Total synthesis of floresolide B and $\Delta^{6,7}$-*Z*-floresolide B†

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The total syntheses of the cytotoxin marine natural product floresolide B (1) and its $\Delta^{6,7}$-*Z* isomer (2) have been achieved through an olefin metathesis-based strategy.

Floresolide B (**1**, Fig. 1) is a recently discovered natural product possessing an intriguing molecular architecture.[1] Isolated from an extract of an ascidian of genus *Aplidium* collected in Pungu Besar, Flores Island, floresolide exhibits cytotoxicity against KB tumor cells and boasts in its structure an aromatic ring weaved within a [10] metacyclophane bridged by a 7-membered lactone. Its structure was deduced from its spectral data and from an X-ray crystallographic analysis of a related natural product. The latter structural analysis revealed only one atropisomer, that shown in Fig. 1, despite the possibility for two such isomers. Although critical, especially from the synthetic point of view, the atropisomerism of floresolide B and its siblings, floresolides A and C, was not mentioned in the isolation and structural elucidation report.[1] In this communication, we disclose a total synthesis of floresolide B (**1**) and its $\Delta^{6,7}$-*Z* isomer (**2**, Fig. 1) by an expedient olefin metathesis-based strategy that delivers both as single atropisomers.

A cursory inspection of the molecule of floresolide B (**1**) reveals the ring closing olefin metathesis[2] substrates **3** or **4** as potential precursors to this considerably strained molecule, as shown retrosynthetically in Fig. 1. *A priori*, however, neither substrate

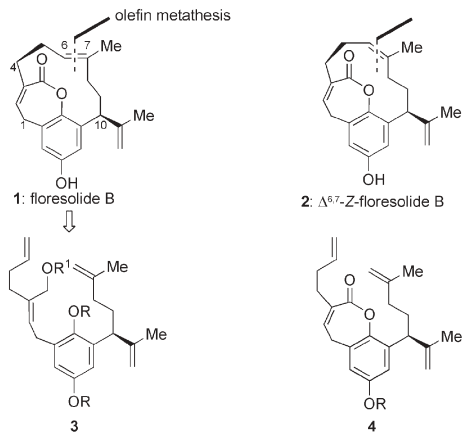

Fig. 1 Molecular structures and retrosynthetic analysis of floresolide B (**1**) and $\Delta^{6,7}$-*Z*-floresolide B (**2**).

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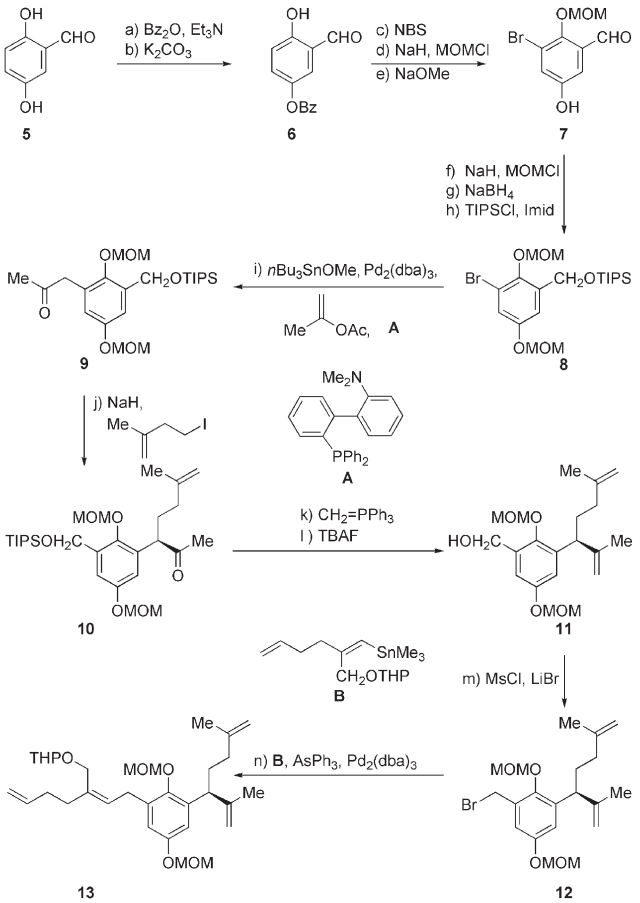
guarantees success in producing a ring, or even if it did, with the proper size and stereochemistry with regard to double bond geometry and atropisomerism. Rather, it was hoped that experimental exploration of this olefin metathesis-based approach would lead to some interesting observations from which a final strategy towards floresolide B might emerge.

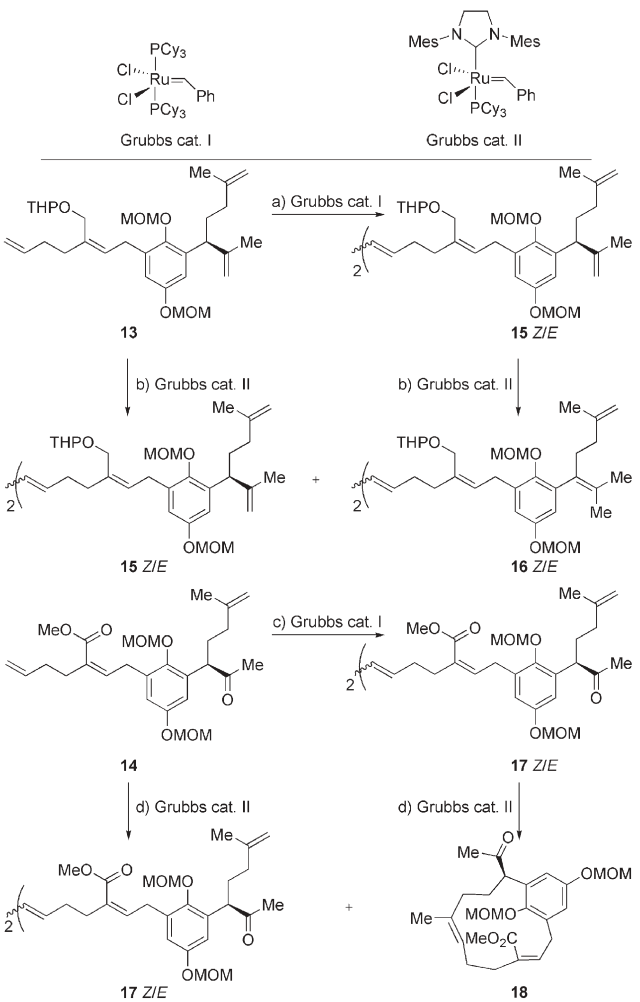
With this anticipation in mind, we set out to first construct substrate **3** as shown in Scheme 1. Thus, commercially available 2,5-dihydroxybenzaldehyde (**5**) was bis-benzoylated (Bz_2O, Et_3N) and selectively mono-debenzoylated (K_2CO_3) by a modification of a literature procedure[3] to afford mono-benzoate hydroxy benzaldehyde derivative **6** in 70% overall yield for the two steps. Sequential *o*-bromination (NBS, 95%), MOM-ether formation (NaH, MOMCl, 90%) and debenzoylation (NaOMe, THF/MeOH, 80%) furnished bromophenol **7**. The latter compound (**7**) was then protected with MOMCl in the presence of NaH, and then reduced with $NaBH_4$ to afford the corresponding benzylic alcohol, which was converted to its TIPS ether derivative **8** (TIPSCl, imidazole) in 65% overall yield for the three steps. Exposure of aryl bromide **8** to isopropenyl acetate and tri-*n*-butyltin methoxide[4] in the presence of catalytic amounts of $Pd_2(dba)_3$ and Buchwald ligand **A**[5] in toluene at 90 °C generated aryl methyl ketone **9** in 85% yield.[6] Alkylation[7] of the thermodynamic enolate derived from ketone **9** and NaH with 4-iodo-2-methylbut-1-ene then afforded compound **10** (73% yield),[8] whose methylenation proceeded smoothly under standard Wittig conditions to give the expected bis-olefin in 75% yield. Removal of the TIPS group from this bis-olefin (TBAF, 80% yield) allowed its conversion to benzylic bromide **12** (MsCl, Et_3N, LiBr, 82% yield)[9] through the corresponding benzylic alcohol **11**. Extension of the short aryl-bound chain of the growing molecule required vinyl stannane **B**, whose construction from the corresponding vinyl iodide relied on lithium–iodine exchange (*t*BuLi) followed by the lithium–tin exchange (Me_3SnCl). Thus **12** and **B** were united under the influence of $Pd_2(dba)_3$ and $AsPh_3$, through a Stille reaction, leading to the olefin metathesis precursor **13** in 85% yield.[10] Note, the choice of the THP as a protecting group in the construction of vinyl stannane **B** from the iodide was crucial for its success.

The behavior of polyolefin **13** and its relative, ketoester **14**, in the presence of the two Grubbs olefin metathesis catalysts (Grubbs cat. I and Grubbs cat. II) is summarized in Scheme 2. Thus, upon treatment with Grubbs cat. I in refluxing CH_2Cl_2 for 48 h, substrate **13** was converted to a 1 : 1 mixture of *E* : *Z* dimeric olefins **15***Z* and **15***E* in 75% combined yield, despite the high dilution conditions (0.5 mM) employed. When Grubbs cat. II was employed under the same conditions, the reaction was complete within 48 h, and the two dimeric olefins **15***Z* : **15***E* were obtained, again in a 1 : 1 ratio, and in 35% combined yield. Along with them, however, this time the two hydride-shift products **16***Z* : **16***E* were also obtained (1 : 1 ratio, 20% combined yield).[11] The same



Scheme 1 Synthesis of advanced intermediate **13**. *Reagents and conditions*: (a) Bz_2O (2.1 equiv), Et_3N (2.3 equiv), 4-DMAP (0.1 equiv), CH_2Cl_2, 25 °C, 12 h, 85%; (b) K_2CO_3 (1.5 equiv), THF : MeOH (1 : 1), 0 °C, 2 h, 83%; (c) NBS (1.05 equiv), CH_2Cl_2, 25 °C, 1 h, 95%; (d) NaH (2.0 equiv), MOMCl (1.0 equiv), DMF, 25 °C, 2 h, 90%; (e) NaOMe (1.1 equiv), THF : MeOH (1 : 1), −40 °C, 2 h, 80%; (f) NaH (2.0 equiv), MOMCl (1.0 equiv), DMF, 25 °C, 2 h, 85%; (g) $NaBH_4$ (2.5 equiv), MeOH, 0 °C, 30 min, 90%; (h) TIPSCl (1.5 equiv), imidazole (2.0 equiv), 4-DMAP (0.1 equiv), DMF, 25 °C, 12 h, 85%; (i) isopropenyl acetate (1.4 equiv), nBu$_3$SnOMe (1.4 equiv), $Pd_2(dba)_3$ (0.1 equiv), Buchwald ligand **A** (0.4 equiv), toluene, 90 °C, 2 h, 85%; (j) NaH (1.2 equiv), THF, 0 °C, 0.5 h; then 4-iodo-2-methylbut-1-ene (1.6 equiv), 0 °C, 4 h, 73%; (k) $CH_3P^+Ph_3$ Br^- (1.5 equiv), NaHMDS (1.5 equiv), THF, 0 °C, 1 h; then **10** added to the generated ylide, 0 °C, 0.5 h, 75%; (l) TBAF (1.1 equiv), THF, 0 °C, 15 min, 80%; (m) LiBr (20 equiv), Et_3N (2.5 equiv), MsCl (1.5 equiv), THF, −10 °C, 30 min, 82%; (n) $Pd_2(dba)_3$ (0.1 equiv), $AsPh_3$ (0.8 equiv), THF, 25 °C, 20 min; then vinyl tin compound **B** (1.2 equiv), **12** (1.0 equiv), 70 °C, 1 h, 85%. Bz = benzoyl, 4-DMAP = 4-dimethylaminopyridine, NBS = *N*-bromosuccinimide, MOM = methoxymethyl, DMF = *N*,*N*-dimethylformamide, TIPS = triisopropylsilyl, dba = dibenzylideneacetone, HMDS = hexamethyldisilazane, TBAF = tetra-*n*-butylammonium fluoride, Ms = methanesulfonyl, THP = tetrahydropyranyl.

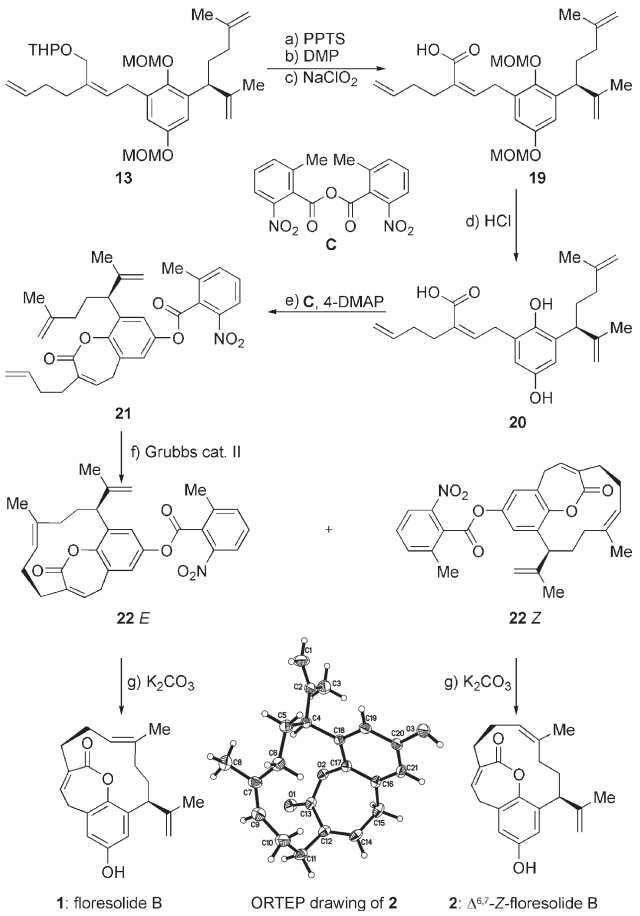
distribution of products **15***Z* : **15***E* and **16***Z* : **16***E* was obtained from **15***Z* : **15***E* (1 : 1 ratio) under the same conditions. Faced with the reluctance of **13** to cyclize, and given the hydride shift side-products arising from the action of the Grubbs cat. II on its activated olefin, we chose ketoester **14** as the next olefin metathesis precursor to be explored. It was reasoned that the absence of the bulky THP group and of the isopropenyl moiety next to the aromatic ring would perhaps allow ring closure and avoid



Scheme 2 Attempted ring closing metathesis of open chain substrates **13** and **14**. *Reagents and conditions*: (a) Grubbs cat. I (0.2 equiv), CH_2Cl_2, 0.5 mM, 40 °C, 48 h, **15***Z* : **15***E* = 1 : 1, 75% combined yield; (b) Grubbs cat. II (0.2 equiv), CH_2Cl_2, 0.5 mM, 40 °C, 48 h, **15***Z* : **15***E* = 1 : 1, 35% combined yield, **16***Z* : **16***E* = 1 : 1, 20% combined yield; (c) Grubbs cat. I (0.2 equiv), CH_2Cl_2, 0.5 mM, 40 °C, 8 h, **17***Z* : **17***E* = 1 : 1, 90% combined yield; (d) Grubbs cat. II (0.2 equiv), CH_2Cl_2, 0.5 mM, 40 °C, 8 h, **17***Z* : **17***E* = 1 : 1, 70% combined yield, **18**, 9%.

alternative pathways for the reaction. In the event, Grubbs cat. I (CH_2Cl_2 reflux, 8 h) resulted in the formation of only the dimeric materials **17***Z* : **17***E* as a 1 : 1 mixture and in 90% combined yield. When Grubbs cat. II was used under the same conditions, however, the cyclic product **18** was obtained, albeit in low yield (9%, single isomer), in addition to **17***Z* : **17***E* (1 : 1 ratio, 70% combined yield). Exposure of the dimeric mixture **17***Z* : **17***E* to Grubbs cat. II under the same conditions led to the same ratio of products **17***Z* : **17***E* and **18**.

The failure of substrates **13** and **14** to advance to cyclic products in a synthetically useful way prompted us to modify our approach to floresolide B (**1**), so as to enforce the desired olefin metathesis-based cyclization reactions. It was reasoned that such enforcement would, perhaps, emerge from a lactone bridge installed within the molecule prior to the olefin metathesis step,[12] and thus the design of precursor **4** (Fig. 1). Removal of the THP group from compound **13** (PPTS, MeOH, 75% yield) proceeded smoothly as shown in Scheme 3 to afford the corresponding alcohol, which was



Scheme 3 Total synthesis of floresolide B (**1**) and $\Delta^{6,7}$-*Z*-floresolide B (**2**) and ORTEP drawing of $\Delta^{6,7}$-*Z*-floresolide B (**2**). (Only the (*S*)-enantiomer is shown from the two enantiomers present in the crystal.) *Reagents and conditions*: (a) PPTS (5.0 equiv), 0.2 M in MeOH, 25 °C, 6 h, 75%; (b) DMP (1.2 equiv), $NaHCO_3$ (20 equiv), CH_2Cl_2, 25 °C, 92%; (c) $NaClO_2$ (4.0 equiv), NaH_2PO_4 (2.0 equiv), 2-methyl-2-butene (5.0 equiv), *t*BuOH/H_2O (4 : 1), 25 °C, 4 h, 95%; (d) HCl in MeOH (0.1 M), 25 °C, 4 h, 75%; (e) 2-nitro-6-methyl-benzoic anhydride (2.0 equiv), 4-DMAP (4.0 equiv), 0.5 mM in CH_2Cl_2, then **20** was added *via* syringe pump over 12 h, 25 °C, 66%; (f) Grubbs cat. II (0.1 equiv), 0.5 mM in CH_2Cl_2, 40 °C, 15 min, 22*E* (23%), 22*Z* (66%); (g) K_2CO_3 (10.0 equiv), MeOH/H_2O (1 : 1), 25 °C, 2 h, 90%. PPTS = pyridinium *p*-toluenesulfonate, DMP = Dess–Martin periodinane.

converted to carboxylic acid **19** through a two-step oxidation procedure (DMP, $NaClO_2$, 66% overall yield). Cleavage of the MOM group from the latter compound (**19**) was effected under acidic conditions (aqueous HCl, MeOH, 75% yield), furnishing carboxy dihydroquinone **20**, which was reacted with 2-nitro-6-methyl-benzoic anhydride in the presence of 4-DMAP to afford lactone **21** in 66% overall yield.[13] Exposure of **21** to Grubbs cat. II in refluxing CH_2Cl_2 pleasantly resulted, within 15 min, in the formation of cyclic olefins **22***Z* and **22***E* in *ca.* 2.9 : 1 ratio, and 89% combined yield. Finally, cleavage of the nitrobenzoate group from these compounds with K_2CO_3 in MeOH furnished, after HPLC separation, floresolide B (**1**)[14] (20% overall yield from **21**) and its $\Delta^{6,7}$-*Z* isomer (**2**) (59% overall yield from **21**).† The structure of the latter compound (**2**) was further confirmed by X-ray crystallographic analysis (see ORTEP drawing, Scheme 3).[15,16]

It is of interest that both products of the ring olefin metathesis reaction were formed exclusively as single atropisomers and of the same form as the natural product (**1**). This observation is in line with severe steric congestion for the transition states leading to the unnatural atropisomers for both *E* and *Z* isomers, whereas those leading to the natural isomers are relatively free of such interactions (manual molecular models). It is also of interest that several modifications of the experimental conditions (solvent, temperature, catalyst) thus far have failed to change the ratio of the geometrical isomers of the metathesis ring closing reaction.

The described chemistry demonstrates the power of the olefin metathesis reaction in total synthesis, exposing at the same time its dependence on substrate structure with regard to product geometry. Further studies to improve the stereochemical outcome of the ring closing reaction in this case and in pursuit of other members of the floresolide family of natural products are in progress.

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15 CCDC 290049 (**2**). For crystallographic data in CIF or other electronic format see DOI: 10.1039/b517385j.
16 Chemical formula ($C_{21}H_{24}O_3$), formula weight (324.40), crystal system (monoclinic), unit cell dimensions (a = 27.321 (6) Å, b = 8.7467 (17) Å, c = 15.029 (3) Å, β = 97.75 (3)°), unit cell volume (3558.5 (12) Å^3), Z = 8, temperature (296 (2) K), space group (*C*2/*c*), absorption coefficient (0.080 mm^{-1}), reflections collected (12624), independent reflections (3134), R_{int} = 0.0506, $R1$ = 0.0813, $wR2$ = 0.1693 for observed data, $I > 2\sigma$ (I).

