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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-S₃ cells with IC₅₀s 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-S₃ cells with IC₅₀s 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 chemists³ 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 alcoholysis⁵ with alcohol **4** and *t*-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-crotylsilylation⁶ proceeded stereospecifically to provide, after quenching with methyl lithium, 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•SMe₂ and DMPU initiated a Brook-like 1,4 carbon (sp²) 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 *t*-butylsilane serves multiple purposes before being morphed into the desired *t*-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 (2 steps). Asymmetric aldol coupling⁸ with 5-hexenal then gave aldol **11** in 85% yield and with >10:1 diastereoselectivity. *Anti*-diastereoselective (>10:1 *dr*) β-hydroxyketone reduction⁹ then gave **12** in 91% yield. Protection of the diol as a cyclopentylidene ketal¹⁰ gave **13** and TBS removal provided fragment **2** in 50% yield (2 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**, 2 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 hydroboration¹³ gave alcohol **22** with 13:1 *dr*. A 4 step oxidation-oxidation-protection-deprotection sequence then provided aldehyde **23** in 79% overall yield. 1,5-*Anti* selective aldol coupling¹⁴ 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 triethylsilyl (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 (2 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 ¹³C NMR, IR, HRMS, [α]_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 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

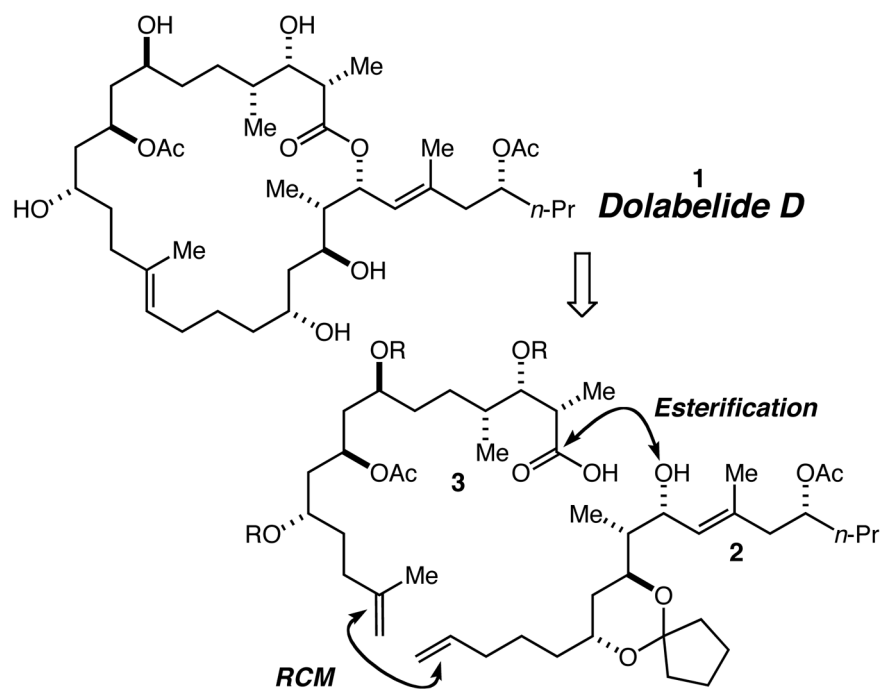
Acknowledgements

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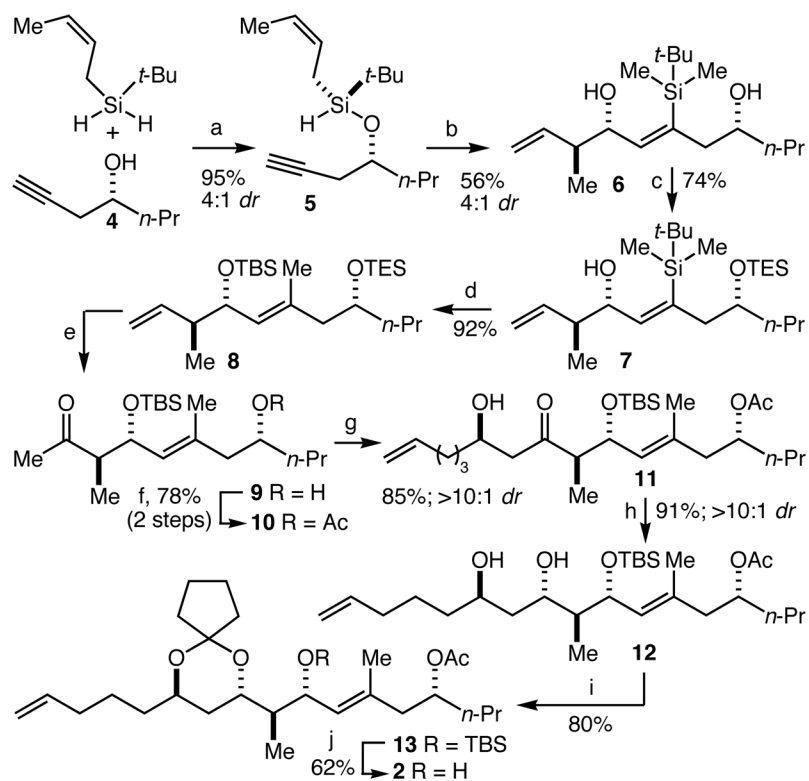
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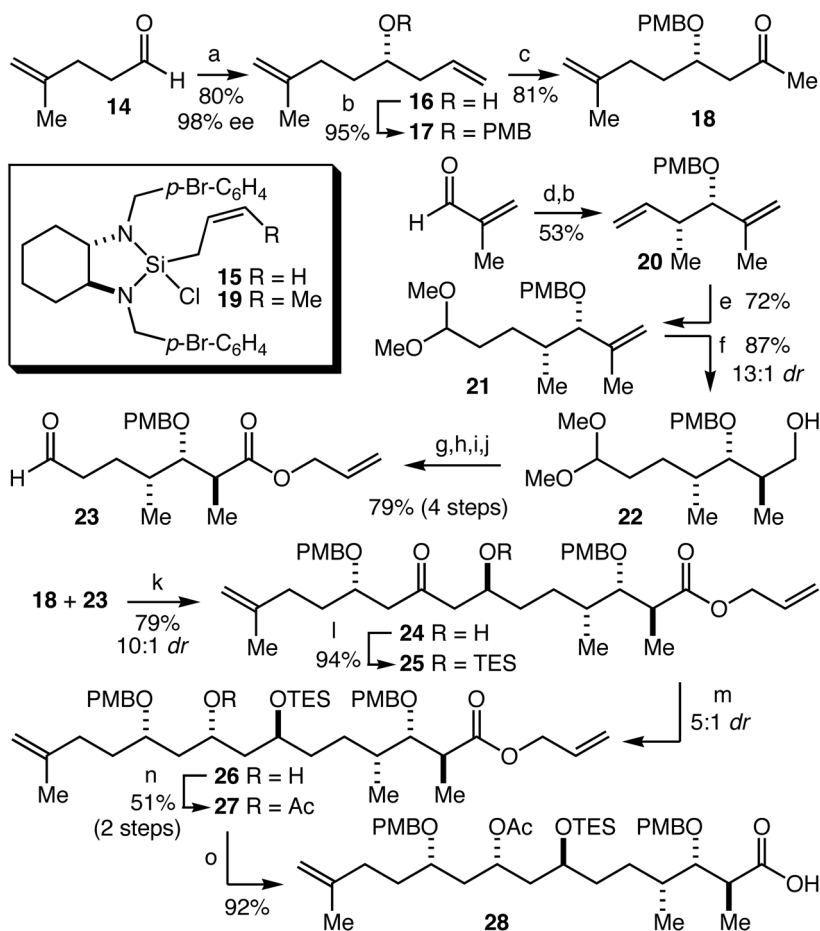
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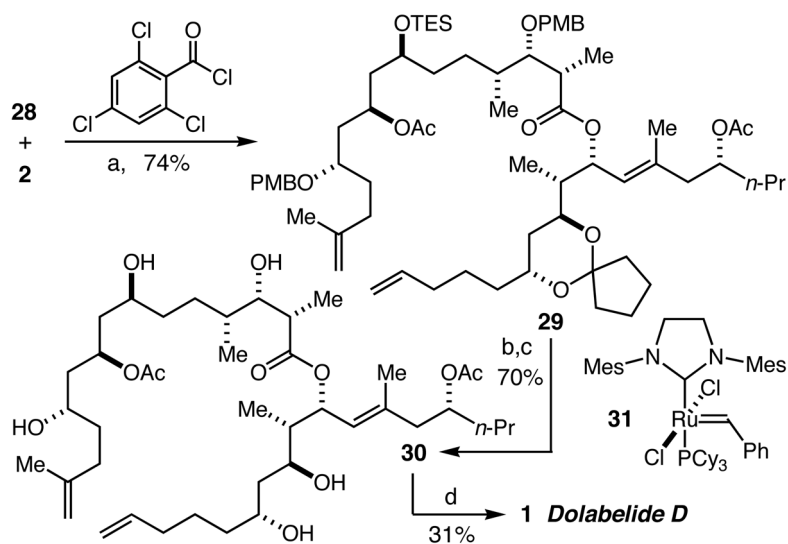
Scheme 1.

**Scheme 2.**

(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]BF₄, CO, PhH, 60 °C; ii. MeLi, Et₂O -78 to 23 °C. (c) TESCl, Et₃N, CH₂Cl₂, -20 °C. (d) *n*-BuLi, THF, -78 °C; CuBr•Me₂S, DMPU, 23 °C; MeI, -78 to 23 °C. (e) 25 mol% PdCl₂, CuCl, DMF, THF, H₂O, O₂. (f) Ac₂O, pyridine, DMAP, CH₂Cl₂. (g) (+)-(*ipc*)₂BCl, Et₃N, 5-hexenal, Et₂O -78 to 23 °C. (h) Me₄NBH(OAc)₃, AcOH, CH₃CN, THF, -40 to -20 °C. (i) 1,1-dimethoxycyclopentane, PPTS, CH₂Cl₂. (j) *n*-Bu₄NF, THF.

**Scheme 3.**

(a) **15**, CH₂Cl₂, -20 °C. (b) NaH, PMBBBr, THF, reflux, (c) 25 mol% PdCl₂, CuCl, DMF, H₂O, O₂. (d) *ent*-**19**, CH₂Cl₂. (e) 2 mol% Rh(acac)(CO)₂, 10 mol% PPh₃, H₂/CO, 2,2-dimethoxypropane, PPTS, 60 °C. (f) 9-BBN, THF, -78 to 23 °C; H₂O₂, NaOH. (g) (COCl)₂, DMSO, Et₃N, CH₂Cl₂, -78 °C. (h) NaClO₂, NaH₂PO₄, 2-methyl-2-butene, *t*-BuOH, H₂O. (i) K₂CO₃, CH₂=CHCH₂Br, acetone, reflux, (j) PPTS, acetone, H₂O, reflux, (k) *n*-Bu₂BOTf, *i*-Pr₂NEt, Et₂O, -110 °C. (l) TESCl, imidazole, CH₂Cl₂. (m) L-Selectride, CH₂Cl₂, -78 °C. (n) Ac₂O, pyridine, DMAP, CH₂Cl₂. (o) 10 mol% Pd(PPh₃)₄, morpholine, THF.

**Scheme 4.**

(a) Et_3N , DMAP, toluene, -78 to 0 $^\circ\text{C}$. (b) PPTS, MeOH. (c) DDQ, CH_2Cl_2 , pH 7 buffer, (d) 25 mol% **31**, CH_2Cl_2 , reflux.