ORGANIC LETTERS

2008
Vol. 10, No. 7
1421−1424

A Multifaceted Phosphate Tether: Application to the C15–C30 Subunit of Dolabelides A–D

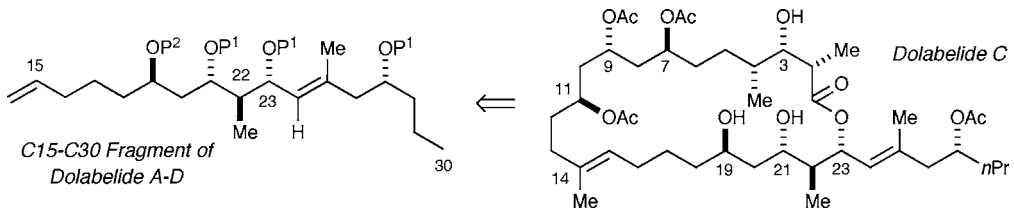
Alan Whitehead, Joshua D. Waetzig, Christopher D. Thomas, and Paul R. Hanson*

Department of Chemistry, University of Kansas, 1251 Wescoe Hall Drive, Lawrence, Kansas 66045

phanson@ku.edu

Received January 25, 2008

ABSTRACT



Construction of the C15–C30 subunit of dolabelide utilizing a temporary phosphate tether is described. Two routes are reported that make use of the orthogonal protecting- and leaving-group properties innate to phosphate esters. One route relies on a selective terminal oxidation, while a second utilizes a CM/selective hydrogenation sequence. Both routes depend on a highly regio- and diastereoselective cuprate addition to set the requisite stereochemistry at C22.

Dolabelide A and B[1] are 22-membered macrolides collected and characterized from the sea hares *Dolabella auricularia*. Upon further investigation of these extracts, researchers uncovered two additional 24-membered macrolide analogs of dolabelide A and B and termed them dolabelide C (**1**) and D (Scheme 1).[2] Dolabelides A−D show cytotoxicity against human cervical cancer HeLa-S_3 cells with IC_{50} values of 6.3, 1.3, 1.9, and 1.5 μg/mL, respectively. Despite this promising activity, their mechanism of action remains unknown. The biological activity and stereochemical complexity of this family present worthy and formidable synthetic challenges and warrant continued synthetic studies directed at this family of macrolides.

Several synthetic studies[3] have recently been reported for the dolabelide family, including one total synthesis of dolabelide D by Leighton and co-workers in 2006.[4] Among these efforts, two reports toward the C15−C30 fragment have been presented, with Leighton and co-workers publishing the only complete C15−C30 fragment bearing the requisite stereochemistry.[3d]

Retrosynthetic analysis reveals a logical disconnection at C1−C14 and C15−C30 (**2**, Scheme 1) for the entire family of dolabelides. A key acid coupling between the C1 carboxylic acid and either the C23 or C21 carbinol centers will serve to join the two major subunits. Subsequent RCM macrocyclization, following the precedent established by Leighton[4] will deliver the C14/C15 trisubstituted olefin moiety.

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

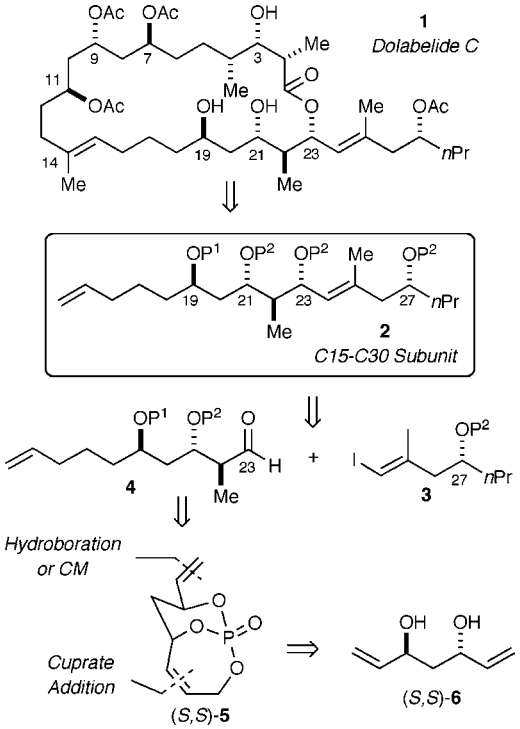
(2) Suenaga, K.; Nagoya, T.; Shibata, T.; Kigoshi, H.; Yamada, K. *J. Nat. Prod.* **1997**, *60*, 155−157.

(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.; Genêt, 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. (e) Keck, G. E.; McLaws, M. D. *Tetrahedron Lett.* **2005**, *46*, 4911−4914. (f) Vincent, A.; Prunet, J. *Synlett* **2006**, 2269−2271.

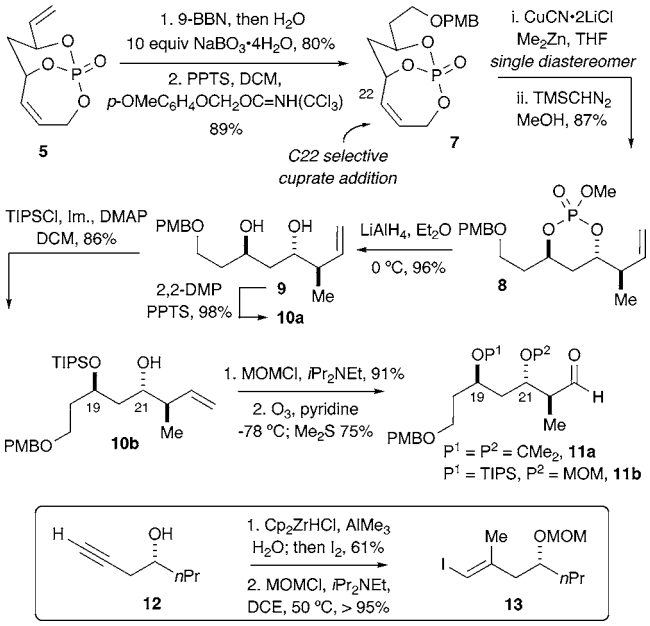
(4) Park, P. K.; O'Malley, S. J.; Schmidt, D. R.; Leighton, J. L. *J. Am. Chem. Soc.* **2006**, *128*, 2796−2797.

10.1021/ol8001865 CCC: $40.75
Published on Web 03/07/2008

Scheme 1. Retrosynthetic Analysis of Dolabelide C



Scheme 2. Synthesis of Aldehyde **11**



Convergent assembly of the C15−C30 subunit via the C23−C24 bond is envisioned to occur through vinylate coupling of metalated **3** with aldehyde **4** (Scheme 1). The 1,3-anti diol moiety contained within subunit **2** (C19 and C21) can be derived from phosphate triester building block (*S*,*S*)-**5**,[5] assembled via phosphate tether mediated desymmetrization of C_2-symmetric anti-diol (*S*,*S*)-**6**. The complimentary phosphate tether approach to the C1−C14 subunit of the dolabelide family has been recently reported and highlights a cross-metathesis and phosphate-mediated regioselective olefin transposition strategy emanating from (*R*,*R*)-**5**.[6] Herein we report ongoing progress toward the dolabelide family of macrolides through preparation of the C15−C30 subunit.

Initial efforts toward the construction of the C15−C30 subunit of dolabelide began with the enantiomeric bicyclic phosphate (*S*,*S*)-**5** (Scheme 2). Mild $NaBO_3$ oxidation conditions were employed following a chemoselective hydroboration of the exocyclic olefin of (*S*,*S*)-**5**. A perborate oxidation protocol developed by Burke and co-workers was implemented[7] and optimized for bicyclic phosphate **5**. Yields in this study were highly dependent on the amount of oxidant, equivalents of H_2O, and reaction time. Subsequent PMB ether formation using the *p*-methoxybenzyl trichloroacetimidate of PMBOH produced **7** in good yields and highlights the acid stability of bicyclic phosphate (*S*,*S*)-**5**. A regio- and diastereoselective S_N2' cuprate addition[5] to **7** followed by methylation ($TMSCHN_2$ and MeOH) afforded cyclic phosphate ester **8** in excellent overall yield (87%, ds = >95:5). The unique orbital alignment within bicyclic phosphate **7**, in synergy with its concave nature, dictates the high selectivity in this S_N2' cuprate reaction.[8]

The remaining steps to aldehyde **11** were non-problematic and involved an intitial reductive cleavage of the monocyclic phosphate ester with $LiAlH_4$ in Et_2O to provide diol **9** as a single diastereomer in excellent yield (96%). Quantitative acetonide formation and subsequent ozonolysis afforded **11a** in good yield. Alternatively, selective mono-TIPS protection (**9**, TIPSCl, imidazole, rt)[9] followed by MOM protection and ozonolysis produced **11b** in good to excellent yields over three steps.

Construction of the C24−C30 vinyl iodide fragment **13** was achieved in two steps from known **12** (Scheme 2).[3d] Alkyne **12** was produced from commercially available *R*-(−)-epichlorohydrin, employing the Yamaguchi protocol for oxirane alkynylation.[10] Subsequent zirconocene-promoted carboalumination, utilizing Wipf's water-accelerated procedure[11] and iodine quench, provided trisubstituted vinyl iodide in 61% yield. Methylmethoxy (MOM) protection ultimately afforded **13** in >95% yield.

(5) (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. (c) Waetzig, J. D.; Hanson, P. R. *Org. Lett.* **2006**, *8*, 1673−1676.

(6) Waetzig, J. D.; Hanson, P. R. *Org. Lett.* **2008**, *10*, 109−112.

(7) Burke and coworkers have shown this protocol to be compatible with multiple acetate protecting groups; see: Lucas, B. S.; Luther, L. M.; Burke, S. D. *Org. Lett.* **2004**, *6*, 2965−2968.

(8) This reaction occurs via a highly regio- and stereoselective *anti*-S_N2' attack at the C(22) olefinic carbon within bicyclic phosphate **7** where proper orthogonal alignment of the C=Cπ^* and C−OP(O)σ^* orbitals allows for *anti*-S_N2' attack to proceed exclusively on the convex face of **7**; see Scheme 4 in ref 5a.

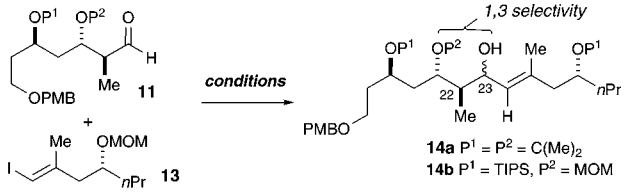
(9) For selective silylation of similar 1,3-diols, see: (a) Soltani, O.; De Brabander, J. K. *Org. Lett.* **2005**, *7*, 2791−2793.

(10) (a) Yamaguchi, M.; Hirao, I. *Tetrahedron Lett.* **1983**, *24*, 391−394. (b) See also: Morris, J.; Wishka, D. G. *Tetrahedron Lett.* **1986**, *27*, 803−806.

(11) (a) Wipf, P.; Lim, S. *Angew. Chem.* **1993**, *105*, 1095−1097; *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1068−1071. (b) Rand, C. L.; Van Horn, D. E.; Moore, M. W.; Negishi, E. *J. Org. Chem.* **1981**, *46*, 4093−4096.

With **11a**/**11b** and vinyl iodide **12** in hand, methods for the construction of both the C23−C24 C−C bond and C23 stereochemistry were investigated (Scheme 3). Reaction of

Scheme 3. Asymmetric Vinylate Additions into **11a/11b**



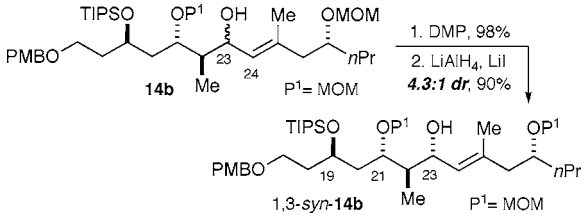
conditions	yield	dr desired 1,3-syn:1,3-anti
11a $P^1 = P^2 = C(Me)_2$		
*t*BuLi, -78 °C	78%	1:2
*t*BuLi, $MgBr_2 \cdot Et_2O$, -78 °C	78%	1:4
*s*BuLi, *i*PrMgCl; $MgBr_2 \cdot Et_2O$, -78 °C	68%	1:6-8
11b P^1 = TIPS, P^2 = MOM		
*t*BuLi, -78 °C	70%	1:1
*t*BuLi, $ZnBr_2$; *n*BuLi, (*R,S*)-*NME*	55%	11:1

acetonide-protected **11a** with the lithium−halogen exchange metalate of **13** (*t*BuLi, −78 °C to rt) or the vinyl Grignard of **13** (*t*BuLi, −78 °C, $MgBr_2 \cdot Et_2O$) provided Felkin C22/C23-*syn* selectivity of the undesired C21−C23 1,3-*anti* product **14a** in modest diastereoselectivity (2−4:1 dr). Selectivity for the undesired C23 epimer was highest when employing Oshima protocol[12] using vinyl magnesiate formation in the presence of $MgBr_2 \cdot Et_2O$, where selectivities of ∼8:1 were observed in favor of the undesired C23 epimer, 1,3-*anti*-**14a**.[13]

To circumvent this selectivity issue we employed reagent controlled asymmetric addition to **11b** using Oppolzer's zinc vinylate-lithium alkoxy *N*-methylephedrine complex[14] recently described by Marshall[15] and co-workers for vinylate additions to α-chiral aldehydes. Under these conditions **14b** was formed in an 11:1 ratio of diastereomers favoring the desired C21−C23-*syn* product in moderate yield.

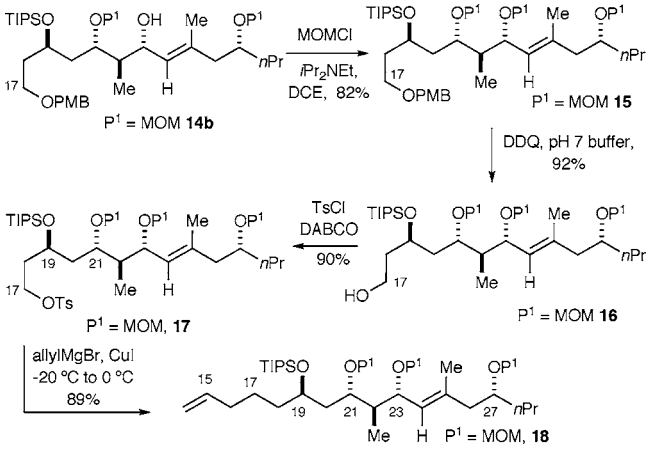
Despite this success, difficulties in reaction reproducibility (also recently noted by Marshall)[16] and low product yields prompted investigation of an alternative oxidation/hydride reduction sequence for the formation of the requisite 1,3-*syn* diol within **14**. Thus, Dess−Martin periodinane oxidation of the C23 epimers of **14b**, followed by reduction of the resulting ketone using Suzuki's 1,3-*syn* selective, chelation-controlled reduction conditions ($LiAlH_4$, LiI)[17] afforded the desired 1,3-*syn* diastereomer (**14b**) as a 4.3:1 mixture of diastereomers in 90% yield.[18]

Scheme 4. Construction of Alcohol **14b**



With **14b** in place, only the installation of the C14−C15 terminal olefin was needed to complete the C15−C30 subunit of dolabelide. Following MOM-protection of the C23 alcohol (**15**), DDQ removal of the PMB ether proceeded in good yield to afford alcohol **16** (Scheme 5). Tosylation of the

Scheme 5. Completion of the C15−C30 Subunit of Dolabelide



primary alcohol provided **17** in 90% yield. Treatment of **17** with an allyl Grignard in the presence of stoichiometric CuI led to the formation of allylated product **18** in 89% yield. Overall, the sequence represents a 12-step synthesis to **18** from **5**, bearing the requisite stereochemistry for the C15−C30 subunit of dolabelide.

An alternative approach to the C15−C30 side chain was additionally investigated employing previously established cross metathesis (CM) methodology (Scheme 6).[5c] As anticipated, **5** underwent CM with **19** in the presence of 6 mol % H-G catalyst[19] in DCE (90 °C) providing *E*-configured **20** in 82% yield (>95:5, *E*:*Z*).[5c] Selective reduction of the

(12) Inoue, A.; Kitagawa, K.; Shinokubo, H.; Oshima, K. *J. Org. Chem.* **2001**, *66*, 4333−4339.

(13) These results are in accordance with literature precedence that larger counterions effect the Felkin selectivity; see: Mengel, A.; Reiser, O. *Chem. Rev.* **1999**, *99*, 1191−1223.

(14) Oppolzer, W.; Radinov, R. N. *Tetrahedron Lett.* **1991**, *32*, 5777−5780.

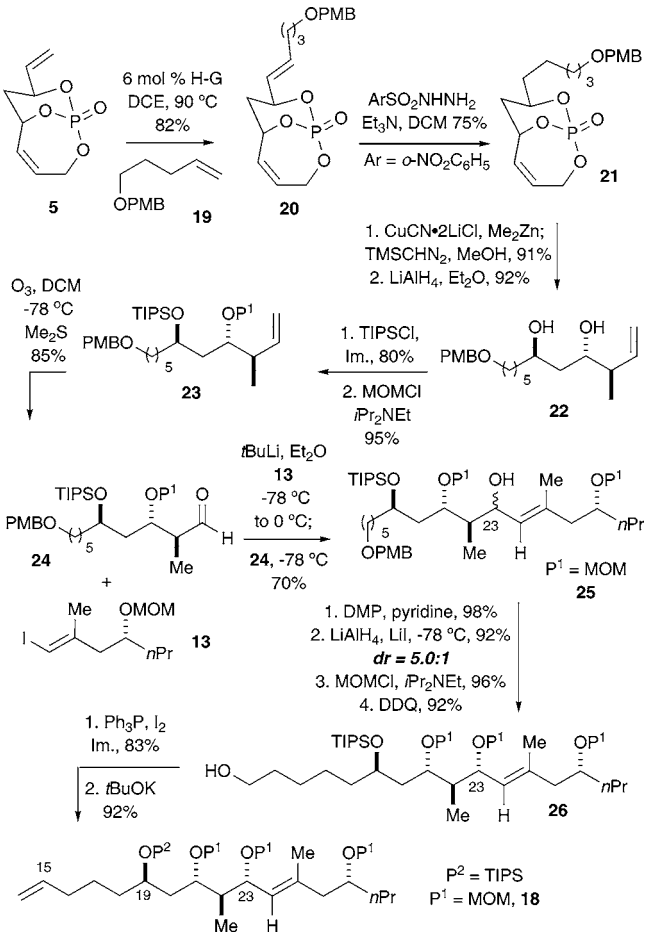
(15) Marshall, J. A.; Eidam, P. M. *Org. Lett.* **2004**, *6*, 445−448.

(16) Marshall and coworkers reported protonolysis products under Oppolzer conditions with similar homoallylic protected vinyl iodides, which we witnessed in unsuccessful reactions, along with decomposed aldehyde; see: Marshall, J. A.; Eidam, P. M. *Org. Lett.* **2008**, *10*, 93−96.

(17) (a) Mori, Y.; Kuhara, M.; Takeuchi, A.; Suzuki, M. *Tetrahedron Lett.* **1988**, *29*, 5419−22. (b) Ghosh, A. K.; Lei, H. *J. Org. Chem.* **2002**, *67*, 8783−8788.

(18) Additional reductions using a variety of reducing agents (DIBAL-H, $LiAlH_4$, $Zn(BH_4)_2$, $NaBH_4$) failed to generate the desired C23 stereochemistry. (a) Evans, D. A.; Ng, H. P.; Rieger, D. L. *J. Am. Chem. Soc.* **1993**, *115*, 11446−59. (b) Oishi, T.; Nakata, T. *Acc. Chem. Res.* **1984**, *17*, 338−344. (c) Evans, D. A.; Kim, A. S.; Metternich, R.; Novack, V. J. *J. Am. Chem. Soc.* **1998**, *120*, 5921−5942.

Scheme 6. CM Route to the C15−C30 Subunit of Dolabelide



external olefin was achieved with *o*-nitrobenzenesulfonylhydrazine,[20] which provided **21** in (>95:5) regioselectivity and 75% yield.[21] Regio- and diastereoselective methyl cuprate addition into **21**, under the aforementioned conditions, followed by phosphate tether removal afforded diol **22** in good yield.

Aldehyde **24** was rapidly accessed using a three-step TIPS-MOM-ozonolysis sequence (Scheme 6). Lithiate addition into aldehyde **24** produced **25** as a 1:1 mixture of C23 epimers in 70% yield (Scheme 6). Subsequent employment of the aforementioned oxidation/Suzuki reduction conditions generated the desired diastereomer of **25** in 92% yield (ds = 5:1 at C23).[17] Substrate **25** was MOM-protected and the PMB-ether removed using DDQ to produce primary alcohol **26**. Iodination of the C14 primary alcohol occurred in 83% yield, followed by facile E2 elimination of a primary iodide in the presence of *t*BuOK (THF, 30 min, rt) afforded **18**, in 92% yield. Given the success, and convenience of the alternative elimination approach to the C14/C15 olefin, we are currently investigating selective vinylate addition with **24** for stereocontrolled formation of C23 within **25**.

In conclusion, we have successfully completed the synthesis of the C15−C30 subunit of dolabelides A−D using two routes relying on a temporary phosphate tether methodology developed in our laboratories. Both pathways make use of the orthogonal protecting- and leaving-group properties innate to phosphate esters. Ongoing efforts toward the completion of dolabelide are currently in progress and will be reported in due course.

Acknowledgment. This investigation was supported by funds provided by NSF CHE-0503875, NIH RO1 GM077309, and the NIH Dynamic Aspects in Chemical Biology Training Grant (A.W., J.D.W.). The authors would also like to thank Materia for supplying metathesis catalyst.

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.

OL8001865

(19) Second generation Hoveyda−Grubbs catalyst: Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168−8179.

(20) Myers, A. G.; Zheng, B.; Movassaghi, M. *J. Org. Chem.* **1997**, *62*, 7505−7507.

(21) For examples of diimide reductions in synthesis, see: (a) Haukaas, M. H.; O'Doherty, G. A. *Org. Lett.* **2002**, *4*, 1771−1774. (b) Buszek, K. R.; Brown, N. *J. Org. Chem.* **2007**, *72*, 3125−3128.