A Concise Route to alpha '-Methoxy-gamma-pyrones and Verticipyrone Based Upon the Desymmetrization of alpha,alpha '-Dimethoxy-gamma-pyrone

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A Concise Route to α′-Methoxy-γ-pyrones and Verticipyrone Based Upon the Desymmetrization of α,α′-Dimethoxy-γ-pyrone

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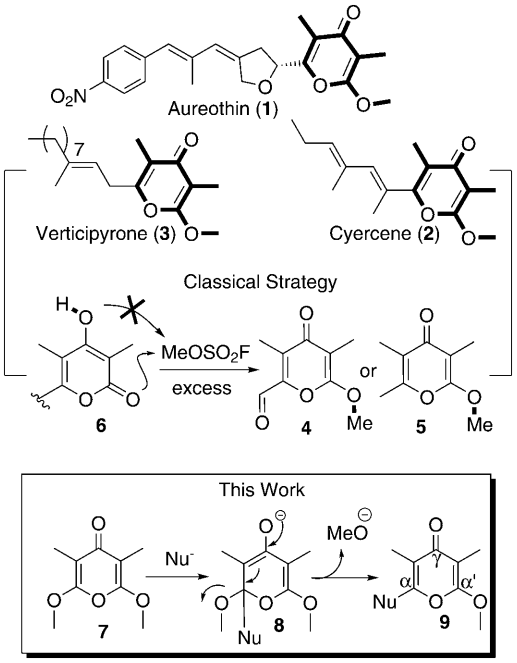
Bacterial and parasitic diseases are two of the leading causes of death worldwide, with 175 000 deaths attributed to hospital-acquired infections each year in Europe alone, stressing the need for innovative antibiotic research.[1,2] Unsaturated pyrone polyketides constitute a broad family of molecules produced by various marine microorganisms from the *Actinomycete* family that, in some cases, exhibit interesting antifungal, antibiotic, or antitumor activities.[3] New molecules belonging to this class are frequently discovered and a concise strategy to synthesize such γ-pyrone cores is highly desirable.[4] For instance, aureothin (**1**),[5] cyercene A (**2**),[6,7] and verticipyrone (**3**) (Scheme 1) are unsaturated γ-pyrone polyketides that exhibit interesting bioactivities.[8,9] Omura et al. recently described the first synthesis of **3**, which can be isolated from *Verticillium* sp. FKI 1083 and possesses potent and selective activity against *Ascaris suum* ($IC_{50}=4.1$ nM) and anthelmintic activity against *Caenorhabditis elegans* and *Artemia salina*.[10]

α-Carboxaldehyde **4** and α-methyl-α′-methoxy-γ-pyrone **5** (Scheme 1) are typical building blocks for the synthesis of compounds **1**–**3**. However, accessing these polyfunctionalized synthons involves several steps for the moderately efficient preparation of intermediate γ-hydroxy-α-pyrone **6**. Then, the known approach to the α′-methoxy-γ-pyrone scaffold in both **4** and **5** relies upon the methylation of ambident **6** with a large excess of methyl fluorosulfonate.[11,12] If performed with dimethyl sulfate, the reaction is not chemoselective and *O*-alkylation isomers are produced in almost equal amounts. Herein, we report a new method for the synthesis of building blocks **4** and **5**, and verticipyrone **3**. Our strategy, outlined in Scheme 1, is based upon the conjugate addition of a nucleophile to desymmetrize α,α′-dimethoxy-γ-pyrone **7**, followed by an elimination of methoxide to furnish unsymmetrical α′-methoxy-γ-pyrone **9**.



Scheme 1. The formation of the α′-methoxy-γ-pyrone ring by the classical strategy and our approach.

With respect to previous approaches, the advantages of such a strategy are that it 1) overcomes the need for a regioselective methylation of intermediates like **6**, 2) allows the versatile synthesis of various α′-methoxy-γ-pyrone scaffolds

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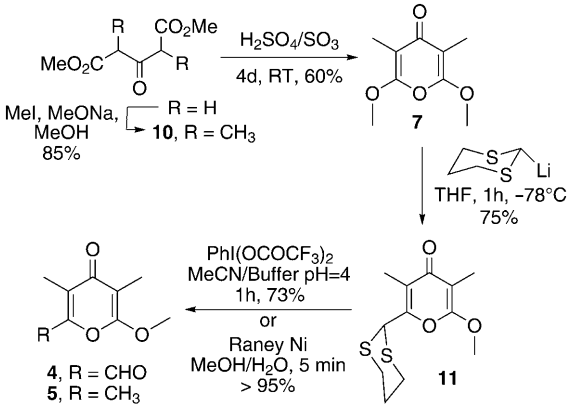
such as **9** by simply varying the nature of the nucleophile, and 3) shortens the preparation of natural products by starting from a readily available and common scaffold (**7**). The preparation of this substrate was first reported by Woodward and Small who used an acid promoted cyclization of keto diester **10** with sulfuric acid and oleum.[13] However, yields remained low and reproducibility poor (Scheme 2).



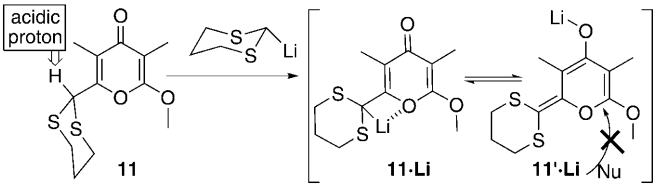
Scheme 2. Preparation of **4** and **5** by desymmetrization of **7** with 2-lithio-1,3-dithiane.

To improve the efficiency of this procedure, we examined several acids (H_3PO_4, CF_3SO_3H) and dehydrating agent P_2O_5 without success. Eventually, the cyclization of **10** was attempted in neat oleum and γ-pyrone **7** was obtained with an improved yield of 60%. These conditions can be routinely applied on a decagram scale to produce **7** after basic aqueous washing and crystallization.

To validate our strategy, the condensation of **7** with a standard nucleophile was investigated next. The umpolung chemistry of 2-lithio-1,3-dithiane is well known and we anticipated that this nucleophile could be a good candidate for our procedure. Our first experiments were particularly encouraging, since treating **7** with 2-lithio-1,3-dithiane (2 equiv) yielded 60% of expected product **11**. Since **11** is acidic, 2 equivalents of the lithiated nucleophile were required to reach full conversion. Quenching the reaction at −78°C with an excess of MeOH and stirring for 30 min at room temperature further enhanced the yield to 75%. The reaction was carried out on multigram scales and **11** was recovered after trituration with cold pentane/iPr_2O.

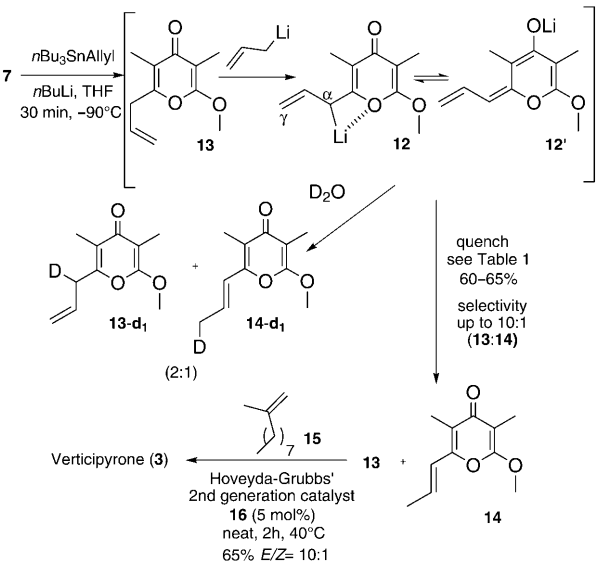
The unmasking of the aldehyde was complicated by its vicinity to a ketone and the resulting acidity of the geminal proton of the dithiane group. After considerable screening of conditions, [bis(trifluoroacetoxy)iodo]benzene (PIFA) was selected to smoothly achieve this transformation. Hence, aldehyde **4** can be prepared on a gram scale from **11** in 73% yield. On the other hand, the reduction of the dithiane proceeded very efficiently in the presence of a slurry of Raney nickel, yielding α-methyl-α′-methoxy-γ-pyrone **5** in nearly quantitative yield. These results constitute an appreciable improvement to the known approaches to these two building blocks.

Notably, this desymmetrization step occurs only once, even if **7** is exposed to 2 equivalents of nucleophile. Since **11** possesses an acidic proton (vide supra), it is probable that deprotonation of this product by the second equivalent of 2-lithio-1,3-dithiane prevents an extra conjugate addition after delocalization of the negative charge into the γ-pyrone ring (Scheme 3, **11·Li/11′·Li**).



Scheme 3. A possible explanation for the mono conjugate addition of 2-lithio-1,3-dithiane to **7**.

Next, we turned our attention to the synthesis of verticipyrone **3**. Successful desymmetrization of **7** by an allylating reagent would, indeed, secure access to an advanced intermediate en route to the synthesis of **3**. For the aforementioned reasons, the condensation was carried out with commercially available allyltributylstannane (2 equiv), in combination with *n*BuLi (2.2 equiv), to generate the allyl lithium (2 equiv; Scheme 4).[14] The reaction proceeded quickly at −90°C, yielding, after quenching of intermediate **12**, a mixture of two isomers, **13** and (*E*)-**14**, in 60–65% yield with an initial ratio of 2:1. These isomers were hypothesized to arise from competition between α- and γ-protonation of **12**. To ascertain the veracity of this hypothesis, D_2O was used for



Scheme 4. Preparation of verticipyrone **3** after desymmetrization of **7** and cross-metathesis.

the quenching and deuterated **13-d$_1$** and **14-d$_1$** were observed, by NMR spectroscopy, in a ratio of 2:1.

If MeOH was used to quench **12**, **14** became the main product (**13**/**14**, 1:3, Table 1, entry 1). Thermodynamic product **14** can be obtained as the only isomer after 1 h of stirring at room temperature in the presence of MeOLi, which is generated during the quenching. On the other hand, acidic quenching by using aqueous HCl prevented the isomerization process and led to a ratio of 3.5:1 in favor of unconjugated product **13**. To improve the regioselectivity of the protonation, kinetic quenching of **12** was envisaged. The quenching of the reaction by slow transfer onto a precooled (−90 °C) mixture of acid in Et_2O was then attempted. Acetic acid gave satisfying results with an improved ratio of 5:1, although trifluoroacetic acid (Table 1, entry 4) reached a higher selectivity of 10:1. The combination of both the acid and the slow transfer at −90 °C appears to favor the formation of **13**.

Table 1. Quenching of lithiated intermediate **12**.

Entry	Conditions	Yield [%]	Product ratio [**13**/**14**][a]
1	MeOH (excess)	60	1:3
2	HCl aq. (excess)	60	3.5:1
3	AcOH (3 equiv)[b]	65	5:1
4	CF_3CO_2H (3 equiv)[b]	65	10:1

[a] Determined by NMR spectroscopy of the crude reaction mixture. [b] Quenching by slow transfer onto a mixture of acid in Et_2O (−90 °C).

With allylated γ-pyrone **13** in hand, we proceeded towards the synthesis of verticipyrone by using an intermolecular olefin cross-metathesis (CM) reaction of **13** with 2-methyldec-1-ene (**15**); this disubstituted olefin is easily prepared from commercially available 2-decanone.[15] The preparation of electron-rich trisubstituted olefins possessing specific configuration by CM remains challenging, especially if one reagent features a double bond prone to migration to a more stable position. Numerous reports indicate that double-bond migrations may interfere with metathesis reactions and, to inhibit this side process, additives may be particularly effective.[16] Alternatively, CM of a monosubstituted olefin by using a large excess of a 1,1-disubstituted olefin partner has been established to overcome these side reactions.[17] The initial attempt at CM of **13** (ratio **13**/**14**, 3.5:1) and **15** (3 equiv) in the presence of Hoveyda–Grubbs' 2nd generation catalyst (**16**, 5 mol %, CH_2Cl_2, RT) resulted in the formation of **14**, due to isomerization of the double bond, contaminated with small amounts of verticipyrone **3** (ratio **13**/**14**/**3**, 0:1:0.2). After screening catalysts, solvents, and conditions, we found that the CM of a mixture of **13** and **14** with a large excess of **15** (50 equiv) can be carried out successfully by using catalyst **16** (5 mol %) in neat conditions.[18] The stereoselectivity of the reaction was good (10:1) but the yields remained medium (55–65 % based upon **13**). It must be noted that up to 90 % of unreacted **15** can be recovered by simple filtration of the crude mixture and elution with pentane. The synthesis of verticipyrone has, thus, been completed in four steps (20 % overall yield) starting from commercially available 1,3-dimethylacetone dicarboxylate. This constitutes the shortest synthesis described so far and is the first application of a CM reaction to allylic pyrones, substrates prone to isomerization.

In summary, a short, practical route to versatile building blocks **4** and **5**, for the synthesis of α′-methoxy-γ-pyrone-containing bioactive molecules, has been unveiled. This new strategy is based upon a versatile desymmetrization of α,α′-dimethoxy-γ-pyrone **7** by 2-lithio-1,3-dithiane to form **11**. This approach is a solution to the long standing problem of chemoselective methylation of protomeric tautomer γ-hydroxy-α-pyrone **6**. From **11**, α-carboxaldehyde **4** or α-methyl-α′-methoxy-γ-pyrone **5** can be obtained, in four steps, and be used as an electrophile or nucleophile, respectively. From a retrosynthetic point of view, we have also introduced readily available α,α′-dimethoxy-γ-pyrone **7** as a cornerstone for new strategies that could allow the direct preparation of α′-methoxy-γ-pyrone natural products. In this regard, the very concise synthesis—four steps—of verticipyrone **3** constitutes a forceful demonstration.

Experimental Section

Synthesis of 11: 1,3-dithiane (0.130 g, 1.09 mmol, 2 equiv) was dissolved in anhydrous THF (4 mL), under an argon atmosphere, in a single-necked round-bottom flask (20 mL) equipped with a magnetic stirrer. The flask was cooled to −78 °C and *t*BuLi in pentane (1.7 M, 670 μL, 1.14 mmol, 2.1 equiv) was added. The deep yellow mixture was stirred for 10 min at this temperature. Then, a solution of **7** (0.100 g, 0.54 mmol, 1 equiv) in THF (6 mL) was added via a cannula over 10 min and the mixture was stirred for 50 min at −78 °C. The reaction was terminated by the addition of methanol (4 mL, technical grade) and the mixture was allowed to warm to RT and agitated for a further 30 min at this temperature. Water was added and the aqueous layer extracted with dichloromethane (3×10 mL). The organic layers were washed with brine, dried (Na_2SO_4), and concentrated under vacuum. The residue was triturated with pentane (20 mL×2, stored at 0 °C for 30 min) and with *i*Pr_2O (20 mL, stored at −20 °C for 30 min) to yield compound **11** as a white powder (0.107 g, 73 %). The *i*Pr_2O layers can be concentrated and purified by flash column chromatography (pentane/AcOEt, 2:1→1:1) to deliver additional **11** (3 mg, 2 %). Alternatively, **11** can be directly purified on silica gel in comparable yield. R_f=0.45 (pentane/AcOEt, 1:1; SiO_2, UV, $KMnO_4$); m.p. 149 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS), δ= 5.30 (s, 1H), 4.04 (s, 3H), 3.12–3.03 (m, 2H) 2.96 (dt, ^3J(H,H)=14.3, 3.9 Hz, 2H), 2.21–2.16 (m, 1H), 2.01 (s, 3H), 2.01–1.95 (m, 1H), 1.84 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS), δ=184.3, 162.4, 153.0, 119.7, 100.2, 56.05, 46.7, 31.5, 29.9, 25.3, 10.25, 7.2 ppm; IR (film) 2952, 1661, 1592, 1463, 1408, 1377, 1323, 1158 cm^{-1}; HRMS (IE, 70 eV): *m*/*z* calcd for $C_{12}H_{16}O_3S_2$: 272.0541; found: 272.0544.

Acknowledgements

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