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Approach to the Synthesis of Dolabelides A and B: Fragment Synthesis by Tandem Silylformylation–Crotylsilylation

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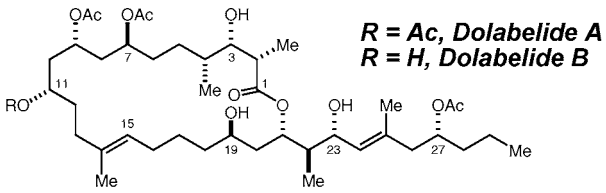
ABSTRACT

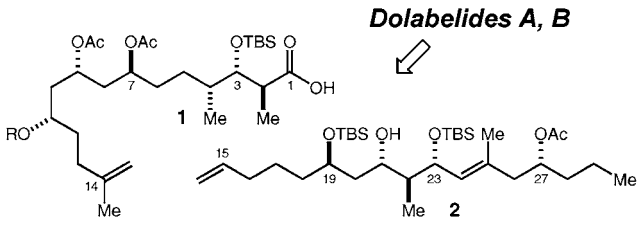


A synthesis of the C(15)–C(30) fragment of Dolabelides A and B has been achieved. The recently developed asymmetric silane alcoholysis and tandem silylformylation–crotylsilylation reactions were used as the key steps to establish the C(23)–C(27) 1,5-*syn*-diol. In addition, the flexibility of this methodology has been demonstrated with an efficient synthesis of the C(24)–C(25) trisubstituted olefin.

Dolabelides A−D comprise a closely related family of marine macrolides that exhibit cytotoxicity against HeLa−S_3 cells with IC_{50} values in the range of 1−6 μg/mL.[1] Due to the activity and scarcity of these natural products, we have embarked on a program targeting the synthesis of dolabelides A and B.[2]

Our retrosynthetic analysis posited a macrocyclization by way of a ring-closing metathesis to form the C(14)−C(15) trisubstituted olefin (Scheme 1). This would allow for a simple esterification as the fragment coupling event and breaks the target into the two similarly complex fragments **1** and **2**. Herein we describe the successful development of an efficient synthesis of the C(15)−C(30) fragment **2**.

Scheme 1



Further analysis suggested that **2** might arise from diene **3** by a number of potential approaches, including asymmetric aldol and allylation reactions (Scheme 2). The central issue in designing a synthesis of fragment **3** was whether the remote C(23) and C(27) stereocenters might somehow be related or established separately using asymmetric synthesis. We have recently reported the tandem alkyne silylformylation/allylsilylation reaction, which delivers 1,5-*anti*-diols in an efficient manner.[3] To have access to the 1,5-syn diastereomer needed for the dolabelide synthesis, we have also developed a catalytic asymmetric silane alcoholysis that allows the diastereoselective synthesis of chiral silanes such as **4**.[4] Stereospecific transfer of chirality from silicon to

(1) (a) Ojika, M.; Nagoya, T.; Yamada, K. *Tetrahedron Lett.* **1995**, *36*, 7491−7494. (b) Suenaga, K.; Nagoya, T.; Shibata, T.; Kigoshi, H.; Yamada, K. *J. Nat. Prod.* **1997**, *60*, 155−157.

(2) For other approaches to the synthesis of the dolabelides, see: (a) Grimaud, L.; de Mesmay, R.; Prunet, J. *Org. Lett.* **2002**, *4*, 419−421. (b) Desroy, N.; Le Roux, R.; Phansavath, P.; Chiummiento, L.; Bonini, C.; Genêt, J.-P. *Tetrahedron Lett.* **2003**, *44*, 1763−1766.

(3) (a) O'Malley, S. J.; Leighton, J. L. *Angew. Chem., Int. Ed.* **2001**, *40*, 2915−2917. (b) Zacuto, M. J.; O'Malley, S. J.; Leighton, J. L. *J. Am. Chem. Soc.* **2002**, *124*, 7890−7891.

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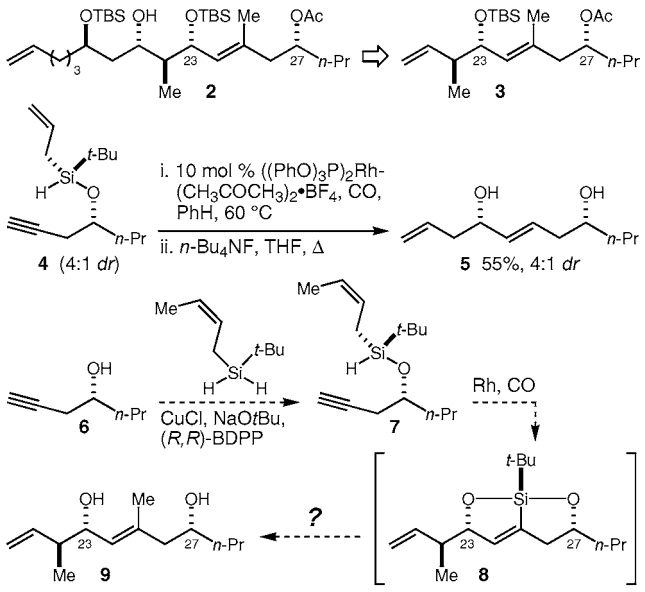
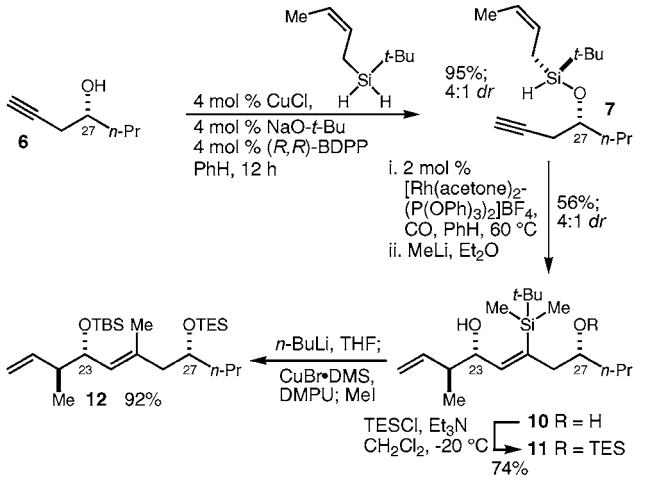
Scheme 2



carbon in the tandem reaction allows access to the 1,5-*syn*-diol **5**. We were intrigued by the possibility of employing these methods in a synthesis of **3** (e.g., **6** → **7** → **8**). In so doing we would be required to develop a method to parlay the vinylsilane **8** into the requisite trisubstituted alkene **9**.

In optimizing the catalytic asymmetric silane alcoholysis with alcohol **6** and *tert*-butyl-*cis*-crotylsilane, we were delighted to find that the reaction is highly efficient, requiring only 4 mol % of the (*R*,*R*)-2,4-bisdiphenylphosphinopentane (BDPP)-modified copper catalyst to provide silane **7** as a 4:1 mixture of diastereomers in 95% yield (Scheme 3). This

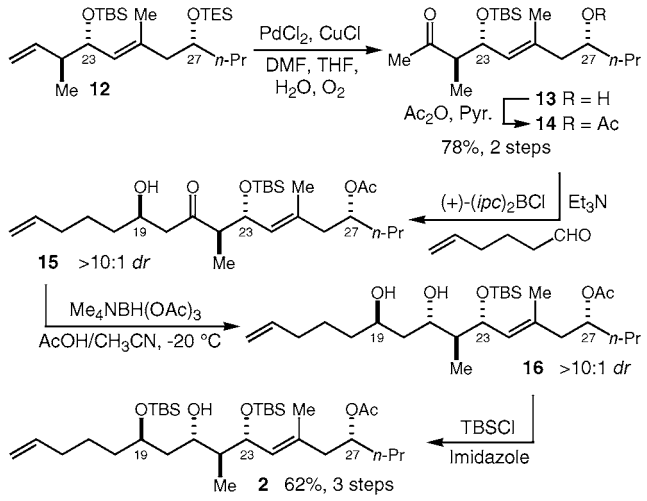
Scheme 3



mixture was subjected to the rhodium-catalyzed tandem silylformylation/ crotylsilylation, and upon quenching with MeLi, the vinylsilane **10** was isolated as a 4:1 mixture of diastereomers in 56% yield. Selective protection of the less hindered alcohol as a triethylsilyl (TES) ether led to alcohol **11**. Diastereomer separation was conveniently accomplished at this point, and **11** was obtained as single diastereomer in 74% yield. Denmark has established that vinylsilanes of this type may be employed in palladium-catalyzed cross-coupling reactions.[5] Extensive attempts along these lines using MeI as the electrophile did provide the desired trisubstituted olefin, but in unacceptably low yields. As our protecting group strategy called for the use of a *tert*-butyldimethylsilyl (TBS) ether for the C(23) alcohol, an intriguing alternative presented itself in the form of a Brook-like 1,4 carbon (sp^2) to oxygen silyl migration. Indeed, treatment of alcohol **11** with *n*-BuLi followed by the addition of CuBr•Me_2S and *N*,*N*′-dimethylpropyleneurea (DMPU) and then addition of MeI led to the clean formation of trisubstituted olefin **12** in 92% yield.[6] The *tert*-butyl silane thus serves two important purposes, and a required protecting group installation is combined with a key carbon−carbon bond formation in a single highly efficient step. In addition, although the yield of the tandem silylformylation/allylsilylation step (**7** → **10**) is quite moderate, it is noteworthy that this single operation establishes two carbon−carbon bonds, two stereocenters, and the vinylsilane precursor for the key Brook rearrangement.

Completion of the synthesis of fragment **2** was straightforward as described in Scheme 4. Wacker oxidation was

Scheme 4



accompanied by a fortuitous hydrolysis of the TES protecting group. Upon optimization, hydroxy ketone **13** could be obtained smoothly, and acetylation then proceeded uneventfully to deliver acetate **14** in 78% overall yield for the two-step sequence. Asymmetric aldol coupling with 5-hexenal

(4) Schmidt, D. R.; O'Malley, S. J.; Leighton, J. L. *J. Am. Chem. Soc.* **2003**, *125*, 1190−1191.

(5) (a) Denmark, S. E.; Pan, W. *Org. Lett.* **2001**, *3*, 61−64. (b) Denmark, S. E.; Pan, W. *Org. Lett.* **2002**, *4*, 4163−4166. (c) Denmark, S. E.; Kobayashi, T. *J. Org. Chem.* **2003**, *68*, 5153−5159.

(6) These conditions are a modification of the procedure reported by Takeda. See: Taguchi, H.; Ghoroku, K.; Tadaki, M.; Tsubouchi, A.; Takeda, T. *Org. Lett.* **2001**, *3*, 3811−3814.

under the conditions established by Paterson[7] proceeded smoothly to deliver β-hydroxy ketone **15** with good diastereoselectivity (>10:1 dr). Although separation of the oxidized chiral auxiliary was difficult at this stage, it proved to be highly convenient to simply carry the mixture through the final two steps. Thus, anti-diastereoselective β-hydroxyketone reduction using the often employed method of Evans[8] proceeded uneventfully to give diol **16** (>10:1 dr), and selective silylation of the C(19) alcohol then delivered the completed fragment **2**. Purification was trivial at this stage, and **2** was isolated in 62% overall yield from **14** (three steps).

The synthesis of the C(15)−C(30) fragment of dolabelides A and B **2** has been accomplished in nine steps and 18% overall yield from alcohol **6**. The synthesis highlights the utility of the catalytic asymmetric silane alcoholysis and tandem alkyne silylformylation/crotylsilylation reactions and also demonstrates the versatility of the method by engaging the initially formed vinylsilane in an additional carbon−carbon bond-forming reaction. With access to **2** secured, we are actively pursuing the completion of the synthesis of dolabelides A and B.

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

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(7) (a) Paterson, I.; Goodman, J. M.; Lister, M. A.; Schumann, R. C.; McClure, C. K.; Norcross, R. D. *Tetrahedron* **1990**, *46*, 4663−4684. (b) Paterson, I.; Florence, G. J.; Gerlach, K.; Scott, J. P.; Sereinig, N. *J. Am. Chem. Soc.* **2001**, *123*, 9535−9544.

(8) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560−3578.