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Studies directed toward the synthesis of caylobolide A: convergent synthesis of C21–C40 subunit

J. S. Yadav *, N. Swapnil, M. Venkatesh, A. R. Prasad

Centre for SemioChemicals, CSIR-Indian Institute of Chemical Technology, Hyderabad 500 007, India

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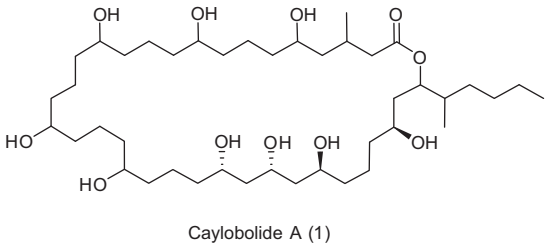
ABSTRACT

Stereoselective synthesis of the C21–C40 core segment of caylobolide A has been achieved following a highly efficient convergent strategy. The key reactions featured in the synthesis are Prins cyclization, reductive radical cyclization, Sharpless asymmetric epoxidation and olefin cross metathesis.

Marine natural products have become a major source of new chemical entities in the discovery of potential anticancer agents that potently suppress various molecular targets.[1] These entities give the synthetic chemist, a challenge in the area of the total synthesis of natural products viz., the exponential probability of number of diastereomers. A new 36 membered macrolactone caylobolide A (**1**) was one of such natural products which was isolated via bioassay-guided purification from the Bahamian cyanobacterium *Lyngbya majuscule* by Molinski and MacMillan.[2] It exhibits potent cytotoxicity toward the human colon tumor cell line HCT-116 (IC_{50} 9.9 μM). As shown in Figure 1, caylobolide A contains eight undefined stereogenic centers, thus giving several structural diastereomeric possibilities with repeating 1,5-diol motif. Undoubtedly, this scarce natural product has attracted top schools of synthesis to embark on its synthesis.[3] Our group is engaged in the synthesis of biologically active natural products[4] and was attracted to the fascinating biological profile of caylobolide. In this Letter, we report our preliminary studies that resulted in the synthesis of the southern (C21–C40) domain of caylobolide A.

As shown in Scheme 1, our overall retrosynthetic strategy for the target fragment **2** involved disconnection at the C20–C21 and the ester bonds, affording two subtargets **3** and **4**, respectively. The subtarget **3** as represented was derived from **5** obtainable by Prins cyclization from homoallylic alcohol **7**, whereas subtarget **4** was realized from **6**, obtainable by radical cyclization. With this strategy in mind, the target fragment **2** could be synthesized via cross metathesis of olefin **3** and allylic alcohol **4**, having arbitrarily chosen the *R*-configuration at C36. With this strategy we can build directly *syn* and *anti* 1,5-diol motif.



Caylobolide A (1)

Figure 1. Structure of caylobolide A.

The synthesis of fragment **3**, the core intermediate is outlined in Scheme 2. This is initiated from the known aldehyde **8** using a two-step sequence.[5] Aldehyde **8** is engaged in allylation under Keck's conditions[6] to produce homo-allylic alcohol **9** in 87% yield.[7] The resulting alcohol **9** is then converted to benzyl ether **10** in 89% yield. Ozonolytic cleavage of the olefinic bond of the compound **10** afforded the required aldehyde **11**, which on Prins cyclization with **7** in the presence of TFA followed by hydrolysis of the resulting trifluoroacetate gave trisubstituted pyran **12** in 52% yield.[8] The primary hydroxyl group in **12** is transformed to its corresponding tosylate using *p*-TsCl and triethylamine followed by protection of the secondary hydroxyl group as its silyl ether

* Corresponding author. Fax: +91 40 27160512.
E-mail address: yadavpub@iict.res.in (J.S. Yadav).

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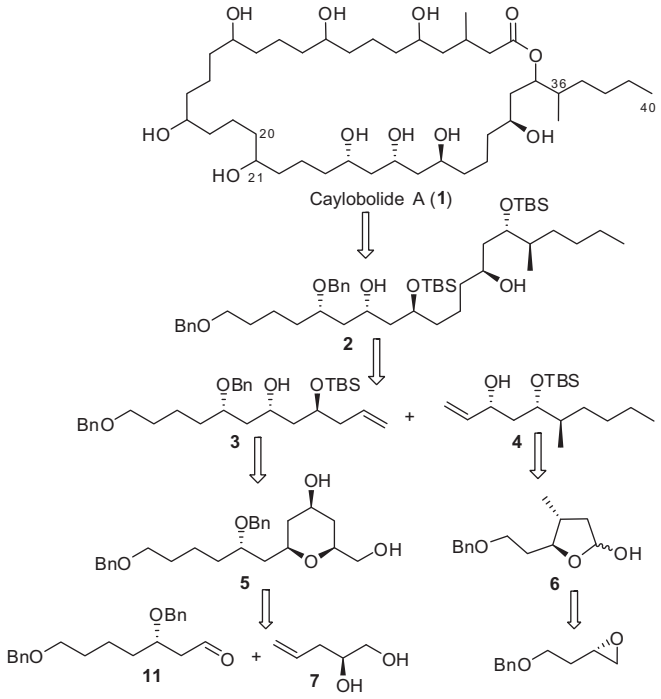
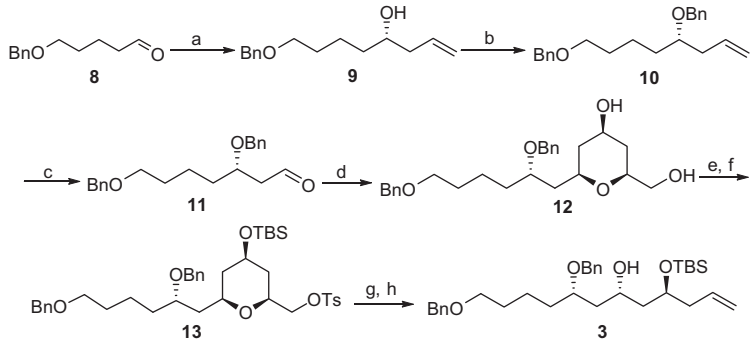


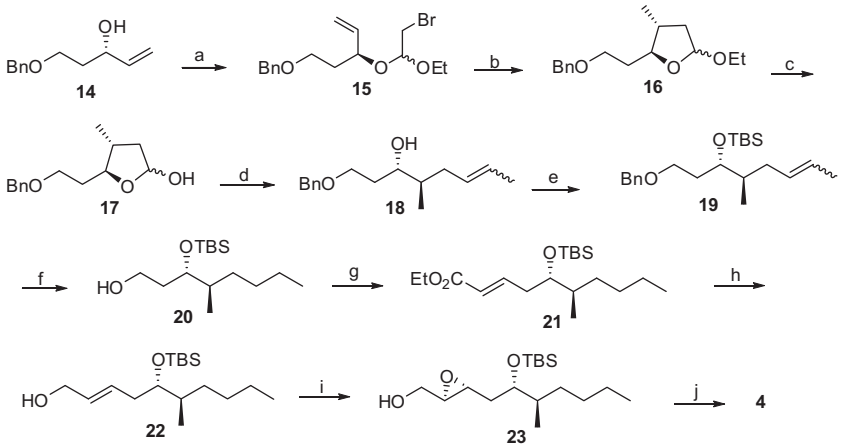
Scheme 1. Retrosynthetic analysis of caylobolide A.

using TBSCl, and imidazole to obtain silyl ether **13** in 80% yield in two steps. Substitution of the tosyl group in **13** using NaI in acetone followed by reductive opening produced alcohol **3** in 83% overall yield (two steps).[8b,d]

The synthesis of fragment **4** commenced from alcohol **14** (Scheme 3). Compound **14**[9] is subsequently reacted with ethyl vinyl ether and NBS, which resulted in bromoacetal **15** as a 1:1 mixture of diastereomers.[10] It was converted into cyclic ethyl acetal **15** (80% for two steps) with a preferential trans geometry of the new stereogenic center via a radical cyclization using *n*-Bu_3SnH in refluxing benzene with catalytic AIBN as a radical initiator.[11] The hydrolysis of ethyl acetal **16** using 60% acetic acid under reflux conditions afforded the lactol **17**, which on two carbon Wittig olefination furnished the hydroxy derivative **18** as mixture of diastereomers in 64% yield in two steps. The resulting alcohol **18** is protected as its silyl ether followed by simultaneous reduction of olefin and benzyl group furnished primary alcohol **19** in 86% yield. Subsequently, oxidation of the alcohol **20** followed by two-carbon Wittig olefination gave the α,β-unsaturated ester **21** in 74% yield in overall two steps. The ester **21** is reduced with DIBAL-H at −20 °C to afford allylic alcohol **22** in 92% yield. The requisite chiral epoxide was introduced at this stage via a Sharpless asymmetric epoxidation[12] reaction, using (−)-diisopropyl tartrate to yield epoxide **23** in 88% yield. Furthermore, titanocene induced regioselective deoxygenation[13] of epoxy alcohol **23** afforded allylic alcohol **4** in 80% yield.



Scheme 2. Reagents and conditions: (a) *R*-BINOL, $Ti(O^iPr)_4$, allyltributylstannane, 4° MS, −78 °C, −20 °C, 72 h, 87%; (b) NaH, BnBr, cat. TBAI, THF, 0 °C to rt, 89%; (c) O_3, CH_2Cl_2, TPP, −78 °C, 1 h, 84%; (d) **7**, TFA, CH_2Cl_2, 0 °C to rt, 3 h then K_2CO_3, MeOH, rt, 30 min, 52%; (e) *p*-TsCl, Et_3N, CH_2Cl_2, 0 °C to rt, 3 h, 88%; (f) TBDMSCl, imidazole, DMAP, CH_2Cl_2, 0 °C to rt, 2 h, 91%; (g) NaI, acetone, reflux, 24 h, 90%; (h) Zn, EtOH, reflux, 2 h, 92%.



Scheme 3. Reagents and conditions: (a) ethyl vinyl ether, NBS, CH_2Cl_2, 0 °C to rt, 5 h, 88%; (b) *n*-Bu_3SnH, AIBN (cat.), benzene, reflux, 2 h, 90%; (c) 60% AcOH, reflux, 2 h, 85%; (d) $C_2H_5PPh_3^+Br^-$, *n*-BuLi, THF, −20 °C, 75%; (e) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C to rt, 90%; (f) H_2, Pd/c, EtOAc, rt, 96%; (g) (i) IBX, DMSO, CH_2Cl_2, 0 °C to rt, 2 h; (ii) $Ph_3P{=}CHCO_2Et$, benzene, rt, 2 h, 92%; (h) DIBAL-H, CH_2Cl_2, −20 °C, 2 h, 92%; (i) (−)-DIPT, $Ti(O^iPr)_4$, TBHP, 4 Å MS, CH_2Cl_2, −20 °C, 12 h, 88%; (j) $(C_5H_5)_2TiCl_2$, Zn, $ZnCl_2$, THF, rt, 10 min, 80%.