic acid monoprotected esters are desirable as these are useful in the synthesis of biological phosphate analogues,[13] including RNA/DNA,[14] phosphonopeptides,[15] amino acid analogues,[16] pro-drugs,[17] and natural products.[18] A less likely mechanistic hypothesis for the transesterification involves a pinacol-pinacolone rearrangement of the protonated phosphonate **14** followed by collapse to the meta phosphate **17** (Scheme 6),[19] and interception of the reactive meta phosphate

SCHEME 6



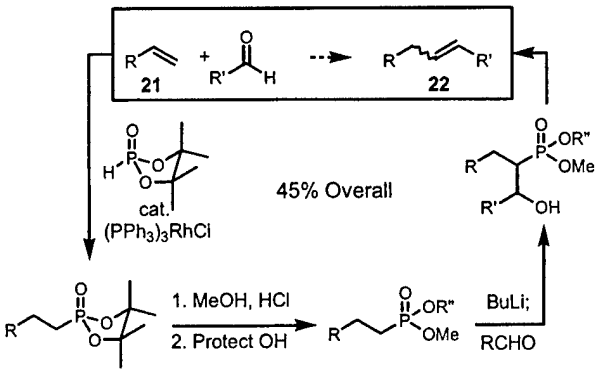
intermediate by methanol would give the half-ester **18**. According to this mechanism pinacol cleavage should occur in the absence of methanol, but the phosphonate **14** was stable to both dry HCl in dioxane and triflic acid in CH_2Cl_2. When stoichiometric methanol was added to these reactions at room temperature, less than 20% conversion to **18** occurred after 2 days. The stability of the pinacol phosphonate in the absence of methanol, and the qualitative rate dependence on the methanol concentration suggested a more likely mechanism in which the rate-limiting step will be the formation of phosphorane **19** by reaction with MeOH.[20] Proton-induced pinacol–pinacolone rearrangement will result in the formation of phosphonic acid mono methyl ester **18**. The poor results obtained at low methanol concentration are consistent with the equilibrium lying on the side of pinacol phosphonate **14** instead of pentavalent phosphorane **19**.[21,22]

Conclusion

Benzylic and *tert*-butyl mixed phosphonate esters were introduced to complete a set of orthogonal protective groups for phosphonic acids that further enhances the synthetic utility of olefin hydrophosphorylation and phos-

(12) Armstrong, A.; Brackenridge, I.; Jackson, R. F. W.; Kirk, J. M. *Tetrahedron Lett.* **1988**, *29*, 2483–2486.
(13) For a review, see: Blackburn, M. G. *Chem. Ind. (London)* **1981**, 134–144.
(14) For a review, see: (a) Eckstein, F.; Thomson, J. B. *Methods Enzymol.* **1995**, *262*, 189–202. (b) Egli, M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1894–1909. (c) De Clercq, E. *Biomed. Pharmacother.* **1996**, *50*, 207–215.
(15) For a review, see: Failla, S.; Finocchiaro, P.; Consiglio, G. A. *Heteroatom Chem.* **2000**, *11*, 493–504.
(16) Kafarski P.; Lejczak, B.. *Phosphorus, Sulfur Silicon Relat. Elem.* **1991**, *63*, 193-215.
(17) For a review, see: Krise, J. P.; Stella, V. J. *Adv. Drug. Deliv. Rev.* **1996**, *19*, 287–310.
(18) For a review, see: Fields, S. C. *Tetrahedron* **1999**, *55*, 12237–12273.
(19) Westheimer, F. H. *Chem. Rev.* **1981**, *81*, 313–326.
(20) Perreault, D. M.; Anslyn, E. V. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 432–450.
(21) (a) Ando, K. *J. Org. Chem.* **1999**, *64*, 6815–6821. (b) Brandt, P.; Norrby, P.-O.; Marin, I.; Rein, T. *J. Org. Chem.* **1998**, *63*, 1280–1289.
(22) See also: (a) Motoyoshiya, J.; Kusaura, T.; Kokin, K.; Yokoya, S.-I.; Takaguchi, Y.; Narita, S.; Aoyama, H. *Tetrahedron* **2001**, *57*, 1715–1721. (b) Kluger, R.; Davis, P. P.; Adawadkar, P. D. *J. Am. Chem. Soc.* **1979**, *101*, 5995–6000.

SCHEME 7



phonate coupling reactions with aldehydes and ketones. The overall sequence detailed herein can be routinely executed on multigram scales in ~45% overall yield from starting olefin **21** through to coupled product **22** (Scheme 7). The transesterification of pinacol phosphonates provides a new and efficient method for accessing phosphonic acid mono methyl esters.

Experimental Section[23]

Compounds **3**,[3] and **4**[3] were prepared according to literature procedures. Compounds **8**, **9b–e**, **10**, and **12** were prepared by one of the following general methods:

Phosphonic Acid Monomethyl Ester 8a from 4. To a solution of **4** (9.1 mmol) and BHT (3.0 mmol) in MeOH (10 mL) was added 4 M HCl in dioxane (10 mL). The solution was stirred at 50 °C for 3 h and concentrated in vacuo to yield crude **8a**, which was used in the next step without further purification: ^{1}H NMR (CD_3CN, 300 MHz) δ 0.90 (t, J = 6.5 Hz, 3H), 1.30–1.53 (m, 10H), 1.53–1.77 (m, 4H), 3.67 (d, J = 10.8 Hz, 3H); ^{1}H NMR (CD_3OD, 300 MHz) δ 0.92 (t, J = 6.0 Hz, 3H), 1.32–1.42 (m, 10H), 1.56–1.81 (m, 4H), 3.70 (d, J = 10.5 Hz, 3H); ^{13}C NMR (CD_3CN, 75.5 MHz) δ 14.5 (CH_3), 23.5 (CH_2), 23.6 (CH_2), 23.7 (CH_2), 23.9 (CH_2), 25.3 (CH_2), 27.2 (CH_2), 20.2 (CH_2), 31.5 (CH_2), 31.8 (CH_2), 31.9 (CH_2), 33.0 (CH_2), 52.1 (CH_3); ^{13}C NMR (CD_3OD, 75.5 MHz) δ 17.3 (CH_3), 26.3 (CH_2), 26.4 (CH_2), 26.5 (CH_2), 28.1 (CH_2), 29.6 (CH_2), 29.9 (CH_2), 33.1 (CH_2), 34.4 (CH_2), 34.6 (CH_2), 35.8 (CH_2), 55.0 (CH_3), 55.1 (CH_3); ^{31}P NMR (CD_3OD, 121.5 MHz) δ 34.3; ^{31}P NMR (CD_3Cl, 121.5 MHz) δ 38.2; MS (EI) m/z 209 $[M + H]^+$.

Phosphonic Acid Dimethyl Ester 9a from 8a. To a solution of crude **8a** and Cs_2CO_3 (10 mmol) in MeCN (15 mL) was added MeI (26 mmol). The resulting suspension was stirred at 50 °C for 48 h. The reaction mixture was diluted with EtOAc and washed with 10% aqueous HCl (2×), aqueous saturated $NaHCO_3$, and brine, dried ($MgSO_4$), and concentrated in vacuo. Purification by flash chromatography gave **9a** as a colorless oil in 73% yield: R_f 0.47 (EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.80 (t, J = 6.6 Hz, 3H), 1.19–1.31 (m, 8H), 1.47–1.72 (m, 4H), 3.66 (d, J = 10.8 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 14.2 (CH_3), 22.4 (CH_2), 22.5 (CH_2), 22.8 (CH_2), 23.9 (CH_2), 25.7 (CH_2), 29.2 (CH_2), 30.6 (CH_2), 30.8 (CH_2), 31.9 (CH_2), 52.3 (CH_3), 52.4 (CH_3); ^{31}P NMR ($CDCl_3$, 121.5 MHz) δ 36.2; MS (EI) m/z 223 $[M + H]^+$; HRMS (EI) calcd for $C_{10}H_{23}O_3P$ $[M + H]^+$ 223.1463, found 223.1462.

Phosphonic Acid Benzyl Ester Methyl Ester 9b from 8b. To a solution of crude **8b** (10 mmol) and Cs_2CO_3 (10 mmol) in MeCN (15 mL) was added BnBr (26 mmol). The resulting suspension was heated at reflux for 48 h, allowed to cool, and then diluted with EtOAc. The organic solution was washed with 10% aqueous HCl (2×), aqueous saturated $NaHCO_3$, and brine, dried ($MgSO_4$), and concentrated in vacuo. Purification of the residue by flash chromatography afforded **9b** as a colorless oil in 82% yield: R_f 0.70 (EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.89 (t, J = 6.8 Hz, 3H), 1.26–1.36 (m, 10H), 1.54–1.80 (m, 4H), 3.68 (d, J = 10.8 Hz, 3H), 5.09 (d, J = 8.4 Hz, 2H), 7.28–7.42 (m, 5H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 14.3 (CH_3), 22.5 (CH_2), 22.6 (CH_2), 22.9 (CH_2), 24.7 (CH_2), 26.6 (CH_2), 29.2 (CH_2), 30.7 (CH_2), 30.9 (CH_2), 32.1 (CH_2), 52.3 (CH_3), 67.3 (CH_2), 67.4 (CH_2), 128.1 (CH), 128.6 (CH), 128.8 (CH), 136.8 (C), 136.9 (C); ^{31}P NMR ($CDCl_3$, 121.5 MHz) δ 35.7; MS (CI) m/z 299 $[M + H]^+$; HRMS (CI) calcd for $C_{16}H_{27}O_3P$ $[M + H]^+$ 299.1776, found 299.1773.

β-Hydroxy Phosphonates 10a from 9a. To a cooled (−78 °C) solution of **9a** (0.80 mmol) in THF (2.5 mL) was added *n*-BuLi in hexanes (0.80 mmol). After the mixture was stirred at −78 °C for 15 min, the aldehyde (0.80 mmol) in THF (1 mL) was added. After 60 min at −78 °C, aqueous NH_4Cl was added to the cold mixture. After being warmed to room temperature, the mixture was extracted with EtOAc, and the organic layer was washed with brine and dried ($MgSO_4$). Purification by flash chromatography afforded **10a** as a colorless oil in 60% yield: R_f 0.65 (EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.80–0.87 (m, 9H), 1.15–1.68 (m, 16 H), 1.97–2.09 (m, 1H), 3.65–3.73 (m, 6H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 7.5 (CH_3), 7.6 (CH_3), 14.2 (CH_3), 22.8 (CH_2), 26.5 (CH_2), 28.6 (CH_2), 28.7 (CH_2), 29.2 (CH_2), 30.0 (CH_2), 30.5 (CH_2), 30.6 (CH_2), 32.0 (CH_2), 43.6 (CH), 52.2 (CH_3), 52.3 (CH_3), 52.4 (CH_3), 75.3 (C); ^{31}P NMR ($CDCl_3$, 121.5 MHz) δ 39.1; MS (CI) m/z 309 $[M + H]^+$, 291 $[M - H_2O + H]^+$.

Olefins 12b from 10b. A solution of **10b** (1.1 mmol) in EtOH (5 mL) containing a catalytic amount of Pd/C was shaken at room temperature for 16 h under an H_2 atmosphere (250 psi), and the resulting mixture was concentrated in vacuo to afford crude **11**. Without further purification, **11** was dissolved in $CHCl_3$ (5 mL) and DIC (2.2 mmol) was added. After being stirred at room temperature for 4 h, the reaction mixture was concentrated in vacuo, and the residue was purified by flash chromatography to give **12b** as a colorless oil in 68% yield: R_f 0.73 (hexane/EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.13 (t, J = 7.5 Hz, 6H), 2.18 (q, J = 7.5 Hz, 2H), 2.26 (q, J = 7.5 Hz, 2H), 3.48 (d, J = 7.2 Hz, 2H), 5.39 (t, J = 7.2 Hz, 2H), 7.25–7.41 (m, 5H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 12.8 (CH_3), 13.2 (CH_3), 23.3 (CH_2), 29.2 (CH_2), 33.8 (CH_2), 121.1 (CH), 125.7 (CH), 128.3 (CH × 2), 141.9 (C), 143.8 (C).

Phosphonic Acid *tert*-Butyl Ester Methyl Ester 9d from 8b. To a solution of crude **8b** (4.3 mmol) in CH_2Cl_2 (10 mL) and cyclohexane (10 mL) was added *tert*-butyl 2,2,2-trichloroimidate (43 mmol) portionwise. The resulting slurry was stirred for 16 h and then concentrated in vacuo. Purification of the residue by flash chromatography afforded **9d** as a colorless oil in 62% yield: R_f 0.30 (EtOAc/hexane 1:1); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.52 (s, 9H), 1.98–2.10 (m, 2H), 2.87–2.95 (m, 2H), 3.71 (d, J = 11.1 Hz, 3H), 7.23–7.36 (m, 5H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 28.69 (d, J = 143 Hz, CH_2), 28.72 (d, J = 4.4 Hz, CH_2), 30.24 (d, J = 3.9 Hz, CH_3), 51.79 (d, J = 6.6 Hz, CH_3), 82.26 (d, J = 9.4 Hz, C), 126.1 (CH), 127.9 (CH), 128.4 (CH), 141.02 (d, J = 17.6 Hz, C); ^{31}P NMR ($CDCl_3$, 121.5 MHz) δ 39.1; MS (CI) m/z 401 $[M + H]^+$; HRMS (CI) calcd for $C_{13}H_{21}O_3P$ $[M + H]^+$ 257.1307, found 257.1317.

Olefins 12e from 10e. To a solution of **10e** (0.68 mmol) in MeOH (2.5 mL) was added 4 M HCl in dioxane (2.5 mL). The reaction mixture was stirred for 2 h and then concentrated in vacuo. The residue was dissolved in $CHCl_3$, and DIC (1.36 mmol) was added. The reaction mixture was stirred for 2 d and then concentrated in vacuo. Purification of the residue by flash chromatography afforded **12e** as a colorless oil in 42% yield: R_f 0.31 (hexane/EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.42–2.49 (m, 1H), 2.55–2.62 (m, 1H), 2.77–2.84 (m, 2H), 3.42 (t, J = 5.1 Hz, 2H), 5.64–5.69 (m, 2H), 7.18–7.41 (m, 10H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 29.6 (CH_2), 33.8 (CH_2), 34.7

(23) For general experimental details, see: Reichwein, J. F.; Iacono, S. T.; Pagenkopf, B. L. *Tetrahedron* **2002**, *58*, 3813–3822.

(CH_2), 36.2 (CH_2), 39.3 (CH_2), 126.1 (CH), 126.2 (CH), 128.6 (CH), 128.7 (CH), 128.8 (CH), 129.2 (CH), 129.9 (CH), 130.0 (CH), 131.3 (CH), 141.3 (C), 142.2 (C), 142.3 (C).

Acknowledgment. We thank the DOD Prostate Cancer Research Program DAMD17-01-1-0109, the Robert A. Welch Foundation, and the Texas Advanced Research Program 003658-0455-2001 for financial support.

Supporting Information Available: Preparation and characterization data for **5**–**10** and **12**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO026834C

J|A|C|S
COMMUNICATIONS

Published on Web 06/13/2003

Formal [3 + 2] Cycloadditions of Donor–Acceptor Cyclopropanes and Nitriles

Ming Yu and Brian L. Pagenkopf*

Department of Chemistry and Biochemistry, The University of Texas at Austin, Austin, Texas 78712

Received December 12, 2002; E-mail: pagenkopf@mail.utexas.edu

Lewis acid promoted [3 + 2] cycloaddition reactions of donor–acceptor cyclopropanes are valuable synthetic processes for the construction of heterocyclic and carbocyclic structures (Scheme 1).[1–3] In an effort to extend the versatility of cyclopropanes to the synthesis and functionalization of carbohydrate derived systems, we have recently reported the facile, stereospecific preparation of **4** and established its utility for the asymmetric synthesis of natural products.[4] Investigations into the unique chemistry of glycal-derived cyclopropanes prepared by intramolecular cyclopropanation revealed novel reactivity, and herein we report the highly stereoselective formal [3 + 2] cycloaddition of these cyclopropanes with a wide variety of nitriles, affording synthetically versatile dihydropyrroles in high yield (see Tables 1 and 2). To the best of our knowledge, dipolar cycloaddition reactions of donor–acceptor cyclopropanes with nitriles are unknown.[5–7] The efficient and stereoselective assembly of densely functionalized amine-containing heterocycles is an active area of investigation due to wide occurrence of these species in natural products and synthetic materials. The 2*H*-3,4-dihydropyrrole products from the cycloaddition contain an aminal, a functional group that has classically served as a latent iminium ion.[8]

We have found that successfully revealing the dipolar nature of glycal-derived cyclopropanes is highly dependent upon the Lewis acid employed.[9,10] Activation with Me_3SiOTf, even in the presence of potential nucleophiles such as allyltrimethylsilane, gave the anhydrosugar **5** (Scheme 2). In stark contrast, when benzonitrile was added to the reaction mixture, activation of **4** by Me_3SiOTf at room temperature gave the imine **6a** in 81% isolated yield.[11,12] The structural assignment of **6a** was unambiguously established by X-ray crystallography (Figure 1).

A wide variety of nitriles were found to participate in the cycloaddition reaction (Table 1).[13] Aliphatic nitriles ranging from MeCN to the much larger *t*-BuCN all gave the expected imine adduct (entries 2–6). The nitrile could be used as solvent, and where this was impractical, the use of $MeNO_2$ or CH_2Cl_2 with 5 to 10 equiv of nitrile also gave excellent yields (compare entries 2 and 3). The cycloaddition of α,β-unsaturated nitriles in nitromethane occurred exclusively at the nitrile functional group (entries 7–9).[7a] Reaction with β-methoxy acrylonitrile proved useful for introducing an aldehyde functional group (entry 9), and the vinylogous amide **6h** was isolated in 78% yield. All the cycloaddition reactions reported herein were highly stereoselective, providing solely one diastereomeric product.

The di-*tert*-butylsilylene protective group is not a necessary structural feature for successful [3 + 2] cycloaddition, and cyclopropanes with distal acetate and benzyl ether protective groups were equally effective substrates (Table 2, entries 1 and 2). In addition to carbohydrate-derived substrates, cyclopropanes prepared from other readily available γ-hydroxy dihydropyrans participate in the cycloaddition reaction (entries 3 and 4).[14] This and related processes offer a new approach to the functionalization and utilization of the growing number of enantiomerically pure dihydropyrans available from hetero-Diels–Alder cycloadditions.[15] Ring expansion of the pyran to the seven-membered oxacycle was not observed from any of these cycloaddition reactions.[16,17] Reaction with the furanose substrate in entry 5 gave the imine addition product in 43% yield. Intramolecular cyclopropanation of dihydrofuran substrates was not possible due to facile furan formation.[4,18]

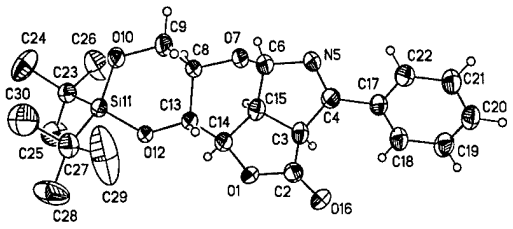
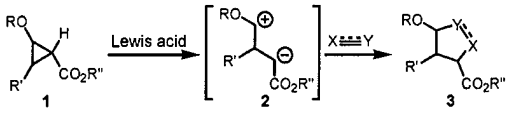


Figure 1. X-ray structure of **6a**.

Scheme 1



Scheme 2

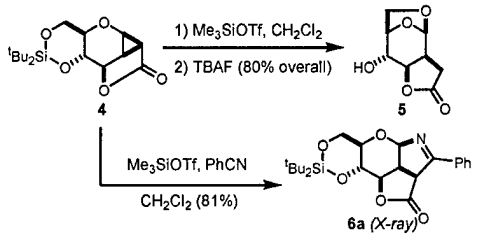
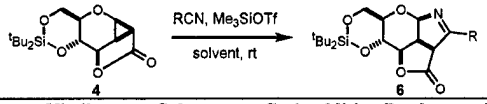
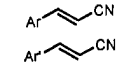
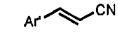
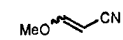
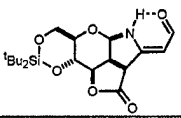


Table 1. Nitrile Additions to Cyclopropane 4

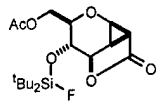
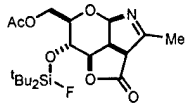
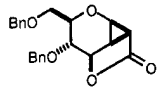
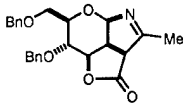
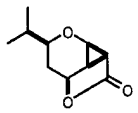
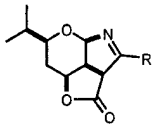
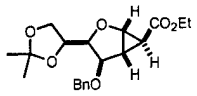
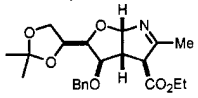


Entry	Nitrile	Solvent	Cycloaddition Product	Yield[a]
1	PhCN	CH_2Cl_2	**6a**, R = Ph	81%
2	MeCN	MeCN	**6b**, R = Me	96%
3	MeCN	CH_2Cl_2	**6b**, R = Me	84%
4	PrCN	CH_2Cl_2	**6c**, R = Pr	95%
5	^{t}BuCN	CH_2Cl_2	**6d**, R = ^{t}Bu	79%
6	$Cl(CH_2)_3CN$	CH_2Cl_2	**6e**, R = $(CH_2)_3Cl$	87%
7[b]		$MeNO_2$	**6f**, R = CHCHAr, X = H	60%
8[b]		$MeNO_2$	**6g**, R = CHCHAr, X = OMe	75%
9		CH_2Cl_2	**6h**, 	78%

[a] Isolated yields. [b] Nitrile =

10.1021/ja029716f CCC: $25.00

Table 2. Nitrile [3 + 2] Cycloadditions Acetonitrile

Entry	Substrate	Nitrile	Cycloaddition Product	Yield[a]
1[b]		MeCN		92%
2		MeCN		90%
3	 **7**	MeCN	 **8a**, R = Me	96%
4[b]	"	PhCN	**8b**, R = Ph	92%
5		MeCN		43%

[a] Isolated yields. [b] Reaction solvent = CH_2Cl_2.

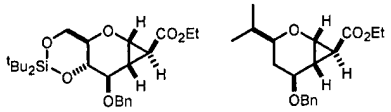


Figure 2.

The intramolecular glycal cyclopropanation strategy[4] appears to have been an important advance necessary for accessing the 3,4-dihydro-2*H*-pyrrole cycloaddition products. The substrates in Figure 2 were prepared by intermolecular cyclopropanation,[19] but attempted nitrile [3 + 2] cycloaddition reactions with these cyclopropanes gave multiple products. The ^{1}H NMR spectra of the crude reaction mixtures suggested imine formation, but decomposition occurred before purification was possible.

In summary, a novel Me_3SiOTf-activated [3 + 2] cycloaddition reaction between donor–acceptor cyclopropanes and nitriles has been described. Excellent yields of 3,4-dihydro-2*H*-pyrrole cycloaddition products are generally observed with aliphatic, aromatic, and α,β-unsaturated nitriles.

Acknowledgment. We thank the Robert A. Welch Foundation, the Texas Advanced Research Program 003658-0455-2001, and the DOD Prostate Cancer Research Program DAMD17-01-1-0109 for partial financial support. M.Y. thanks the Dorothy B. Banks Charitable Trust Fund for a graduate scholarship.

Supporting Information Available: X-ray structure data, CIF file for **6a**, and detailed experimental procedures and characterization of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Donor–acceptor cyclopropane reviews: (a) Wenkert, E. *Acc. Chem. Res.* **1980**, *13*, 27–31. (e) Danishefsky, S. *Acc. Chem. Res.* **1979**, *12*, 66–72. (b) Paquette, L. A. *Chem. Rev.* **1986**, *86*, 733–750. (c) Reissig, H.-U. In *The Chemistry of the Cyclopropyl Group*; Rappoport, Z., Ed.; John Wiley & Sons: Chichester, 1987; Chapter 8, pp 375–443. (d) Reissig, H. U. *Top. Curr. Chem.* **1988**, *144*, 73–135. (e) Wong, H. N. C.; Hon, M.-Y.; Tse, C.-W.; Yip, Y.-C.; Tanko, J.; Hudlicky, T. *Chem. Rev.* **1989**, *89*, 165–198. (f) de Meijere, A.; Wessjohann, L. *Synlett* **1990**, 20–32. (g) Kulinkovich, O. G. *Russ. Chem. Rev.* **1993**, *62*, 839–850. (h) Carbocyclic Three- and Four-Membered Ring Compounds. In *Houben-Weyl, Methods of Organic Chemistry*, 4th ed.; de Meijere, A., Ed.; Thieme Verlag: Stuttgart, 1997; Vols. E17a, E17b, E17c, E17d. (i) Salaün, J. *Top. Curr. Chem.* **2000**, *207*, 1–67. (j) de Meijere, A.; Kozhushkov, S. I.; Khlebnikow, A. F. *Top. Curr. Chem.* **2000**, *207*, 89–147. (k) de Meijere, A.; Kozhushkov, S. I.; Hadjiarapoglou, L. P. *Top. Curr. Chem.* **2000**, *207*, 149–227. (l) Reissig, H. Y.; Zimmer, R. *Chem. Rev.* **2003**, *103*, 1151–1196. (m) Gnad, F.; Reiser O. *Chem. Rev.* **2003**, *103*, 1603–1624;

(2) Dipolar cycloaddition reviews: (a) *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley: New York, 1984. (b) Wade, P. A. In *Comprehensive Organic Synthesis*; Trost, B. M., Flemming I., Eds.; Pergamon Press: Oxford, 1991; Vol. 4, p 1111. (c) Padwa, A. In *Comprehensive Organic Synthesis*; Trost, B M., Flemming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 4, p 1069. (d) *Synthetic applications of 1,*3-dipolar cycloaddition chemistry toward heterocycles and natural products; Padwa, A., Pearson, W. H., Eds.; New York: Wiley: 2002.

(3) (a) Komatsu, M.; Suehiro, I.; Horiguchi, Y.; Kuwajima, I. *Synlett* **1991**, 771–773. (b) Saigo, K.; Shimada, S.; Shibasaki, T.; Hasegawa, M. *Chem. Lett.* **1990**, 1093–1096. (c) Shimada, S.; Hashimoto, Y.; Sudo, A.; Hasegawa, M.; Saigo, K. *J. Org. Chem.* **1992**, *57*, 7126–7133.

(4) Yu, M.; Lynch, V.; Pagenkopf, B. L. *Org. Lett.* **2001**, *3*, 2563–2566.

(5) For a conceptually similar nitrile [4 + 2] cycloaddition, see: Stevens, R. V.; Kenny, P. M. *J. Chem. Soc., Chem. Commun.* **1983**, 384–385.

(6) For similar products from diazoester methodology, see: Doyle, M. P.; Yan, M.; Hu, W.; Gronenberg, L. S. *J. Am. Chem. Soc.* **2003**, *125*, 4692–4693.

(7) Cycloaddition reactions with the cyano group have been reviewed, see: (a) Myers, A. I.; Sircar, J. C. In *The Chemistry of the Cyano Group*; Rapporport, Z., Ed.; John Wiley: Belfast, 1970, Chapter 8. For a recent example, (b) see: Broggini, G.; Garanti, L.; Molteni, G.; Zecchi, G. *Heterocycles* **1999**, *51*, 1295–1302.

(8) (a) Hepworth, J. D.; Gabbutt, C. In *Comprehensive Organic Functional Group Transformations*; Katritzky, A. R., Meth-Cohn, O., Rees, C. W., Eds.; Kirby, G. W., Volume Ed.; Pergamon: Oxford, 1995; Vol. 4. (b) Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817–3856. For recent examples, see: (a) Sugiura, M.; Hagio, H.; Hirabayashi, R.; Kobayashi, S. *J. Am. Chem. Soc.* **2001**, *123*, 12510–12517. (b) Fleming, J. J.; Fiori, K. W.; Du Bois, J. *J. Am. Chem. Soc.* **2003**, *125*, 2028–2029.

(9) Reactions with BF_3·OEt_2: Yu, M.; Pagenkopf, B. L. *J. Org. Chem.* **2002**, *67*, 4553–4558.

(10) Reactions with $TiCl_4$: Yu, M.; Pagenkopf, B. L. *Tetrahedron* **2003**, *59*, 2765–2771.

(11) Traditional dipolarophiles are compatible, including aldehydes, imines, and silyl enol ethers. These results will be described elsewhere.

(12) For examples of nitriles as glycosyl acceptors, see: (a) Ratcliffe, A. J.; Mootoo, D. R.; Andrews, C. W.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1989**, *111*, 7661–7662. (b) Nair, L. G.; Fraser-Reid, B.; Szardenings, A. K. *Org. Lett.* **2001**, *3*, 317–319.

(13) Standard procedure: To a solution of cyclopropane (1 mmol) in CH_2Cl_2 (4 mL) at room temperature were added the nitrile (5.0 equiv) and trimethylsilyl trifluoromethanesulfonate (TMSOTf) (1.0 equiv) sequentially. After 5 min the reaction mixture was poured into vigorously stirred saturated aqueous $NaHCO_3$ (10 mL). Pure product is obtained by standard purification and silica gel chromatography (See Supporting Information).

(14) Huang, Y.; Rawal, V. H. *Org. Lett.* **2000**, *2*, 3321–3323.

(15) (a) Bednarski, M. D.; Lyssikatos, J. P. In *Comprehensive Organic Synthesis*; Trost, B. M., Heathcock, C. H., Eds.; Pergamon: New York, 1991; Vol. 2, pp 661–706. (b) Schmidt, R. R. *Acc. Chem. Res.* **1986**, *19*, 250–259. (c) Danishefsky, S. J.; DeNinno, M. P. *Angew. Chem., Int. Ed. Engl.* **1987**, *15*, 5–23. (d) Kametani, T.; Hibino, S. *Adv. Heterocycl. Chem.* **1987**, *42*, 245–333.

(16) Ramana, C. V.; Murali, R.; Nagarajan, M. *J. Org. Chem.* **1997**, *62*, 7694–7703.

(17) Cousins, G. S.; Hoberg, J. O. *Chem. Soc. Rev.* **2000**, *29*, 165–174.

(18) Timmers, C. M.; Verheijen, J. C.; van der Marel, G.; van Boom, J. H. *Synlett* **1997**, 851–853.

(19) (a) Wenkert, E.; Hudlicky, T.; Showalter, H. D. H. *J. Am. Chem. Soc.* **1978**, *100*, 4893–4894. (b) Hoberg, J. O.; Claffey, D. J. *Tetrahedron Lett.* **1996**, *37*, 2533–2536. (c) Henry, K. J.; Fraser-Reid, B. *Tetrahedron Lett.* **1995**, *36*, 8901–8904.

JA029716F