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Stereocontrolled entry to the tricyclo[3.3.0]oxoheptane core of bielschowskysin by a [2+2] cycloaddition of an allene-butenolide

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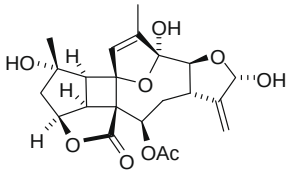
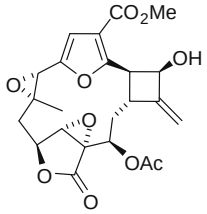
ABSTRACT

As part of ongoing transannulation studies, the practical synthesis of an allene-linked γ-butenolide from L-malic acid and its substrate-controlled [2+2] photocycloaddition to the tricyclic core of bielschowskysin (**1**) are described.

West Indian gorgonian octocorals are rich sources of terpenoids with a high propensity to produce secondary metabolites with promising pharmacological activities.[1] In particular, the Rodríguez group have reported several new classes of marine natural products from *Pseudopterogorgia kallos*; otherwise named *Bielschowsky* after the discoverer of this Caribbean Sea plume.[2,3] Bielschowskysin[4] (**1**) and providencin[5] (**2**), for example, represent new founding members of highly oxygenated cyclobutane-classes of furanocembranoids.



1:bielschowskysin

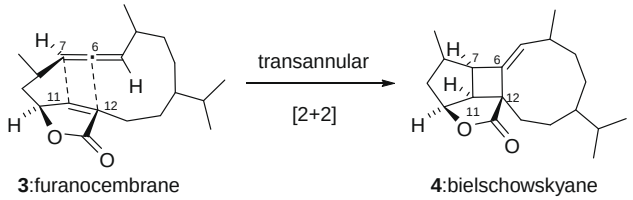


2:providencin

Besides the clear structural challenge, our interest with bielschowskysin (**1**) resides in unlocking the pharmacophoric features and molecular targets that are responsible for its antiplasmodial activity against several drug resistant strains of the malaria-causing protozoan parasite, *Plasmodium falciparum* ($IC_{50} \sim 10\ \mu g\ ml^{-1}$). With a further view to expanding transannulation approaches to natural product frameworks, we have embarked on the total synthesis of **1**, especially since re-isolation efforts from various *P. kallos* sources have proved unfruitful due to seasonal or chemotype variations, and only trace amounts of natural **1** remain.[6] Herein, we describe a biomimetically inspired model study to fuse the tricyclic core of bielschowskysin (cf. **4**) via the [2+2] photocycloaddition of an allenyl-2(5*H*)-furanone (cf. **3**) under high stereocontrol (Fig. 1).

By considering the connective relationships between cembranoid natural products,[1–5] we proposed to mold the bielschowskyane ring system (**4**) through a formal [2+2] transannulation of an allene-butenolide functionalised furanocembrane macrocycle (**3**).[7] Conceivably this may involve successive or concerted bond formations between C7/C11 and C6/C12. Bray and Pattenden, for example, have constructed the cyclobutane moiety of providencin (**2**) by employing an intramolecular C–H insertion reaction.[5] While our work was ongoing,[7] Doroh and Sulikowski published the validity of a [2+2]-photochemical approach to bielschowskysin (**1**) via an enol ether appended butenolide.[8] Indeed, literature examples support similar intramolecular photocycloadditions of double-bonds appended to cyclopentenones[9], and an allene-butenolide photocycloaddition[10] has been applied to the synthesis of solanoeclepin A. Despite these related studies, our focus herein was to develop a reproducible and practical synthesis that could be readily accessed and exploited within a transannular bielschowskyane manifold (cf. **3**).

As a model system, we targeted the allene-butenolide **5** via the benzylidene **6** (Schemes 1 and 2). First, commercially available L-malic acid (**7**) was reduced to triol **8** using borane-dimethyl sulfide.[11] Protection of **8** in acetone with $CuSO_4$ and a catalytic



3:furanocembrane **4**:bielschowskyane

Figure 1. Proposed biomimetic transannulation strategy.

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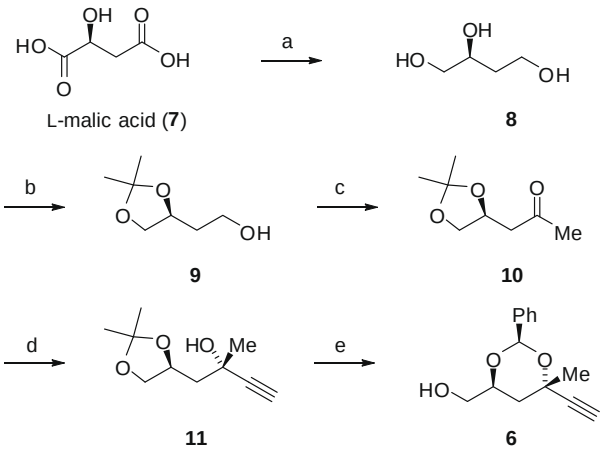
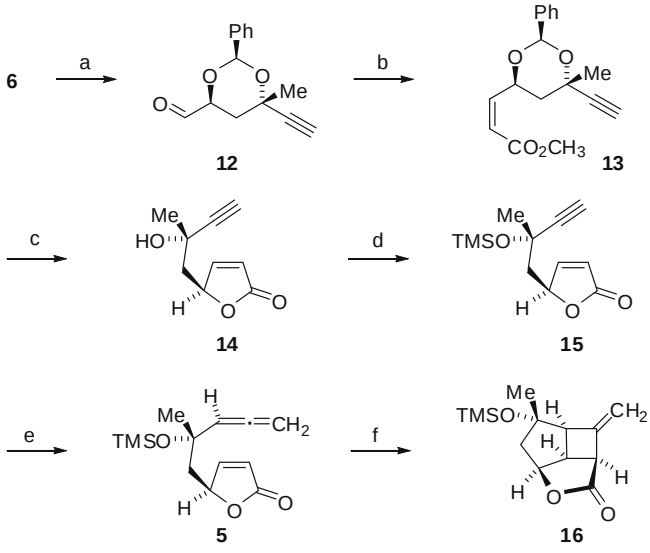


Scheme 1. Reaction conditions: (a) $BH_3{\cdot}SMe_2$, rt, 16 h, 95%; (b) acetone, $CuSO_4$, *p*-TsOH, rt, 18 h, 67%; (c) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C, 1.5 h; MeMgBr, Et_2O, −78 °C, 3 h ; PCC, NaOAc, MS 4 Å, CH_2Cl_2, rt, 5 h, 43%, 3 steps; (d) ethynylmagnesium bromide, Et_2O, −78 °C, 15 min, rt, 5 h, 72%; (e) $PhCH(OMe)_2$, *p*-TsOH, CH_2Cl_2, rt, 75%.



Scheme 2. Reaction conditions: (a) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C, 1.5 h; (b) $Br{\cdot}Ph_3PCH_2CO_2Me$, Et_3N, MeOH, 0 °C, 3 h, 60%, 2 steps (4:1 *Z*/*E*); (c) H_2SO_4, MeOH, rt, overnight, 70 % (d) TMSOTf/2,6-lutidine, CH_2Cl_2, 0 °C to rt, 2 h, 62%, (e) $(CH_2O)_n$, *i*-Pr_2NH, CuBr, dioxane, reflux, 3 h, 68% (f) hν, hexane/CH_2Cl_2, rt, 12 h, 70%.

amount of PTSA subsequently produced the acetonide **9** in 67% yield.[12]

Swern oxidation of **9** followed by the addition of methyl magnesium bromide and subsequent PCC oxidation afforded the methyl ketone **10** in 43% overall yield. Under chelation control, the Grignard addition to ketone **10** with ethynylmagnesium bromide provided a 4:1 separable mixture of propargylic alcohols, giving the major diastereomer **11** in 72% yield. Treatment of the ethynyl carbinol **11** with benzaldehyde dimethylacetal in the presence of *p*-TsOH transformed the acetonide **11** smoothly to the more stable six-membered benzylidene acetal **6**.[13]

Aldehyde formation of **12** from alcohol **6** followed by Wittig homologation in methanol produced a 4:1 cis/trans mixture of α,β-unsaturated esters, with the cis-isomer **13** predominating (Scheme 2). The γ-butenolide **14** was then prepared in 70% yield by cyclising **13** in aqueous sulfuric acid in methanol at room temperature. Protection of the alcohol **14** as its TMS ether **15** and subsequent homologation of the acetylene, with $(CH_2O)_n$, *i*-Pr_2NH and CuBr in refluxing dioxane,[14] directly afforded the allene precursor **5** in 68% yield for cycloaddition studies.

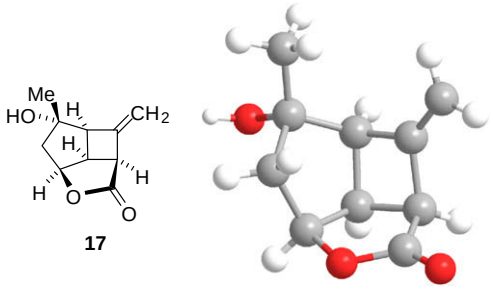


Figure 2. X-ray structure of photoadduct **17**.

Initial thermal [2+2] cycloaddition studies on butenolides akin to **5** were unproductive. Although the free-carbinol form of **5** was found to undergo a photo-induced cyclisation, the silylated substrate **5** cleanly underwent a [2+2] cycloaddition to the photoadduct **16**. Conveniently, we found that the irradiation of **5** in a 1:1 (v/v) solution of dichloromethane/hexane could be performed reliably with three conventional UV lamps (3 × 6 W, λ = 254 nm) over 12 h.[15] This gave a single diastereomeric photoadduct **16** in 70% yield. The photoadduct **16** displayed all characteristic ^1H and ^{13}C NMR cyclobutane peaks, which was confirmed unambiguously by single-crystal X-ray analysis of its desilylated form **17** (Fig. 2).[16] As anticipated,[8,9] the incorporation of a tertiary carbinol into the allenyl-arm of **5** favoured cyclisation to the tricyclo[3.3.0]oxoheptane ring structure **16**, as opposed to alternative modes of closure. Here, the combination of geminal-disubstituted and 1,3-allenylic conformational effects are believed to play a role in determining the stereochemical outcome. For instance, the six-membered cyclised counterparts to **16** can also form with allene-substrates lacking a quaternary centre, whereby exceptions to the 'rule-of-five' can occur and the *exo*-methylene of the allene can react with the butenolide.[9a]

In summary, we have demonstrated the intramolecular feasibility of our biometically inspired strategy to form the tricyclic core (**17**) of bielschowskysin (**1**) by virtue of a substrate-controlled [2+2] photocycloaddition of an allene-butenolide (**5**). In practice, gram-quantities of the butenolide **15** have been prepared reproducibly, and transannular manifolds (cf. furanocembrane **3**) to generate tetracyclo[9.3.3.0]tetradecanes (cf. bielschowskyane **4**) are being explored. Further efforts towards the total synthesis of bielschowskysin (**1**) are actively being pursued in our laboratories and will be published in due course.

Acknowledgements

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Supplementary data

Experimental procedures and characterisation data for compounds **5**, **6**, **10**, **11** and **13**–**17**. Coordinates for **17** have been uploaded to the Cambridge Crystallographic Data Centre (http://

www.ccdc.cam.ac.uk/). Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.01.131.

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15. *Experimental procedure to photoadduct* ***16***: The allene-butenolide **5** (15 mg, 0.06 mmol) was dissolved in a 1:1 (v/v) solvent mixture of hexane/CH_2Cl_2 (2 mL), and the resulting solution was bubbled with N_2 for 15 min. This solution was then irradiated with three UV lamps (3×6 W, $\lambda = 254$ nm) in a quartz test tube without stirring for 12 h. After consumption of the starting material, as indicated by TLC, the solvent was removed and the residue was purified by chromatography (hexane/ethyl acetate = 6:1, v/v) to give the photoadduct **16** as a colourless oil in 70% yield. $[\alpha]_D^{25}$ −23.4 (*c* 0.47, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 500 MHz): 5.30 (d, *J* = 0.9 Hz, 1H), 5.25 (ddd, *J* = 2.3, 5.7, 8.0, 1H), 5.15 (d, *J* = 0.9, 1H), 3.58 (dt, *J* = 2.3, 7.1, 1H), 3.49 (m, 1H), 3.24 (dt, *J* = 2.3, 3.9, 1H), 2.48 (ddd, *J* = 1.6, 8.0, 14.6, 1H), 1.95 (dd, *J* = 5.7, 14.6, 1H), 1.42 (s, 3H), 0.12 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 Hz): δ 176.0, 142.6, 114.6, 85.1, 84.9, 58.7, 49.4, 45.0, 42.1, 23.2, 2.2; IR(CH_2Cl_2): 2958, 1770, 1252, 1149, 1045, 841; MS (FAB): $[M+H]^+$ 253.1; HRMS (FAB) $[M+H]^+$ calcd for $C_{13}H_{21}O_3Si$ 253.1254, found 253.1248.
16. *Experimental procedure to photoadduct* ***17***: Catalytic CSA was added to a solution of compound **16** (10 mg, 0.04 mmol) in 0.5 mL of ethanol, and the resulting mixture was stirred for 2 h. After completion of starting material, as monitored by TLC, the solvent was removed and the residue was purified by chromatography (hexane/ethyl acetate = 1/1, v/v) to give compound **17** as a white solid in 85% yield. This solid was dissolved in a minimal amount of acetone, then CH_2Cl_2 and hexane were added. Slow evaporation at room temperature afforded orthorhombic single crystals (mp = 125–126 °C), one of which was subjected to X-ray crystallography (cf. Supplementary data). $[\alpha]_D^{25}$ −34.4 (*c* 0.5, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 500 MHz): 5.35 (d, *J* = 2.5 Hz, 1H), 5.25 (ddd, *J* = 2.5, 5.1, 8.0, 1H), 5.19 (d, *J* = 2.5, 1H), 3.63 (dt, *J* = 2.5, 7.0, 1H), 3.58 (m, 1H), 3.21 (dt, *J* = 1.9, 5.7, 1H), 2.45 (ddd, *J* = 1.9, 7.6, 15.1, 1H), 2.05 (dd, *J* = 5.1, 15.1, 1H), 1.43 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 Hz): 175.8, 142.2, 115.0, 84.8, 82.6, 58.3, 48.5, 45.2, 42.1, 23.8; IR: IR(CH_2Cl_2): 3406, 2961, 2922, 1746, 1258, 1150, 1011, 798; MS (FAB): $[M+H]^+$ 181.1; HRMS (FAB): $[M+H]^+$ calcd for $C_{10}H_{13}O_3$ 181.0865, found 181.0857.