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Total Synthesis of Dolabelide D

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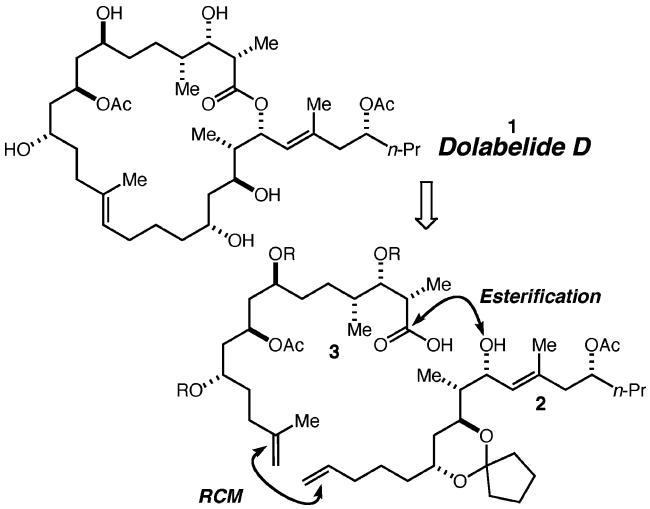
In 1995, researchers reported the isolation and structural characterization of two new 22-membered macrolides they termed dolabelides A and B from Japanese specimens of the sea hare *Dolabella auricularia*.[1] These compounds exhibited cytotoxic activity against HeLa−S_3 cells with IC_{50}'s of 6.3 and 1.3 μg/mL, respectively. Two years later, two new members of this class of natural products, dolabelides C and D, were reported.[2] These 24-membered macrolides are also cytotoxic against HeLa−S_3 cells with IC_{50}'s of 1.9 and 1.5 μg/mL, respectively. This biological activity and the interesting stereostructure of these natural products have combined to elicit attention from synthetic chemists,[3] including our own group.[4] Herein we describe our investigations that have led to the first total synthesis of dolabelide D, by way of the synthesis and coupling of fragments **2** and **3** by esterification and ring-closing metathesis (Scheme 1).

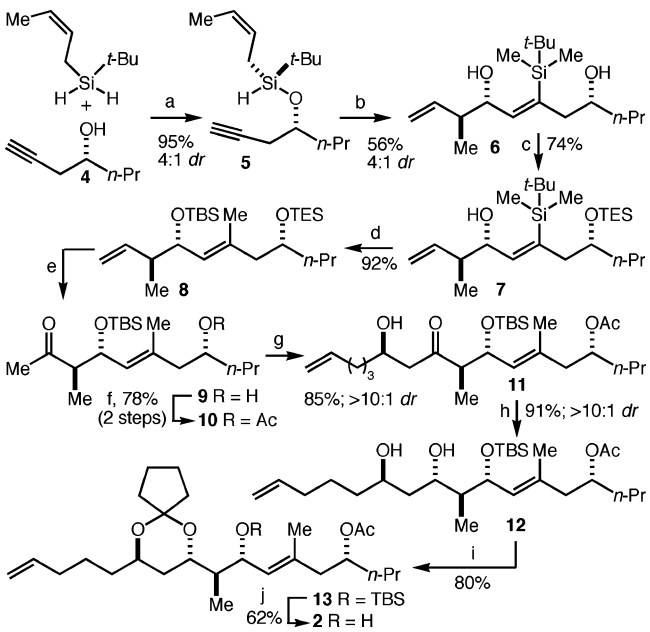
The synthesis of fragment **2**[4] commenced with an application of our recently developed catalytic asymmetric silane alcoholysis[5] with alcohol **4** and *tert*-butyl-*cis*-crotylsilane to provide **5** as the major component of a 4:1 mixture of diastereomers in 95% yield (Scheme 2). Rhodium-catalyzed tandem silylformylation−crotylsilylation[6] proceeded stereospecifically to provide, after quenching with methyllithium, a 4:1 mixture of diastereomers favoring 1,5-*syn*-diol **6** in 56% yield. Selective protection of the less-hindered alcohol as its triethylsilyl (TES) ether led, after separation of the diastereomers, to the isolation of **7** in 74% yield. Treatment of alcohol **7** with *n*-BuLi and then CuBr·SMe_2 and DMPU initiated a Brook-like 1,4-carbon (sp^2) to oxygen silane migration,[7] and the resulting vinylcopper species was then alkylated with MeI to provide **8** in 92% yield. This sequence illustrates the power of the tandem silylformylation chemistry to provide access to different functionalities and substitution patterns in the 1,5-diol products. In addition, it is noteworthy that the *tert*-butylsilane serves multiple purposes before being morphed into the desired *tert*-butyldimethylsilyl (TBS) ether. A Wacker oxidation was optimized for concurrent removal of the TES ether, and the resulting alcohol **9** was acetylated to provide **10** in 78% overall yield (two steps). Asymmetric aldol coupling[8] with 5-hexenal then gave aldol **11** in 85% yield and with >10:1 diastereoselectivity. Anti diastereoselective (>10:1 *dr*) β-hydroxyketone reduction[9] then gave **12** in 91% yield. Protection of the diol as a cyclopentylidene ketal[10] gave **13**, and TBS removal provided fragment **2** in 50% yield (two steps from **12**). The synthesis of **2** was thus achieved in 10 steps and 11% overall yield from **4**.

Allylation of aldehyde **14** with our recently developed reagent **15**[11] proceeded smoothly to provide **16** in 80% yield and 98% ee (Scheme 3). Protection of the alcohol as its *p*-methoxybenzyl (PMB) ether gave **17** in 95% yield and was followed by a Wacker oxidation to give ketone **18** in 81% yield. Crotylation of methacrolein with crotylsilane *ent*-**19**,[12] followed by protection of the resultant alcohol as its PMB ether, produced **20** in 53% yield (based on *ent*-**19**, two steps) and 88% ee. Hydroformylation in the presence of 2,2-dimethoxypropane proceeded smoothly and selectively to give acetal **21** in 72% yield. Still−Barrish hydroboration[13] gave alcohol **22** with 13:1 *dr*. A four-step oxidation−oxidation−protection−deprotection sequence then provided aldehyde **23** in 79% overall yield.

Scheme 1



Scheme 2 [a]



[a] (a) 4 mol % CuCl, 4 mol % NaO-*t*-Bu, 4 mol % (*R*,*R*)-BDPP, PhH. (b) i. 2 mol % $[Rh(acetone)_2$-$(P(OPh)_3)_2]BF_4$, CO, PhH, 60 °C; ii. MeLi, Et_2O, −78 to 23 °C. (c) TESCl, Et_3N, CH_2Cl_2, −20 °C. (d) *n*-BuLi, THF, −78 °C; CuBr·Me_2S, DMPU, 23 °C; MeI, −78 to 23 °C. (e) 25 mol % $PdCl_2$, CuCl, DMF, THF, H_2O, O_2. (f) Ac_2O, pyridine, DMAP, CH_2Cl_2. (g) (+)-$(ipc)_2BCl$, Et_3N, 5-hexenal, Et_2O, −78 to 23 °C. (h) $Me_4NBH(OAc)_3$, AcOH, CH_3CN, THF, −40 to −20 °C. (i) 1,1-Dimethoxycyclopentane, PPTS, CH_2Cl_2. (j) *n*-Bu_4NF, THF.

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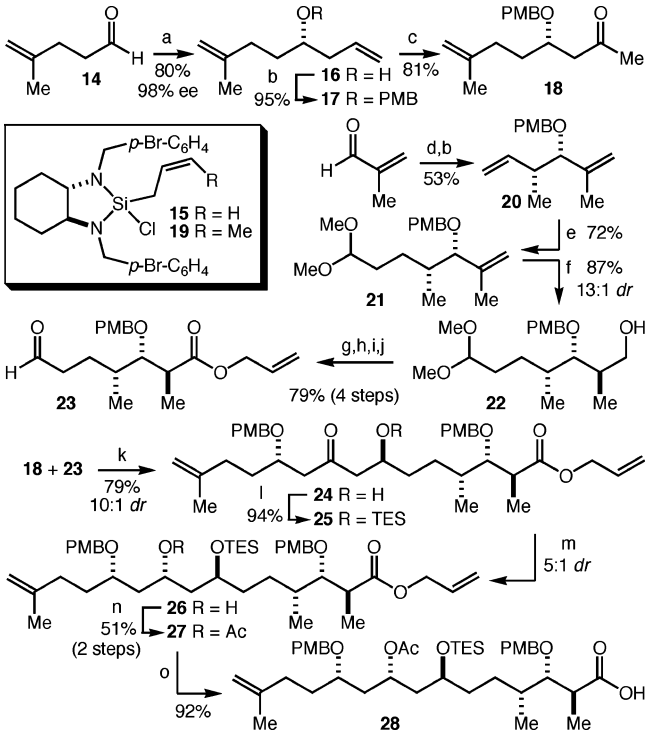
Scheme 3 [a]



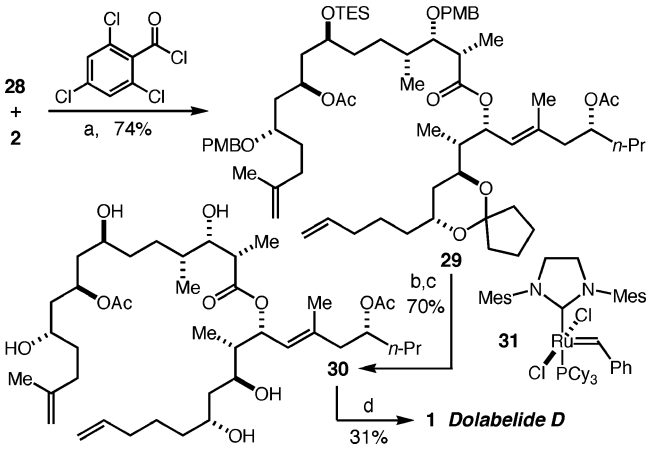
[a] (a) **15**, CH_2Cl_2, −20 °C. (b) NaH, PMBBr, THF, reflux. (c) 25 mol % $PdCl_2$, CuCl, DMF, H_2O, O_2. (d) *ent*-**19**, CH_2Cl_2. (e) 2 mol % Rh(acac)-$(CO)_2$, 10 mol % PPh_3, H_2/CO, 2,2-dimethoxypropane, PPTS, 60 °C. (f) 9-BBN, THF, −78 to 23 °C; H_2O_2, NaOH. (g) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C. (h) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*-BuOH, H_2O. (i) K_2CO_3, $CH_2{=}CHCH_2Br$, acetone, reflux. (j) PPTS, acetone, H_2O, reflux. (k) *n*-Bu_2BOTf, *i*-Pr_2NEt, Et_2O, −110 °C. (l) TESCl, imidazole, CH_2Cl_2. (m) L-Selectride, CH_2Cl_2, −78 °C. (n) Ac_2O, pyridine, DMAP, CH_2Cl_2. (o) 10 mol % $Pd(PPh_3)_4$, morpholine, THF.

1,5-Anti selective aldol coupling[14] of ketone **18** and aldehyde **23** proceeded smoothly to give aldol **24** in 79% yield as a 10:1 mixture of diastereomers. Protection of the alcohol as a TES ether gave **25** in 94% yield and was followed by a diastereoselective (∼5:1) ketone reduction with L-Selectride to give **26**. Following acetylation, the diastereomers were separated, and **27** was isolated in 51% yield. Finally, deprotection of the allyl ester gave the target acid **28** in 92% yield. The synthesis of **28** was carried out with a longest linear sequence of 13 steps from methacrolein in 9% overall yield.

Esterification of alcohol **2** with acid **28** proceeded smoothly to give **29** in 74% yield (Scheme 4). Methanolysis of the TES ether and cyclopentylidene ketal-protecting groups was followed by oxidative cleavage of the PMB ether groups to provide pentaol **30** in 70% overall yield (two steps). Initial attempts at macrocyclization by ring-closing metathesis with the "second-generation" Grubbs catalyst **31** were plagued not only by (not unexpected) low stereoselectivity (∼1.3:1 *E*:*Z*), but also by significant amounts of byproducts presumably derived from olefin isomerization pathways.[15] Despite these setbacks, dolabelide D could be isolated in 31% yield. Although a sample of the natural product was unavailable, comparison (^1H and ^{13}C NMR, IR, HRMS, $[\alpha]_D$) to published data confirmed the identity of our synthetic material.

The first synthesis of dolabelide D (and of any of the dolabelides) has been achieved. Methodologically, the four-step sequence that converts alcohol **4** into protected diol fragment **8** is especially noteworthy and serves as a demonstration of the power of the

Scheme 4 [a]



[a] (a) Et_3N, DMAP, toluene, −78 to 0 °C. (b) PPTS, MeOH. (c) DDQ, CH_2Cl_2, pH 7 buffer. (d) 25 mol % **31**, CH_2Cl_2, reflux.

catalytic asymmetric silane alcoholysis and tandem silylformylation−crotylsilylation methods. That the pathway from alcohol **4** to dolabelide D comprises just 14 linear steps (the longest linear sequence is from methacrolein to dolabelide D in 17 steps) is testament to the efficiency of these methods.

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Supporting Information Available: Experimental procedures, characterization data, and stereochemical proofs. This material is available free of charge via the Internet at http://pubs.acs.org.

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