Pergamon

Tetrahedron Letters 43 (2002) 5249–5253

TETRAHEDRON LETTERS

Synthesis of a novel cyclic pentacovalent phosphoenol ether derived from a dienone. Approaches to the syntheses of phosphonate analogs of sphingomyelin, sphingosine 1-phosphate and ceramide 1-phosphate

Cynthia K. McClure* and Pranab K. Mishra[†]

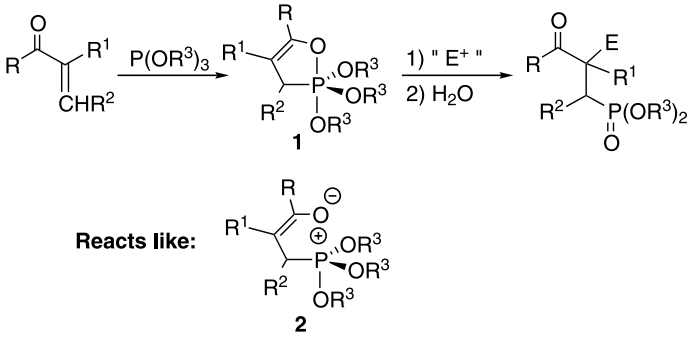
Department of Chemistry and Biochemistry, Montana State University, Bozeman, MT 59717, USA

Received 30 May 2002; accepted 3 June 2002

Abstract—The synthesis of a new pentacovalent oxaphospholene from a dienone, and its use as an enolate equivalent in the approach toward the syntheses of phosphonate analogs of sphingomyelin, sphingosine 1-phosphate and ceramide 1-phosphate are described. Condensation of the new P(V) reagent with an azodicarboxylate, followed by reduction of the ketone produced *cis*- and/or *trans*-oxazolidinones, potential precursors to the sphingomyelin, sphingosine and ceramide molecules. A study of reducing agents to produce the desired *cis*-oxazolidinone is presented. © 2002 Elsevier Science Ltd. All rights reserved.

Introduction of an antimetabolite, an agent which inhibits or perturbs a given metabolic reaction, is a reliable method used to investigate biochemical processes.[1,2] Phosphonate analogs possess a non-hydrolyzable C–P bond in place of the labile O–P bond in organophosphate esters, and as such present this possibility of antimetabolic activity. Phosphonate analogs of biologically active organophosphates *have* been found to be highly biologically active, and are therefore becoming increasingly important in the field of pharmacology and drug design.[1,2]

We are currently applying our pentacovalent oxaphospholene [P(V)] methodology to the preparation of isoteric and non-isosteric phosphonate analogs of various biologically active compounds for metabolic and biological activity studies.[3,4] During our investigation of the chemistry of the pentacovalent 1,2λ^5-oxaphospholenes **1**, prepared from the reaction of an enone with a trialkyl phosphite, we discovered that these P(V) compounds condense under very mild conditions with a variety of electrophiles to produce highly functionalized phosphonates.[3,4] Thus, in two steps or less, we have



Scheme 1.

Keywords: oxaphospholene; pentacovalent phosphorus; dienone; sphingomyelin analogs; phosphonate analogs.

* Corresponding author. Tel.: 406-994-1779; fax: 406-994-5407; e-mail: cmcclure@chemistry.montana.edu

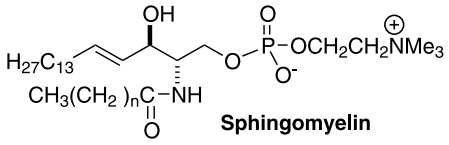
[†] Current address: Tanabe Research Laboratories, USA, Inc., 4540 Towne Center Court, San Diego, CA 92121, USA.

PII: S0040-4039(02)01038-9

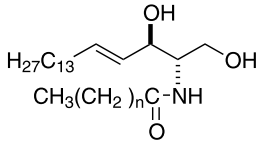
been able to α,β-difunctionalize enones. Our 1,2λ^5-oxaphospholenes **1** can be regarded as cyclic phosphoenol ethers. While their reactivities are of the 'open' enolate/phosphosphonium species such as **2**, they clearly exist as the cyclic pentacovalent species **1** as evidenced by ^{31}P NMR spectroscopy (see Scheme 1).

Herein, we report our progress on the preparation of phosphonate analogs of sphingomyelin, sphingosine 1-phosphate, and ceramide 1-phosphate via our P(V) methodology. The importance of sphingomyelins, ceramides and sphingosines in metabolism and cellular signalling has kept the areas of phospholipid biosynthesis, activation and catabolism under intense investigation.[5,6] Sphingomyelin is a major component of mammalian cell membranes, and ceramide, its catabolite formed during a sphingomyelinase-catalyzed reaction, is an important second messenger that can affect cell growth, cell differentiation and cell death. Ceramide is further metabolized by ceramidase to sphingosine, which can be phosphorylated to sphingosine 1-phosphate by sphingosine kinase. Recently, sphingosine 1-phosphate has been found to be a potent mitogen for several cell types, as well as being implicated in calcium mobilization, cell growth and differentiation.[5d,e] While the structural characteristics of inhibitors of the enzyme ceramidase have been delineated to some extent,[5f–h] and the functions of a family of sphingosine 1-phosphate receptors reported,[5d,e] less is known about the structure of sphingomyelinases, or which of the sphingomyelinases (acid or neutral) is most important for the stimulus-induced ceramide production.[5i–k] Thus, metabolically stable analogs or inhibitors would greatly assist in the investigations of these various sphingomyelinases and processes.

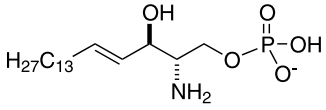
Our model studies toward the syntheses of the sphingomyelin and ceramide 1-phosphate phosphonate analogs utilizing a P(V) reagent derived from methyl vinyl ketone with dialkyl azodicarboxylates as the electrophilic nitrogen sources have been published.[4] While this current work was in progress, other workers in the field have reported on the syntheses of sphingomyelin and sphingosine phosphonates as hydrolytically stable analogs and possible sphingomyelinase inhibitors.[6] In this communication, we report our successful synthesis



Sphingomyelin



Ceramide



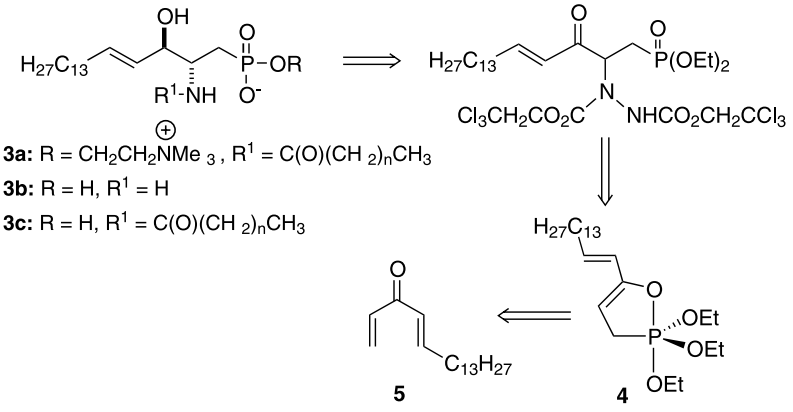
Sphingosine 1-phosphate

of a new P(V) reagent from a dienone and its use toward the production of the title compounds.

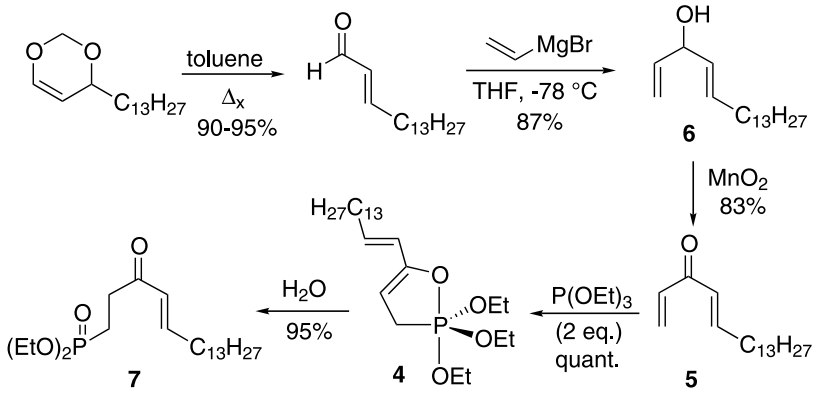
Our retrosynthetic analysis is shown in Scheme 2. For the synthesis of the phosphonate analogs of sphingomyelin (**3a**), sphingosine 1-phosphate (**3b**) and ceramide 1-phosphate (**3c**), we required the pentacovalent oxaphospholene **4** derived from the dienone **5**. To date, we have produced 1,2λ^5-oxaphospholenes (**1**) from enones where R = alkyl, TMS, $SiMe_2Ph$, CH_2OR'; R^1 = H; and R^2 = H or $P(O)(OEt)_2$.[3,4]

The dienone **5** was prepared via addition of vinyl Grignard reagent to *E*-hexadecenal synthesized by Schollkopf[7] via Funk's method, followed by MnO_2 oxidation. This dienone could be purified via flash column chromatography on silica gel, but had to be utilized quickly in subsequent reactions. We found it best to store our dienone precursor as the diene–alcohol **6**, and oxidize it just before use (see Scheme 3).

When we first attempted to form the P(V) **4** from the dienone **5**, we initially assumed that use of more than 1 equiv. of trialkyl phosphite would be detrimental and might lead to other products. However, by monitoring the reaction mixture of triethyl phosphite and the dienone **5** via ^{1}H, ^{31}P and ^{13}C NMR spectroscopies, we discovered that utilization of only 1 equiv. of phosphite led to many different products along with the desired P(V), **4**. Use of 2 equiv. of triethyl phosphite led to the successful formation of the desired P(V) in very high yield with little or no by-products.[8a,9] The excess phosphite could be easily removed in vacuo to produce very



Scheme 2.



Scheme 3.

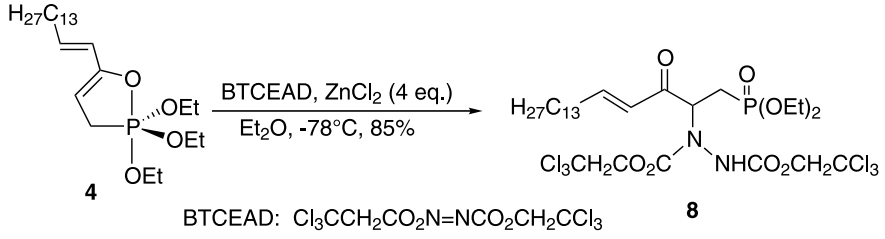
pure **4**. In order to prove that we had indeed produced the correct P(V) compound, **4** was hydrolyzed with water, and the expected phosphonoenone **7** was isolated in 95% yield after purification via column chromato graphy.[8b,9]

The condensation of our new P(V) **4** with an electrophilic nitrogen source was next investigated. The reaction conditions that worked well with the P(V) derived from methyl vinyl ketone were initially utilized, that is, addition of the P(V) to bis(2,2,2-trichloroethyl)azodicarboxylate (BTCEAD) at −78°C in Et_2O.[4] However, with the P(V) **4** derived from the dienone, no reaction was observed when these conditions were used. Warming the reaction mixture to room temperature did induce the reaction between BTCEAD and **4**, but the yield of **8** was very low. Following the protocol of Leblanc and co-workers, the use of Lewis acid activation to induce the reaction was investigated.[10] Of the Lewis acids studied ($TiCl_4$, $BF_3{\cdot}Et_2O$, $MgBr_2{\cdot}Et_2O$, $ZnCl_2$), it was found that the highest yield of **8** (85%) was obtained with $ZnCl_2$ (4 equiv.) in diethyl ether[9] (see Scheme 4).

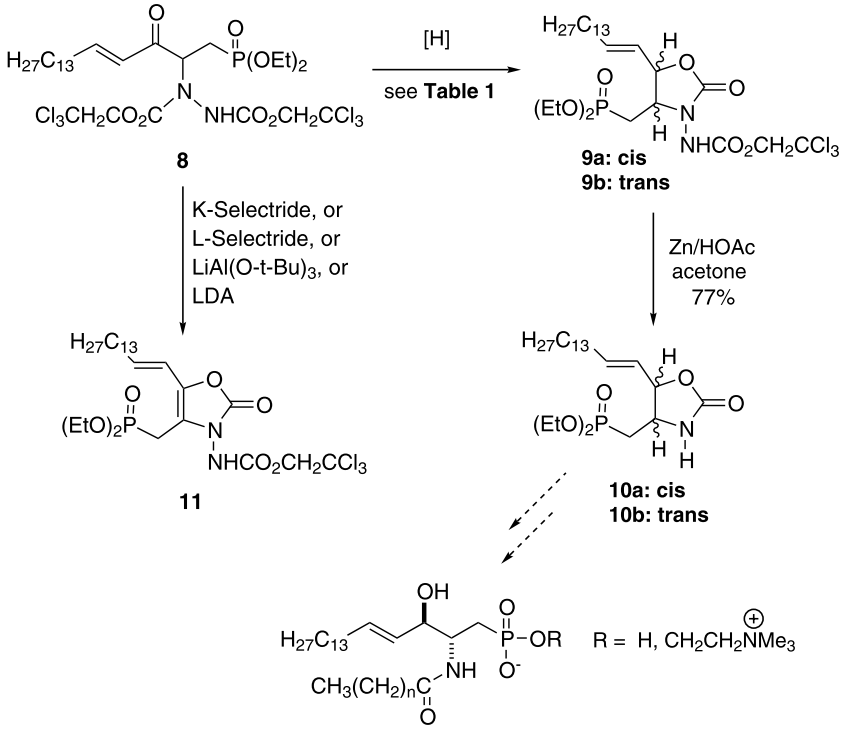
In order to reduce the enone carbonyl in a 1,2-sense to produce the *erythro*-aminoalcohol, several different reducing agents were investigated (Scheme 5 and Table 1). As previously seen in our model studies, the alkoxide formed from the reduction of the carbonyl cyclized onto the hydrazide to form the oxazolidinones **9a** and/or **9b**.[4,9] In order to produce the *erythro*-sphinomyelin isomer, we needed to form the *cis* oxazolidinone **9a**. Unfortunately, the majority of the reducing reagents utilized predominantly produced the undesired *trans* oxazolidinone isomer **9b**. Only the chiral reducing agent *R*-2-methyl-CBS-oxazaborolidine[11] produced the desired *cis* oxazolidinone product **9a** in moderate yield (43%). The other enantiomer of this chiral reducing agent, *S*-2-methyl-CBS-oxazaborolidine, produced the *trans* oxazolidinone product **9b** (40% yield). Kinetic resolution has apparently occurred, as the remaining material in both cases was the starting enone, **8**. We are currently investigating this reaction in more detail.

Interestingly, the reducing agents K-Selectride, L-Selectride and lithium tri-*t*-butoxy aluminum hydride ($LiAlH(O\text{-}t\text{-}Bu)_3$) all produced the same unsaturated oxazolidinone, **11**, most likely via enolization of the ketone followed by oxazolidinone formation. To prove its structure, **11** was independently synthesized by reacting the condensation product **8** with LDA to form the enolate, and allowing the reaction mixture warm to room temperature. The unsaturated oxazolidinone, **11**, was isolated in 88% yield via this method.

Cleavage of the N–N bond in a mixture of the oxazolidinones **9a** and **9b** to produce **10a** and **10b** was accomplished in good yield (77%) under the conditions used in the model system (Zn/AcOH/acetone).[4,10] Further synthetic studies on the reduction reaction, as well as preparation of the choline derivatives of both the *erythro* and *threo* derivatives will be reported in due course.



Scheme 4.



Scheme 5.

Table 1. Reduction of enone **8** to oxazolidinones **9a** and **9b**

Reaction conditions	Yield of **9** (%)	Ratio of **9b**:**9a**
$NaBH_4$, $CeCl_3$, MeOH, 0°C[a]	85 (+10% alcohol)	2:1
$ZnBH_4$, THF, 0°C[b]	89	3:1
$LiBH_3N(i\text{-}Pr)_2$, THF, 0°C[c]	77	4:1
$NaBH_4$, sucrose,[d] THF/H_2O, 0°C–rt	83	7:1
R-CBS, BH_3–DMS, rt	43	**9a** only
S-CBS, BH_3–DMS, rt	40	**9b** only

[a] Luche, J.-L. *J. Am. Chem. Soc.* **1978**, *100*, 2225.
[b] Nakata, T.; Tanaka, T.; Oishi, T. *Tetrahedron Lett.* **1983**, *24*, 2653.
[c] Fisher, G.; Fuller, J.; Harrison, J.; Alvarez, S.; Burkhardt, E.; Goralski, C.; Singaram, B. *J. Org. Chem.* **1994**, *59*, 6378.
[d] Denis, C.; Laignel, B.; Plusquellec, D.; Marouille, J.-Y.; Botrel, A. *Tetrahedron Lett.* **1996**, *37*, 53.

Acknowledgements

We thank the National Science Foundation for partial support of this work under grant CHE-970558. Acknowledgement is also made to the Donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research (27456-AC1).

References

1. (a) *Molecular Mechanisms of Transmembrane Signalling*; Cohen, P.; Houslay, M. D., Eds.; Elsevier: Oxford, 1985; (b) Hilderbrand, R. L. *The Role of Phosphonates in Living Systems*; CRC Press: Boca Raton, FL, 1983; (c) Blackburn, G. M.; Taylor, G. E.; Tattershall, R. H.; Thatcher, G. R. J.; McLennan, A. In *Biophosphates and their Analogues—Synthesis, Structure, Metabolism and Activity*; Bruzik, K. S.; Stec, W. J., Eds.; Elsevier Science: Amsterdam, 1987; p. 451; (d) Kalir, A.; Kalir, H. H. In *The Chemistry of Organophosphorus Compounds*; Hartley, F. R., Ed.; Wiley and Sons: New York, 1996; Vol. 4, pp. 767–780; (e) Engel, R. *Chem. Rev.* **1977**, *77*, 349; (f) Blackburn, G. M. *Chem. Ind.* **1981**, 134; (g) Fields, S. C. *Tetrahedron* **1999**, *55*, 12237; (h) Knowles, J. R.; Orr, G. A. *Biochem. J.* **1974**, *141*, 721; (i) Kim, C. U.; Misco, P. F.; Luh, B. Y.; Hitchcock, M. J. M.; Ghazzouli, I.; Martin, J. C. *J. Med. Chem.* **1991**, *34*, 2286.
2. For some recent relevant examples, see: (a) van Beek, E. R.; Lowik, C. W. G. M.; Ebetino, F. H.; Papapoulos, S. E. *Bone* **1998**, *23*, 437; (b) Pokrovsky, A. G.; Pronayeva, T. R.; Fedyuk, N. V.; Shirokova, E. A.; Khandazhinskaya, A. L.; Tarusova, N. B.; Karpenko, I. L.; Krayevsky, A. A. *Nucleosides Nucleotides Nucleic Acids* **2001**, *20*, 767; (c) Birck, M. R.; Holler, T. P.; Woodard, R. W. *J. Am. Chem. Soc.* **2000**, *122*, 9334 and references cited therein; (d) Chen, J.; Prestwich, G. D. *J. Org. Chem.* **1998**, *63*, 430; (e) Chung, S.-C.; Moon, S.-H. *Carbohydr. Res.* **1994**, *260*, 39; (f) Ezra, A.; Hoffman, A.; Breuer, E.; Alferiev, I. S.; Mönkkönen, J.; Hanany-Rozen, N.; Weiss, G.; Stepensky, D.; Gati, I.; Cohen, H.; Tömälehto, S.; Amidon, G. L.; Golomb, G. *J. Med. Chem.* **2000**, *43*, 3641; (g) Yokomatsu, T.; Shimizu, T.; Sada, T.; Shibuya, S. *Heterocycles* **1999**, *50*, 21 and references cited therein.
3. (a) McClure, C. K.; Jung, K.-Y.; Grote, C. W. *Phosphorus Sulfur Silicon* **1990**, *51/52*, 418; (b) McClure, C. K.; Jung, K.-Y. *J. Org. Chem.* **1991**, *56*, 867; (c) McClure, C.

K.; Jung, K.-Y. *J. Org. Chem.* **1991**, *56*, 2326; (d) McClure, C. K.; Grote, C. W. *Tetrahedron Lett.* **1991**, *32*, 5313; (e) McClure, C. K.; Grote, C. W. *J. Org. Chem.* **1992**, *57*, 5195; (f) McClure, C. K.; Grote, C. W. *Tetrahedron Lett.* **1993**, *34*, 983; (g) McClure, C. K.; Jung, K.-Y.; Grote, C. W.; Hansen, K. B. *Phosphorus Sulfur Silicon* **1993**, *75*, 23; (h) McClure, C. K.; Hansen, K. B.; Herzog, K. J.; Link, J. S.; Arnold, F. P. *Phosphorus Sulfur Silicon* **1996**, *109–110*, 333; (i) McClure, C. K.; Hansen, K. B. *Tetrahedron Lett.* **1996**, *37*, 2149; (j) McClure, C. K.; Herzog, K. J.; Bruch, M. D. *Tetrahedron Lett.* **1996**, *37*, 2153; (k) McClure, C. K.; Boehlow, T. R.; Alegria, L. A.; Madsen, T. A.; Wilkinson, R. A. *Phosphorus Sulfur Silicon* **1999**, *144–146*, 177–180; (l) McClure, C. K.; Hausel, R. C.; Hansen, K. B.; Grote, C. W.; Jung, K.-Y. *Phosphorus Sulfur Silicon* **1996**, *111*, 695; (m) McClure, C. K.; Cai, B.; Spangler, L. H. *Phosphorus Sulfur Silicon* **1999**, *144–146*, 709–712; (n) McClure, C. K.; Boehlow, T. R.; Alegria, L. A.; Madsen, T. A.; Sullivan, P. A.; Wilkinson, R. A. *J. Am. Chem. Soc.* **2002**, *124*, manuscript in preparation.

4. (a) McClure, C. K.; Mishra, P. K. *Phosphorus Sulfur Silicon* **1996**, *111*, 709; (b) McClure, C. K.; Mishra, P. K.; Grote, C. W. *J. Org. Chem.* **1997**, *62*, 2437.
5. (a) Kolter, T.; Sandhoff, K. *Angew. Chem., Int. Ed.* **1999**, *38*, 1532; (b) Sawai, H.; Hannun, Y. A. *Chem. Phys. Lipids* **1999**, *102*, 141 and references cited therein; (c) Krönke, M. *Chem. Phys. Lipids* **1999**, *102*, 157 and references cited therein; (d) Spiegel, S.; Milstien, S. *Biochem. Biophys. Acta* **2000**, *1484*, 107; (e) Im, D.-S.; Clemens, J.; Macdonald, T. L.; Lynch, K. R. *Biochemistry* **2001**, *40*, 14053; (f) Usta, J.; El Bawab, S.; Roddy, P.; Szulc, Z. M.; Hannun, Y. A.; Bielawska, A. *Biochemistry* **2001**, *40*, 9657; (g) Rerejm, M. E.; Chen, H.-C.; Barkovic, B.; Van Wyck, D.; Garidel, P.; Mendelsohn, R.; Moore, D. J. *J. Phys. Chem. B* **2001**, *105*, 9355; (h) He, L.; Byun, H.-S.; Smit, J.; Wilschut, J.; Bittman, R. *J. Am. Chem. Soc.* **1999**, *121*, 3897; (i) Arenz, C.; Gartner, M.; Waschowski, V.; Giannis, A. *Bioorg. Med. Chem.* **2001**, *9*, 2901; (j) Arenz, C.; Giannis, A. *Eur. J. Org. Chem.* **2001**, 137; (k) Murakami, M.; Iwama, S.; Fujii, S.; Ikeda, K.; Katsumura, S. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 1725.
6. (a) Hakogi, T.; Monden, Y.; Iwama, S.; Katsumura, S. *Org. Lett.* **2000**, *2*, 2627 and references cited therein; (b) Yokomatsu, T.; Takechi, H.; Takeshi, A.; Shibuya, S.; Kominato, T.; Soeda, S.; Shimeno, H. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1227; (c) Tarnowski, A.; Bär, T.; Schmidt, R. R. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 573.
7. Groth, U.; Schollkopf, U.; Tiller, T. *Tetrahedron* **1991**, *47*, 2835.
8. (a) Data for **4**: ^{1}H NMR: 5.98 (1H, dt, $J=15.3$, 6.9 Hz), 5.75 (1H, d, $J=15.4$ Hz), 4.68 (1H, dm, $J_{P-H}=47.4$ Hz), 3.87 (6H, m), 2.61 (2H, d, $J_{P-H}=18.6$ Hz), 2.08 (2H, m), 1.37 (2H, m), 1.30 (29H, m), 0.85 (3H, t, $J=6.14$); ^{13}C NMR: 151.7 (d, $J_{P-C}=16.9$ Hz), 131.2, 122.3 (d, $J_{P-C}=3.9$ Hz), 94.2 (d, $J_{P-C}=5.6$ Hz), 62.2 (d, $J_{P-C}=10.6$ Hz), 32.7, 32.3, 31.9, 29.6, 29.5, 29.4 (d, $J_{P-C}=162.5$ Hz), 29.3, 29.2, 28.2, 16.6 (d, $J_{P-C}=7.2$ Hz), 14.1. ^{31}P NMR: −23.8 ppm. IR (neat, cm^{-1}): 2930, 1730, 1695, 1627, 1606, 1467, 1261, 1220, 1159, 1059. HRMS (EI) calcd for $C_{24}H_{47}O_4P$: 430.3211; found: 430.3218; (b) Data for **7**: ^{1}H NMR: 6.87 (1H, dt, $J=8.95$, 6.9 Hz), 6.08 (1H, d, $J=15.9$ Hz), 4.08 (4H, m), 2.80 (2H, m), 2.20 (2H, m), 2.04 (2H, m), 1.44 (2H, m), 1.42 (20H, m), 1.09 (3H, t, $J=6.2$ Hz); ^{13}C NMR: 197.2, 148.2, 129.5, 63.4 (d, $J_{P-C}=5.4$ Hz), 61.5 (d, $J_{P-C}=4.6$ Hz), 32.50, 31.99 (d, $J_{P-C}=46.4$ Hz), 29.4, 29.3, 29.2, 29.0, 27.8, 27.3, 27.0, 22.4, 19.4 (d, $J_{P-C}=144.4$ Hz), 16.2, 15.9 (d, $J_{P-C}=6.4$ Hz), 13.9; ^{31}P NMR: 32.4 ppm. IR (neat, cm^{-1}): 3473, 2925, 2853, 1699, 1682, 1633, 1031. HRMS (EI) calcd for $C_{22}H_{43}O_4P$: 402.2894; found: 402.2898.
9. Mishra, P. K. Ph.D. Thesis, Montana State University, Bozeman, MT, 1997.
10. Mitchell, H.; Leblanc, Y. *J. Org. Chem.* **1994**, *59*, 682.
11. (a) Corey, E. J.; Bakshi, R. K.; Shibata, S.; Chen, C. P.; Singh, V. K. *J. Am. Chem. Soc.* **1987**, *109*, 7925; (b) Corey, E. J.; Gavai, A. V. *Tetrahedron Lett.* **1988**, *29*, 3201; (c) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551; (d) Martens, J.; Wallbum, S. *Tetrahedron: Asymmetry* **1992**, *3*, 1475.