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Total Synthesis and Stereochemical Revision of Phacelocarpus 2-Pyrone A

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Abstract: The first total synthesis of phacelocarpus 2-pyrone A is reported. The original natural compound was tentatively assigned (by NMR spectroscopy) as containing two *cis*-alkenes and a *trans*-vinyl ether connected to a 2-pyrone ring motif. Our computational predictions indicated that a *cis*-vinyl ether motif was equally feasible. Attempts to prepare the *trans*-vinyl ether were met with no success. The all *cis*-target compound was synthesised in nine steps, employing key regio- and stereoselective reactions including Au^{I}-catalysed vinyl etherification, Wittig alkenylation and end-game Stille macrocyclisation. Analysis of the NMR data enabled identification and confirmation of the correct structure of phacelocarpus 2-pyrone A, containing a *cis*-vinyl ether. Our studies pave the way for future development of methodologies to these structurally distinct pyrone skipped-polyenyne natural products.

The phacelocarpus pyrones (e.g. **1**–**5**, Figure 1) are a family of remarkable pyrone-containing macrocycles isolated from *Phacelocarpus labillardieri*, a marine red algae found abundantly around the coasts of southern Australia.[1] Despite limited biological studies on these compounds,[2] their distinctive arrangement of skipped alkenes around a macrocyclic ring containing an embedded 2- or 4-pyrone moiety makes them intriguing and challenging targets for synthetic chemists. Indeed, no total synthesis of any member of this family had been completed since their isolation in the 1980s until earlier this year when the first synthesis of brominated ether **3** was reported by Fürstner's group.[3]

Of particular note amongst this unusual family of compounds is phacelocarpus 2-pyrone A (**1**), the only member to contain an unprecedented 2-pyronyl enol ether substructure as part of the skipped unsaturated system. The incorporation of these features into a 19-membered macrocycle makes the construction of this compound a formidable synthetic challenge. The structure of **1** was assigned on the basis of NMR spectroscopic data and also by comparison to compounds ***E*-2** and ***Z*-2**, and the stereochemistry at the enol ether bond tentatively assigned as the *E*-isomer.[1b] Since no total synthesis of **1** has thus far been reported, and following our recent successful completion of a model compound,[4] we undertook to develop a convergent strategy for the synthesis of **1** to determine its authentic stereochemistry.

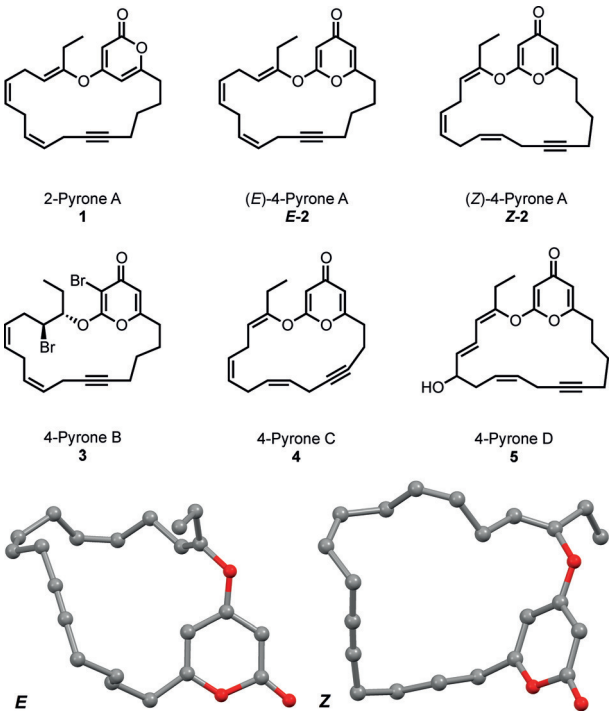

Figure 1. Top: Various members of the phacelocarpus pyrone family including phacelocarpus 2-pyrone A **1** (proposed structure); Bottom: Computed lowest energy molecular structures of the *E*- and *Z*-vinyl ethers of phacelocarpus 2-pyrone A **1**.

Molecular models revealed that the macrocycle containing the *E*-vinyl ether was more strained than that containing the *Z*-vinyl ether. DFT calculations (see the Supporting Information for methodology) indicate that the energy difference between the *E*/*Z* stereoisomers is small and that both should therefore be viable.

We anticipated that the major challenge in any synthetic route aimed towards **1** would be the construction of the vinyl ether linked to the electron-withdrawing 2-pyrone motif. The

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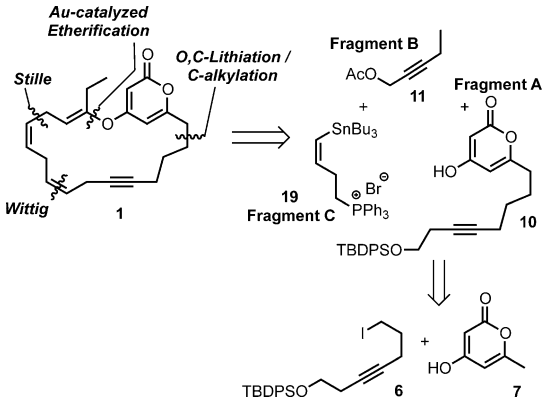
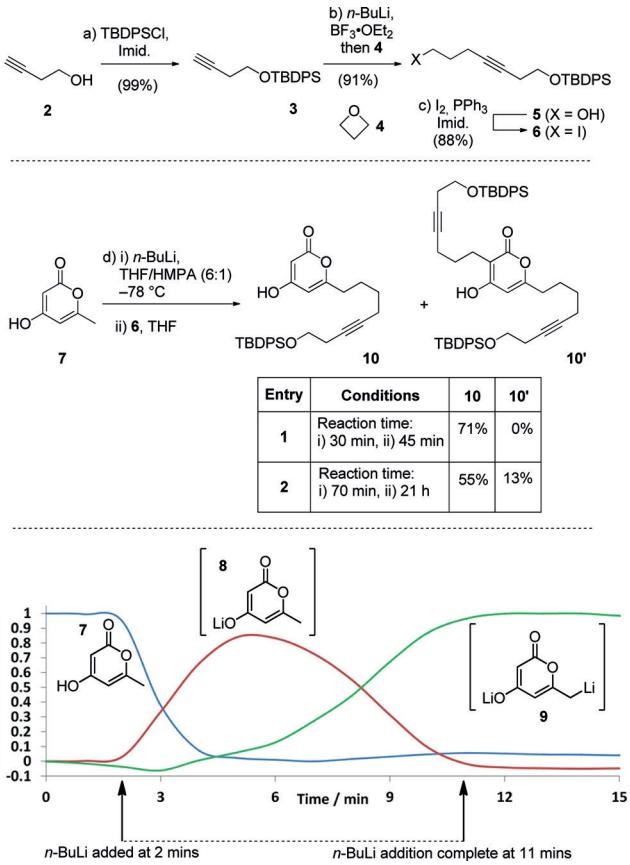
computational results detailed above indicated that it would be desirable to prepare both *E*- and *Z*-vinyl ether isomers of **1**, and the route was mapped out with this in mind. In principle, the vinyl ether can be formed in several ways, including a Pd-catalysed Hartwig–Buchwald-type etherification reaction, as we demonstrated in the synthesis of the arene mimetic of **1**.[4a] However, 4-hydroxy-2-pyrones possess limited nucleophilicity ($pK_a \approx 5$) in these Pd-mediated reactions and do not form the desired coupling products (see the Supporting Information for details). Nolan's Au^I-catalysed etherification methodology[5] for the reaction of substituted phenols with internal alkynes was identified as a potentially efficient way to access this type of motif, although at the point we initiated this work, no phenol with a pK_a lower than 7.15 (p-$NO_2C_6H_4OH$) had been evaluated as a coupling partner. This adventurous step would also raise questions over the regio- and stereochemical outcome of the reaction; we thus envisaged that a vinyl ether isomerization reaction might become necessary later in the route.

Given the considerations above, the retrosynthetic analysis of **1** was formulated as detailed in Scheme 1. Fragments A and B would first be unified using the Au^I-catalysed etherification step. We recognised that fragment A could be synthesised by selective *C*-alkylation of the dilithium salt derived from 4-hydroxy-6-methyl-2-pyrone (**7**).[6] The route then exploits the double nucleophilic reactivity of (*Z*)-1-tributylstannyl-but-1-en-4-triphenylphosphonium bromide (fragment C),[4a,7] allowing Wittig and Stille cross-coupling reactions to be assessed sequentially as the closing steps in the synthesis. Obtaining good regio- and stereochemical control would be crucial in both of these intricate final steps.



Scheme 1. Retrosynthetic analysis to compound **1**.

The forward synthesis of **1** begins with alkyne **6**, which can be accessed in excellent yield from commercially available but-3-yn-1-ol **2** (Scheme 2).[4a] We found that the reaction of iodide **6** with the dilithium salt derived from **7**,[6] that is, intermediate **9**, was blighted by lower than expected yields of the desired product **10**, while formation of the unwanted C3-alkylation side product **10′** was also observed. Given these issues, qualitative kinetic information about the formation of mono-lithium species **8** and dilithium species **9**, under working reaction conditions,[8] was gathered to provide a deeper understanding of the process.

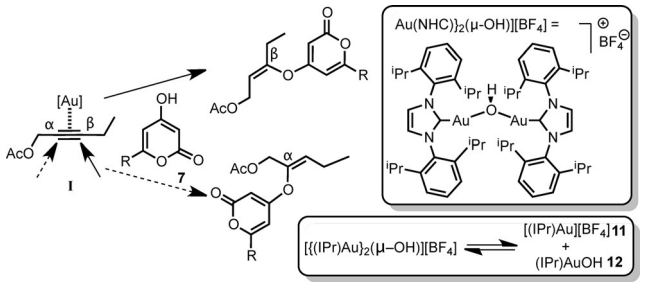


Entry	Conditions	10	10'
1	Reaction time: i) 30 min, ii) 45 min	71%	0%
2	Reaction time: i) 70 min, ii) 21 h	55%	13%

Scheme 2. Synthesis of compound **10** (fragment A). Real-time infrared spectroscopic analysis showing the formation of mono- and di-lithiated 2-pyrone intermediates **8** and **9** (both are likely solvated species); conversions are normalised against relative absorbance of each species (following IR bands at 1740 (**7**), 1698 (**8**) and 1634 (**9**) cm^{-1}). Reagents and conditions: a) TBDPSCl (1 equiv), imidazole (1 equiv), CH_2Cl_2, RT, 26 h, 99%; b) **3** (2 equiv), *n*BuLi (2 equiv), THF, −78 °C, 30 min, then $BF_3{\cdot}OEt_2$ (2 equiv), 15 min, then **4** (1 equiv), 2 h, 91%; c) PPh_3 (1.1 equiv), I_2 (1.1 equiv), imidazole (2.2 equiv), CH_2Cl_2, RT, 3 h, 88%; d) *n*BuLi (2.3 equiv), THF/HMPA (6:1), −78 °C, 30 min, then **6** (1.5 equiv), 45 min, 71%. TBDPS = *tert*-butyldiphenylsilyl, Imid = imidazole, THF = tetrahydrofuran, HMPA = hexamethylphosphoramide.

Reaction monitoring with real-time infrared spectroscopic analysis (using ReactIR™ IC10 with fixed Si probe) of **7** with *n*BuLi in THF/HMPA at −78 °C, showed that the initial deprotonation of the hydroxyl group occurred within approximately 4 min, giving mono-lithium salt intermediate **8**. The depletion of **8** was concomitant with formation of dilithium species **9**; the reaction reached completion within 12 min. When the lithiation time in a preparative reaction was adjusted accordingly, the desired product **10** could be obtained in 71% yield, with no formation of the dialkylation side product **10′** observed.

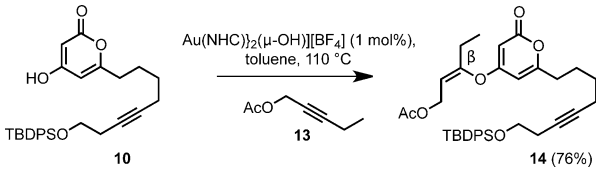
With the synthesis of **10** completed, its utility in the Au-catalysed etherification reaction of alkyne **13** was examined (Scheme 3). The Au catalyst $[\{(IPr)Au\}_2(\mu\text{-}OH)][BF_4]$ is unusual, existing in equilibrium with the Lewis acidic and Brønsted basic monomeric Au^I species (**11** and **12**).[5] Complexation of Au^I to alkyne **13** is envisaged to form π-complex **I**. Here it can be seen that two regioisomers can result by addition to either



Scheme 3. Possible reaction pathways of pyrone **7** with alkyne **13**.

the α or β carbon centres. The stereochemistry in previously reported reactions of internal alkynes is most commonly *Z*, but we envisaged that a subsequent isomerisation at a late stage might be feasible. Given that the construction of a trisubstituted vinyl ether containing a 2-pyrone by other methods had previously proven inefficient or impossible (see the Supporting Information for details),[9] the Au-methodology[5] was deemed the most promising potential route.

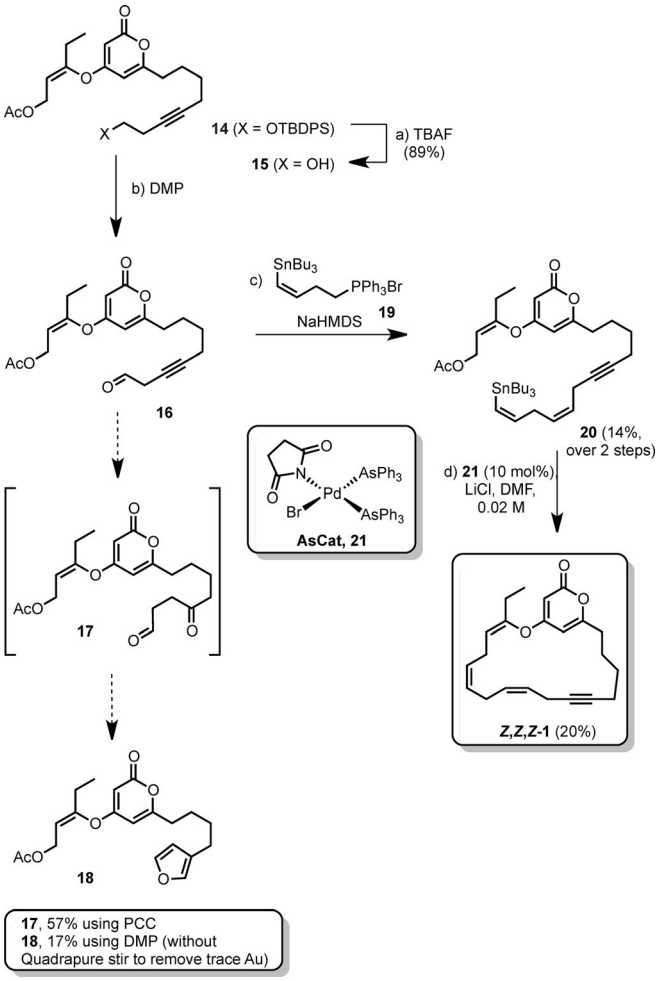
We were pleased to establish that the reaction between **10** and **13** (5 equiv), catalysed by 1 mol% of $[\{(IPr)Au\}_2(\mu\text{-OH})][BF_4]$, gave **14** with excellent regioselectivity ($\beta:\alpha = 10:1$) and complete *Z*-stereoselectivity in a yield of 76%. Moreover, intra- or intermolecular addition of the 4-hydroxyl group to the internal alkyne present within **10** was successfully avoided by using alkyne **13** in excess (Scheme 4). At this stage a number of different isomerisation conditions were screened in an attempt to obtain the *E*-enol ether from compound **14**, but no isomerisation could be detected under any of the conditions screened (see the Supporting Information for details). We thus resolved to proceed with the total synthesis of ***Z*-1** from compound **14**, which has a vinyl ether possessing *Z*-stereochemistry.



Scheme 4. Au-catalysed reaction of **10** with **13** to give **12**.

The end-game synthesis of ***Z*-1** is depicted in Scheme 5. Alcohol **15** was revealed by silyl deprotection of **14** using standard TBAF conditions, but initial attempts to oxidise the primary alcohol **15** to aldehyde **16** under Dess–Martin conditions[10] were not straightforward. The high polarity of the 2-pyrone **16** meant that it was difficult to separate the desired aldehyde cleanly from excess DMP and DMP-derived byproducts. Noted also was decomposition and side-product formation (e.g., furan **18** was isolated in 17% yield). Other oxidants, for example, PDC and TPAP, led to the decomposition of **15**, whereas the use of PCC led to formation of 1,4-dicarbonyl compound **17**, in 57% yield.

Dicarbonyl compound **17** is an obvious precursor to furan **18**, thus pointing to unwanted alkyne hydration as a major side reaction. This process could be catalysed by residual gold remaining from the prior vinyl etherification step, which according to literature reports can occur with as little as 10 ppm Au.[11] We therefore carried out the oxidation reaction with DMP using starting material that had been treated with a thiourea-based resin (Quadrapure-TU) specifically designed to scavenge trace metal atoms; in this way, alcohol **15** was cleanly oxidised to aldehyde **16**. The latter compound is rather prone to degradation, and thus **16** was used immediately in the subsequent reaction.



Scheme 5. End-game synthesis of ***Z*,*Z*,*Z*-1**. Reagents and conditions: a) TBAF (1.1 equiv), THF, RT, 1.5 h, 89%; b) DMP (1.4 equiv), CH_2Cl_2, 0 °C to RT, 1 h; c) **19** (2 equiv), NaHMDS (1.9 equiv), THF, −78 to 0 °C, then **16**, −78 to RT, 1 h, 14% over two steps; d) **21** (10 mol%), LiCl (10 equiv), DMF, 35 °C, 18 h, 20%. TBAF = tetrabutylammonium fluoride, DMP = Dess–Martin periodinane, NaHMDS = sodium hexamethyldisilazide, DMF = *N*,*N*-dimethylformamide, PCC = pyridinium chlorochromate.

The Wittig reaction with stannane–phosphonium salt **19** was hampered by the particular sensitivity of aldehyde **16**. At low temperature (−78 °C), no reaction occurs between the ylide formed from **19** and the aldehyde **16**; upon warming, product formation is observed but with accompanying decomposition. Nevertheless, compound **20** could be prepared in 14% yield over two steps, directly from compound **15**. A detailed study using NMR spectroscopic analysis of the Wittig reaction under

working conditions showed that ylide oxidation was the primary side reaction. Other attempts to optimize this reaction were met with limited success.

The Pd^{II} precatalyst, AsCat (**21**), which contains arsine, bromide and succinimidyl groups, has previously been developed by our groups.[12] It is a particularly active precatalyst for mild Stille cross-coupling reactions, and was also applied to complete the synthesis of the arene mimetic of **1**.[4a] The final Stille macrocyclisation reaction of **20**, mediated by AsCat (**21**), gave ***Z,Z,Z*-1** in 20% yield. All of the available NMR spectroscopic data confirmed that the stereochemistry throughout the molecule was all-*cis* (see the Supporting Information for complete analysis and deductions).

With spectroscopic data for synthetic ***Z,Z,Z*-1** in hand, and given that the DFT calculations had indicated that both *Z*- and *E*-vinyl ethers are viable, we compared our data with the reported ^1H and ^{13}C NMR data for **1** (assigned with an *E*-vinyl ether stereochemistry).[1b] To our delight, the data matched very closely; the similarity in the ^{13}C NMR data is particularly striking (Table 1) in that all the carbon signals match within error the reported data for **1**. The stereochemistry of phacelocarpus 2-pyrone A, **1**, is therefore confirmed as all-*cis*. The observation is supported by the computational study, which indicates that the macrocycle with a *Z*-vinyl ether, relative to the *E*-vinyl ether, is a feasible structure.

Table 1. Comparison of reported ^{13}C NMR spectroscopic data for **1** with the data for the synthetic material.

Position	δ (**1**, natural) [ppm][a]	δ (**1**, synthetic) [ppm][b]	$\Delta\delta$ [ppm]
1	165.1	165.1	0
3	151.0	151.1	+0.1
4	114.2	114.3	+0.1
5	23.8	23.8	0
6	126.6	126.7	+0.1
7	128.4	128.5	+0.1
8	25.3	25.3	0
9	130.5	130.6	+0.1
10	124.4	124.4	0
11	16.9	16.9	0
12	78.9	79.0	+0.1
13	79.3	79.4	+0.1
14	18.1	18.1	0
15	27.3	27.3	0
16	25.0	25.0	0
17	32.3	32.4	+0.1
18	166.9	166.9	0
20	169.0	169.0	0
21	89.6	89.6	0
22	99.0	99.0	0
1′	25.5	25.5	0
2′	11.0	11.0	0

[a] From ref. [1b] (50 MHz); reassigned. [b] Referenced to $CDCl_3$ = 77.0 ppm (200 MHz). For the compound numbering system, see the Supporting Information.

In conclusion, we have synthesised phacelocarpus 2-pyrone A, **1**, and in the process have been able to confirm the structural connectivity within this remarkable macrocyclic framework. The stereochemistry of the vinyl ether linked to the 2-pyrone has been revised, by comparison of the reported data of the natural compound with our data for the synthetic natural product. We continue to work toward the synthesis of other members of the 2-pyrone family of macrocycles, in addition to expanding the Au-catalysed vinyl ether formation reactions with 2-pyrones and related derivatives.

Experimental Section

Experimental data for **1**: R_f 0.58 (EtOAc/petrol, 1:1, *v/v*); IR (thin film, cm^{-1}) ν_{max} 2925 s, 2854 m, 1733 s, 1645 m, 1567 m, 1462w, 1417w, 1223 m, 1131w, 821w, 702w; ^1H NMR (700 MHz, $CDCl_3$) δ 6.03 (d, J = 2.2 Hz, 1H, H-22), 5.54–5.47 (m, 1H, H-10), 5.42 (d, J = 2.2 Hz, 1H, H-21), 5.41–5.34 (m, 3H, H-6, 7, 9), 5.16 (t, J = 7.3 Hz, H-4), 2.87 (d, J 7.5 Hz, 2H, H-11), 2.81 (t, J = 7.5 Hz, 2H, H-8), 2.66 (t, J = 7.3 Hz, 2H, H-5), 2.51 (t, J = 6.9 Hz, 2H, H-17), 2.23–2.16 (m, 4H, H-14, 1′), 1.81 (app p, J = 6.9 Hz, 2H, H-16), 1.62–1.53 (m, 2H, H-15), 1.07 (t, J = 7.4 Hz, 3H, H-2′); ^{13}C NMR (see Table 1); MS (ESI) *m/z* (%) 361 ([*M*+Na]$^+$, 100); HRMS (ESI): *m/z* calcd for $C_{22}H_{26}NaO_3$: 361.1761 [*M*+Na]$^+$; found: 361.1774.

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Keywords: dienes · macrocycles · natural products · palladium · total synthesis

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