Total Synthesis of an Antifouling Marine Furanosesquiterpene

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Abstract An antifouling sesquiterpene isolated from Sinularia sp. was synthesized from citronellyl acetate in eight steps and 9% overall yield. The furan moiety was constructed using a multifunctional sulfone reagent.

Key words furans, sulfones, natural products, total synthesis, heterocycles

Biofouling constitutes a significant economic challenge. Fouling organisms are ubiquitous in marine habitats, and they negatively impact shipping operations, water purification, and aquatic recreation.3 Inorganic antifoulants have been the first line of defense for many years,4 but increasing environmental concerns prompted the International Maritime Organization to adopt a ban on the use of organotins and other harmful antifouling systems in marine coatings in 2001.5 Consequently, research into non-bioaccumulating, environmentally benign fouling inhibitors has taken on a renewed sense of urgency, and particular attention has been devoted to natural products of marine origin.6

In this context, the furanosesquiterpene 1 has been isolated from several subspecies of the soft coral Sinularia species,7–11 and preliminary studies have estimated its efficacy against the blue mussel (Mytilus edulis) at a loading of 0.2 mg/mL to be 74% that of copper(II) sulfate, a highly effective (but environmentally persistent) inorganic antifoulant;12,13 moreover, at concentrations of 30 μM it exhibited moderate (26%) inhibition of inducible NO synthase (iNOS) activity in J774 macrophages.14 However, extraction of 1 from natural sources yields low quantities, and to our knowledge a total synthesis has not been reported previously. We were therefore intrigued with this compound as a target for our recently reported sulfone-mediated preparative method for converting 1,3-diketones into 2,4-disubstituted furans.15

Using this approach (Figure 1), we envisioned that furoic acid 1 could be accessed via diketone 2, which in turn could be efficiently constructed from the readily available citronellyl acetate (3).

Figure 1 Retrosynthetic strategy for furanosesquiterpene 1

For the construction of diketone 2, we took inspiration from a synthesis of the insect pheromone methyl 2,6,10-trimethyldodecanoate reported by Zarbin et al.,16 which launched by subjecting citronellyl acetate (3) to selenium dioxide mediated allylic oxidation to provide aldehyde 4 (Table 1). Using superstoichiometric quantities of SeO2, the E-aldehyde 4 was isolated in 41% yield upon reflux in ethanol for 15 min (entry 1). Higher yields and shorter reaction times could be achieved using a microwave protocol (entry 2), albeit with a somewhat more limited scalability. In both of these approaches, a small amount of Z-isomer was observed, which was difficult to remove by chromatography without yield loss. In contrast, the use of substoichiometric amounts of SeO2 adsorbed onto silica in dichloromethane at room temperature in the presence of aqueous tert-butyl hydroperoxide as a terminal oxidant17 (entry 3) provided practically exclusively the E-isomer in yields comparable to those found in entry 1. However, with an eye toward scale-up, we explored the possibility of isolating gram quantities of aldehyde 4 without the high solvent demand associated...
with chromatography. The most effective alternative was found to be Kugelrohr distillation (130 °C/2 Torr), which has a higher throughput than a flash column and delivers the product in significantly higher yield (entry 4). One drawback, however, is that a small amount of E/Z isomerization occurs, which could not be circumvented. To take advantage of its convenience and scalability, we nonetheless carried the material forward with an eye toward removal of the Z-isomer after the next step.

When the oxidation was carried out in the presence of 10 mol% 2,6-di-tert-butyl-4-methylphenol (BHT). Since the conversion is practically quantitative, the BHT was carried forward to avoid yield loss in purification.

The next step was to install the 1,3-diketone moiety necessary for the sulfone-mediated furan formation, which we envisioned to occur via an aldol-oxidation sequence on aldehyde 7. We chose to optimize this reaction using commercially available citronellal (8) (Table 2). As one of the strategies surveyed, we examined the titanocene-catalyzed Reformatsky addition of chloroacetone onto citronellal, which has been previously reported to give a 91% yield of hydroxy ketone 9 as a mixture of diastereomers. Although the chief product was the corresponding enone (entry 1), results could be improved by using superstoichiometric amounts of proline and acetone as a solvent (entry 3).21 Similar yields (53%) could be obtained using catalytic sodium methoxide in methanol at 5 °C.24 (entry 4). Still better results were achieved by changing the base to LDA and using one equivalent of acetone in THF (entry 5).25 Gratifyingly, these conditions worked equally well on substrate 7, providing aldol 10 in 66% yield. Subsequent oxidation to diketone 2 proceeded smoothly using stabilized IBX,26 although the product degraded upon storage and was used immediately for the next step. Again, the addition of BHT was necessary to prevent E/Z isomerization during the oxidation.

### Table 1 Allylic Oxidation of Citronellyl Acetate (3)

<table>
<thead>
<tr>
<th>Entry</th>
<th>SeO₂ (equiv)</th>
<th>t-BuOOH (equiv)</th>
<th>Solvent</th>
<th>Time</th>
<th>T (°C)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.0</td>
<td>0</td>
<td>EtOH</td>
<td>15 min</td>
<td>78</td>
<td>41b</td>
</tr>
<tr>
<td>2</td>
<td>2.0</td>
<td>0</td>
<td>EtOH</td>
<td>10 min</td>
<td>100e</td>
<td>50b</td>
</tr>
<tr>
<td>3</td>
<td>0.5d</td>
<td>2.5</td>
<td>CH₂Cl₂/H₂O</td>
<td>24 h</td>
<td>r.t.</td>
<td>39</td>
</tr>
<tr>
<td>4</td>
<td>0.5d</td>
<td>2.5</td>
<td>CH₂Cl₂/H₂O</td>
<td>24 h</td>
<td>r.t.</td>
<td>60e</td>
</tr>
<tr>
<td>5f</td>
<td>0.5</td>
<td>3.0</td>
<td>CH₂Cl₂/H₂O</td>
<td>3 h</td>
<td>r.t.</td>
<td>40</td>
</tr>
</tbody>
</table>

*Isolated by column chromatography unless otherwise stated.
*b Approximately 2–4% Z-isomer present (by NMR).
*d Microwave protocol.
*e Isolated by bulb-to-bulb distillation. Z isomer also present.
*f Results reported in ref. 16.

Methylation of the aldehyde functionality was effectuated using standard Wittig chemistry. Thus, treatment of methyltriphenylphosphonium bromide with n-butyllithium, followed by addition of aldehyde 4 resulted in smooth conversion into the corresponding E-diene acetate 5 in 76% yield (Scheme 1). Subsequent deprotection of the alcohol could be accomplished conveniently through potassium carbonate promoted transesterification in methanol, which afforded alcohol 6 in excellent yield on a variety of scales.

Among several protocols screened for the conversion of the primary alcohol into aldehyde 7, oxidation with stabilized IBX (sIBX) in tert-butyl alcohol proceeded with the highest yield. Vexingly, a small amount (ca. 5%) of isomerization was observed about the internal double bond under these reaction conditions. It is unclear whether the E/Z isomerization is induced by sIBX itself or results from traces of iodine in the reagent. To our knowledge, the IBX-mediated isomerization of double bonds has not been reported, although the iodine-promoted variant is well known, and previous studies have shown the efficacy of radical scavengers in retarding the iodine-catalyzed isomerization of dienes. Thus, we were pleased to observe no Z-isomer when the oxidation was carried out in the presence of 10 mol% 2,6-di-tert-butyl-4-methylphenol (BHT). Since the conversion is practically quantitative, the BHT was carried forward to avoid yield loss in purification.
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Table 2 Optimization of Aldol Condensation Using Citronellal (8)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cp2TiCl2 (2 equiv), Mn (8 equiv), chloroacetone (2 equiv), 2,4,6-collidine (8 equiv), TMSCl (4 equiv), THF</td>
<td>58</td>
</tr>
<tr>
<td>2</td>
<td>proline (0.3 equiv), 20% acetone/DMSO</td>
<td>21*</td>
</tr>
<tr>
<td>3</td>
<td>proline (2 equiv), acetone</td>
<td>49</td>
</tr>
<tr>
<td>4</td>
<td>NaOMe (0.33 equiv), acetone (3.6 equiv), MeOH</td>
<td>53</td>
</tr>
<tr>
<td>5</td>
<td>LDA (1.2 equiv), acetone (1.0 equiv), THF</td>
<td>63</td>
</tr>
</tbody>
</table>

* The corresponding enone was produced in 65% yield.

With diketone 2 in hand, the phenylsulfonylmethylfuraran 11 could be accessed by treatment with 2,3-dibromo-1-(phenylsulfonyl)prop-1-ene in the presence of methanolic sodium methoxide. The carboxylic acid functionality could then be installed using an oxidative desulfonylation strategy, in which the sulfonyl dianion formed using potassium hexamethyldisilazanide is allowed to undergo oxidation in dry air, providing the target furansesquiterpene 1 in fair yield.

In summary, we have reported a convenient and scalable synthesis of the potential antifouling compound 1, which is suitable for preparing gram quantities of the synthetic target in 8 steps and 9% overall yield from the readily available citronellyl acetate. Antifouling evaluation of compound 1 is currently underway.

THF was distilled first over CaH2 and then over Na/benzophenone ketyl. Hexanes for chromatography were distilled over CaH2, MeOH, EtoAc, acetone, and CH2Cl2, which were purchased as HPLC grade and used without further purification. n-Butyllithium was titrated against diphenylacetic acid before use. All other reagents were purchased from Aldrich Chemical Company and used as received.

Only diagnostic absorptions in the infrared spectrum are reported. NMR spectra were recorded in CDC13, unless otherwise noted, using a JEOL Eclipse 400+ FT-NMR spectrometer. Elemental analyses were performed at Atlantic Microlabs in Norcross, GA. All air-sensitive reactions were performed under N2 atmosphere. Column chromatography was carried out using SilicaFlash P60 silica gel (40–63 μm) purchased from Silicycle.

(E)-3,7-Dimethyl-8-oxooct-6-ynyl Acetate (4)

To a stirred suspension of 5 wt% SeO2 on silica (15.0 g, 6.75 mmol) in CH2Cl2 (135 mL) was added aq 70 wt% tBuOOH (4.9 mL, 34.1 mmol) as a bolus followed by a solution of citronellyl acetate (3.0 mL, 2.7 g, 13.5 mmol) in CH2Cl2 (12.5 mL) added over a period of 15 min. The resulting suspension was stirred vigorously open to the atmosphere for 24 h, and then filtered through a frit. The filtrate was concentrated in vacuo to yield a yellow oil (3.58 g), which was purified by Kugelrohr distillation (130 °C oven temperature/2 Torr) to afford aldehyde at 2.86 g, 60%) as a pale yellow oil comprised of a 96:4 mixture of E- and Z-isomers. The E-isomer can be isolated using column chromatography (30% Et2O/hexane) to give analytically pure material with spectroscopic data identical to those reported in the literature.

(E)-3,7-Dimethyl-8-oxooct-6-ynyl Acetate (5)

To a stirred suspension of MePPh3Br (3.74 g, 10.5 mmol) in anhyd THF (85 mL) at 0 °C was added dropwise 1.5 M n-ButLi in hexanes (0.8 mL, 10.2 mmol), whereupon the contents immediately turned yellow. The mixture was warmed to 0 °C and allowed to stir for 2.5 h, after which it was transferred dropwise via syringe to a solution of (E)-3,7-dimethyl-8-oxooct-6-ynyl acetate (4, 1.76 g, 8.29 mmol) in anhyd THF (75 mL) at −78 °C. The cooling bath was removed and the yellow solution was stirred at r.t. overnight. The solvent was removed in vacuo, and the resulting oil was passed through a small silica plug (ca. 3 in), eluting with Et2O (250 mL). The eluent was concentrated in vacuo to give an oil (1.62 g), which was purified by column chromatography (10% EtOAc/hexane) to afford diene as a colorless oil with spectroscopic data identical to those reported in the literature.

(E)-3,7-Dimethyl-6,8-dien-1-ol (6)

To a solution of dienyl acetate (1.26 g, 5.98 mmol) in HPLC grade MeOH (19 mL) was added K2CO3 (5.98 mmol). The reaction mixture was stirred at −78 °C for 1 h. Citronellal (85 mL) at 0 °C was added dropwise 1.5 M n-ButLi (2.8 mL, 6.2 mmol) and allowed to stir for 25 min with stirring, after which the mixture was cooled, hexanes (120 mL) were added, and the organics were washed with sat. NaHCO3/brine (5 × 120 mL). The organic layer was dried (Na2SO4), and concentrated in vacuo to provide alcohol (1.00 g, quant.) as a pale straw-colored oil, which was immediately used in the next step without further purification. Spectroscopic data were identical to those reported in the literature.

(E)-3,7-Dimethyl-6,8-dien-1-one (7)

To a solution of dienol (257 mg, 1.53 mmol) and BHT (33.8 mg, 0.15 mmol) in n-ButOH (23 mL) was added stabilized 2-iodoxybenzoic acid (45 wt%, 1.9059 g, 3.06 mmol). The suspension was heated at reflux for 25 min with stirring, after which the mixture was cooled, hexanes (120 mL) were added, and the organics were washed with sat. NaHCO3/brine (5 × 120 mL). The organic layer was dried (Na2SO4), and concentrated in vacuo to provide an oil (289 mg) containing product (754 mg, 99.6%), as well as residual BHT, which was used immediately in the next step. A sample purified by chromatography (5% EtOAc/hexanes) yielded analytically pure material with spectroscopic data identical to those reported in the literature.

4-Hydroxy-6,10-dimethylundec-9-en-2-one (9)

A solution of i-Pr2NH (0.87 ml, 6.2 mmol) in THF (6.0 mL) at −78 °C was treated with 2.2 M n-ButLi (2.8 mL, 6.2 mmol) and allowed to stir at −78 °C for 10 min. A solution of HPLC grade acetone (0.39 mL, 5.2 mmol) in THF (0.8 mL) was added to the LDA thus formed, and the solution was stirred at −78 °C for 1 h. Citronellal (8, 0.864 ml, 4.8 mmol) in THF (1.0 mL) was then added over a period of 15 min. The mixture was stirred for an additional 12 min at −78 °C, quenched by the addition of sat. aq NH4Cl (3 mL) and partitioned between sat. aq NH4Cl (40 mL) and Et2O (2 × 30 mL). The combined organic extracts were washed with brine (2 ×), dried (Na2SO4), and concentrated in vacuo to give an oil, which was purified by column chromatography...
(30% EtOAc/hexane) to afford product 9 (678 mg, 63%) as a straw-colored oil with spectroscopic properties identical to those reported in the literature.21

(E)-4-Hydroxy-6,10-dimyldodeca-9,11-dien-2-one (10)

A solution of 1-Pr₂NH (0.87 mL, 6.2 mmol) in THF (6.0 mL) at –78 °C was treated with 2.2 M i-Pr₂Li (2.8 mL, 5.6 mmol) and allowed to stir at –78 °C for 10 min. A solution of HPLC grade aceton (0.39 mL, 5.2 mmol) in THF (0.8 mL) was added to the LDA thus formed, and the solution was stirred at –78 °C for 1 h. Unpurified dienal was treated with 2.2 M MeOH (1 ml, 22 mmol), and the mixture was stirred for an additional 12 min at –78 °C, quenched by the addition of sat. aq NH₄Cl (3 mL), and partitioned between sat. aq NH₄Cl (40 mL) and Et₂O (2 × 30 mL). The combined organic extracts were washed with brine (2 × 50 mL), dried (Na₂SO₄), and concentrated in vacuo to give an oil, which was purified by column chromatography (30% EtOAc/hexane) to afford product 10 (708 mg, 66%) as a clear oil (mixture of diastereomers).

IR (neat, NaCl): 3436, 3088, 2925, 1713 cm⁻¹.

1H NMR (CDCl₃, 400 MHz): δ = 6.85 (d, J = 7.3 Hz, 1 H), 5.06 (d, J = 17.4, 10.7 Hz, 1 H), 4.91 (d, J = 10.7, 2.9 Hz, 1 H), 2.66–2.55 (m, 1 H), 2.55–2.44 (m, 1 H), 2.17 (s, 3 H), 2.23–2.01 (m, 2 H), 1.73 (m, 3 H), 1.65–1.00 (m, 5 H), 0.92 (d, J = 6.6 Hz, 3 H), 4.22–4.06 (m, 1 H), 2.66–2.55 (m, 1 H), 2.55–2.44 (m, 1 H), 2.17 (s, 3 H), 2.23–2.01 (m, 2 H), 1.73 (m, 3 H), 1.65–1.00 (m, 5 H), 0.92 (d, J = 6.6 Hz, 3 H).

13C NMR (CDCl₃, 100 MHz): δ = 210.1, 141.7, 134.0, 133.9, 133.3, 110.6, 110.5, 65.3, 65.3, 50.8, 50.2, 43.7, 37.4, 36.3, 30.9, 29.1, 28.8, 25.8, 25.6, 20.1, 19.1, 11.8, 11.7.


(E)-6,10-Dimyldodeca-9,11-dien-2,4-dione (2)

Dienone 10 (645 mg, 2.87 mmol) and BHT (164 mg, 0.29 mmol) were dissolved in HPLC grade EtOAc (25 mL). To the solution was added stabilized 2-iodoxybenzoic acid (45 wt%, 5.356 g, 8.61 mmol). The mixture was stirred at reflux for 50 min with stirring, after which the mixture was cooled to r.t. and hexanes (323 mL) was added. The suspension was heated at reflux for 50 min with stirring, after which the mixture was cooled to r.t., treated with 2.2 M NaOMe solution (3.6 mL, 66%) and BHT (41.9 mg, 0.19 mmol) was dissolved in anhyd MeOH (8.5 mL). The solution was cooled to 0 °C and treated dropwise with 0.5 M NaOMe solution (3.6 mL, 1.8 mmol). The solution was stirred for an additional 20 min at rt., cooled again to 0 °C, after which 2,3-dibromo-1-(phenylsulfonyl)prop-1-ene (555.9 mg, 1.64 mmol) was added in one portion. The mixture was stirred at r.t. for 2.5 h, cooled to 0 °C, and treated with a second portion of 0.5 M NaOMe solution (3.9 mL, 1.95 mmol). After stirring for 16 h at r.t., the reaction was quenched with sat. NH₄Cl (6 mL). MeOH was removed in vacuo and the mixture was poured into sat. NH₄Cl (35 mL), extracted with CH₂Cl₂ (3 × 15 mL), washed with water (60 mL), and dried (Na₂SO₄). The organic layers were concentrated in vacuo to provide an oil (713 mg), which was purified by column chromatography (15% EtOAc/hexane) to afford phenylsulfonylmethylene furan 11 (376 mg, 59% from 10) as a light yellow oil.

IR (neat, NaCl): 2957, 2925, 1607, 1458, 1382, 1285, 1240, 990, 843, 777 cm⁻¹.

1H NMR (CDCl₃, 400 MHz): δ = 7.77–7.69 (m, 2 H), 7.65–7.56 (m, 1 H), 7.47 (t, J = 7.8 Hz, 2 H), 7.05 (d, J = 17.4, 10.7 Hz, 1 H), 5.88 (s, 1 H), 5.44 (t, J = 7.3 Hz, 1 H), 5.08 (d, J = 17.5 Hz, 1 H), 4.93 (d, J = 10.7 Hz, 1 H), 4.13 (s, 2 H), 2.54 (dd, J = 14.9, 6.0 Hz, 1 H), 2.38 (dd, J = 14.8, 7.7 Hz, 2 H), 2.24–2.04 (m, 2 H), 1.83–1.72 (m, 1 H), 1.73 (d, J = 1.2 Hz, 3 H), 1.45–1.30 (m, 1 H), 1.28–1.13 (m, 1 H), 0.86 (d, J = 6.7 Hz, 3 H).

13C NMR (CDCl₃, 100 MHz): δ = 156.4, 141.6, 141.2, 137.9, 134.1, 133.8, 133.0, 129.0, 128.7, 113.1, 110.7, 108.0, 53.7, 36.1, 35.3, 32.3, 25.8, 19.5, 11.8.


(E)-2-(2,6-Dimyldoctylocta-5,7-dienyl)-4-furoic Acid (1)

To a solution of furan 9 (173.2 mg, 0.48 mmol) in anhyd THF (5.7 mL) cooled to –78 °C was added dropwise 0.5 M KHMDOS in toluene (2.4 mL). The solution was stirred for 45 min at –78 °C and thereafter sparged with dry air through a 22-gauge needle for 2.5 h. The solution was warmed to r.t. and quenched with sat. NH₄Cl (5 mL), diluted with Et₂O (40 mL), and washed with 0.1 M HCl (2 × 40 mL). The organic phase was dried (Na₂SO₄) and concentrated in vacuo to afford an oil, which was purified using column chromatography (10% MeOH/CH₂Cl₂) to afford natural product 1 (59.1 mg, 50%) as a light straw-colored oil with spectroscopic properties identical to those reported in the literature.

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Supporting Information

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