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# A Multifaceted Phosphate Tether: Application to the C1–C14 Subunit of Dolabelides A–D

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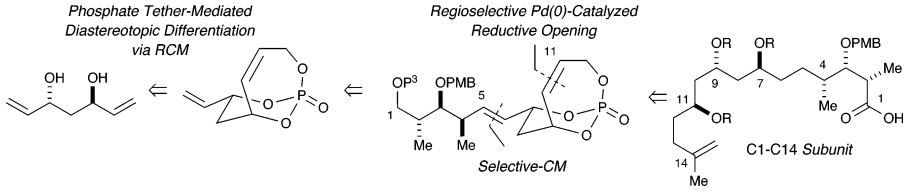
## ABSTRACT




**A phosphate tether approach to the C1–14 subunit of dolabelide is described. The phosphate tether serves a multifaceted role mediating several processes, including (i) diastereotopic differentiation via RCM, (ii) selective CM by imparting Type III behavior to the exocyclic olefin, (iii) regioselective hydrogenation, and (iv) regioselective Pd(0)-catalyzed reductive opening of the bicyclic phosphate. Overall, this strategy uses orthogonal protecting- and leaving-group properties innate to phosphate esters to rapidly assembly the titled subunit.**

In 1995, isolation and structural characterization of two new 22-membered macrolides, dolabelides A (**1**) and B,[1] from the sea hare *Dolabella auricularia* were reported. Isolation of dolabelides C and D,[2] 24-membered macrolides, was achieved from the same source. Cytotoxicity studies of dolabelides A−D revealed promising results against cervical cancer HeLa-$S_3$ cells with $IC_{50}$ values of 6.3, 1.3, 1.9, and 1.5 $\mu$g/mL, respectively. Synthetic studies toward various subunits of dolabelide have recently been reported.[3] These efforts include synthesis of protected intermediates of the C1−C14 subunit, with Leighton and co-workers reporting the properly acetylated C1−C14 fragment and completing the only total synthesis of dolabelide D in 2006.[4] Key features common among the dolabelide family are 11 stereogenic centers, eight of which bear oxygen, and two *E*-configured trisubstituted olefins. Other attributes possessed by this family of molecules include 1,3-*anti*-diol fragments found at C7/C9 and C19/C21, along with an accompanying 1,3-*syn*-diol at C9/C11 and polypropionate fragments at C1/C4 and C22/23. The endgame strategy for ring closure was envisioned to hinge on a key ring-closing metathesis (RCM) of the C14/C15-trisubstitued olefin following a precedent set by Leighton and co-workers.[4] Preceding this macrocyclization is a simple esterification connecting the C1 carboxylic acid and C23 alcohol, thus coupling the C1−C14 (**2**) and C15−C30 (**3**) subunits of dolabelide. The stereochemical complexity and known biological activity of the dolabelide family present a worthy and formidable challenge. In this regard, we herein report the use of a multifaceted phosphate tether toward the synthesis of the C1−C14 subunit of dolabelide.

The cornerstone for the title work hinged on recent studies, countering historical views, which have revealed a function-

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(3) (a) Grimaud, L.; Rotulo, D.; Ros-Perez, R.; Guitry-Azam, L.; Prunet, J. *Tetrahedron Lett.* **2002**, *43*, 7477−7479. (b) Grimaud, L.; de Mesmay, R.; Prunet, J. *Org. Lett.* **2002**, *4*, 419−421. (c) Desroy, N.; Le Roux, R.; Phansavath, P.; Chiummiento, L.; Bonini, C.; Genet, J.-P. *Tetrahedron Lett.* **2003**, *44*, 1763−1766. (d) Schmidt, D. R.; Park, P. K.; Leighton, J. L. *Org. Lett.* **2003**, *5*, 3535−3537. (e) Le Roux, R.; Desroy, N.; Phansavath, P.; Genêt, J.-P. *Synlett* **2005**, 429−432. (f) Keck, G. E.; McLaws, M. D. *Tetrahedron Lett.* **2005**, *46*, 4911−4914. (g) Vincent A.; Prunet, J. *Synlett* **2006**, 2269−2271.

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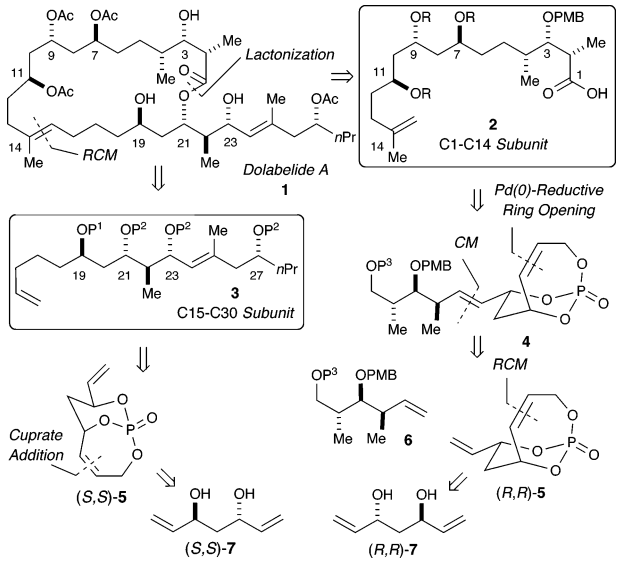
ally active phosphate triester tether[5] within the *P*-chiral bicyclic phosphate **5** (Scheme 1).[6] These studies also revealed

**Scheme 1.** Retrosynthetic Analysis of Dolabelide

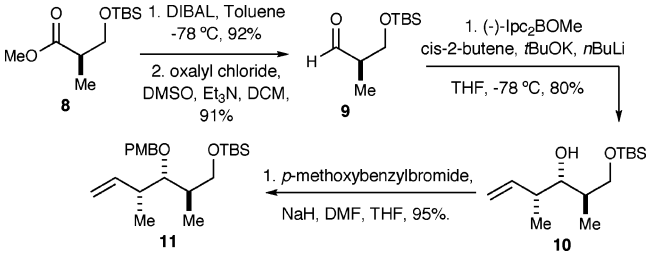



selective cleavage pathways operative through displacement reactions at carbon ($S_N2$, $S_N2'$) and phosphorus, ultimately affording multipositional activation, which extends throughout the bicyclic framework. Overall, rapid access to advanced polyol synthons was attained, thus providing impetus for this study.[5]

Retrosynthetic analysis shows that assembly of the C1−C14 (**2**) portion can be achieved via a Grignard addition into the C11 aldehyde, which is accessed by regioselective hydride opening of the advanced phosphate intermediate **4**. Regioselective cross metathesis (CM) between bicyclic phosphate (*R*,*R*)-**5** and terminal olefin **6** generates the C5−C6 bond and installs five of the six stereocenters found within the C1−C14 subunit of dolabelide. Bicyclic phosphate tether (*R*,*R*)-**5** is readily constructed from the proper enantiomeric, $C_2$-symmetric 1,3-*anti*-diol, (*R*,*R*)-**7** via a *P*-tether-mediated diastereotopic differentiation using RCM. The C15−C30 portion of dolabelide can also be accessed using this phosphate methodology and the enantiomer of the $C_2$-symmetric 1,3-*anti*-diol (*S*,*S*)-**7**.

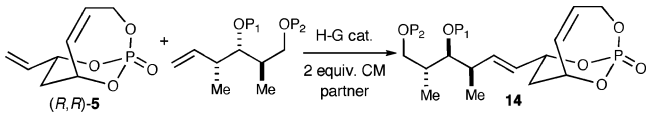
Synthesis of CM partner **11** was achieved through initial reduction of TBS-protected Roche ester **8**, followed by subsequent Swern oxidation of the alcohol, providing the necessary aldehyde **9** (Scheme 2).[7] Reaction of the formed

**Scheme 2.** Synthesis of CM Partner **2.3**




aldehyde with the *Z*-crotyl (−)-Ipc-borane generated enantiopure homoallylic alcohol **10** in 80% yield.[8] PMB-protection of alcohol **10** was achieved using *p*-methoxybenzylbromide and sodium hydride to afford **11** in 95% yield.[9]

**Scheme 3.** CM Studies with Bicyclic Phosphate **5**




| CM-partner | H-G cat. | solvent | temp. (°C) | yield (%) |
|---|---|---|---|---|
| PMBO OTBDPS (**12**) | 6 mol % | Tol | 60 | N.A. |
| | 6 mol % | Tol | 90 | 28 |
| | 12 mol % | Tol | 90 | 31 |
| PMBO OTBS (**11**) | 6 mol % | $CH_2Cl_2$ | 50 | 42 |
| | 6 mol % | Tol | 90 | 45 |
| | 12 mol % | Tol | 90 | 60 |
| | 6 mol % | DCE | 90 | 72 |
| PMP (**13**) | 6 mol % | $CH_2Cl_2$ | 50 | 32 |
| | 6 mol % | Tol | 90 | 63 |
| | 6 mol % | DCE | 90 | 73 |

H-G cat. = Hoveyda Grubbs 2nd Generation Catalyst;
DCE = 1,2-dichloroethane

A key component of the proposed synthesis of dolabelide was the selective CM between bicyclic phosphate (*R*,*R*)-**5**,[5a] and the synthesized homoallylic alcohol **11**. Previous studies have shown CM of bicyclic phosphate (*R*,*R*)-**5**[10] in which the exocyclic olefin was shown to possess Type III olefin behavior, implying that no detrimental homodimerization pathways are operative.[10,11] Other derivatives of **11** (TBDPS (**12**)[12a] and PMP acetal(**13**)[12b]) were synthesized to test their ability to undergo the necessary CM reaction. Utilizing

(5) For examples of P(III)/P(V)-based tethers in synthesis, 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) For use of phosphate tethers in synthesis, see: (a) Whitehead, A.; McReynolds, M. D.; Moore, J. D.; Hanson, P. R. *Org. Lett.* **2005**, *7*, 3375−3378. (b) Whitehead, A.; McParland, J. P.; Hanson, P. R. *Org. Lett.* **2006**, *8*, 5025−5028.

(7) Burke, S. D.; Cobb, J. E.; Takeuchi, K. *J. Org. Chem.* **1990**, *55*, 2138−2151.

(8) (a) Hung, D. T.; Nerenberg, J. B.; Schreiber, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 11054−11080. (b) Ramachandran, P. V.; Srivastava, A.; Hazra, D. *Org. Lett.* **2007**, *9*, 157−160.

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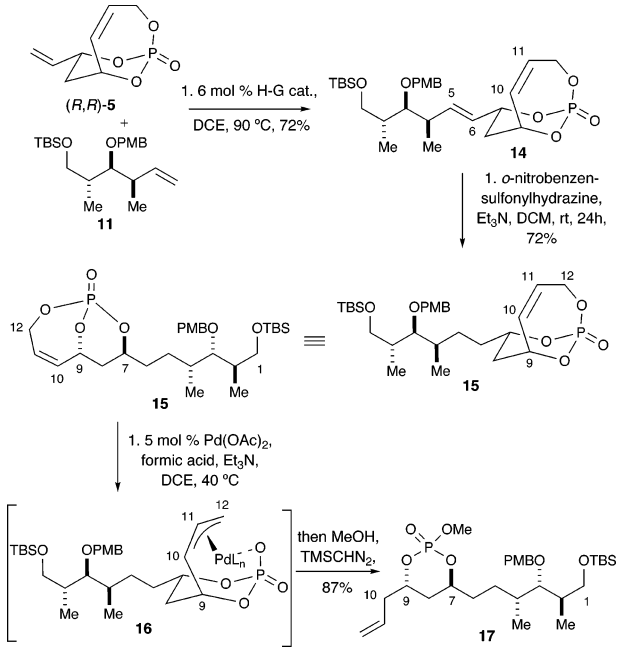
TBDPS as a protecting group (**12**) gave low reactivity, as well as low yields during CM (Scheme 3, entries 1−3). CM was next attempted between (*R*,*R*)-**5** and **11** under the conditions previously reported (6 mol % Hoveyda−Grubbs cat., DCM, 45 °C),[10] but incomplete consumption of the starting phosphate was observed after 6 h (entry 4). Optimizing the reaction conditions with various solvents revealed that use of toluene (90 °C), with the same catalyst loading, gave essentially the same results (entry 5). However, an improved yield of 60% was obtained (entry 6) when 12 mol % catalyst was added to the CM reaction. Switching to DCE (90 °C) and adding only 6 mol % Hoveyda−Grubbs catalyst gave the optimized results for **11**, providing 72% yield of CM product **14** after 2 h. When removing the silyl protecting group altogether, **13** furnished results similar to those with **11**. It should be noted that in all cases excess **11**, **12**, **13**, Type II CM partners, could be recovered in near quantitative yield and recycled in future CM events. This differential reactivity pattern toward CM demonstrates that both proximal and distal steric interactions play vital roles in the success of selective CM reactions.[13]

With optimal CM conditions, **11** was chosen over **13**, owing to the facile removal of the silyl protecting group in the late stages of the synthesis. The CM between (*R*,*R*)-**5** and **11** provided phosphate **14** in 72% yield on multigram scale (Scheme 4). Regioselective hydrogenation of exocyclic

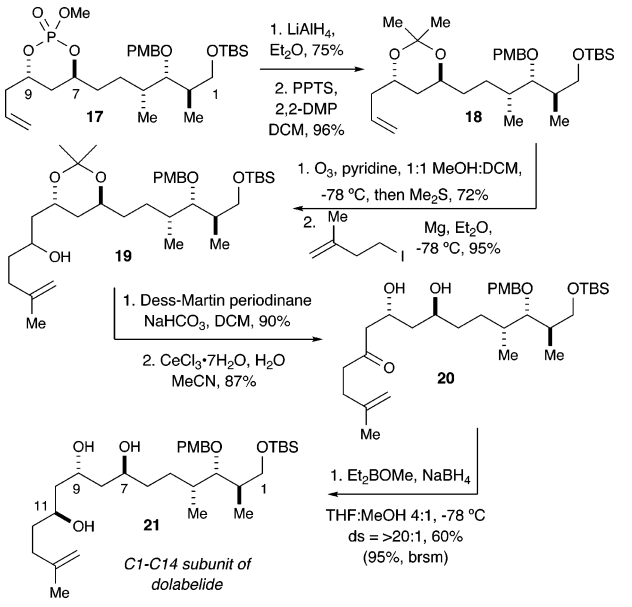
**Scheme 4.** Selective Phosphate Cleavage in the Synthesis of Phosphate **17**




C5−C6 olefin in the presence of the C10−C11 internal olefin was paramount to allow for subsequent regioselective opening of the bicyclic system. Upon investigating several hydrogenation conditions, (Wilkinson's catalyst, Crabtree's catalyst, Pd/C) it was found that an in situ generated diimide reduction under mild conditions (*o*-nitrobenzenesulfonylhydrazine,[14] $Et_3N$, DCM) provided the necessary regioselective hydrogenated phosphate **15** with near complete selectivity for the exocyclic olefin. Other diimide conditions (tosylhydrazine, NaOAc, $H_2O$, DCE, 90 °C) gave drastically lower yields, likely due to bicyclic phosphate instability under basic medium.

With phosphate **15** in hand, efforts were directed to an additional use of the tether in a potential regioselective olefin transposition to the desired terminal olefin. Initial attempts focused on the use of allylic hydride addition employing various reagents (Stryker's reagent, CuCN·LiCl/$PhSiH_3$, $CeCl_3$·$7H_2O$/$NaBH_4$). To our dismay, however, all conditions probed provided only unreacted starting material or total decomposition of the reaction mixture. Pd-catalyzed formate reductions were next investigated for generation of the requisite terminal olefin.[15] Employment of 1.5 equiv of formic acid and 5 mol % palladium acetate at 40 °C in DCE selectively opened phosphate **15** to provide the desired terminal olefin. Methylation of phosphate acid intermediate showed that a highly regioselective process was operative (37:1 ratio of regioisomers as evident by $^{31}P$ NMR analysis). Purification provided phosphate **17** in 87% yield. The remarkable regioselectivity reveals another feature of the phosphate tether, whereby orthogonal orbital alignment[5] within **15** allows for selective Pd(0)-catalyzed allylic phosphate ionization at C12 over C9.

**Scheme 5.** Synthesis of the C1−C15 Subunit of Dolabelide




Installation of the C11−C14 fragment began with cleavage of the phosphate **17** using $LiAlH_4$, which generated a diol

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that was subsequently protected as the acetonide (PPTS, 2,2-methoxypropane, DCM) to yield **18** in 96% yield (Scheme 5). Ozonolysis ($O_3$, pyridine, DCM:MeOH 1:1, $Me_2S$) of the terminal olefin produced the intended aldehyde, which was subjected to the Grignard generated from 1-iodo-3-methyl-3-butene[16] affording **19** in a 95% yield. Dess−Martin periodinane (DMP, $NaHCO_3$, DCM) oxidation of the free alcohol in **19** generated the requisite ketone in 90% yield. Attempts to selectively reduce the acetonide protected ketone, using an assortment of reducing agents, resulted in no diastereoselectivity at C11.[17] This problem seemed likely to be circumvented by deprotection of the acetonide and subsequent *syn* reduction utilizing the C9 free alcohol. Removal of the acetonide was achieved by the addition of $CeCl_3 \cdot 7H_2O$ and water,[18] which efficiently cleaved the acetonide protecting group without loss of the primary TBS group and provided diol **20** in 86% yield. Final chelation-controlled reduction of ketone **20** using $Et_2BOMe$ and $NaBH_4$ afforded triol **21** in 60% (95% based on recovered starting material) with excellent diastereoselectivity (ds ≥ 20:1).

In conclusion, successful completion of the synthesis of the C1−C14 subunit of dolabelides A−D using phosphate tether methodology has been achieved. Overall, the phosphate tether serves a multifaceted role by (i) mediating the initial desymmetrization event leading to (*R*,*R*)-**5**, (ii) a selective Type III CM to couple two major complex fragments in the C1−C14 subunit of dolabelides, (iii) differentiating the two olefins within the bicyclic system **14**, allowing for a selective hydrogenation, and finally (iv) serving as an excellent leaving group in a regioselective Pd(0)-mediated formate reduction. The route outlined above makes use of orthogonal protecting- and leaving group properties innate to phosphate esters. This work provides evidence that counters historical and traditional applications associated with the utilization of phosphates in synthesis. Efforts to complete the total synthesis are ongoing in our laboratories and will be reported in due course.

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**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.

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(17) See Supporting Information for further details.

(18) Umezawa, T.; Hayashi, T.; Sakai, H.; Teramoto, H.; Yoshikawa, T.; Izumida, M.; Tamatani, Y.; Hirose, T.; Ohfune, Y.; Shinada, T. *Org. Lett.* **2006**, *8*, 4971−4974.