A New Synthetic Strategy towards Bioactive Merosesquiterpenoids

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Abstract: The Diels–Alder cycloaddition of the labdane diene methyl trans-communate with various representative dienophiles has been studied. Based on this, a novel strategy for synthesizing bioactive merosesquiterpenes is reported. This methodology affords considerable atom and step economy and makes it feasible to prepare A-ring functionalised compounds. A study on the synthesis of the fungitoxic pycnanthuquinone C has been carried out.

Key words: Diels–Alder reactions, esters, natural products, quinones, terpenoids

Natural products of mixed biosynthetic origin (polyketide-terpenoid) containing a sesquiterpene unit joined to a phenolic or quinone moiety are generally named ‘merosesquiterpenes’.1 Among these substances, which include both marine and terrestrial fungal metabolites, special attention should be paid to those bearing a bicyclic terpene (drimane) moiety, because of the important pharmacological properties most of them exhibit. Representative examples shown in Figure 1 include the cholesteryl ester transfer protein (CETP) inhibitors wiedendiol A (1) and wiedendiol B (2),2 the antibacterial hongoquerin A (3),3 and the antileukemic and antiinflammatory pelorol (4).4

More recently, merosesquiterpenoids with different functionalities on the C-4 of the drimane moiety have been reported. In this respect, we might cite the 15-human lipoxygenase (15-HLO) inhibitor jaspic acid (5), found in the Papua New Guinea marine sponge Jaspis cf. johnstoni,5 the antileishmanial disulfated meroterpenoid ilhabrene (6), isolated from the Brazilian marine sponge Callyspongia sp.,6 and the fungitoxic terpenoid-quinone pycnanthuquinone C (7), obtained from Pycnanthus angolensis (Welw.).7

The relevant biological properties and the natural scarcity of these metabolites have prompted chemists to investigate their synthesis. In general, two different strategies have been utilized to achieve merosesquiterpenes: (a) the biomimetic cyclization of farnesylphenols, as used by Ishibashi et al.,8 for the synthesis of wiedendiol A (1), and (b) a two-synthon strategy, which usually involves the reaction of a drimane electrophile with a nucleophilic phenol derivative (Scheme 1). Of these, the two-synthon strategy has been the most frequently employed; thus, syntheses of 1–3, and related compounds, utilizing this process have been reported.9 Very recently, an alternative strategy for preparing tetracyclic metabolites, with a benzopyran fragment such as that presented by compound 3, was reported by us. The key step is the Diels–Alder cycloaddition of a C19 dienol ether, derived from sclareol oxide, with a suitable dienophile.10

The preceding methodologies have some drawbacks. In the two general strategies mentioned above, a nucleophilic aromatic synthon must be utilized, which prevents the straightforward access to compounds bearing electrophilic groups (COOR, COR and CN) in the phenolic moiety, for example the immediate precursors of metabolites 3–5. Moreover, the two-synthon strategy involves the use of a drimane electrophile, which is usually prepared in a multistep synthetic sequence from a labdane diterpene.

Figure 1 Some representative bioactive merosesquiterpenes and derivatives
Table 1  Diels–Alder Cycloaddition of Ester 8b with Various Dienophiles; Cycloadducts and Aromatic Derivatives

<table>
<thead>
<tr>
<th>Entry</th>
<th>Dienophile</th>
<th>Reaction conditions</th>
<th>Product (Yield, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>ClCN</td>
<td>toluene, reflux, 48 h</td>
<td>9 (88%)</td>
</tr>
<tr>
<td>2</td>
<td>PhO&lt;sub&gt;2&lt;/sub&gt;S = SO&lt;sub&gt;2&lt;/sub&gt;Ph</td>
<td>DMF, reflux, 3 h DMF, reflux, 3 d</td>
<td>10 (85%)&lt;sup&gt;a&lt;/sup&gt; (80)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>3</td>
<td>COOMe</td>
<td>xylene, reflux, 12 h</td>
<td>11a (94%, 1:1)&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>4</td>
<td>MeOOC  = = = COOMe</td>
<td>xylene, reflux, 6 h</td>
<td>12 (95%)&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>toluene, reflux, 4 h</td>
<td>13 (71%)&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>toluene, reflux, 4 h</td>
<td>14a (68%, 1:1)&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
</tbody>
</table>
Continuing our research into the synthesis of bioactive merosesquiterpenes from abundant natural terpenoids, we planned a novel strategy to achieve these compounds, avoiding the aforementioned drawbacks. Under this approach, the aromatic ring of the target compound is formed through the Diels–Alder cycloaddition of a suitable labdane diene, such as methyl trans-communate (8b) (see scheme on Table 1). In this way, the merosesquiterpene carbon skeleton is formed in a single step; after aromatization, the appropriate transformation of the ester, X, Y and methyl groups and, if necessary, the electrophilic substitution on the aromatic ring will provide the final compound. This new methodology, besides involving considerable atom- and step-economy, enables direct access to compounds with electrophilic groups in the benzene ring and, furthermore, makes feasible the synthesis of A-ring-functionalised compounds, such as the natural products 4–7, or others similar to those isolated from natural sources (e.g., compounds 1–3) bearing a functional group on the A ring, which could exhibit interesting biological activities.

Bearing this synthetic strategy in mind, we studied the behaviour of the methyl ester 8b towards some representative dienophiles (Table 1). Treatment with 2-chloro-2-propenenitrile, under the described conditions, afforded a chloronitrile 9 as a 4:1 mixture of C-1 epimers, in high yield; it is noteworthy that this cycloadduct was obtained with complete regioselectivity.

The reaction of diene 8b with the other dienophiles led to mixtures of stereoisomer cycloadducts, which were characterized after aromatization under different conditions. The treatment of ester 8b with trans-1,2-bis(phenylsulfonyl)ethylene in DMF under reflux for three hours gave a mixture of adducts, which was transformed into the phenyl derivative 10 after refluxing with 6% sodium amalgam in ethanol for two hours; compound 10 was also

Table 1  Diels–Alder Cycloaddition of Ester 8b with Various Dienophiles; Cycloadducts and Aromatic Derivatives (continued)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Dienophile</th>
<th>Reaction conditions</th>
<th>Product (Yield, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td></td>
<td>toluene, 90 °C, 8 h</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td></td>
<td>toluene, reflux, 4.5 h</td>
<td></td>
</tr>
</tbody>
</table>

a Obtained after treatment of adducts with 6% Na–Hg in EtOH under reflux for 2 h.
b After prolonged reaction time.
c After treatment with DDQ (1.1 equiv) in dioxane at reflux.
d With further treatment with DDQ (2.2 equiv) in refluxing dioxane.

Scheme 1  Synthetic strategies towards merosesquiterpenes
obtained when the reaction was prolonged for three days (entry 2).

Methyl ester 8b also underwent Diels–Alder cycloaddition with methyl propiolate and dimethyl acetylenedicarboxylate by refluxing in toluene or xylene; the aromatization of adducts was accomplished by refluxing with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ; 1.1 equiv) in dioxane (entries 3–4). Compounds 11a and 11b were separated by selective reaction of the latter with methyl propiolate and dimethyl acetylenedicarboxylate by refluxing in toluene at 90 °C for eight hours (entry 7). The compounds obtained when the reaction was prolonged for three days (entry 2).

The behaviour of diene 8b towards different 1,4-benzoquinone derivatives was also studied (entries 5–8, Table 1). The resulting mixture of cycloadducts was characterized after dehydrogenation by treatment with 2.2 equivalents of DDQ in refluxing dioxane; in this way, naphthoquinones 13–16 were obtained in good yields. The cycloaddition with commercial 2-methyl-1,4-benzoquinone was not regioselective, affording a 1:1 mixture of quinones 14a,b (entry 6). However, surprisingly, the reaction with 2-methoxy-1,4-benzoquinone took place with complete regioselectivity under controlled conditions; the regioisomer 15a was the only product obtained after reaction in toluene at 90 °C for eight hours (entry 7). The structure of this compound was established on the basis of an INADEQUATE NMR experiment. This behaviour could probably be attributed to electronic effects. The 6′-OMe regioisomer (15b) was also obtained in variable proportions when the reaction was carried out at higher temperatures. Finally, 2-methyl-3-methoxy-1,4-benzoquinone was utilized as the dienophile; in this case, a 1:1 mixture of regioisomers 16a,b resulted (entry 8).

α-Chloronitrile 9 was easily transformed into the aromatic nitrile 17 after dehydrohalogenation by treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in refluxing benzene and subsequent aromatization with DDQ in dioxane under reflux. Alternatively, chloronitrile 9 was converted into the corresponding α,β-unsaturated ketone 18 by refluxing with potassium hydroxide in tert-butanol; all attempts to transform this ketone into the phenol derivative were unsuccessful; however, salicylate 19 resulted after methoxycarbonylation and further aromatization (Scheme 2).

The aromatic derivatives 10–12 and 17–19, obtained after 1–3 steps from the easily accessible trans-communic acid (8a), are suitable intermediates for the synthesis of bioactive A-ring-functionalised merosequiterpenoids, such as compounds 5 and 6.

On the other hand, compound 16a is the dimethyl derivative of 1-epipycnanthuquinone, which means that the natural fungitoxic 7 could be synthesized through the Diels–Alder process reported here utilizing trans-oxic acid, the 4-epimer of trans-communic acid (8a), as the diene. However, the results of our study reveal that the synthesis of this metabolite would be addressed through the reaction with 2-methoxy-1,4-benzoquinone (see entry 7), with the further introduction of a methyl group. The last steps in this synthetic study towards the natural pycnanthuquinone C (7) must involve the demethylation of the corresponding dimethyl derivative, such as compound 16a. This transformation was studied utilizing the pure regioisomer 15a as a model (Scheme 3). The treatment of this compound with methanolic potassium hydroxide at room temperature for 12 hours gave the hydroxy derivative 20 in 95% yield. The hydroxy ester 20 was transformed into acid 21 by reaction with sodium ethanethiolate (NaSEt) in DMF at 60 °C for 12 hours. Under similar conditions, the mixture of regioisomers 16a–b was converted into the 1-epimer of pycnanthuquinone C (7) and its regioisomer.

Scheme 2 Transformation of chloronitrile 9 into aromatic derivatives

Scheme 3 Demethylation of quinone 15a
In summary, a new synthetic strategy towards bioactive merosesquiterpenes, based on the Diels–Alder cycloaddition of the methyl ester of trans-communic acid (8b), has been developed. This new methodology affords significant atom- and step-economy and makes it possible to synthesize A-ring-functionalised compounds. A study on the synthesis of fungitoxic pycnanthuquinone C (7), utilizing 8b as a model, has been carried out.

\[ ^1H \text{ and } ^13C \text{ NMR spectra were recorded on Varian 400 and } 500 \text{ spectrometers. IR spectra were obtained using Perkin-Elmer Spectru} \]

\[ \text{mum to give a crude product which was dissolved in Et}_2\text{O (30 mL), stirred at reflux for 12–15 h. The solvent was removed under vacu} \]

\[ \text{Dehydrogenation Reaction; General Procedure} \]

\[ \text{To a stirred solution of methyl trans-communate (8b; 1 mmol, 316 mg) in either toluene or xylene (8 mL), was added the appropriate dienophile (2 mmol) and the mixture was stirred at reflux for the specified time (monitored by TLC). The solvent was removed under vacuum and the crude product was either used directly or purified by column chromatography to provide the desired adduct.} \]

\[ \text{Diels–Alder Reaction; General Procedure} \]

\[ \text{To a solution of the crude adduct (1 mmol) in dioxane (10 mL), was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (1.1 mmol or 2.2 mmol, as indicated in each case) and the reaction mixture was stirred at reflux for 12–15 h. The solvent was removed under vacuum and the crude product was extracted with Et}_2\text{O (2 mL) and brine (2 × 15 mL)), and the organic layer was dried over anhyd Na}_2\text{SO}_4, \text{filtered and concentrated to afford the crude product.} \]

\[ \text{1H NMR (400 MHz, CDCl}_3): \delta = 0.48 (s, 3 H), 1.04 (ddd, } J = 13.4, 13.4, 4.0 \text{ Hz, 1 H), 1.12 (s, 3 H), 1.70 (s, 3 H), 1.18–1.42 (m, 16 H), 2.45 (br d, } J = 10.9 \text{ Hz, 1 H), 2.62 (dd, } J = 9.2, 2.8 \text{ Hz, 1 H), 3.55 (s, 3 H), 4.52 (s, 1 H), 4.57 (s, 1 H), 5.36 (br s, 1 H).} \]

\[ \text{13C NMR (100 MHz, CDCl}_3): \delta = 12.3 (\text{CH}_3), 20.1 (\text{CH}_3), 22.3 (\text{CH}_3), 23.1 (\text{CH}_3), 26.5 (\text{CH}_3), 27.5 (\text{CH}_3), 28.8 (\text{CH}_3), 33.5 (\text{CH}_3), 38.2 (\text{CH}_3), 38.7 (\text{CH}_3), 41.0 (C), 44.5 (C), 47.5 (CH), 51.2 (CH), 52.6 (CH), 56.5 (CH), 59.9 (C), 106.9 (CH), 119.8 (C), 121.0 (CH), 122.1 (C), 133.5 (C), 148.5 (C), 178.1 (C).} \]

\[ \text{HRMS (FAB): } \text{m/z calcd for C}_3\text{H}_7\text{SNO}_2\text{Na: 426.2176; found: 426.2184.} \]

\[ \text{Methyl (1S,4aR,5S)-1,4a-Dimethyl-5-(2-methylbenzyl)-6-methylenedecahydronaphthalene-1-carboxylate (10)} \]

\[ \text{To a solution of 8b (1 g, 3.16 mmol) in DMP (25 mL), was added (E)-1,2-bis(phenylsulfonyl)ethene (1.3 g, 4.22 mmol) and the reaction mixture was stirred at reflux for 3 h, at which time TLC showed no starting material remained. The mixture was warmed to r.t., then diluted with Et}_2\text{O (30 mL) and washed with H}_2\text{O (3 × 10 mL)) and brine (3 × 10 mL). The organic layer was dried over anhyd Na}_2\text{SO}_4, \text{filtered and concentrated to afford the crude adduct (2.2 g).} \]

\[ \text{Yield: 0.91 g (85%); colourless oil; } [\theta]_D^{25} = 44.7 (c 1.36, CHCl}_3). \]

\[ \text{IR (film): 1724, 1645, 1604, 1449, 1383, 1311, 1227, 1154, 1092, 1031, 987, 888, 804, 820, 738 cm}^{-1}. \]

\[ \text{HRMS (FAB): } \text{m/z calcd for C}_{23}\text{H}_{32}\text{O}_2\text{Na: 363.2300; found: 363.2300.} \]

\[ \text{Methyl (1S,4aR,5S)-5-(2-Methoxy carbonyl)-6-methylbenzyl]-1,4a-dimethyl-6-methylenedecahydronaphthalene-1-carboxylate (11a) and Methyl (1S,4aR,5S)-5-(5-Methoxy carbonyl)-2-methylbenzyl]-1,4a-dimethyl-6-methylenedecahydronaphthalene-1-carboxylate (11b)} \]

\[ \text{Following the general procedure described for the Diels–Alder reaction, utilizing diene 8b (5 g, 15.8 mmol) and methyl propiolate (2.66 g, 31.6 mmol), the crude product (6.8 g) was obtained, which was used in the next step without purification.} \]

\[ \text{The crude adduct was treated following the general procedure described for the dehydrogenation reaction, utilizing DDQ (1.1 equiv). The crude product was purified by column chromatography (Et}_2\text{O-hexanes, 10%) to provide a 1:1 mixture of 11a and 11b.} \]

\[ \text{Yield: 5.91 g (94%); yellow syrup.} \]

\[ \text{Compound 11a was isolated unreacted after treatment of the mixture with MeMgBr as follows: To a solution of the above mixture (1.2 g, 3.0 mmol) in anhyd Et}_2\text{O (30 mL) was added, dropwise, a solution of MeMgBr (5 mL, 7 mmol, 1.4 M solution in toluene–THF) at 0 °C. The mixture was stirred under an argon atmosphere for 1 h. HCl (2 N, 2 mL) was added slowly to the mixture cooled to 0 °C, which was extracted with Et}_2\text{O (2 × 20 mL). The combined organic layers were washed with H}_2\text{O (3 × 15 mL)) and brine (3 × 15 mL), dried over anhyd Na}_2\text{SO}_4, \text{and concentrated under vacuum. Purification by silica gel column chromatography (Et}_2\text{O-hexanes, 10%) gave 11a.} \]

\[ \text{Yield: 0.52 g (43%); } [\theta]_D^{25} = -21.9 (c 1.0, CHCl}_3). \]

\[ \text{IR (film): 1723, 1646, 1436, 1384, 1278, 1226, 1012, 1104, 1164, 1122, 1092, 981, 884, 806, 820, 738 cm}^{-1}. \]
Dimethyl 3-[[15(S),8aR]-5-(Methoxycarbonyl)-5,8a-dimethyl-2-methylene decahydronaphthalen-1-yl]methyl-4-methyldicarboxylate (12)

Following the general procedure described for the Diels–Alder reaction, utilizing diene 8b (370 mg, 1.17 mmol) and dimethyl acetylenedicarboxylate (272 mg, 2.35 mmol), the crude product (0.6 g) was obtained, which was used in the next step without purification.

The crude adduct was treated according to the general procedure described for the dehydrogenation reaction, using DDQ (1.1 equiv). The resulting crude product was purified by column chromatography (Et2O–hexanes, 35%) to provide 12.

**Yield:** 507 mg (95%); colourless syrup; [α]25D = −16.6 (c 1.0, CHCl3).

**IR (film):** 1725, 1660, 1615, 1580, 1466, 1368, 1220, 1080, 1028, 1015, 966, 883, 835, 755 cm−1.

**HRMS (FAB):** m/z calcd for C29H30O4Na: 479.2410; found: 479.2413.

**Methyl (1S,4aR,5S)-1,4a-Dimethyl-5-[(2-methyl-5,8-dioxo-5,8-dihydronaphthalen-1-yl)methyl]-6-methylene decahydronaphthalene-1-carboxylate (13)**

Following the general procedure described for the Diels–Alder reaction, utilizing diene 8b (1.0 g, 3.16 mmol) and 1,4-benzoquinone (683 mg, 3.62 mmol), the crude product (1.35 g) was obtained, which was used in the next step without purification.

The above crude product was treated following the general procedure described for the dehydrogenation reaction, using DDQ (2.2 equiv). Flash chromatography on silica gel (Et2O–hexanes, 15%) of the resulting crude material gave 13.

**Yield:** 0.94 g (71%); yellow syrup.

**IR (film):** 1723, 1658, 1617, 1578, 1463, 1369, 1311, 1226, 1155, 1075, 1031, 886, 804, 757, 666 cm−1.

**1H NMR (500 MHz, CDCl3):** δ = 0.66 (s, 3 H), 0.87 (ddd, J = 13.5, 13.5, 4.3 Hz, 1 H), 0.98 (ddd, J = 13.4, 13.4, 4.0 Hz, 1 H), 1.14 (s, 3 H), 1.27 (dd, J = 12.1, 2.8 Hz, 1 H), 1.37 (m, 1 H), 1.53 (br d, J = 13.0, 1 H), 1.72–2.00 (m, 4 H), 2.06 (t, J = 6.6 Hz, 1 H), 2.10 (br d, J = 13.4 Hz, 1 H), 2.34 (dt, J = 12.0, 3.4 Hz, 1 H), 2.38 (s, 3 H), 3.13 (d, J = 7.5 Hz, 2 H), 3.61 (s, 3 H), 3.85 (s, 3 H), 4.50 (s, 1 H), 4.66 (s, 1 H), 7.08 (dd, J = 7.5, 7.2 Hz, 1 H), 7.20 (d, J = 7.2 Hz, 1 H), 7.44 (d, J = 7.5 Hz, 1 H).

**13C NMR (125 MHz, CDCl3):** δ = 127.8 (CH), 21.3 (CH3), 26.2 (CH2), 29.1 (CH), 38.3 (CH3), 39.0 (CH), 39.3 (CH), 41.7 (C), 44.5 (C), 51.3 (CH2), 52.3 (CH2), 56.8 (CH), 56.9 (CH), 107.1 (CH), 125.3 (CH), 127.8 (CH), 132.3 (C), 133.7 (CH3), 137.6 (C), 140.5 (C), 149.6 (C), 170.8 (C), 177.6 (C).

**HRMS (FAB):** m/z calcd for C29H30O4Na: 479.2410; found: 479.2413.

**Methyl (1S,4aR,5S)-5-[(2,7-Dimethyl-5,8-dioxo-5,8-dihydronaphthalen-1-yl)methyl]-1,4a-dimethyl-6-methylene decahydronaphthalene-1-carboxylate (14a)**

Following the general procedure described for the Diels–Alder reaction, utilizing diene 8b (540 mg, 1.71 mmol) and 2-methyl-1,4-benzoquinone (415 mg, 3.4 mmol), a crude product (620 mg) was obtained, which was used in the next step without purification.

The crude material was treated following the general procedure described for the dehydrogenation reaction, utilizing DDQ (2.2 equiv). The resulting crude product was purified by column chromatography (Et2O–hexanes, 20%) to provide an unsolvable 1:1 mixture of compounds 14a and 14b.

**Yield:** 505 mg (68%); colourless oil.

**IR (film):** 1725, 1660, 1615, 1580, 1466, 1368, 1220, 1080, 1028, 799, 750, 658 cm−1.

**1H NMR (500 MHz, CDCl3):** δ (selected data for the mixture) = 0.71 (s, 3 H), 1.14 (s, 3 H), 1.25 (s, 3 H), 2.12 (s, 3 H), 2.16 (s, 3 H), 2.46 (s, 3 H), 3.42 (dd, J = 14.6, 6.8 Hz, 1 H), 3.44 (dd, J = 14.6, 6.4 Hz, 1 H), 3.61 (s, 3 H), 4.75 (s, 1 H), 4.78 (s, 1 H), 6.71 (s, 1 H), 6.73 (s, 1 H), 7.40 (d, J = 7.9 Hz, 1 H), 7.82 (d, J = 7.8 Hz, 1 H), 7.89 (d, J = 7.8 Hz, 1 H).

**13C NMR (125 MHz, CDCl3):** δ (selected signals for the mixture) = 11.6 (CH3), 14.6 (CH3), 16.1 (CH), 18.9 (CH), 20.8 (CH), 27.8 (CH), 37.1 (CH3), 37.5 (CH2), 37.6 (CH3), 40.6 (C), 43.3 (C), 50.1 (CH), 55.4 (CH), 55.6 (CH2), 105.9 (CH3), 123.2 (CH), 123.1 (CH), 132.6 (CH), 133.9 (CH), 136.7 (C), 143.6 (C), 143.8 (C), 144.3 (C), 148.9 (C), 149.0 (C), 176.0 (C), 181.4 (C), 184.9 (C), 187.1 (C), 188.3 (C).

**HRMS (FAB):** m/z calcd for C29H31O4Na: 457.2355; found: 457.2339.

**Methyl (1S,4aR,5S)-5-[(7-Methoxy-2-methyl-5,8-dioxo-5,8-dihydronaphthalen-1-yl)methyl]-1,4a-dimethyl-6-methylene decahydronaphthalene-1-carboxylate (15a)**

Following the general procedure described for the Diels–Alder reaction, utilizing diene 8b (0.6 g, 1.9 mmol) and 2-methoxy-1,4-benzoquinone (525 mg, 3.8 mmol), a crude product (1.1 g) was obtained, which was used in the next step without purification.

The crude material was treated following the general procedure described for the dehydrogenation reaction, utilizing DDQ (2.2 equiv). The resulting crude product was purified by column chromatography (Et2O–hexanes, 25%) to provide 15a.

**Yield:** 0.77 g (89%); yellow syrup.

**IR (film):** 1722, 1676, 1649, 1621, 1569, 1460, 1239, 1210, 1155, 1081, 883, 835, 755 cm−1.
Methyl (1S,4aR,SS)-5-[7-Methoxy-2,6-dimethyl-5,8-dioxo-5,8-
dihydropthalen-1-yl)methyl]-1,4a-dimethyl-6-methylene-
decahydropthalene-1-carboxylate (16a) and Methyl (1S,4aR,SS)-5-[6-Methoxy-2,7-dimethyl-5,8-dioxo-5,8-
dihydropthalen-1-yl)methyl]-1,4a-dimethyl-6-methylene-
decahydropthalene-1-carboxylate (16b)

Following the general procedure described for the Diels–Alder reaction, utilizing diene 8b (675 mg, 2.13 mmol) and 2-methoxy-1-methyl-1-benzoxquinone (643 mg, 4.23 mmol), a crude product (0.85 g) was obtained, which was used in the next step without purification.

The above crude product was treated following the general procedure described for the dehydrogenation reaction, using DDQ (2.2 equiv). Flash chromatography on silica gel (Et2O–hexanes, 1:3) gave an unresolved 1:1 mixture of compounds 16a and 16b.

Yield: 672 mg (68%); yellow syrup.

IR (film): 1723, 1662, 1610, 1581, 1470, 1368, 1224, 1123, 1080, 1024, 801, 750 cm⁻¹.

1H NMR (500 MHz, CDCl₃): δ = 0.72 (s, 3 H), 0.92–1.04 (m, 2 H), 1.14 (s, 3 H), 1.29 (dd, J = 12.4, 3.3 Hz, 1 H), 1.37 (br d, J = 14.0 Hz, 1 H), 1.57 (br d, J = 13.0 Hz, 1 H), 1.73–1.98 (m, 4 H), 2.10 (br d, J = 13.4 Hz, 1 H), 2.17 (t, J = 6.6 Hz, 1 H), 2.30 (m, 1 H), 2.48 (s, 3 H), 3.39 (dd, J = 14.5, 7.0 Hz, 1 H), 3.53 (dd, J = 14.5, 6.6 Hz, 1 H), 3.61 (s, 3 H), 3.90 (s, 3 H), 4.36 (s, 1 H), 4.60 (s, 1 H), 6.06 (s, 1 H), 7.43 (d, J = 7.8 Hz, 1 H), 7.88 (d, J = 7.8 Hz, 1 H).

13C NMR (125 MHz, CDCl₃): δ = 12.6 (CH₂-C₆a), 19.8 (C-3), 21.8 (CH₂-C₇), 26.0 (C-8), 26.9 (CH₃-C₈), 28.8 (CH₂-C₉), 35.8 (C-7), 37.9 (C-2), 38.9 (C-4), 41.4 (C-4a), 44.2 (C-1), 51.0 (COOMe), 56.08 (C-8a), 56.12 (C-5), 56.4 (C-OMe), 107.7 (C=CH₂), 107.7 (C=CH₂), 124.2 (C-14), 129.6 (C-8a), 132.1 (C-1′a), 135.6 (C-3′), 144.3 (C-2′), 146.0 (C-1′), 149.5 (C-6), 161.1 (C-7), 177.4 (COOMe), 182.3 (C-3′), 184.7 (C-5′).

HRMS (FAB): m/z calcd for C₂₃H₂₃NO₃Na: 383.1582; found: 383.1584.

Methyl (1S,4aR,SS)-1,4a-Dimethyl-5-(2-Hydroxy-3-methoxycarbonyl)-6-methylenedeca-
hydropthalen-1-carboxylate (19)

KOH (2 g, 35.7 mmol) was added to solution of ketone 3 (2.25 g, 5.58 mmol) in i-BuOH (40 mL) and the reaction mixture was stirred under reflux for 3 h, at which time TLC showed the disappearance of compound 9. The mixture was poured into Et₂O–H₂O (30:1 mL), which was then extracted with CH₂Cl₂ (2 × 15 mL). The organic phase was washed with brine (2 × 10 mL), dried over anhyd Na₂SO₄ and the solvent was evaporated to give 18.

Yield: 1.65 g (82%); brown syrup; [α]D⁰ = –6.7 (c 1.3, CHCl₃).

IR (film): 1723, 1660, 1449, 1379, 1328, 1228, 1154, 1092, 1033, 985, 884, 808, 755, 666 cm⁻¹.

1H NMR (500 MHz, CDCl₃): δ = 0.57 (s, 3 H), 1.04 (dd, J = 13.4, 4.1 Hz, 1 H), 1.15 (s, 3 H), 1.26 (dd, J = 13.1, 13.1, 4.1 Hz, 1 H), 1.33 (dd, J = 12.2, 2.8 Hz, 1 H), 1.50 (m, 1 H), 1.70–1.90 (m, 7 H), 1.94 (s, 3 H), 2.10–2.18 (m, 2 H), 2.22–2.32 (m, 5 H), 2.42 (br d, J = 14.1, 3.8 Hz, 1 H), 2.51 (dd, J = 14.1, 9.4 Hz, 1 H), 3.59 (s, 3 H), 4.50 (s, 1 H), 4.70 (s, 1 H).

13C NMR (125 MHz, CDCl₃): δ = 12.5 (CH₃), 20.3 (CH₂), 21.0 (CH₂), 22.0 (CH₂), 22.2 (CH₂), 26.6 (CH₃), 29.1 (CH₃), 33.4 (CH₃), 38.4 (CH₃), 38.9 (CH₂), 39.0 (CH₁), 39.1 (CH₁), 41.2 (C), 44.5 (C), 51.3 (CH₂), 54.9 (CH₆), 107.0 (CH₆), 136.5 (C), 149.0 (C), 155.1 (C), 177.9 (C), 199.2 (C).


Methyl (1S,4aR,SS)-5-[2-Hydroxy-3-(methoxycarbonyl)-6-methylene]
-deca-
hydropthalen-1-carboxylate (19)

-n-BuLi (3.5 mL, 5.6 mmol) in hexanes was added to DIPA (0.8 mL, 5.69 mmol) in THF (20 mL) at ~78 °C under an argon atmosphere. The reaction mixture was stirred for 20 min, warmed to 0 °C and stirred for a further 5 min. The solution was cooled to ~78 °C and a solution of ketone 18 (1 g, 2.79 mmol) in THF (12 mL) was added. The reaction mixture was stirred for 30 min then a solution of methyl cyanoformate (0.25 mL, 3.15 mmol) in THF (8 mL) was added and the reaction was stirred for another 2 h. The reaction mixture was poured into H₂O (2 mL), extracted with Et₂O (3 × 20 mL) and the combined organic extracts were washed with HCl (2 N, 3 × 10 mL), H₂O (10 mL) and brine (10 mL), then dried over anhyd...
Na₂SO₄. Concentration under vacuo gave a crude product (1.2 g), which was used directly in the next step without further purification.

The crude β-ketoester was treated following the general procedure described for the dehydrogenation, using DDQ (2.2 equiv.). Flash chromatography on silica gel (Et₂O–hexanes, 15%) of the resulting crude material gave 19.

Yield: 1.04 g (90%); yellow syrup; [α]D25 –36.6 (c 1.3, CHCl₃).

IR (film): 3104, 1723, 1671, 1618, 1574, 1440, 1333, 1249, 1199, 1154, 1092, 1030, 948, 885, 757, 686 cm⁻¹.

1H NMR (500 MHz, CDCl₃): δ = 0.70 (s, 3 H), 1.03 (ddd, J = 13.2, 13.2, 4.0 Hz, 1 H), 1.13 (dd, J = 13.0, 13.0, 4.2 Hz, 1 H), 1.17 (s, 3 H), 1.37 (dd, J = 12.5, 2.9 Hz, 1 H), 1.45 (m, 1 H), 1.76–2.02 (m, 5 H), 2.14 (br, d, J = 13.5 Hz, 1 H), 2.34 (m, 1 H), 2.26 (s, 3 H), 2.54 (t, J = 6.7 Hz, 1 H), 2.87 (d, J = 7.4 Hz, 2 H), 3.63 (s, 3 H), 3.90 (s, 3 H), 4.73 (s, 1 H), 4.79 (s, 1 H), 7.52 (d, J = 8.1 Hz, 1 H), 7.50 (d, J = 8.1 Hz, 1 H), 11.26 (s, 1 H).

13C NMR (125 MHz, CDCl₃): δ = 125.8 (C₅), 20.3 (C₈), 21.5 (C₆), 22.7 (C₁₀), 26.7 (C₄a), 29.2 (C₂), 38.5 (C₈), 38.9 (C₈), 39.3 (C₉), 41.5 (C₄), 44.6 (C₄), 51.4 (C₄), 52.3 (C₇), 54.3 (C₃), 56.9 (CH₃), 107.0 (C₇a), 109.8 (C₁), 121.7 (C₁₂), 126.9 (C₁₀), 129.6 (C₉), 145.3 (C₅), 149.6 (C₆), 160.1 (C₁), 171.5 (C₄), 178.0 (C₃).

HRMS (FAB): m/z calculated for C₂₅H₅₅O₂Na: 437.2304; found: 437.2311.

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