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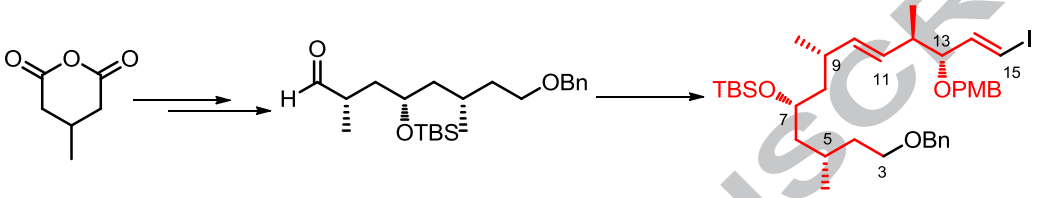

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Stereoselective Synthesis of the C3-C15 Fragment of Callyspongiolide

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ABSTRACT

The synthesis of C3-C15 fragment of callyspongiolide, a 14-membered macrolides isolated from the marine sponge *Callyspongia sp.*, which was collected from the Indonesia, is reported. Highlights of the synthesis include construction of *E*-olefin through Julia-Kocienski olefination, Brown asymmetric allylation and base-induced elimination reactions for propargyl alcohol synthesis.

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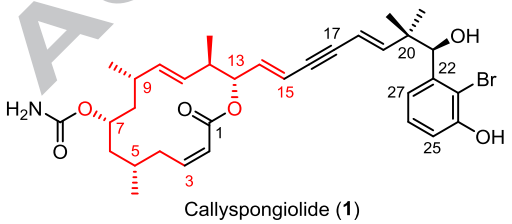
Callyspongiolide (**1**) is a marine sponge derived macrolide, isolated from the methanolic extract of the sponge *Callyspongia* sp. collected in Indonesia by Proksch and co-workers in 2014 as a light yellowish amorphous solid.[1] Callyspongiolide possesses significant *in vitro* cytotoxicity against human Jurkat J16 T and Ramos B lymphocytes (IC_{50} 70 and 60 nM, respectively). Importantly, callyspongiolide is 13-fold more active than kahalalide F.[1] As such callyspongiolide could serve as a promising lead compound for the development of new anticancer agents, provided a sustainable supply can be generated by chemical synthesis.



Callyspongiolide (**1**)

Figure 1. Structure of callyspongiolide (**1**).

From a structural perspective, callyspongiolide contain a 14-membered macrocyclic lactone ring connected with a conjugated dieneynic system side chain terminating at a brominated benzene ring. This unique structure incorporates six stereocenters, including five in the macrocyclic ring and one in the side chain. Also the macrolactone core features one *E*-olefin and one *Z*-olefin. The structure and relative stereochemistry of the macrocyclic part was established by detailed NMR and HRMS spectroscopy.[1] However, the relative stereochemistry of the C-21 stereocenter was not disclosed. Later absolute stereochemistry of callyspongiolide was established by Ye et al.[2] and Ghosh et al.[3] by its total synthesis. The interesting biological activity, structural novelty and low natural abundance of callyspongiolide (**1**) have attracted attention of synthetic organic chemists worldwide. There are two more synthesis of macrocyclic ring by Ghosh et al.[4] and synthesis of the unsaturated fragment of callyspongiolide by Kotora et al.[5] reported. Very recently total synthesis of callyspongiolide was reported by Harran et al.[6]

Our retrosynthetic plan for the synthesis of C3-C15 fragment of callyspongiolide is illustrated in Scheme 1. To construct *E*-olefin in compound **4**, we planned to couple aldehyde **5** and sulphone **6** through Julia-Kocienski olefination. The aldehyde fragment **5** could be obtained from homoallylic alcohol **7**, which could be easily amenable from commercially available 3-methylglutaric anhydride (**8**). The sulphone fragment **6** could be obtained from propargylic alcohol (**9**), which in turn could be prepared from commercially available (*R*)-Roche ester (**10**).

The synthesis of lactone **16** commenced from ester **11** (Scheme 2), which was prepared from commercially available 3-methylglutaric anhydride (**8**) following reported protocol.[7] The hydroxyl group in **11** was protected as its *tert*-butyldimethylsilyl (TBS) ether using *tert*-butyldimethylsilyl chloride (TBSCl), imidazole to afford compound **12** in 91% yield. Subsequent reduction of isopropyl ester in compound **12** using DIBAL-*H* followed by protection of corresponding primary alcohol using

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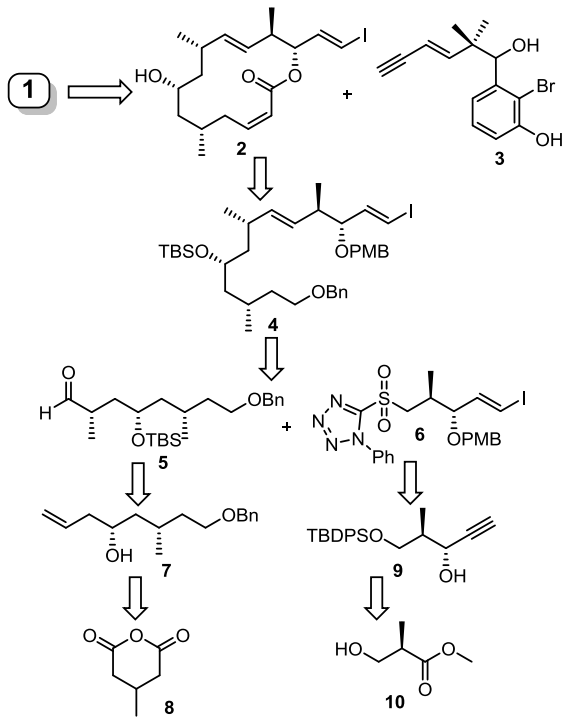
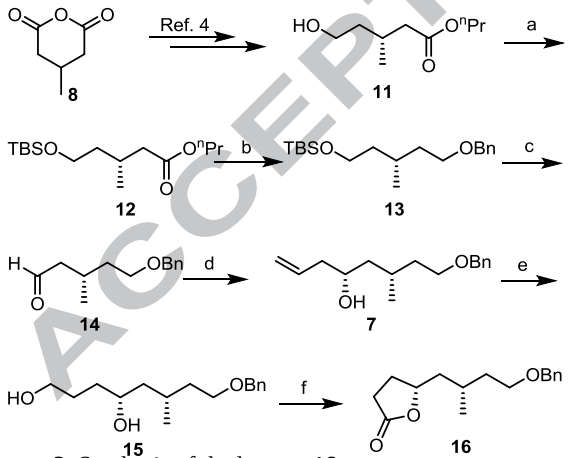
benzyl bromide afforded benzyl ether **13** in 81% yield over two steps. Deprotection of TBS group by treating with *p*-toulenesulfonic acid (PTSA) gave corresponding primary alcohol, which was oxidized under Swern conditions (oxalyl chloride, DMSO, Et_3N) to furnish aldehyde **14** in 95% yield. The



Scheme 1. Retrosynthetic analysis

aldehyde **14** was immediately treated with (+)-Ipc_2BOMe and allyl magnesium bromide to obtain homo allyl alcohol **7** in 85% yield (dr 98.6:1.4).[8] Hydroboration of compound **7** by treatment with $BH_3{\cdot}Me_2S$, followed by oxidation with H_2O_2 and NaOH afforded 1,4-diol **15**

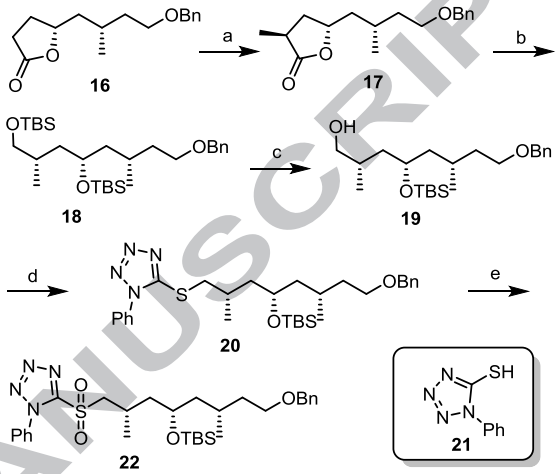


Scheme 2. Synthesis of the lactone **16**.

Reagents and conditions: a) TBSCl, imidazole, CH_2Cl_2, 4 h, 0 °C-rt, 91%; b) i) DIBAL-*H*, CH_2Cl_2, −40 °C, 2 h, 89%; ii) BnBr, NaH, THF, 0 °C-rt, 92%; c) i) PTSA, CH_3OH, 0 °C-rt, 1 h, 88%; ii) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, −78 °C, 1 h, 95%; d) (+) Ipc_2BOMe, allylMgBr, ether, −78 °C, 12 h; ii) H_2O_2, NaOH, 0 °C-rt, 4 h, 85%; e) i) $BH_3.SMe_2$, THF, 0 °C-rt, 12 h; ii) H_2O_2, NaOH, 0 °C-rt, 3 h, 79% (over two steps); f) TEMPO, $PhI(OAc)_2$, CH_2Cl_2, rt, 3 h, 71%.

in 79% yield. Compound **15** was readily converted into lactone **16** by chemo-selective oxidation under 2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) and (diacetoxyiodo) benzene (BAIB) conditions in 71% yield.[9]

With good quantities of lactone **16** in hand, our next task was to introduce methyl stereo center at C9, which was accomplished through a stereoselective methylation of **16** by using LDA and MeI to afford *trans*-lactone **17** as the major component (4:1 separable mixture of diastereomers) in 68% yield.[10] Lactone **17** was reduced by LAH to produce the corresponding diol in 92% yield which was protected as di-TBS ether **18** using TBSCl

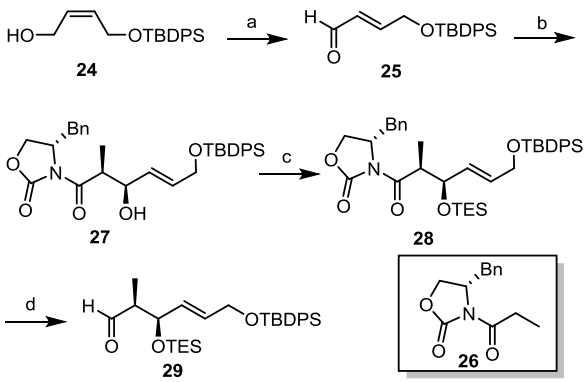


Scheme 3. Synthesis of the sulphone **22**.

Reagents and conditions: a) LDA, MeI, THF, −78 °C, 2 h, 68%; b) i) $LiAlH_4$, THF, 0 °C-rt, 1 h, 92%; ii) TBSCl, imidazole, CH_2Cl_2, 0 °C-rt, 4 h, 95%; c) PPTS, CH_2Cl_2:CH_3OH, 0 °C, 2 h, 85%; d) **21**, PPh_3, DIAD, THF, 0 °C-rt, 2 h, 87%; e) $(NH_4)_6Mo_7O_{24}$, H_2O_2, EtOH, rt, 12 h, 77%.

in 95% yield. Selective deprotection of primary TBS ether using pyridinium *p*-toluenesulfonate (PPTS) in MeOH/CH_2Cl_2 (1:1) produced the primary alcohol **19** in 85% yield. Finally, Mitsunobu reaction of **19** with 1-phenyl-1*H*-tetrazole-5-thiol (**21**) provided sulphide **20** in 87% yield and subsequent molybdenum catalyzed peroxide oxidation afforded sulfone **22** in 77% yield (Scheme 3).[11]

After successful synthesis of sulfone fragment **22**, our attention was turned to the synthesis of other coupling partner, aldehyde **29** for Julia-Kocienski olefination reaction. The synthesis of aldehyde **29** was initiated from mono protected



Scheme 4. Synthesis of the aldehyde **29**.

Reagents and conditions: a) PCC, Celite, CH_2Cl_2, 0 °C-rt, 8 h, 78%; b) **26**, *n*-Bu_2BOTf, Et_3N, CH_2Cl_2, 0 °C, 2 h, 76%; c) TESOTf, DIPEA, CH_2Cl_2, 0 °C, 2 h, 88%; d) i) $NaBH_4$, THF/H_2O, 0 °C, 2 h, 87%; ii) DMP, $NaHCO_3$, CH_2Cl_2, 0 °C, 2 h, 72%.

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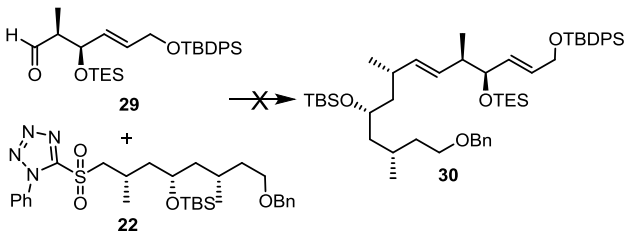
cis-2-butene-1,4-diol **(24)**[12] (Scheme 4). Silylether **24** was oxidized by treating with pyridinium chlorochromate (PCC) and Celite to provide *E*-enal **25** in 78% yeild.[13] The resulting aldehyde **25** underwent asymmetric aldol reaction[14] with the known chiral auxiliary (*S*)-4-benzyl-3-propionyloxazolidin-2-one (**26**) to furnish hydroxyimide **27** in 76% yield as single diastereomer. Protection of hydroxyl group in compound **27** using TESOTf afforded compound **28** in 88% yield. Reductive cleavage of the chiral auxiliary in compound **28** using $NaBH_4$ in MeOH produced corresponding primary alcohol in 87% yield. Oxidation of the resulting alcohol with Dess-Martin periodinane (DMP) gave required aldehyde **29** in 72% yield.



Scheme 5. Coupling of aldehyde **29** and sulphone **22**

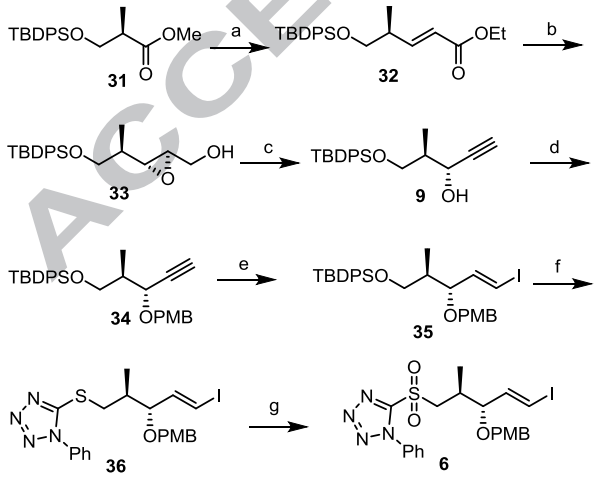
With both the coupling partners aldehyde **29** and sulfone **22** in hand, we then carried out Julia-Kocienski olefination[11,15] (Scheme 5) under different reaction conditions (Table 1), but failed to isolate required coupling product **30**.

Table 1: Different conditions for Julia-Kocienski olefination

entry	reagent	conditions	time	yield[a]
1	LHMDS	THF/HMPA, –78 °C-rt	12	NR
2	KHMDS	THF/HMPA, –78 °C-rt	12	NR
3	LHMDS	DME, –78 °C-rt	12	NR
4	KHMDS	DME, –78 °C-rt	12	NR

[a]Starting material recovered

To circumvent the above problem, we changed the strategy. Accordingly, we planned to prepare sulfone **6** (Scheme 6) as one of the coupling partner and earlier sulfone fragment became aldehyde fragment in this case. The synthesis started from the



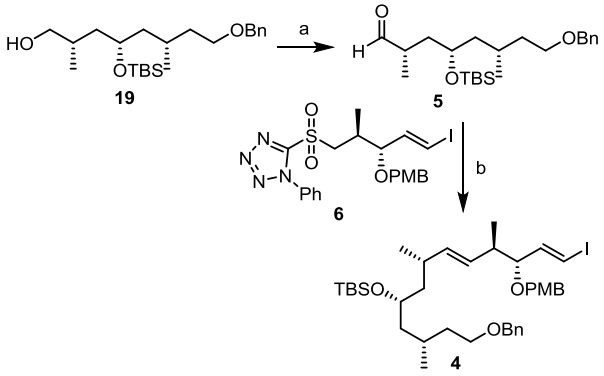
Scheme 6. Synthesis of sulphone **6**

Reagents and conditions: a) i) DIBAL-*H*, −78 °C, 30 min; ii) Ph_3P=CHCOOEt, C_6H_6, rt, 5 h, 80% (over 2 steps); b) i) DIBAL-*H*, CH_2Cl_2, −20 °C, 30 min, 87%; ii) (−)-DET, $Ti(O^iPr)_4$, TBHP, CH_2Cl_2, −20 °C, 10 h, 85%; c) i) PPh_3, $NaHCO_3$, CCl_4, reflux, 5 h; ii) *n*-BuLi, THF, −78 °C, 3 h, 81% (over 2 steps); d) PMBBr, NaH, TBAI, THF, 0 °C-rt, 6 h, 87%; e) i) Cp_2ZrCl_2, DIBAL-*H*, THF, 0 °C, 1 h; ii) I_2, THF, −78 to 0 °C, 30 min, 72%; f) i) TBAF, THF, 0 °C-rt, 4 h, 86%; ii) **21**, PPh_3, DIAD, THF, 0 °C-rt, 6 h, 87%; g) $(NH_4)_6Mo_7O_{24}$, H_2O_2, EtOH, rt, 12 h, 77%.

silyl protected Roche ester **31**.[16] Controlled reduction of ester **31** with DIBAL-*H* at −78 °C afforded corresponding aldehyde,[16] which was immediately treated with (ethoxycarbonylmethylene) triphenylphosphorane in benzene at room temperature to furnish *α,ß*-unsaturated ester **32** with *E*-configuration in 80% yield over two steps. The ester group in compound **32** was reduced with DIBAL-*H* to provide the corresponding allylic alcohol in 87% yield. The Sharpless asymmetric epoxidation[17] of resulting allylic alcohol using (−)-DET and $Ti(O^iPr)_4$ in CH_2Cl_2 at −20 °C furnished epoxy alcohol **33** in 85% yield (≥98% de). Epoxy alcohol **33** was converted to the corresponding (chloromethyl) oxirane using CCl_4-Ph_3P under reflux conditions followed by base-induced elimination reaction[18] to afford the chiral propargylic alcohol **9** in 81% yield over two steps.

Propargyl alcohol **9** was protected as its *p*-methoxybenzyl (PMB) ether with *p*-methoxybenzyl bromide (PMB-Br) and NaH to afford corresponding alkyne **34** in 87% yield. The terminal alkyne of **34** was subjected to a hydrozirconation-iodination sequence by treatment with Schwartz reagent[19] (Cp_2ZrHCl) prepared from Cp_2ZrCl_2 and DIBAL-*H* in situ followed by exposure to an electrophilic iodine source to incorporate *trans*-vinyl iodide **35** in 72% yield. Vinyl iodide **35** was next transformed into sulfide **36** in 74% yield by a two-step sequence involving removal of the *tert*-butyldiphenylsilyl (TBDPS) protecting group using tetrabutylammonium fluoride **(**TBAF) and Mitsunobu reaction of the resulting primary alcohol with 1-phenyl-1*H*-tetrazole-5-thiol (**21**), triphenylphosphine (TPP) and diisopropyl azodicarboxylate (DIAD). Oxidation of sulfide **36** with ammonium heptamolybdate and H_2O_2 afforded sulfone fragment **6** in 77% yield.[11]

Now, the stage is set to couple the sulphone **6** and aldehyde **5** through Julia–Kocienski olefination.[11,15] Aldehyde **5** was prepared from alcohol **19** by oxidation with Dess-Martin periodinane (DMP) in 91% y−ield. Coupling of sulfone **6** with aldehyde **5** in presence of LiHMDS and HMPA/THF (1:4) at −78 °C for 2 h and stirring at room temperature over 5 h, furnished coupled product **4** with (*E*)-olefin (E/Z > 9:1 as per ^{1}H NMR) in 70% yield. The coupling product was assigned on the basis of its ^{1}H NMR in which four peaks appeared due the resonance of olefinic protons at δ 6.44, 6.21, and 5.33 ppm, benzylic methyle protons at δ 4.56 ppm and methoxy methyl protons of PMB group at δ 3.80 ppm, respectively. Furthermore, ^{13}C NMR and mass spectral data were in good agreement with the product.



Scheme 6. Synthesis of the C3 to C15 fragment of callyspongiolide (**1**)

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Reagents and conditions: a) i) DMP, $NaHCO_3$, CH_2Cl_2, 0 ^oC, 1 h, 91%; b) LHMDS, THF/HMPA, −78 ^oC-rt, 6 h, 70%.

In summary, we have achieved the synthesis C3-C15 fragment of callyspongiolide with 9.5% overall yield in 14 longest linear sequence starting from **11** following Julia-Kocienski for *E*-selective olefination, Brown asymmetric allylation and base-induced elimination reaction for chiral propargyl alcohol synthesis as key reactions.

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Supporting Information

Supplementary data associated with this article can be found, in the online version, at http://dx.doi/xxxxxx.

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