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A simple approach to the construction of the core structure present in bielschowskysin and hippolachnin A

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Abstract. A convenient route for the synthesis of oxacyclobutapentalene, the tricyclic bridged core structure present in bioactive marine diterpene bielschowskysin and the polyketide hippolachnin A, is reported. The key steps involve ring closing metathesis of a triene derived from D-mannitol to produce selectively the dihydrofuran derivative instead of the cyclopentene derivative and a Cu(I)-catalyzed intramolecular [2+2] photocycloaddition of the dihydrofuran derivative.

Keywords. Asymmetric synthesis; marine natural products; olefin metathesis; photochemistry.

1. Introduction

The marine diterpene bielschowskysin **1**,[1] isolated from the Caribbean gorgonian octocoral *Pseudopterogorgia kallos* and the polyketide hippolachnin A **2**[2] (figure 1), recently isolated from the South China Sea sponge *Hippospongia lachne* elicited considerable interest amongst the organic chemist community. Bielschowskysin exhibits antiplasmodial activity against *Plasmodium falciparum* and strong cytotoxicity against human lung cancer and renal cancer cell lines while hippolachnin A is a potent antifungal agent. The latter is also capable of curing diseases such as renal and heart failure. Both these compounds are densely functionalized with a high degree of stereochemical complexity and possess oxacyclobutapentalene as the core structure. Since their isolation these compounds and their analogues became attractive synthetic targets. A number of approaches for synthesis of bielschowskysin[3] and hippolachnin A[4] have been reported. The majority of these approaches mainly used [2+2] photocycloaddition as the key step and provided access either to bielschowskysin **1** or to hippolachnin A **2** (scheme 1). We considered the possibility of developing a route likely to lead an entry to both these compounds.

Retrosynthetically, an intramolecular [2+2] photocycloaddition of the dienone **4** should provide the core oxacyclobutapentalene **3** stereoselectively (scheme 2). With appropriately designed **3** ($R^5 = O$), the substituents R^3 and R^4 can be employed to build either the medium rings for **1** or to provide directly the ethyl groups for **2**. The lactone carbonyl of the tricycle **3** can be employed to provide the unsaturated ester present in **2**.[5] The dienone **4** may be obtained from site selective ring closing metathesis (RCM)[6] of the triene **5**. The triene **5** can in turn be synthesised from the D-mannitol derived known unsaturated ester **6**.[7] This route thus has the provision for incorporation of substituents that can be elaborated to lead to the synthesis of **1** as well as **2** (scheme 2). We herein describe the synthesis of the tricyclic lactone **3** ($R^1 = R^3 = R^4 = H$, $R^5 = O$, $R^2 =$ functionalized substituent) to demonstrate the feasibility of the synthetic plan.

2. Experimental

All reactions were carried out under an atmosphere of argon. PE refers to the fraction of petroleum ether having bp 60–80°C. EA refers to ethyl acetate. Column chromatography was carried out with silica gel (100–120 mesh). ^{13}C peaks assignment is based on the DEPT experiment. Optical rotation values are given in 10^{-1} deg cm^2 g^{-1}. High resolution mass spectra (HRMS) were recorded on a QTOF I (quadrupole-hexapole-TOF) mass spectrometer with an orthogonal Z-spray–electrospray interface. Infrared spectra were recorded as thin films.

2.1 *(S)-2-((3S,5S)-5-(Allyloxy)hepta-1,6-dien-3-yl)-1,4-dioxaspiro[4.5]decane (**10**)*

A solution of the known hydroxy compound **8**[8] (390 mg, 1.55 mmol) in anhydrous THF (10 mL) was

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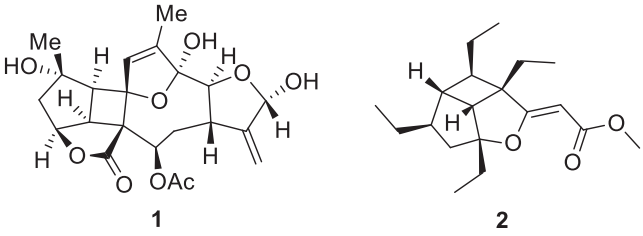
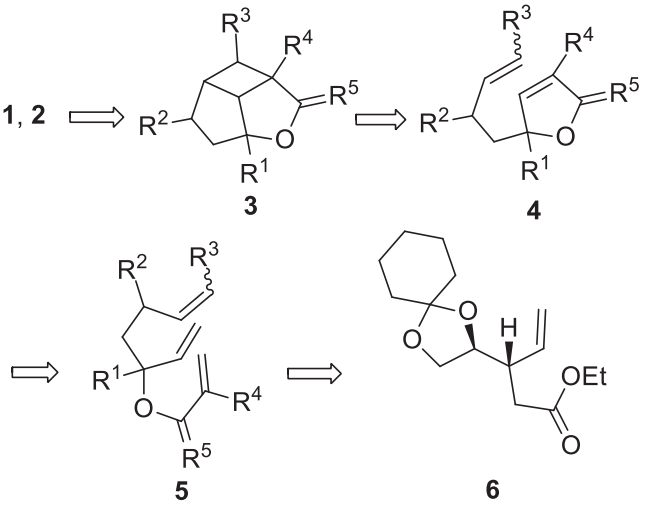


Figure 1. Structures of bielschowskysin and hippolachnin A.

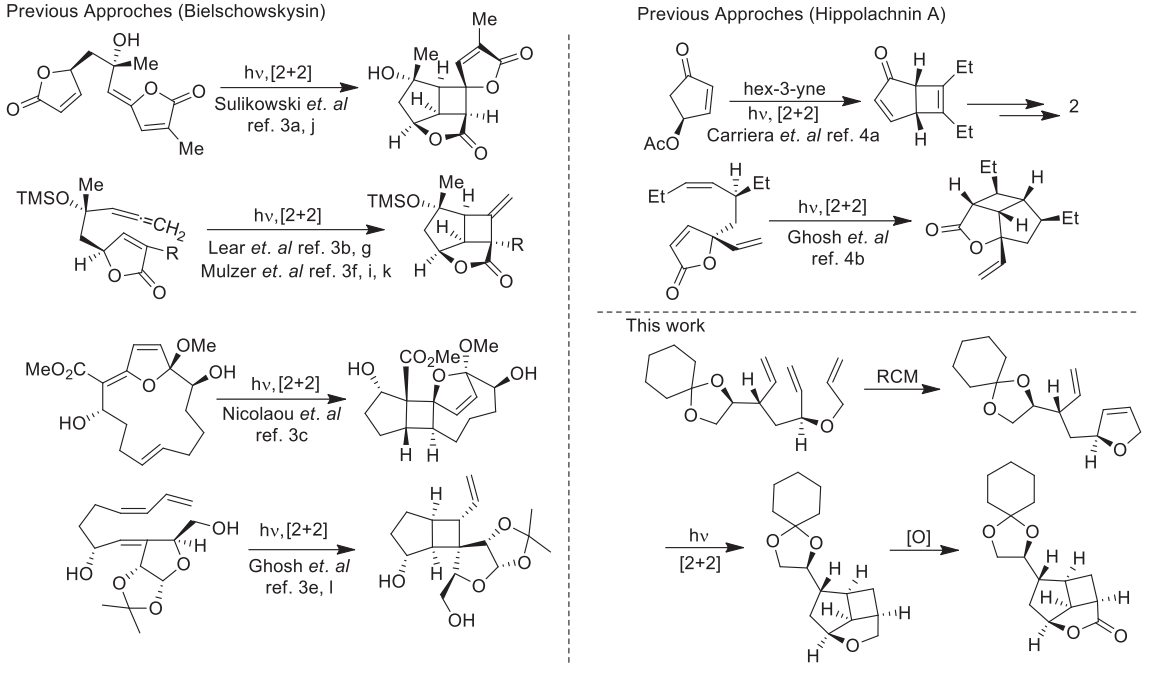
added to a stirred suspension of sodium hydride (112 mg, 2.32 mmol, 50% suspension in oil) in anhydrous THF (5 mL) at 0°C. After 15 min, allyl bromide (0.27 mL, 3.09 mmol) was added to it at 0°C. The reaction mixture was stirred at rt for 2 h and then quenched with saturated aqueous ammonium chloride solution (5 mL). The reaction mixture was extracted with diethyl ether (3 × 10 mL). The combined organic layer was washed with water, brine and dried. Evaporation of solvent furnished the crude product which was purified by column chromatography (5% ether-PE) to furnish the pure product **10** (429 mg, 95%); $[\alpha_D^{25}+8.7$ (*c* 2.3, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.95–5.82 (1H, m), 5.68–5.50 (2H, m), 5.27–5.01 (6H, m), 4.04–3.97 (1H, m), 3.93–3.87 (2H, m), 3.83–3.72 (2H, m), 3.66-3.59 (1H, m), 2.27-2.17 (1H, m), 1.94-1.86 (1H, m), 1.71-1.63 (1 H, m), 1.58-1.56 (8H, m), 1.38–1.34 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.7 (CH), 138.2 (CH), 135.3 (CH), 118.0 (CH_2), 117.3(CH_2), 116.6 (CH_2), 109.8 (C), 79.3 (OCH), 78.2 (OCH), 69.1 (OCH_2), 67.6 (OCH_2), 45.0 (CH), 36.7 (CH_2), 36.6 (CH_2), 35.3 (CH_2), 25.4 (CH_2), 24.2 (CH_2), 24.0 (CH_2); HRMS(ESI) m/z calcd for $C_{18}H_{28}O_3Na$ $(M+Na)^+$, 315.1936; found: 315.1935.



Scheme 2. Retrosynthetic analysis.

2.2 *(S)-2-((S)-1-((S)-2,5-Dihydrofuran-2-yl)but-3-en-2-yl)-1,4-dioxaspiro[4.5]decane (**11**)*

To a solution of the compound **10** (172 mg, 0.59 mmol) in degassed anhydrous toluene (20 mL), catalyst G I (25 mg, 0.029 mmol) was added and the reaction mixture was stirred at rt for 4 h. The solvent was evaporated and the residual mass was chromatographed (5% diethyl ether/PE) to afford the dihydrofuran derivative



Scheme 1. Summary of previous works and present work.

11 (134 mg, 87%) along with recovered starting material (9 mg, 6%); α_D^{25} − 30.7 (*c* 2.4, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.89-5.82 (2H, m), 5.63 (1H, ddd, J = 9, 10.5, 17.4 Hz), 5.17-5.07 (2H, m), 4.90-4.84 (1H, m), 4.69-4.54 (2H, m), 3.99-3.90 (2H, m), 3.68-3.62 (1H, m), 2.33-2.22 (1H, m), 1.92-1.84 (1H, m), 1.73-1.65 (1H, m), 1.60-1.56 (8H, m), 1.42-1.35 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$)δ 138.2 (CH), 129.8 (CH), 126.6 (CH), 117.1 (CH_2), 109.8 (C), 84.6 (OCH), 78.2 (OCH), 74.9 (OCH_2), 67.6 (OCH_2), 45.7 (CH), 37.9 (CH_2), 36.6 (CH_2), 35.3 (CH_2), 25.4 (CH_2), 24.1 (CH_2), 24.0 (CH_2); HRMS (ESI) m/z calcd for $C_{16}H_{24}O_3Na$ $(M+Na)^+$, 287.1623; found : 287.1624.

2.3 *5-(1,4-Dioxaspiro[4.5]decan-2-yl)octahydro-3-oxacyclobuta[cd]pentalene (**12**)*

Copper triflate-benzene complex was prepared following the literature procedure:[9] A mixture of Cu_2O (0.6 g, 4.19 mmol) and triflic anhydride (1.68g, 5.95 mmol) in anhydrous benzene was refluxed under argon atmosphere till all Cu_2O goes into solution (~1 h). On cooling to rt copper(I) triflate-benzene complex crystallizes out. The white solid thus obtained was filtered through a sintered glass funnel under argon atmosphere. The solid was then washed with anhydrous benzene (2 × 5 mL) and dried under a stream of argon.

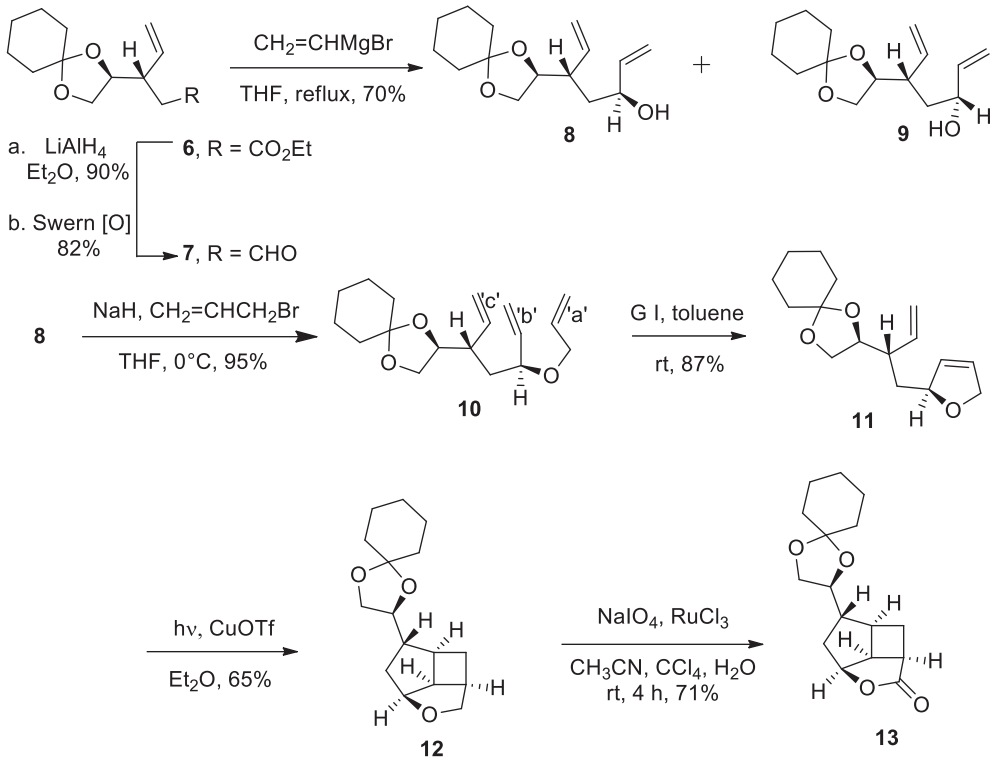
A solution of the diene **11** (200 mg, 0.76 mmol) in diethyl ether (100 mL) was poured into a pyrex cell. The ethereal solution was then degassed by bubbling argon through it for 30 min. Freshly prepared $2CuOTf{\cdot}C_6H_6$ (8 mg, 0.015 mmol) was added to the reaction mixture. The reaction mixture was then irradiated internally under argon with a Hanovia 450 W medium pressure mercury vapor lamp through a water cooled quartz immersion well for about 5 h. After completion (TLC), the reaction mixture was poured into ice cold ammonia solution (10 mL) in a separating funnel. The ether layer was separated, dried over Na_2SO_4 and concentrated under vacuum. The residual mass was purified through column chromatography using 5% ether-PE as the eluent to afford the cyclobutane derivative **12** (130 mg, 65%); α_D^{25} − 2.4 (*c* 1.8, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 442–4.39 (1H, m), 4.03-3.92 (2H, m), 3.78-3.75 (1H, m), 3.63-3.59 (1H, m), 3.55-3.46 (1H, m), 3.14 (1H, q, J = 6.6 Hz), 2.79-2.71 (1H, m), 2.60–2.49 (1H, m), 2.38–2.29 (2H, m), 2.24–2.12 (1H, m), 1.60–1.45 (10H, m), 1.42–1.34 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 109.5 (C), 85.7 (OCH), 79.0 (OCH), 75.7 (OCH_2), 68.2 (OCH_2), 50.7 (CH), 49.2 (CH), 38.3 (CH_2), 36.6 (CH_2), 36.3 (CH), 35.7 (CH), 35.3 (CH_2), 32.7 (CH_2), 25.4 (CH_2), 24.1 (CH_2), 24.0 (CH_2); HRMS (ESI) m/z calcd for $C_{16}H_{24}O_3Na$ $(M+Na)^+$, 287.1623; found : 287.1625.

2.4 *5-(1,4-Dioxaspiro[4.5]decan-2-yl)hexahydro-3-oxacyclobuta[cd]pentalen-2(1a1H)-one (**13**)*

The photoadduct **12** (39 mg, 0.15 mmol) was taken in a solvent mixture made of CH_3CN, CCl_4 and water (0.5 mL, 0.5 mL, 1 mL, respectively). To it sodium metaperiodate (126 mg, 0.59 mmol) and ruthenium trichloride (4 mg, 0.015 mmol) were added at rt and stirred for 4 h. After completion (TLC) the reaction mixture was worked up with diethyl ether (3 × 15 mL). The combined ether extract was washed with water, brine and dried over Na_2SO_4. The residual mass obtained after evaporation of ether was purified by column chromatography (30% EA-PE) to afford the pure lactone **13** (29 mg, 71%); α_D^{25} 29.8 (*c* 0.75, $CHCl_3$); ν_{max} (neat) 2937, 1762 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$)δ5.07–5.04 (1H, m), 4.06-3.97 (2H, m), 3.55-3.49 (1H, m), 3.40 (1H, q, J = 7.2 Hz), 3.09–3.02 (1H, m), 2.90-2.80 (1H, m), 2.58-2.51 (1H, m), 2.44-2.30 (2H, m), 1.87–1.80 (1H, m), 1.78-1.68 (1H, m), 1.66–1.23 (10H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.4 (CO), 109.9 (C), 85.7 (OCH), 77.8 (OCH), 67.8 (OCH_2), 49.3 (CH), 44.7 (CH), 38.6 (CH), 38.5 (CH_2), 36.5 (CH_2), 36.3 (CH), 35.1 (CH_2), 30.7 (CH_2), 25.3 (CH_2), 24.1 (CH_2), 24.0 (CH_2); HRMS (ESI) m/z calcd for $C_{16}H_{22}O_4Na$ $(M+Na)^+$, 301.1416; found : 301.1415.

3. Results and Discussion

The synthesis began with the transformation of the known unsaturated ester **6** to the dienol **8** following the protocol established earlier in this laboratory.[8] The unsaturated ester **6** was converted to the aldehyde **7** through a reduction-oxidation sequence in excellent yield (scheme 3). Addition of vinyl magnesium bromide to the enal **7** led to a mixture of the hydroxy compounds **8** and **9** in *ca.* 1:1 ratio. The hydroxy compound **8** was isolated in 35% yield after column chromatography. The structure of the hydroxy compound **8** was established by comparison of the NMR spectra with those reported in literature.[8] The compound **8** was then allylated on treatment with NaH-allyl bromide to afford the triene **10** in excellent yield. The triene **10** in toluene was treated with Grubbs' 1st generation catalyst G I $[Cl_2(PCy_3)_2Ru{=}CHPh]$ at room temperature to afford exclusively the five-membered oxacycle **11** in 87% yield. That RCM produced the dihydrofuran derivative **11** involving ring closure between the vinyl



Scheme 3. Synthesis of the tricycle **13**.

groups 'a' and 'b' was clearly evident from the presence of the vinyl group 'c' in ^{1}H NMR spectra. Thus, in ^{1}H NMR spectra of **11** the vinylic methine proton appeared at δ 5.63 as a ddd (J = 9, 10.5 and 17.4 Hz) while the two vinylic methylene protons appeared at δ 5.07–5.17 as a multiplet. In ^{13}C NMR spectra, the presence of a methine carbon at δ138.2 and a methylene carbon at δ117.1 indicated the presence of the vinyl group 'c'. Exclusive formation of the five-membered oxa-cycle is attributed to be the result of the entropic preference favoring the formation of the common ring oxa-cycle rather than the seven-membered oxacycle which could arise through RCM involving the vinyl groups 'a' and 'c'.

With the dihydrofuran derivative **11** ready in hand, we made an attempt to convert it to the corresponding butenolide **4** (R^1 = R^3 = R^4 = H, R^5 = O) (scheme 2), the required precursor for photocycloaddition using the commonly employed oxidation with PCC or PDC.[10] However, an intractable mass was obtained instead of the expected butenolide. We thus decided to change the reaction sequence. We chose to accomplish the photocycloaddition of the diene **11** first and then oxidation of the resulting photoadduct. Photocycloaddition[11,12] of **11** could be achieved only under Cu(I) catalysis. Thus, an ethereal solution of the diene **11** was irradiated in presence of 2CuOTf.C_6H_6 complex as catalyst (scheme 3). The tricyclic adduct **12** was formed in 65% yield after column chromatography.

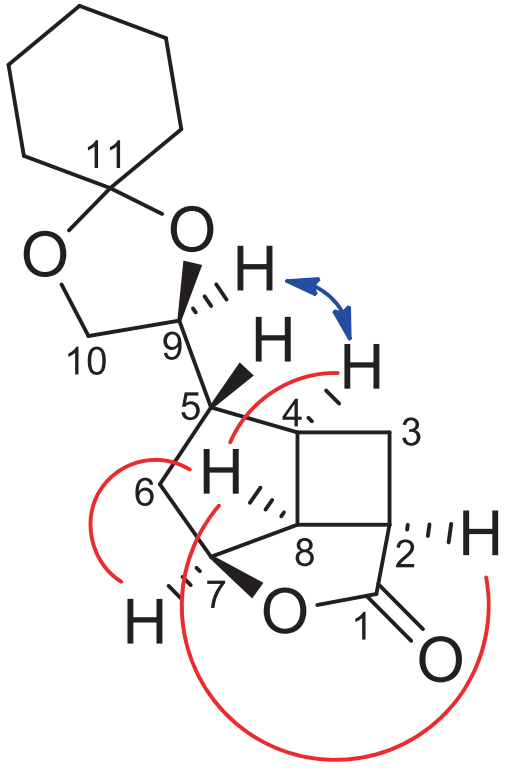


Figure 2. ^{1}H-^{1}H COSY (⌒) and NOESY (⌒) correlation of **13**.

The gross structure of the photo-adduct was established through NMR and mass spectra. The stereochemical

assignment could be made only after its transformation to the lactone **13**. Oxidation of the tetrahydrofuran ring in **12** with RuO_4 afforded the tricyclic lactone **13** in 71% yield. The structure of the lactone **13** was established through analysis of its 2D NMR spectra (figure 2). In COSY spectrum the C-8 H appearing at δ 3.40 (q, $J = 7.2$ Hz) reveals cross peaks with C-7 H at δ 5.05 (m), C-2 H at δ 3.05 (m) and C-4 H at δ 2.54 (m) indicating their *syn* relationship with each other (see Supplementary Information) while in NOESY spectrum a cross peak was observed between the C-4 H and C-9 H at δ 4.04 (m). These observations led to the structural assignment to the lactone **13**. The assignment of stereochemistry of the lactone **13** establishes also the stereochemistry of the photo-adduct as **12**.

4. Conclusion

We have developed a convenient route to the oxacyclobutapentalene core present in bielschowskysin **1** and hippolachnin A **2**. The key steps involve a site selective RCM of a triene and intramolecular [2+2] photocycloaddition of the resulting 2,5-dihydrofuran derivative. The route is flexible and can be extended for the synthesis of **1** and **2** with an appropriately designed triene.

Supplementary Information (SI)

All additional information regarding characterisation of the new compounds using ^{1}H NMR, ^{13}C NMR and 2D NMR spectra are given in the supplementary information, available at www.ias.ac.in/chemsci.

Acknowledgements

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