ORGANIC
LETTERS

2006
Vol. 8, No. 8
1673−1676

Temporary Phosphate Tethers: A Metathesis Strategy to Differentiated Polyol Subunits

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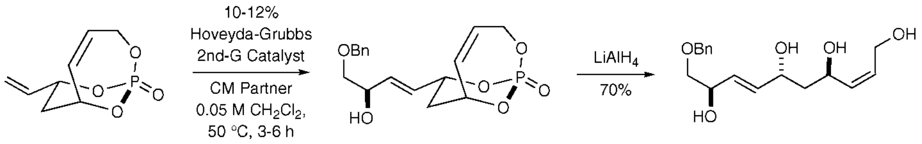
Received February 1, 2006

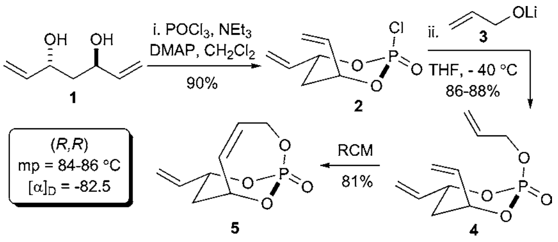
ABSTRACT



Studies probing reactivity and selectivity of cross metathesis (CM) with an exocyclic olefin in a *P*-chiral bicyclo[4.3.1]phosphate triester are described. Studies have revealed a Type III CM reactivity pattern for the exocyclic olefin within this phosphate triester. This versatile method allows for simple, selective manipulation of a *P*-chiral building block en route to advanced polyol subunits.

Exploiting temporary tethers[1] as a tactic to join complex synthetic building blocks has emerged as a versatile approach to rapidly access biologically relevant targets. Previous use of temporary tethers in synthesis has centered largely around silicon.[1] We have reported the use of phosphinamide, phosphonamide, phosphonamidate,[2] and phosphate tethers (*P*-tethers),[5] each possessing a number of salient features that can be exploited in synthesis. In particular, we have demonstrated that phosphate tethers provide not only orthogonal protective attributes but also multivalent activation of the corresponding phosphate ester appendages by providing innate leaving group ability within the tether. Using a phosphate tether, we constructed the unique *P*-chiral bicyclo[4.3.1]phosphate triester **5** (Scheme 1) and demonstrated its utility in a myriad of regio-, chemo-, and stereoselective transformations.[5] In light of this advance, we now report an extension of the phosphate tether methodology in which additional functionalization via highly selective cross metathesis (CM) of **5** allows for facile assembly of a diverse array of complex differentiated polyol subunits.

Scheme 1



Olefin CM is a powerful technique to access highly substituted olefins in a rapid, mild, and selective manner.[3] CM has emerged as a versatile synthetic tool and continues to showcase its utility in compliment to its widely used metathesis counterparts. Issues concerning olefin partner selectivity[4] continue to warrant further development in this

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(1) (a) Gauthier, D. R., Jr.; Zandi, K. S.; Shea, K. J. *Tetrahedron* **1998**, *54*, 2289−2338. (b) For reviews on temporary silicon-tethered (Si-tethered) reactions, see: Fensterbank, L.; Malacria, M.; Sieburth, S. M. *Synthesis* **1997**, *8*, 813−854. (c) White, J. D.; Carter, R. G. *Science of Synthesis: Houben-Wehl Methods of Molecular Transformations*; Thieme Verlag: New York, 2001; Vol. 4, pp 371−412 and references therein.

(2) (a) Sprott, K. T.; McReynolds, M. D.; Hanson, P. R. *Org. Lett.* **2001**, *3*, 3939−3942. (b) McReynolds, M. D.; Sprott, K. T.; Hanson, P. R. *Org. Lett.* **2002**, *4*, 4673−4676. (c) McReynolds, M. D.; Dougherty, J. M.; Hanson, P. R. *Chem. Rev.* **2004**, *104*, 2239−2258.

(3) For recent reviews on CM, see: (a) Grubbs, R. H. *Handbook of Metathesis*; Wiley-VCH: Weinheim, Germany, 2003. (b) Connon, S. J.; Blechert, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 1900−1923.

(4) Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360−11370.

10.1021/ol0602809 CCC: $33.50

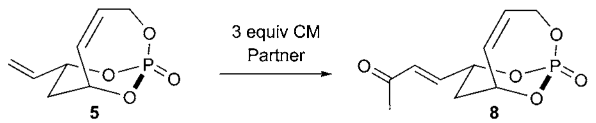
area. Uncovering amenable partners for selective CM opens opportunities for the stereoselecive synthesis of interesting targets. With this goal in mind, we set out to expand the utility of our previously reported bicyclic phosphate triester **5**[5] via selective CM and further functionalization.

The scope of olefin CM has expanded as the reactivity of various catalysts and selectivity issues continue to be resolved.[3] The proper choice of olefin partners which must account for steric and electronic differences, in accord with a suitable catalyst, allows for a highly selective CM.[4] Grubbs and co-workers have categorized various olefins by their relative rates of homodimerization correlating with the catalyst being used for CM.[4,6] These types range from Type I olefins, classified by rapid, reversible, homodimerization, to Type IV olefins which are spectators to CM. Varying product ratios can be observed when pairing different olefin types; mixing Type I olefins yields a statistical mixture of CM and homodimerization, whereas CM between Type I and Type II olefin pairs is very selective and high yielding of CM products. Using differential reactivity of olefins allows one to design selective CM by properly pairing olefin partners.

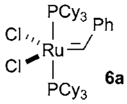
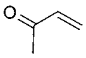
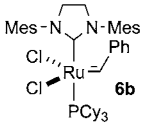
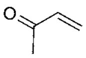
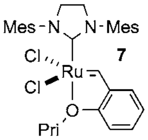
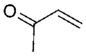
Bearing in mind these features of CM, we set out to explore the scope and utility of CM reactions between the terminal olefin in **5** and olefinic partners. Construction of *P*-chiral bicyclic[4.3.1]phosphate triester **5** began with coupling of C_2-symmetric diene 1,3-diol **1**[7] and phosphoryl trichloride producing the pseudo-C_2-symmetric compound **2** possessing interchangeable, homotopic Cl and $P{=}O$ groups. Concurrent addition of lithium allyloxide **3** into phosphoryl monochloride **2** yields phosphate triester triene **4**. Ring-closing metathesis (RCM) using the Grubbs second-generation catalyst **6b**[8] afforded desired phosphate **5** in good yield.

Our work started by screening metathesis catalysts **6a**, **6b**, and **7** for viability in CM between **5** and suitable olefinic partners (Scheme 2). We employed methyl vinyl ketone under refluxing CH_2Cl_2 as a standard system for a preliminary proof-of-concept experiment. Various catalytic loads and reaction concentrations produced disappointingly low yields, < 5% and 26%, when using both Grubbs first- and second-generation catalysts **6a**[9] and **6b**, respectively. We next studied the use of the Hoveyda−Grubbs second-generation catalyst **7**,[10] which Blechert and co-workers employed in successful CM with electron-deficient systems.[11] Using Blechert's conditions, we produced a selective CM between **5** and methyl vinyl ketone yielding **8** (75%) with high olefin selectivity (E:Z = 44:1). At a concentration of 0.1 M, similar yields were achieved, yet the E:Z ratio decreased to 15:1.

Scheme 2



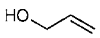
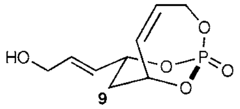
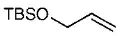
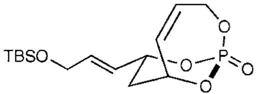
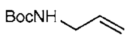
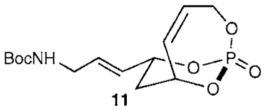
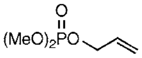
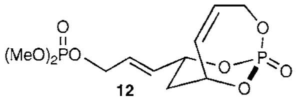
5 **8**

entry	10% catalyst	CM partner	conc./ solvent	% yield
1	 **6a**		0.05 M/ CH_2Cl_2	<5[a]
2	 **6b**		0.05 M/ CH_2Cl_2	25[a]
3			0.1 M/ CH_2Cl_2	26[a]
4	 **7**		0.05 M/ CH_2Cl_2	75[b]
5			0.1 M/ CH_2Cl_2	71[b,c]

[a] Yields determined by ^{31}P NMR. [b] Yields determined by isolated, purified products. [c] Used 4.0 equiv of MVK.

With this result in hand, other CM partners were studied. Beginning with Type I olefins (Table 1), CM of **5** with 1.1 equiv of allyl alcohol and TBS-protected allyl alcohol proceeded smoothly with excellent yield and selectivity (86% and 87% yields, >99:1 E:Z selectivity) using 10 mol % of

Table 1

entry	CM partner	product	% yield	*E/Z*
1		 **9**	86	>99:1
2		 **10**	87	>99:1
3		 **11**	69	>99:1
4		 **12**	80	2:1

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(5) Whitehead, A.; McReynolds, M. D.; Moore, J. D.; Hanson, P. R. *Org. Lett.* **2005**, *7*, 3375−3378.

(6) Hoveyda, H. R.; Vezina, M. *Org. Lett.* **2005**, *7*, 2113−2116.

(7) (a) 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.

(8) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953−956.

(9) (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.

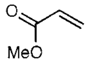
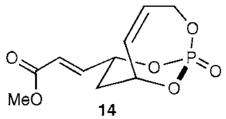
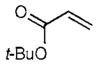
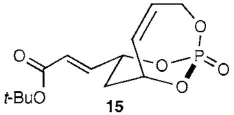
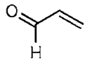
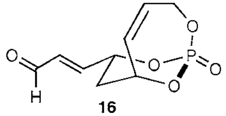
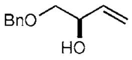
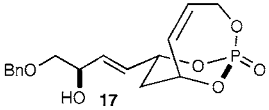
(10) (a) For a review, see: Hoveyda, A. H.; Gillingham, D. G.; Van Veldhuizen, J. J.; Kataoka, O.; Garber, S. B.; Kingsbury, J. S.; Harrity, J. P. A. *Org. Biol. Chem.* **2004**, *2*, 8−23 and references therein. (b) A study of the CM reaction using the Hoveyda−Grubbs catalyst was reported by: Cossy, J.; BouzBouz, S.; Hoveyda, A. H. *J. Organomet. Chem.* **2001**, *624*, 327−332.

(11) Dewi, P.; Randl, S.; Blechert, S. *Tetrahedron Lett.* **2005**, *46*, 577−580.

Hoveyda–Grubbs catalyst **7** in refluxing CH_2Cl_2 over a 3–6 h period. When the CM partner was switched to a Boc-protected allylamine, the yield of the corresponding protected amino phosphate triester **11** decreased, but selectivity was maintained (>99:1). Coupling allyloxy dimethoxyphosphate with bicyclic phosphate **5** produced **12** in good yield, albeit with diminished *E*:*Z* selectivity (2:1). Again, when **6a** and **6b** were used in these CMs with Type I olefin partners, yields were noticeably lower.

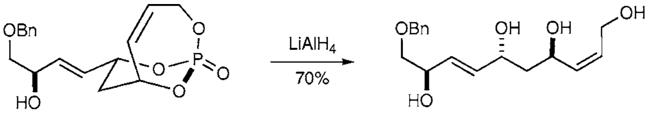
With the success of Type I olefins in hand, we next turned toward screening CM between Type II olefin coupling partners and **5** (Table 2). With electron-deficient Type II olefins, 4–5 equiv of the CM partner were needed to obtain the best yields. Optimized conditions were found to occur again with 10–12 mol % of Hoveyda–Grubbs catalyst **7**. Having achieved CM with methyl vinyl ketone, we employed other electron-deficient olefin partners. Treatment of **5** with methyl acrylate occurred in good yield and selectivity (78% yield, *E*:*Z* = 8:1) (Table 2, entry 1). Interestingly, when *tert*-butyl acrylate was used, the yield dropped to 60% and the *E*:*Z* ratio decreased to 5:1 (Table 2, entry 2). When acrolein was used, CM proceeded smoothly to afford **16** in good yield and with excellent selectivity (Table 2, entry 3).

Table 2

entry	CM partner	product	% yield	*E/Z*
1		 **14**	78	8:1
2		 **15**	60	5:1
3		 **16**	78	>99:1
4	 **13**	 **17**	72	>99:1

The use of more elaborate coupling partners provides an attractive extension of this chemistry. Thus, treatment of **5** with readily prepared (*R*)-1-(benzyloxy)but-3-en-2-ol **13**[12] (Table 2, entry 4) gave phosphate **17** in good yield and high selectivity. Furthermore, convenient removal of the tether in **17** was realized with $LiAlH_4$[13] affording the advanced polyol subunit **18** in 70% yield (Scheme 3). Overall, **18** is readily derived from **1** in a concise five-step sequence.

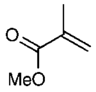
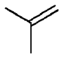
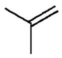
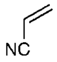
Scheme 3



17 **18**

To complete the reactivity profile of **5**, Type III olefins were surveyed as CM partners. When treated with methyl methacrylate for 12 h, **5** was unreactive and could be cleanly recovered (Table 3, entry 1). Using isobutylene afforded only trace amounts of product when the reaction was run at varying equivalents (Table 3, entries 2 and 3). CM between bicyclic phosphate **5** and electron-deficient acrylonitrile[6] also yielded no product (Table 3, entry 4). Attempted homodimerization of bicyclic phosphate **5** produced no observable product after 24 h under the aforementioned CM conditions. This result, when coupled with the data complied in Table 3, suggests Type III character for the external olefin within phosphate **5**.

Table 3

entry	CM partner	equivalents	% yield
1		4.0	<5
2		4.0	<5
3		Neat	<5
4		4.0	N.R.

We next undertook the construction of complex polyketide fragment **23** (Scheme 4) possessing a key stereotriad found in a number of natural products,[14] including Dolabelides A and B.[15] In this alternative method, we envisioned that a selective hydrogenation would be possible at the external olefin if we imposed additional steric constraints via incorporation of a geminal dimethyl group in **19** and **20**.

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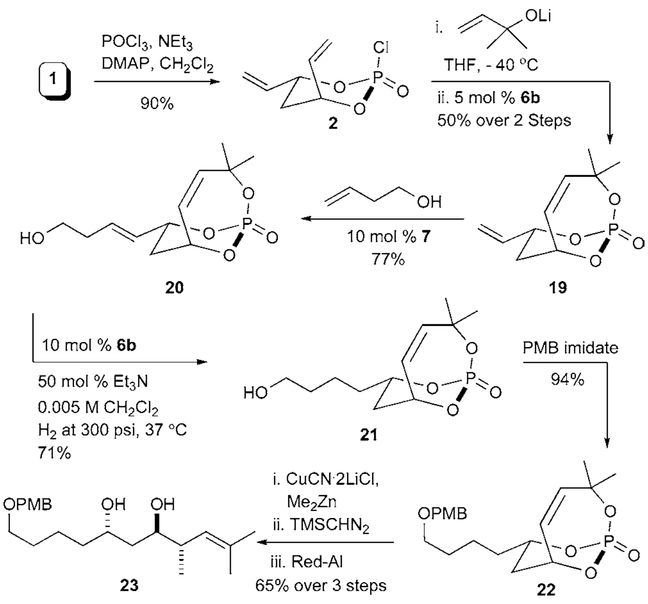
(12) Olefin **13** was produced in high yield following the Davoille protocol. See: Davoille, R. J.; Rutherford, D. T.; Christie, S. D. R. *Tetrahedron Lett.* **2000**, *41*, 1255–1259. Thus, (*R*)-(−)-benzyloxy glycidol ether in THF was added to Me_3SI/BuLi (−40 °C to room temperature).

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

(14) Salicylihalamides: (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. Bitungolides A–F: (d) 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. Rhizoxin D: (e) Lafontaine, J. A.; Provencal, D. P.; Gardelli, C.; Leahy, J. W. *Tetrahedron Lett.* **1999**, *40*, 4145–4148. (+)-Discodermolide: (f) Smith, A. B., III; Kaufman, M. D.; Beauchamp, T. J.; LaMarche, M. J.; Arimoto, H. *Org. Lett.* **1999**, *1*, 1823–1826.

(15) (a) Ojika, M.; Nagoya, T.; Yamada, K. *Tetrahedron Lett.* **1995**, *36*, 7491–7494. (b) Schmidt, D. R.; Park, P. K.; Leighton, J. L. *Org. Lett.* **2003**, *5*, 3535–3537.

Scheme 4



Thus, utilizing the lithium alkoxide of 2-methylbut-3-en-2-ol as a coupling partner with diol **1** and $POCl_3$ provided a phosphate triene that underwent smooth RCM to afford **19**. CM of phosphate **19** with homoallyl alcohol using Hoveyda–Grubbs catalyst **7** generated functionalized phosphate **20**. Subjection of **20** to 10 mol % of Grubbs catalyst **6b**, in the presence of 0.5 equiv of triethylamine[16] at 300 psi H_2, achieved selective hydrogenation of the external olefin in good yield. PMB protection of alcohol **21** using a PMB-imidate produced **22** in 94% yield. Final diversification of this substrate using a highly regio- and diastereoselective methyl cuprate addition,[5] followed by phosphate removal, produced the differentiated polyol fragment **23** as the sole product in good yield over three steps.

In conclusion, we have demonstrated the utility of CM in bicyclic phosphates **5** and **19** with application to rapid assembly of advanced polyol subunits. Moreover, we have determined a Type III olefinic character with respect to CM for the exocyclic olefin in both **5** and **19**. This is significant in that Type III behavior is ideal for the precious CM partner where homocoupling pathways are nonexistent (i.e., precious component will not dimerize). This empirical observation illustrates deficiencies in our knowledge of cross metathesis in complex molecules and points to additional studies. Further methodology studies probing reactivity and manipulations of the intriguing bicyclic phosphates **5** and **19** and analogues thereof continue. Applications to total synthesis are ongoing and will be reported in due course.

Acknowledgment. This investigation was generously supported by funds provided by the NSF CHE-0503875 and the NIH Dynamic Aspects in Chemical Biology Training Grant (J.D.W.). The authors thank Dr. David Vander Velde and Sarah Neuenswander for assistance with NMR measurements and Dr. Todd Williams for HRMS analysis. The authors kindly acknowledge Daiso Co., Ltd., Fine Chemical Department, for donating 100 g of each antipode of both benzyl- and trityl-protected glycidols (e-mail:akkimura@daiso.co.jp) and Materia, Inc. for supplying metathesis catalyst and helpful suggestions.

Supporting Information Available: Experimental details and spectroscopic data of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0602809

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[16] (a) Drouin, S. D.; Zamanian, F.; Fogg, D. E. *Organometallics* **2001**, *20*, 5495–5497. (b) Bielawski, C. W.; Louie, J.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 12872–12873.