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Total Synthesis of an Exceptional Brominated 4-Pyrone Derivative of Algal Origin: An Exercise in Gold Catalysis and Alkyne Metathesis

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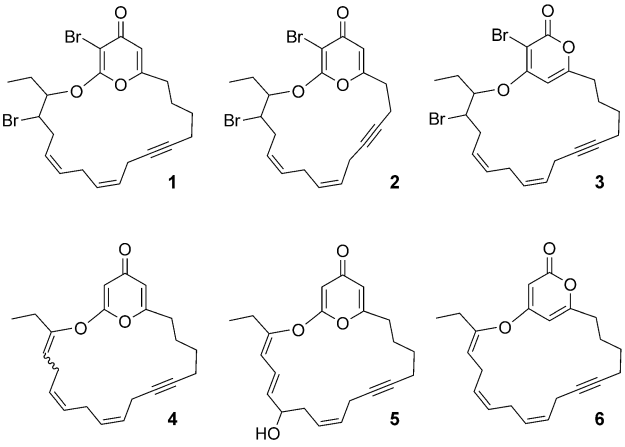
Abstract: A concise approach to the algal metabolite **1** is described, which also determines the previously unknown stereostructure of this natural product. Compound **1** is distinguished by a rare brominated 4-pyrone nucleus linked as a ketene–acetal to a polyunsaturated macrocyclic scaffold comprising an extra homoallylic bromide entity. The synthesis of **1** is based on the elaboration and selective functionalization of the linear precursor **23** endowed with no less than six different sites of unsaturation including the highly enolized oxo-alkanoate function. Key to success was the formation of the 2-alkoxy-4-pyrone ring by a novel gold-catalyzed transformation which engages only the acetylenic β-ketoester substructure of **23** but leaves all other π-bonds untouched. The synthesis was completed by a ring-closing alkyne metathesis to forge the signature cycloalkyne motif of **1** followed by selective bromination of the ketene–acetal site in the resulting product **27** without touching the skipped diene–yne substructure resident within the macrocyclic tether.

Although the secondary metabolites **1**–**6** isolated from southern Australian red algae of the genus *Phacelocarpus labillardieri* are unique in structural terms,[1–3] they escaped total synthesis for more than three decades.[4] This paradox may perhaps be attributed to the missing stereochemical assignment of the chiral centers in **1**–**3** and **5**, as well as to the only limited information about their biological properties and ecological functions.[5] From a synthetic viewpoint, these truly exceptional pyrone derivatives constitute attractive targets for the ensemble of unorthodox structural elements comprised within their macrocyclic frames. While skipped polyenes (enynes) are per se often fragile and difficult to work with, the presence of the unusual enol ether linkages in **4**–**6** or the homoallylic bromide functions in **1**–**3** with latent non-classical carbocation reactivity certainly augment the task. Likewise, the proper buildup of two different brominated sites within a polyunsaturated backbone including a rare cycloalkyne motif needs careful consideration.



For these very reasons, compound **1** was deemed synthetically most challenging. While the formation of the cycloalkyne substructure of **1** by ring-closing alkyne metathesis (RCAM) seemed fairly obvious (**B** → **A**, Scheme 1),[6,7] it was hoped that the peculiar ketene–acetal motif linking the heterocyclic ring in **1** to the lipophilic tether renders this site sufficiently electron rich to broker a selective late-stage bromination of a precursor of type **A** even in the presence of other potentially reactive π-systems. Although this projected maneuver bore considerable risk,[8] the formation of the 2-alkoxy-4-pyrone ring itself under conditions that allow the resident functionality to endure was even less intuitive. 4-Pyrones are privileged motifs for chemical biology and medicinal chemistry,[9] but only few methods are known for their synthesis, especially for the subset containing a 2-alkoxide substituent.[10] Because these procedures usually require fairly harsh conditions and/or are inherently limited to the formation of 4-methoxy-2-pyrones,[11] none of them seemed adequate for an application to the total synthesis of **1**.

For this very reason it was planned to forge this characteristic heterocyclic ring system by re-programming a gold catalyzed procedure previously developed by our group for the preparation of 2-pyrones **G** (Scheme 1, bottom).[12–14] This transformation hinges on a 6-*endo-dig* cyclization of alkynoic β-ketoesters ($R^2 = t$Bu). Complexation of the triple bond with a π-acidic catalyst,[15,16] as shown in **D**, leads to a first cyclic inter-

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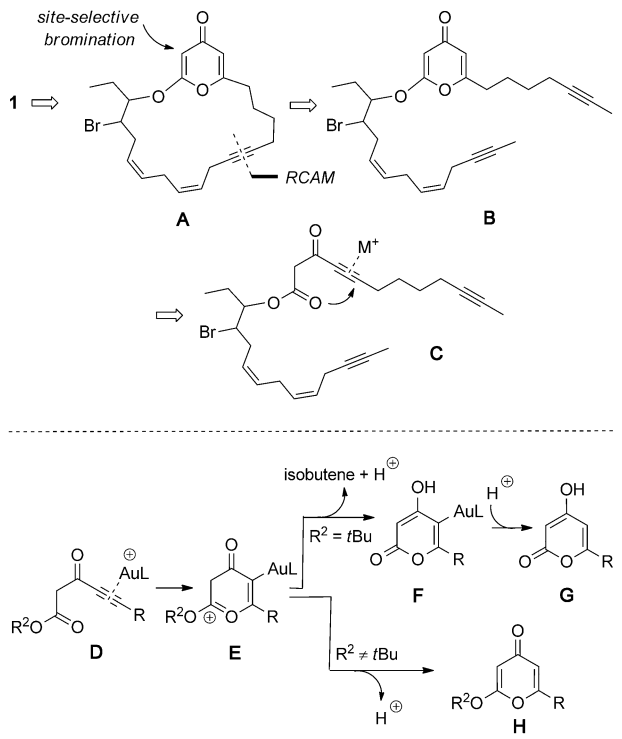
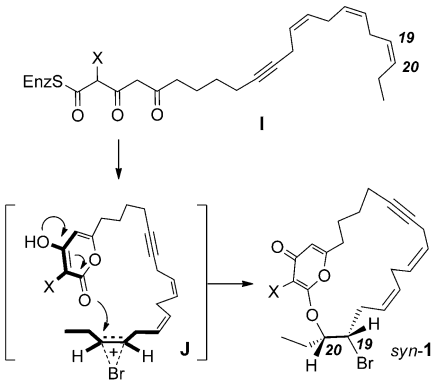


Scheme 1. Retrosynthetic analysis of **1** (top) and rationale of the envisaged synthesis of 2-alkoxy-4-pyrones by a gold catalyzed cycloisomerization of an acetylenic β-ketoester (bottom).

mediate of type **E**, which is prone to rapid loss of isobutene and a proton as necessary for product release and catalyst recycling. Because an analogous intermediate **E** with $R^2 \neq t$Bu cannot collapse in this way, it should be longer lived and might therefore give tautomerization to the corresponding 2-alkoxy-4-pyrone **H** a chance. Even if successful, however, the challenge of imposing this novel transformation onto an inherently labile precursor of type **C** remains, which might have many other options to react (or decompose) upon activation of the different π-bonds by a carbophilic Lewis acid catalyst.

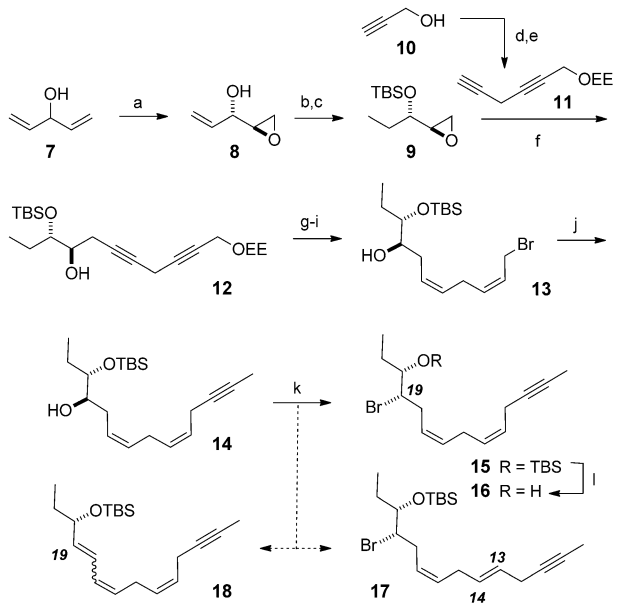
Under the premise that the gold-catalyzed cyclization can eventually be steered towards the required 4-pyrone tautomer,[17] we embarked on the total synthesis of **1**. Although the relative and absolute configuration of the two resident chiral centers had remained unassigned by the different isolation teams,[1–3] *syn*-**1** was deliberately chosen as our prime target. Because of the likely biosynthetic origin of **1** from a polyunsaturated fatty acid precursor of type **I**, its bromohydrin entity is thought to derive from the attack of the pyrone (or its immediate progenitor) onto a *Z*-alkene activated by a bromonium cation equivalent (see intermediate **J**, Scheme 2). This hypothetic scenario is in accord with the oxidative halogenation paradigm accounting for the biosynthesis of most halogen-containing natural products[18] and necessarily leads to a *syn*-configured linkage. For preparative purposes however, it was planned to introduce the bromide substituent at C19 by an S_N2 -type inversion of an *anti*-configured secondary alcohol precursor. However, this transformation might be far from trivial, given the homoallylic environment of the C19 position in **1**. Our apprehension was further raised by the fact that a literature search gave only very few hits of homoallyl bromides made in such a way.[19]



Scheme 2. Biosynthetic hypothesis, suggesting that the bromohydrin junction in **1** is *syn*-configured (only the relative stereochemistry is implied).

The actual synthesis commenced with the desymmetrization of cheap **7** by the Sharpless epoxidation protocol (Scheme 3).[20] TBS-protection of the resulting product **8** followed by hydrogenation of the remaining double bond over palladium on charcoal furnished multigram quantities of compound **9**. A Lewis-acid assisted opening of the epoxide ring[21] by the lithiated skipped diyne **11**[22] followed by cleavage of the acetal protecting group in the resulting product **12** gave a labile diol, which was immediately processed by catalytic semi-reduction of both triple bonds over nickel boride (P2-Ni),[23] followed by conversion of the primary hydroxyl group into the corresponding bromide. Although the resulting product **13** is sensitive and can only be kept in frozen benzene glass for limited periods of time, it was amenable to a highly selective nucleophilic substitution on treatment with propynylmagnesium bromide in the presence of sub-stoichiometric amounts of CuI; provided that the temperature was carefully controlled, the competing S_N2' attack of the nucleophile was suppressed and the stereochemical integrity of the *Z*-configured allylic bond fully preserved to give the skipped diene–yne **14** in respectable yield.[12,24]

Substantial optimization was necessary to find a reliable method for the conversion of **14** into the homoallylic bromide **15**. In the end, surprisingly harsh conditions gave the best results and allowed **15** to be obtained in well reproducible 60% yield. Complications arose from partial elimination of the alcohol as well as from competing *Z*/*E* isomerization, which—somewhat unexpectedly—affected the distal $\Delta^{13,14}$-bond more than the homoallylic alkene. For analytical purposes, the resulting by-products **17** and **18** were removed and the integrity of **15** was unambiguously confirmed; in the preparative context, however, this tedious homework was unnecessary as the isomeric compounds could be separated in the final steps of the synthesis. It is also emphasized that all attempts to install the bromide function in the tether at a later stage met with decomposition of the precious material.[25]

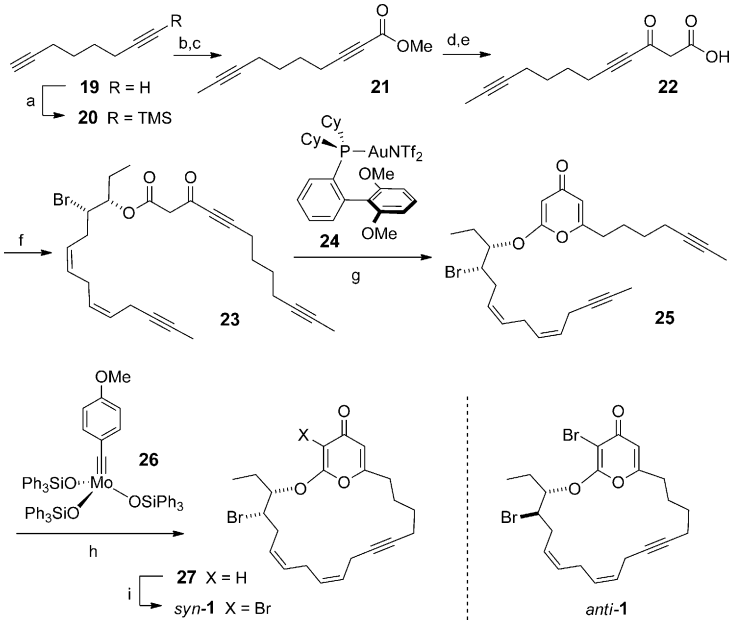


Scheme 3. a) Ti(O*i*Pr)$_4$ (10 mol%), (+)-diisopropyl tartrate (13 mol%), cumene hydroperoxide, CH_2Cl_2, MS 4 Å, −25 °C, 82%; b) TBSCl, imidazole, DMF, 0 °C → RT, 90%; c) H_2 (1 atm), Pd/C (10 mol% Pd), EtOAc, 95%; d) ethyl vinyl ether, *p*TsOH·H_2O (10 mol%), 0 °C, 84%; e) (i) EtMgBr, THF, 45 °C; (ii) CuCl (5 mol%), propargyl bromide, 60 °C, 68%; f) (i) **11**, *n*BuLi, THF, −78 °C; (ii) BF_3·Et_2O, then **9**, −78 °C, 72%; g) PPTS, MeOH, 30 °C, 98%; h) H_2 (1 atm), P2-Ni (25 mol%), EtOH, 79%; i) CBr_4, PPh_3, CH_2Cl_2, 0 °C, 91%; j) propynylmagnesium bromide, CuI (50 mol%), THF, −15 °C → −10 °C, 81%; k) CBr_4, PPh_3, toluene, 65 °C, **15** (60%), **17** (ca. 12%), **18** (ca. 11%); l) HF·pyridine, THF, 0 °C, 83%; EE = 1-ethoxyethyl; MS = molecular sieves; PPTS = pyridinium *p*-toluenesulfonate; TBS = *tert*-butyldimethylsilyl.

With a good amount of this delicate building block in hand, the stage was set for the key strategic maneuvers to close the pyrone ring and the macrocyclic scaffold (Scheme 4). To this end, alcohol **16** was esterified with the alkynoic β-ketoacid **22**, which in turn was obtained from commercial 1,7-octadiyne (**19**) in a few robust operations. Although the resulting ester **23** contains five different sites of unsaturation in addition to the highly enolized β-ketoester unit, treatment with catalytic amounts of the cationic gold complex **24**[12,26] resulted in exclusive and almost quantitative formation of the desired 2-alkoxy-4-pyrone derivative **25**. The reaction was best performed in MeCN/HOAc (4:1); the Brønsted acid is believed to assist in the protodeauration of an intermediate of type **E** (see Scheme 1) as the likely rate-determining step of the catalytic cycle.[27] In any case, the excellent preparative outcome is the result of a favorable kinetic selectivity profile: although the triple bond flanked by the carbonyl group is the least electron-rich of the unsaturations in substrate **23** and therefore a priori the least affine to the π-acidic catalyst,[15] it is the only one poised for being attacked by the internal nucleophile; this opens an irreversible pathway that siphons the substrate off to the desired pyrone nucleus.

Equally gratifying was the outcome of the subsequent ring-closing alkyne metathesis (RCAM)[6] of the sensitive diyne **25** which eventually degrades even upon storage in a freezer. Yet, treatment of this compound with the molybdenum alkylidyne **26** (5 mol%) at ambient temperature in the presence of MS 5 Å to sequester the released 2-butyne furnished cycloalkyne **27** in excellent yield.[28] As expected, the chosen catalyst rigorously distinguished between the alkene and the alkyne groups of **25**. Moreover, the chemical character of this formally high-valent metal species is obviously sufficiently tempered by the ancillary silanolate ligands not to cause any configurational or migratory isomerization of the highly susceptible skipped diene-yne motif.[29,30]

At this point, only the selective bromination of the 4-pyrone ring in **27** was missing. A screening of different [Br^+] sources under a variety of experimental conditions showed that the reaction indeed favored the ketene-acetal site, as originally hoped;[8] however, rapid *Z* → *E* isomerization turned out to be a serious complication, again mostly at the $\Delta^{13,14}$-double bond. Upon lowering the temperature, the desired bromination would stall while the isomerization continued to compromise the sterochemical integrity of the material. Therefore the total synthesis was completed on treatment of **27** with freshly recrystallized NBS at ambient temperature; the conversion was closely monitored and the reaction stopped as soon as the starting material was consumed, because extended stirring aggravated the isomerization problem. Under these conditions, *syn*-**1** was isolated in well reproducible 40% yield, which we deemed acceptable in view of the unusual sensitivity of sub-



Scheme 4. a) LiHMDS, THF, −78 °C, then TMSCl, −78 °C → RT, 52%; b *n*BuLi, THF, −78 °C, then MeI, −78 °C → RT, 91%; c) MeLi, THF, −78 °C, then ClC(O)OMe, −78 → 0 °C, 86%; d) *t*BuOAc, LDA, −78 °C, then **21**, 87%; e) TFA, CH_2Cl_2, 99%; f) **16**, DCC, DMAP cat., CH_2Cl_2, 0 °C, 70%; g) **24** (3 mol%), MeCN/HOAc (4:1), 97%; h) **26** (5 mol%), MS 5 Å, toluene, 82%; i) NBS, THF, 40%; DCC = dicyclohexylcarbodiimide; DMAP = 4-dimethylaminopyridine; LDA = lithium diisopropylamide; LiHMDS = lithium hexamethyldisilazide; NBS = *N*-bromosuccinimide; TFA = trifluoroacetic acid; TMS = trimethylsilyl.

strate and product and of the associated chemical challenges referred to above.

The recorded ^{13}C NMR data of *syn*-**1** matched those of the natural product very well,[2,31] thus establishing the stereostructure of this algal metabolite and confirming our biosynthetic hypothesis.[32] To exclude any doubt, we also prepared *anti*-**1** by an analogous route,[33] the spectral data of which deviated from those of the authentic compound. Finally, crystals of *syn*-**1** suitable for X-ray diffraction could be grown, which confirmed the assignments. Figure 1 shows the puckered conformation imposed on the macrocycle by the two *Z*-alkenes and the essentially linear alkyne unit. Interestingly, the large dihedral angle between the protons H19 and H20 at the bromohydrin junction ($\Theta = 179.09^{\circ}$) observed in the crystal structure has no correspondence in the recorded coupling constant of these protons in $CDCl_3$ solution (Figure 2); rather, a $^{3}J_{19,20} = 2.5$ Hz indicates a synclinal orientation and therefore suggests that the conformations adopted by *syn*-**1** in the solid state and in solution are substantially different.

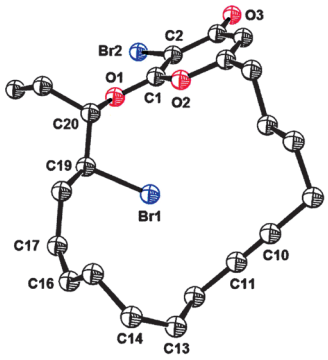


Figure 1. Structure of compound **1** in the solid state; co-crystallized MeCN has been removed for clarity (the entire structure is contained in the Supporting Information).

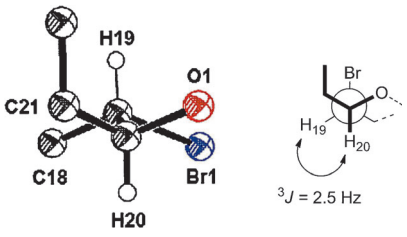


Figure 2. A Newman-like projection along the C19–C20 bond of compound *syn*-**1** shows the antiperiplanar orientation of H19 and H20 in the solid state; in contrast, these protons are most likely synclinal to each other in solution as suggested by the recorded coupling constant.

To summarize, the present investigation established, by way of total synthesis, the stereostructure of a marine metabolite that is fairly unique in structural terms and highly challenging for its chemical character. This goal was reached by a gold-catalyzed cyclization that allows readily available alkynoic β-ketoesters to be converted into pyrones under mild conditions that no other known entry into these privileged scaffolds can assure. The fact that this novel transformation was deliberately implemented at a very late stage shows our growing trust in π-acid catalysis in general, a field that has seen exponential growth in the recent past but remained surprisingly short of convincing applications to elaborate and precious substrates.[34] From a somewhat larger perspective, this study therefore also helps illustrate the tremendous opportunities that π-acid catalysis provides for heterocyclic chemistry and natural product synthesis.[35] Together with the selective triple-bond metathesis event as the other key step en route to **1**, it adds a new entry into a now rapidly growing list of examples featuring the strategic advantages of contemporary (catalytic) alkyne chemistry, to which our group is strongly committed.[36]

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Keywords: alkyne metathesis · biosynthesis · gold · heterocycles · molybdenum · natural products

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[25] Details will be reported in a future full paper.

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[31] The ^{1}H NMR data are also matching, but the comparison is less informative because the recorded data of the natural product are not sufficiently precise (for all multiplets, only the median was given); our data resolve the uncertainty about the shift of H19 at the foot of the bromine substituent, which was reported to resonate at $\delta_H = 4.74$ ppm in ref.[1a], but at $\delta_H = 4.14$ ppm in ref. [2]; for details see the Supporting Information.

[32] Because the $[\alpha]_D$ of **1** has not been reported, the absolute configuration cannot be defined.

[33] For the sake of brevity, the -OH group in **16** was inverted and the resulting alcohol 20-*epi*-**16** advanced to *anti*-**1**; for details, see the Supporting Information.

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[35] For other instructive cases from our group, see: a) G. Valot, C. S. Regens, D. P. O'Malley, E. Godineau, H. Takikawa, A. Fürstner, *Angew. Chem. Int. Ed.* **2013**, *52*, 9534 – 9538; *Angew. Chem.* **2013**, *125*, 9713 – 9717; b) S. Benson, M.-P. Collin, A. Arlt, B. Gabor, R. Goddard, A. Fürstner, *Angew. Chem. Int. Ed.* **2011**, *50*, 8739 – 8744; *Angew. Chem.* **2011**, *123*, 8898 – 8903; c) K. Gebauer, A. Fürstner, *Angew. Chem. Int. Ed.* **2014**, *53*, 6393 – 6396; *Angew. Chem.* **2014**, *126*, 6511 – 6514; d) L. Hoffmeister, P. Persich, A. Fürstner, *Chem. Eur. J.* **2014**, *20*, 4396 – 4402; e) L. Brewitz, J. Llaveria, A. Yada, A. Fürstner, *Chem. Eur. J.* **2013**, *19*, 4532 – 4537; f) G. Valot, D. Mailhol, C. S. Regens, D. P. O'Malley, E. Godineau, H. Takikawa, P. Philipps, A. Fürstner, *Chem. Eur. J.* **2015**, *21*, 2398 – 2408.

[36] A. Fürstner, *Angew. Chem.* **2014**, *126*, 8728 – 8740; *Angew. Chem. Int. Ed.* **2014**, *53*, 8587 – 8598.

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Natural Products

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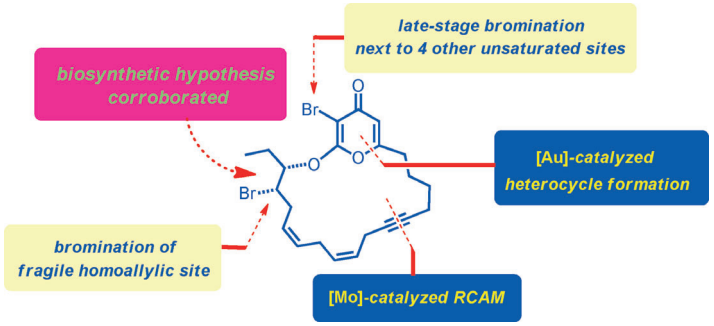
Total Synthesis of an Exceptional Brominated 4-Pyrone Derivative of Algal Origin: An Exercise in Gold Catalysis and Alkyne Metathesis



The gentle way: Certain red algae produce highly unusual 4-pyrone derivatives which cluster several remarkable functionalities into a macrocyclic frame. The first member of this series (see figure) has now been conquered and a biosynthetic hypothesis predicting its relative stereochemistry has been confirmed. The successful route is based on the selective transformation of an acyclic precursor containing six different sites of unsaturation, without scrambling the labile skipped π-systems.