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# Multivalent Activation in Temporary Phosphate Tethers: A New Tether for Small Molecule Synthesis

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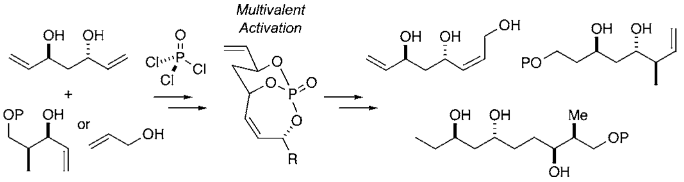
## ABSTRACT



**A new tether for small molecule synthesis is reported. This functionally active tether mediates the desymmetrization of a pseudo-$C_2$-symmetric tris-allylic phosphate triester to generate a *P*-chiral bicyclo[4.3.1]phosphate containing ample steric and stereoelectronic differentiation for investigating chemo-, regio-, and stereoselective transformations. Overall, the method reported herein demonstrates a fundamentally new role of phosphates in synthesis and provides differentiated polyol building blocks for use in natural product synthesis.**

The use of temporary tethering of two advanced intermediates is a powerful approach to streamline synthetic sequences en route to efficient asymmetric syntheses of complex biologically active targets. Historically, silicon has been the most widely used tether,[1] in which its orthogonal protecting group properties and coupling characteristics have served as the cornerstone of several synthetic strategies.[2−4] In contrast, use of phosphorus-based tethers (*P*-tethers) has been relatively limited, *with use of phosphate tethers being completely void in the literature.*[5] This is a surprising observation when one considers the potential of phosphorus tethers to mediate both di- and tripodal coupling and provide multivalent activation within the phosphate ester appendages for further transformations.

Despite enormous research on organophosphorus compounds, the general use of phosphate triesters in synthesis has been relatively limited. The use of phosphate triesters in complex synthesis has focused primarily on nucleophilic displacement reactions of allylic phosphates[6] and cross-coupling/reduction reactions with enolphosphates.[7] These reaction processes utilize the leaving group ability of a phosphate monoanion,[8] where a single ester moiety is

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[1] For a comprehensive review on disposable tethers, see: (a) Gauthier, D. R., Jr.; Zandi, K. S.; Shear, K. J. *Tetrahedron* **1998**, *54*, 2289−2338. (b) For a review on temporary silicon-tethered (Si-tethered) reactions, see: Fensterbank, L.; Malacria, M.; Sieburth, S. M. *Synthesis* **1997**, *8*, 813−854.

[2] For a recent review on temporary silicon-tethered (TST) strategies, see: (a) White, J. D.; Carter, R. G. In *Science of Synthesis: Houben-Wehl Methods of Molecular Transformations*; Fleming, I., Ed.; Georg Thieme Verlag: New York, 2001; Vol. 4, pp 371−412 and references therein.

[3] For use of Si tethers in metathesis reactions, see: (a) Fu, G. C.; Grubbs, R. H. *J. Am. Chem. Soc.* **1992**, *114*, 5426−5427. (b) Evans, P. A.; Cui, J.; Gharpure, S. J.; Polossoukhine, A.; Zhang, H.-R. *J. Am. Chem. Soc.* **2003**, *125*, 14702−14703 and references therein. (c) Maifeld, S. V.; Miller, R. L.; Lee, D. *J. Am. Chem. Soc.* **2004**, *126*, 12228−12229 and references therein.

[4] (a) Leighton, J. L.; Chapman, E. *J. Am. Chem. Soc.* **1997**, *119*, 12416−12417. (b) Wang, X.; Meng, Q.; Nation, A. J.; Leighton. J. L. *J. Am. Chem. Soc.* **2002**, *124*, 10672−10673. (c) Hackman, B. M.; Lombardi, P. J.; Leighton J. L. *Org. Lett.* **2004**, *6*, 4375−4377 and references therein.

[5] For examples of other P(III)/P(V)-based tethers, see: (a) Rubinstenn, G.; Esnault, J.; Mallet, J.-M.; Sinay, P. *Tetrahedron: Asymmetry* **1997**, *8*, 1327−1336. (b) Sprott, K. T.; McReynolds, M. D.; Hanson, P. R. *Org. Lett.* **2001**, *3*, 3939−3942.

[6] (a) Yanagisawa, A.; Noritake, Y.; Nomura, N.; Yamamota H. *Synlett* **1991**, 251−253. (b) Kacprzynski, M. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2004**, *126*, 10676−10681 and references therein.

[7] (a) Takai, K.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1980**, *21*, 2531−2534. (b) Sato, M.; Takai, K.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1981**, *22*, 1609−1612. (c) Nicolaou, K. C.; Shi, G.-Q.; Gaertner, P.; Gunzner, J. L.; Agrios, C.; Huber, R.; Chadha, R.; Huang, D. H. *J. Am. Chem. Soc.* **1997**, *119*, 8105−8106.

[8] Phosphate monoanions possess a p$K_a$ of roughly 1.5.

10.1021/ol0512886 CCC: $30.25

activated (monovalent activation) and the remaining ester positions serve as ancillary substituents. Our interest in the development of new methods in phosphorus chemistry[9] has led us to investigate the possibility of exploiting both multipodal coupling and multivalent activation in phosphate triesters, which by their nature present opportunities to investigate selective processes. We now report a new method that embodies several underdeveloped areas of phosphate chemistry, namely their use as removable, functionally active tethers capable of multipodal coupling and multivalent activation and their subsequent role as latent leaving groups in a number of unprecedented selective cleavage reactions. In addition, stereoelectronic effects within the bicyclic framework lend orthogonal protecting group stability. Overall, the method demonstrates a fundamentally new role of phosphates in synthesis and provides a facile approach to differentiated polyol building blocks for use in natural product synthesis.

We chose to utilize the tether desymmetrization method developed by Burke and co-workers[10] in order to construct the *P*-chiral bicyclo[4.3.1]phosphate **1** (Figure 1) containing ample steric and stereoelectronic differentiation for investigating chemo-, regio-, and stereoselective transformations. Overall, **1** possesses electrophilic character at seven of its nine non-oxygen atoms allowing for nucleophilic attack at phosphorus or any of six carbinol and allylic phosphate carbons [C(3), C(6), and C(8)] and [C(4), C(5), and C(12)], respectively.

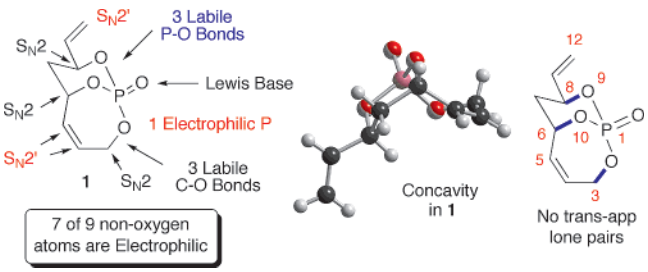
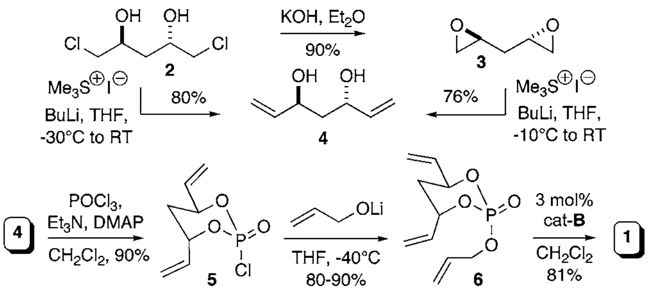


**Figure 1.**

In an optimized procedure, diol **4** is produced directly from the reaction of dichloro-1,3-*anti*-diol **2**[11] with a 9-fold excess of sulfonium ylide, generating **4** (80%) and circumventing the isolation of volatile epoxide **3**. Coupling of diol **4** with $POCl_3$ afforded phosphoryl monochloride **5** in excellent yield (Scheme 1). Subsequent reaction with lithium allyloxide afforded phosphate triester **6**. Final ring-closing metathesis (RCM) using $[(IMesH_2)(PCy_3)(Cl)_2Ru{=}CHPh$; cat-**B**$]$[12] produced **1** (81%) as confirmed by X-ray crystallographic analysis. Use of Grubbs' first-generation catalyst $(PCy_3)_2(Cl)_2Ru{=}CHPh$ (cat-**A**)[13] gave poorer yields.

**Scheme 1**



With **1** in hand, we initially examined hydrolytic protocols for tether removal. Although hydrolysis of phosphate esters, using both acid and base, has been extensively studied,[14] selective phosphate hydrolysis[15] is quite limited.[16] Exposure of **1** to a variety of acidic hydrolysis conditions [MeOH/HCl, 10% HCl (aq)/dioxane, and TMSCl], revealed a remarkable stability profile in **1**. This enhanced acid stability can be rationalized by the lack of lone pairs on the adjacent oxygen atoms antiperiplanar (app) to the P═O as shown in Figure 1, and as evident in previously studied bicyclic phosphate systems.[17]

Alternatively, basic hydrolysis conditions are known to stop at the stage of the monoanion salt due to decreased electrophilicity at the P═O moiety.[18] Hydrolysis of **1** was thus anticipated to stop at one or more of the regioisomeric phosphate mono-acid salts **7a**−**c** (Figure 2).

Experimentally, treatment of **1** with LiOH (aq) in dioxane led to quantitative and selective cleavage as evidenced by the appearance of a major singlet appearing at −0.06 ppm in the $^{31}P$ NMR spectrum (rs = 44:1). A $^{13}C$ NMR

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[9] McReynolds, M. D.; Dougherty, J. M.; Hanson, P. R. *Chem. Rev.* **2004**, *104*, 2239−2258.

[10] (a) Burke, S. D.; Muller, N.; Beaudry C. M. *Org. Lett.* **1999**, *1*, 1827−1829. (b) Burke, S. D.; Voight, E. A. *Org. Lett.* **2001**, *3*, 237−240. (c) Lambert, W. T.; Burke, S. D. *Org. Lett.* **2003**, *5*, 515−518.

[11] Following the protocol of Rychnovsky and co-workers, we have synthesized **2** on a 100-g scale starting from 2,4-pentanedione; see: Rychnovsky, S. D.; Griesgraber, G.; Powers, J. P. *Org. Synth.* **2000**, *77*, 1−11.

[12] Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953−956.

[13] (a) Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100−110. (b) Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2039−2041.

[14] (a) Cox, J. R., Jr.; Ramsay, J. O. B. *Chem. Rev.* **1964**, *64*, 317. (b) Bunton, C. A. *Acc. Chem. Res.* **1970**, *3*, 257−265. (b) Westheimer, F. *Acc. Chem. Res.* **1968**, *1*, 70−78. (c) Gorenstein, D. G.; Rowell, R.; Taira, K. Stereoelectronic Effects in Phosphate Esters. *ACS Symp. Ser.* **1981**, *171*, 69−75. (d) Fanni, T.; Taira, K.; Gorenstein, D. G.; Vaidyanathaswamy, R.; Verkade, J. G. *J. Am. Chem. Soc.* **1986**, *108*, 6311−6314 and references therein.

[15] Thatcher, G. R. J.; Kluger, R. Mechansim and Catalysis of Nucleophilic Substitution in Phosphate Esters. *Adv. Phys. Org. Chem.* **1989**, *25*.

[16] The most prominent synthetic case is a recent report by Imanishi and co-workers; see: Miyashita, K.; Ikejiri, M.; Kawasaki, H.; Maemura, S.; Imanishi, T. *J. Am. Chem. Soc.* **2003**, *125*, 8238−8243.

[17] It is known that when oxygen lone pairs occupy a trans-app position to an adjacent polar bond (P−OR), they donate electron density from their lone pair orbital, n, to the antibonding O−P $\sigma^*$, thus weakening the P═O bond and increasing the basicity at O. Conversely, lack of app lone pairs imparts orthogonal stability to hydrolysis with acid. (a) Deslongchamps, P. *Stereoelectronic Effects In Organic Chemistry*; Pergamon Press: Oxford, 1983. (b) Vande Griend, L. J.; Verkade, J. G.; Pennings, J. F. M.; Buck, H. M. *J. Am. Chem. Soc.* **1977**, *99*, 2459−2463.

[18] The half-life of trimethyl phosphate $(MeO)_3PO$ in a 1 M solution of NaOH in water at 35 °C is 30 min; the corresponding half-life of the resulting hydrolyzed phosphate salt $(MeO)_2PO_2Na$ is 11 years. Westheimer, F. H. *Science* **1987**, *235*, 1173−1178.

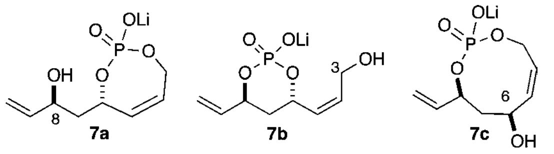
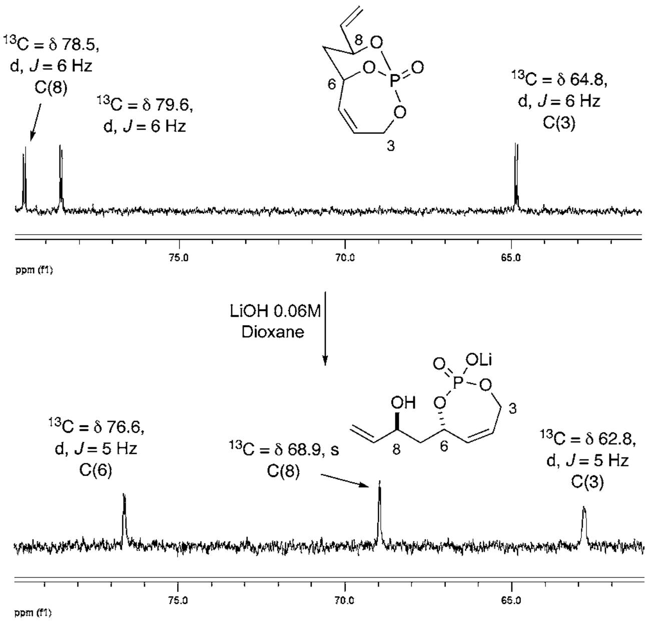


**Figure 2.**

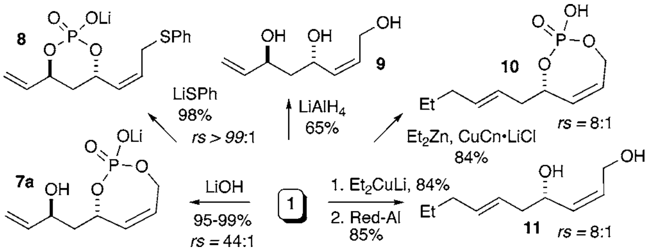
comparative analysis of both the product and **1** showed a diagnostic upfield shift of the resonance corresponding to the C(8) carbinol, indicating regioisomer **7a** as the major cleavage product (Scheme 2). Further evidence for **7a** is seen in the loss of C−P coupling at the C(8) carbinol position, as expected for cleavage of the C(8)O−P bond to form **7a**. Studies focusing on mechanistic details of this selective hydrolysis event are underway. In contrast, treatment of **1** with PhSLi showed remarkable quantitative and complete selectivity (rs = >99:1) for phosphate displacement at C(3), leading to **8** containing the differentiated 1,3-*anti* diol subunit (Scheme 3). This transformation is in agreement with precedent showing soft nucleophilic preference for attack at *C* vs *P*.[14a]

**Scheme 2**



We next examined reductive removal using conditions previously developed by Bartlett.[19] Reaction with LiAlH$_4$ (Et$_2$O at 0 °C, 15 min) led to exhaustive removal of the phosphate tether to produce triol **9**, a building block for the central subunit in the potent phosphatase inhibitor fostriecin.[16,20] This result is consistent with the addition of hard hydride anions at phosphorus and subsequent cleavage of all P−O ester bonds. Phosphate **1** was completely stable to Super Hydride (Et$_3$BHLi), LiBH$_4$, and BH$_3$·THF in THF at rt, demonstrating no product decomposition.

**Scheme 3**



Interest in revealing additional selective processes led us to examine regioselective and potentially diastereoselective S$_N$2′ cuprate displacement reactions. Initial use of ethyl cuprate[21] resulted in S$_N$2′ attack at the more accessible external terminal olefin of **1** to yield phosphonic acid **10** in excellent yield (rs ∼ 8:1). Subsequent reduction with Red-Al removed the phosphonic acid tether to yield diol diene **11**.

With this latter example in hand, we next turned to investigating stereofacial bias and stereoelectronic effects in cuprate additions to phosphate triester **1** with the goal of producing 1,3,4-stereotriads **13** and **15** found in the southern hemisphere of dolabelides A−D.[22] This stereotriad is also found in a number of other biologically active natural products including salicylihalamides A and B,[23] bitungolides A−F,[24] rhizoxin and rhizoxin D,[25] and discodermolide.[26] Initially, we studied the reactivity of the partially hydrogenated analogue **12** which was treated with ethyl cuprate, followed by Red-Al to provide diol **13** as the sole product (Scheme 4). This reaction occurs via a highly regio- and stereoselective *anti*-S$_N$2′ attack[27] at the C(5) olefinic carbon (rs = >99:1, ds = >99:1), where proper orthogonal alignment of the C=C $\pi^*$ and C−OP(O) $\sigma^*$ orbitals in path A allows for *anti*-S$_N$2′ attack to proceed exclusively at C(5) on the convex face of **12**.

Having established the high selectivity for the cuprate addition into **1**, we turned our attention to generating more elaborate systems via preferential functionalization of the external olefin. Therefore, hydroboration of **1** with 9-BBN

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(19) Bartlett, P. A.; Jernstedt, K. K. *Tetrahedron Lett.* **1980**, *21*, 1607−1610.

(20) (a) Boger, D. L.; Ichikawa, S.; Zhong, W. *J. Am. Chem. Soc.* **2001**, *123*, 4161−4167. (b) Chavez, D. E.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2001**, *40*, 3667−3670.

(21) Calaza, M. I.; Hupe, E.; Knochel, P. *Org. Lett.* **2003**, *5*, 1059−1061.

(22) Ojika, M.; Nagoya, T.; Yamada, K. *Tetrahedron Lett.* **1995**, *36*, 7491−7494.

(23) (a) Wu, Y.; Seguil, O. R.; De Brabander, J. K. *Org. Lett.* **2000**, *2*, 4241−4244. (b) Holloway, G. A.; Hugel, H. M.; Rizzacasa, M. A. *J. Org. Chem.* **2003**, *68*, 2200−2204. (c) Snider B.; Song, F. *Org. Lett.* **2001**, *3*, 1817−1820.

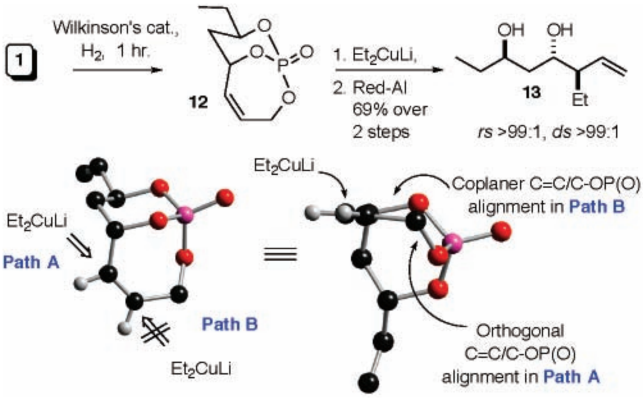
(24) Sirirath, S.; Tanaka, J.; Ohtani, I. I.; Ichiba, T.; Rachmat, R.; Ueda, K.; Usui, T.; Osada, H.; Higa, T. *J. Nat. Prod.* **2002**, *65*, 1820−1823.

(25) Lafontaine, J. A.; Provencal, D. P.; Gardelli, C.; Leahy, J. W. *Tetrahedron Lett.* **1999**, *40*, 4145−4148.

(26) Smith, A. B., III; Kaufman, M. D.; Beauchamp, T. J.; LaMarche, M. J.; Arimoto, H. *Org. Lett.* **1999**, *1*, 1823−1826 and references therein.

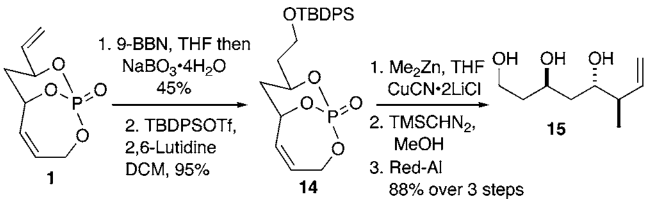
(27) Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1984**, *25*, 3063−3066.

**Scheme 4**



followed by mild oxidation of the borane with sodium perborate and subsequent TBDPS-protection afforded silyl protected primary alcohol **14** in moderate yield (Scheme 5).

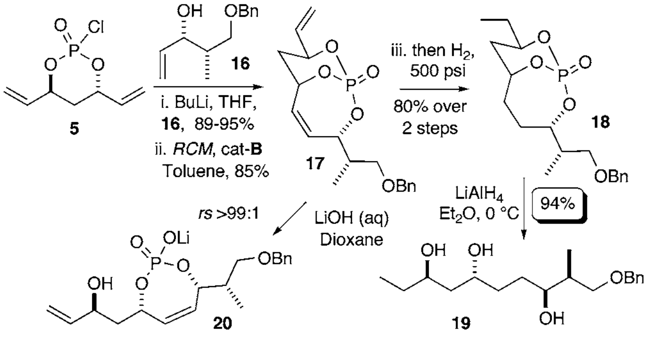
**Scheme 5**



As anticipated, treatment with a $Me_2Zn$-derived cuprate produced the corresponding phosphate acid as a single product as witnessed by $^{31}P$ NMR. Subsequent methylation to the phosphate ester, followed by reductive cleavage of the phosphate ester with Red-Al, led to fully deprotected triol **15** in excellent yields.[28]

Further potential of this method was showcased in the rapid assembly of tetrol **19**, which represents an advanced intermediate in the synthesis of feigrisolide B,[29] with direct application to tetranactin[30] (Scheme 4). In this example, the phosphate tether serves to mediate both the RCM desymmetrization event and to parlay the stereochemical complexity of diol **16** onto chloride **5**. Tandem RCM/exhaustive hydrogenation[31] using the second-generation Grubbs catalyst, afforded saturated bicyclic phosphate **18**. Reduction of **18** with $LiAlH_4$ produced triol **19** in excellent yield (94%). Alternatively, selective hydrolysis using the aforementioned LiOH conditions generated **20** with quantitative conversion and complete regioselectivity (rs = >99:1), further demonstrating the ability to generate complex differentiated polyol subunits (Scheme 6).

**Scheme 6**



In conclusion, we have demonstrated the utility of multivalent activation via a phosphate tether where latent leaving group ability has been harnessed in selective cleavage reactions within the bicyclic framework of **1**. Taken collectively, these features uncover new dimensions in phosphate chemistry. Additional studies probing mechanistic features, as well as applications in total synthesis, are underway and will be reported in due course.

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**Supporting Information Available:** Experimental details and spectroscopic data of new compounds, including X-ray crystallographic analysis of **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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[28] The TBDPS protecting group unexpectedly was removed.

[29] Tang, Y.-Q.; Sattler, I.; Thiericke, R.; Grabley, S.; Feng, X.-Z. *J. Antibiot.* **2000**, *53*, 934−943.

[30] Ando, K.; Oishi, H.; Hirano, S.; Okutomi, T.; Suzuki, K.; Okazaki, H.; Sawada, M.; Sagawa, T. *J. Antibiot.* **1971**, *24*, 347−352.

[31] Louie, J.; Bielawski, C. H.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 11312.