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Convergent enantioselective syntheses of two potential C25–C40 subunits of (−)-caylobolide A

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ABSTRACT

The convergent syntheses of two possible diastereomers of the C25–C40 subunit resident in (−)-caylobolide A have been accomplished. The key reaction featured a chemoselective Ru-catalyzed cross-metathesis between a fully elaborated type I and two functionalized type II α,β-unsaturated ketones.

Marine sources continually provide the synthetic community a variety of structurally challenging natural products.[1] One aspect that makes the total synthesis of natural products so challenging is the uncertain configuration of multiple stereogenic centers within a target compound. It is well known that diastereomeric possibilities increase exponentially by a factor of 2^n, where n is equal to the number of chiral centers. Thus, the greater number of undefined stereogenic centers can rapidly complicate a synthetic approach. One such natural product, termed caylobolide A (**1**), was isolated via bioassay-guided purification in 2002 from the marine cyanobacteria *Lyngbya majuscule* collected at Cay Lobos, Bahamas by Molinski and MacMillan.[2] As shown in Scheme 1, caylobolide A contains eight undefined stereocenters, thus 256 diastereomeric structural possibilities. Another interesting feature of **1** is the repeating 1,5-diol motif present along the 36-membered lactone core. In addition to its intriguing macrocyclic structure, caylobolide A has shown cytotoxic properties against the human colon tumor cell line HCT 116 (IC_{50} = 9.9 μM). Based on the limited biological data and very unique and challenging structural features of caylobolide A, we sought to undertake the synthesis of **1**. Herein, we disclose our synthetic approach to the C25–C40 subunit of **1**.

The retrosynthetic strategy of caylobolide centered on a highly convergent approach is highlighted in Scheme 1. Thus, we envisaged esterification at C35 (either standard or macrocyclic) and olefin metathesis (either cross or ring-closing) process at C23–C24 to forge the 36-membered ring of **1**. We initially decided to focus on constructing the C25–C40 segment of **1** due to the defined stereocenters (relative configuration via the Kishi universal NMR database and absolute configuration by Mosher analysis) at C25, C27, C29, and C33.[3,4]

With this idea in mind, the two potential C25–C40 segments **2** and **3** would be synthesized via a cross-metathesis of homoallylic alcohol **4** and the two α,β-unsaturated ketones **5** and **6**. We arbitrarily chose the *S*-configuration at C36 for compounds **5** and **6** to simply illustrate the synthetic approach to **2** and **3**.

With the initial synthetic plan in hand, our focus was turned to completing the homoallylic diol **4**. As shown in Scheme 2, treatment of the known TBS protected aldehyde **7**[5] with (+)-Ipc_2Ballyl under the standard reaction conditions as pioneered by Brown furnished the requisite homoallylic alcohol.[6] An ensuing protection of the free hydroxyl group with BnBr, NaH, and Bu_4NI afforded benzyl ether **8** in 69% yield over two steps from **7**. Oxidative cleavage with O_3 and PPh_3 mediated reductive quench of the olefin moiety resident in **8** was readily accomplished and provided the aldehyde **9** in 60% yield. With the required aldehyde in hand, we envisioned a chelation-controlled allylation with an appropriate stannane utilizing the benzyl directing group and $TiCl_4$.[7] Much to our delight, treatment of **9** with $TiCl_4$ and $Bu_3Snallyl$ at −78 °C furnished the desired *anti*-homoallylic alcohol with excellent diastereoselectivity (~12:1 dr) as deduced by ^1H NMR.

An ensuing protection of the free hydroxyl moiety as a TBS ether was readily accomplished under standard reaction conditions (TBSCl and imidazole) to afford the protected diol **4** in 75% yield over two steps from **9**.[8]

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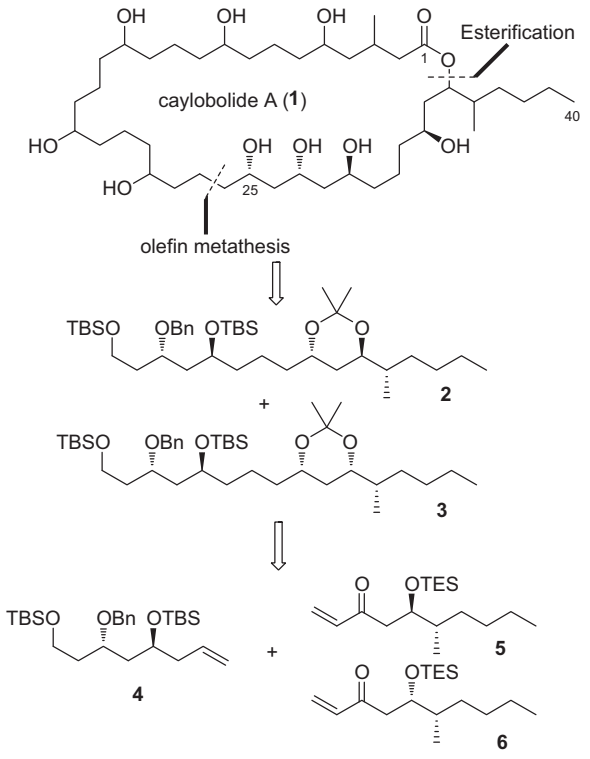
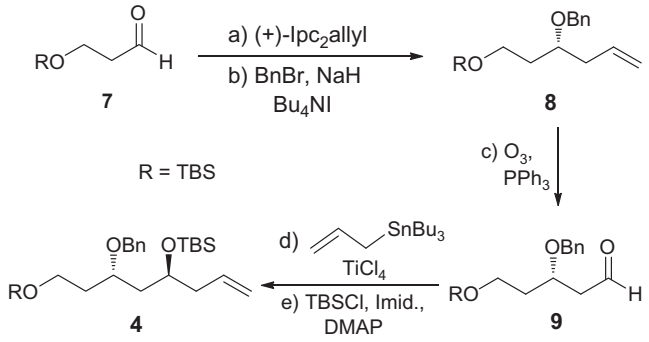
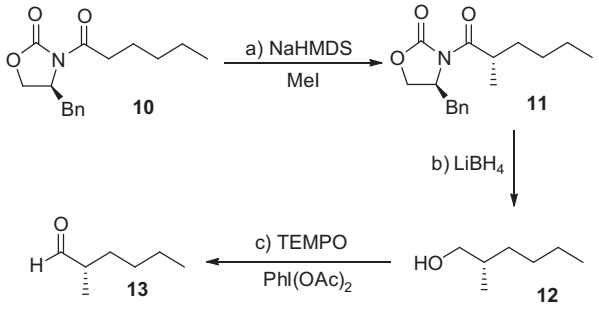


Scheme 1. Retrosynthetic analysis of caylobolide (**1**).



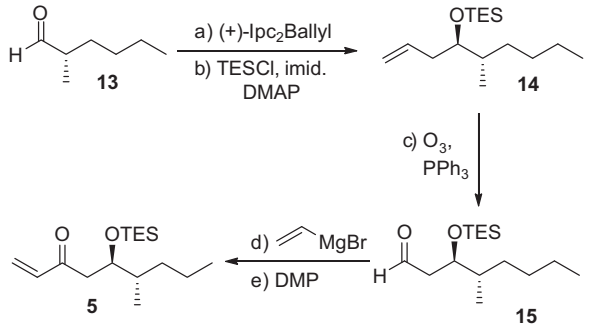
Scheme 2. Synthesis of intermediate **4**. Reagents and conditions: (a) (+)-Ipc$_2$BOMe (1.6 equiv), allylMgBr (1.5 equiv) Et$_2$O, 0 °C to −78 °C to rt, 6 h, 83%; (b) BnBr (1.1 equiv), NaH (2.0 equiv), Bu$_4$NI (0.1 equiv), DMF, rt, 24 h, 83%; (c) CH_2Cl_2, −78 °C, then PPH_3 (4.0 equiv), rt, 6 h, 60%; (d) allylSnBu$_3$ (2.0 equiv), $TiCl_4$ (1.0 equiv), CH_2Cl_2, −78 °C, 8 h, 81%; (e) TBSCl (2.0 equiv), imidazole (4.0 equiv), DMAP (0.2 equiv), DMF, rt, 24 h, 92%.



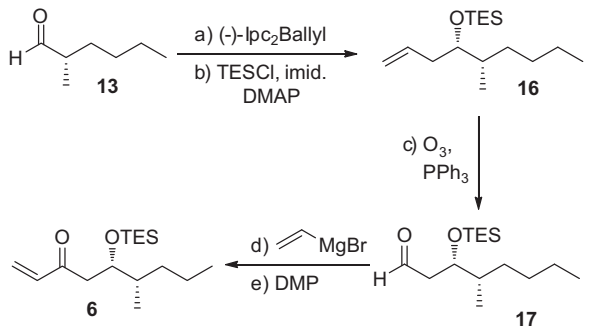
Scheme 3. Synthesis of intermediate **13**. Reagents and conditions: (a) NaHMDS (1.2 equiv), MeI (2.5 equiv), THF, −78 to −20 °C, 2 h, 81%; (b) LiBH$_4$ (3.0 equiv), MeOH (3.0 equiv), Et$_2$O, rt, 6 h, 93%; (c) TEMPO (0.15 equiv), PhI(OAc)$_2$ (1.1 equiv), CH_2Cl_2, rt, 20 h, 82%.

Our outline to the C25–C40 segment of **1** required the synthesis of chiral aldehyde **13** as delineated in Scheme 3. Hence, an asymmetric alkylation of the known chiral oxazolidinone **10** with NaHMDS and MeI provided **11** in 81% yield with excellent diastereoselectivity (>15:1 dr).[9] Subsequent reduction of the oxazolidinone moiety with LiBH$_4$ readily afforded the chiral primary alcohol **12** in 93% yield. Final oxidation of the hydroxyl group of **12** with TEMPO and PhI(OAc)$_2$ furnished the desired aldehyde **13** in 82% yield and set the stage for building the subunits **5** and **6**.[10]

With the chiral aldehyde **13** readily in hand and in multi-gram quantities, we next focused our effort on the completion of the cross-metathesis precursor ketones **5** and **6** as delineated in Schemes 4 and 5. Thus, treatment of the chiral aldehyde **13** with (+)-Ipc$_2$Ballyl provided the corresponding homoallylic alcohol with a respectable 66% yield and dr of ~10:1. Ensuing protection of the free hydroxyl group with TESCl, DMAP, and imidazole furnished the triethylsilyl ether **14** in 73% yield. Ozonolysis of the terminal olefin followed by the addition of PPh_3 resulted in the formation of the requisite aldehyde **15** in 63% yield. In order to complete the cross-metathesis coupling type II olefin **5**, a vinyl addition and subsequent oxidation to furnish the α,β-unsaturated ketone **5** were required. Thus, the addition of vinyl Grignard reagent to **15** provided the allylic alcohol as an extraneous mixture of diastereomers and ensuing oxidation of the hydroxyl moiety with Dess–Martin periodinane (DMP) afforded ketone **5** in 38% yield over two steps from **15**.[11] Access to ketone **6** followed a very similar synthetic pathway, but differed only in utilizing the (−)-Ipc$_2$Ballyl reagent as shown in Scheme 5. All of the other steps (b–e) were



Scheme 4. Synthesis of intermediate **5**. Reagents and conditions: (a) (+)-Ipc$_2$BOMe (1.6 equiv), allylMgBr (1.5 equiv), Et$_2$O, −78 °C to rt, 3 h 66%; (b) TESCl (1.5 equiv), imidazole (3.0 equiv), DMAP (0.1 equiv), CH_2Cl_2, rt, 12 h, 73%; (c) CH_2Cl_2 −78 °C, 1 h, then PPh_3 (4.0 equiv), rt, 6 h, 63%; (d) vinylMgBr, (2.0 equiv), Et$_2$O, −78 °C, 4 h, 60%; (e) DMP (2.0 equiv), pyridine (5.0 equiv), CH_2Cl_2, rt, 15 h, 63%.



Scheme 5. Synthesis of intermediate **6**. Reagents and conditions: (a) (−)-Ipc$_2$BOMe (1.6 equiv), allylMgBr (1.5 equiv), Et$_2$O, −78 °C to rt, 3 h 86%; (b) TESCl (1.5 equiv), imidazole (3.0 equiv), DMAP (0.1 equiv), CH_2Cl_2, rt, 12 h, 75%; (c) CH_2Cl_2, −78 °C, 1 h, then PPh_3 (4.0 equiv), rt, 6 h, 60%; (d) vinylMgBr, (2.0 equiv), Et$_2$O, −78 °C, 4 h, 75%; (e) DMP (2.0 equiv), pyridine (5.0 equiv), CH_2Cl_2, rt, 15 h, 70%.