Convenient synthesis of C75, an inhibitor of FAS and CPT1†

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A new approach to the enzyme inhibitor C75 and its temporary transformation into a phenylseleno ether derivative is disclosed. This procedure facilitates the purification, manipulation and storage of C75.
Abstract

C75 is a synthetic racemic $\alpha$-methylene-$\gamma$-butyrolactone exhibiting antitumoural properties \textit{in vitro} and \textit{in vivo} as well as to inducing hypophagia and weight loss in rodents. These interesting properties are thought to be a consequence of the inhibition of the key enzymes FAS and CPT1 in lipid metabolism. The need for larger amounts of this compound for biological evaluation prompted us to develop a convenient and reliable route to multigram quantities of C75 from easily available ethyl penta-3,4-dienoate 6. A recently described protocol for the addition of 6 to a mixture of dicyclohexylborane and nonanal followed by acidic treatment of the crude afforded lactone 8, as a mixture of \textit{cis} and \textit{trans} isomers, in good yield. The DBU-catalyzed isomerization of the methyl esters 9 arising from 8 gave a 10:1 \textit{trans/cis} mixture from which the \textit{trans} isomer was isolated and easily transformed into C75. The temporary transformation of C75 into a phenylseleno ether derivative makes its purification, manipulation and storage easier.

Introduction

C75 is a synthetic racemic compound that acts as a potent inhibitor of mammalian type I fatty acid synthase (type I FAS) and, in its CoA-adducted form, inhibits carnitine palmitoyltransferase 1 (CPT1) activity \textit{in vivo}. Over the last few years, C75 as a racemic mixture of its \textit{trans} diastereoisomers has been used extensively in the study of fatty acid synthesis in metabolic disorders and cancer.\textsuperscript{1}

In the course of our ongoing search for potential new drugs against obesity and type 2 diabetes,\textsuperscript{2} we required multigram quantities of racemic \textit{trans} C75 for biological testing and as starting material for the preparation of new analogues. Although C75 is commercially available, its very high price prompted us to consider the preparation of C75 in our own laboratory. Surprisingly, only one procedure for its preparation has been reported by Kuhajda \textit{et al}.\textsuperscript{3} This procedure was based on previous work\textsuperscript{4} by Carlson \textit{et al}. that uses itaconic anhydride and \textit{p}-methoxybenzyl alcohol as starting materials. Under these conditions C75 is obtained as a separable mixture of C75 and its \textit{cis} isomer 1. In our hands, the laborious column chromatography process required for this separation caused significant isomerization of the exocyclic double bond to the endocyclic position to give inactive
isomer 2 (Fig. 1). Herein, we proposed an alternative straightforward scalable method for the preparation of C75 and its separation from 1 and 2.

![Structures of C75 and compounds 1-3.](image)

**Figure 1.** Structures of C75 and compounds 1–3.

According to our retrosynthetic analysis of C75, the methylene group would be introduced in the last step from lactone *trans*-4 that would arise from the appropriate γ-hydroxyester *anti*-5 (Scheme 1). Taking advantage of our recent studies on the stereoselective addition of allenes to aldehydes,\(^5\) we envisaged that the hydroboration of ethyl penta-3,4-dienoate 6 with dicyclohexylborane in the presence of nonanal could afford the required *anti*-5.\(^6\)

Herein, we report our findings in this respect.

![Scheme 1. Retrosynthetic analysis of C75.](image)

**Scheme 1.** Retrosynthetic analysis of C75.

**Results and discussion**

The allylation and crotylation of aldehydes with 2-alkenyl boranes provide attractive and versatile routes to homoallylic secondary alcohols. 2-Alkenylides derived from alkali and alkaline earth metals generally serve as the starting points for the generation of 2-alkenyl boranes. However, hydroboration of allenes might be a milder alternative for obtaining such boron reagents. Initially, the borane adds to the sterically less hindered face of the allene to
form a transient \((Z)\)-2-alkenylborane. However, this kinetically formed borane reagent suffers fast isomerization to the thermodynamically more stable \((E)\)-2-alkenylborane at room temperature. The addition of an aldehyde to this then affords a \textit{syn} homoallylic alcohol as the major product, through a 6-membered transition state. Recently, we demonstrated that the hydroboration of the allene is also possible in the presence of the aldehyde.\textsuperscript{5b} In such conditions, the \((Z)\)-borane reagent can be trapped immediately by the aldehyde leading to \textit{anti} adducts. Accordingly, we expected that the treatment of a mixture of ethyl penta-3,4-dienoate 6 and nonanal with Chx\textsubscript{2}BH would lead to \textit{anti}-5 by trapping the transient \((Z)\)-2-alkenylborane, \((Z)\)-7 (Scheme 2). In contrast, the hydroboration of 6 with dicyclohexylborane (Chx\textsubscript{2}BH) followed by the addition of nonanal would afford selectively the \(\gamma\)-hydroxyester \textit{syn}-5.

\[\text{Scheme 2. Mechanism of hydroboration of 6 followed by nonanal addition.}\]

In practice, the addition of allene 6 to a mixture of Chx\textsubscript{2}BH (1.2 equiv) and nonanal (1.2 equiv) in CH\textsubscript{2}Cl\textsubscript{2} gave, after work-up (triethanolamine) and chromatographic separation, a separable mixture of hydroxyester \textit{syn}-5 and the lactone \textit{trans}-8 arising from \textit{anti}-5 but in a disappointing 6:4 ratio (Scheme 3). Apparently, the minor \textit{anti}-5 isomer formed suffers a selective lactonization during the work-up and/or chromatographic processes to give \textit{trans}-
The unexpected abundance of the syn isomer suggests that after the hydroboration step, isomerization of (Z)-7 to (E)-7 was faster than we expected. It is known that the allylic isomerization of the crottylboranes strongly depends on the steric hindrance of both allylic positions and the isomerization in (Z)-7 seems to be easier than in the more hindered protected allenols used in our previous work.\textsuperscript{5h} When we heated the mixture in MeOH to reflux with acid catalysis, only 8 was obtained in 68\% overall yield as a 6:4 cis/trans mixture that was difficult to separate. As expected, isolated syn-5 afforded only cis-8 under acidic conditions.

\textit{Scheme 3. One-pot synthesis of lactones 8}

In an effort to improve the proportion of trans-8, the experimental conditions were revised. Lower temperatures (0 °C or –20 °C) slowed down Z/E isomerization of 7 but hydroboration was incomplete and yields diminished. Neither changing the solvent (THF, Et\textsubscript{2}O), or work-up (triethanolamine or H\textsubscript{2}O\textsubscript{2}) nor a fine tuning of the allene/aldehyde/Chx\textsubscript{2}BH ratio were satisfactory. Consequently, we considered the use of more hindered hydroborating agents. Both (–)-Ipc\textsubscript{2}BH\textsuperscript{7} (Ipc = isopinocampheyl), and disiamylborane\textsuperscript{8} were tested since these bulky reagents are less prone to undergo boratropic isomerization providing a greater opportunity for trapping the Z reagent. Furthermore, by using an enantiopure boron reagent, the reaction could, in principle, become enantioselective. Unfortunately, neither of the reagents improved the trans-8/syn-5 ratio significantly but also led to lower yields (40-45\%). In addition, the GC analysis of the trans-8 obtained with (–)-Ipc\textsubscript{2}BH revealed low enantioselectivities (55:44 ratio).
On the other hand, when we performed the alternative stepwise process for comparative purposes, i.e. hydroboration of 6 (CH₂Cl₂ or THF) with (Chx)₂BH (1.2 equiv.) followed by addition of nonanal at –78 °C, only complex reaction mixtures containing compounds 5 or 8 in low yield (<15%) were obtained. These results are in sharp contrast with previous ones both from our laboratory⁵ and others⁹ in which terminal allenes undergo addition to aldehydes in good yields under similar conditions. Our results suggest that, although the starting allene readily disappeared in the hydroboration step (as observed by TLC), the resulting alkenylborane decomposed at 0 °C giving a mixture of by-products.¹⁰

Consequently, we turned our attention to the former one-pot hydroboration with Chx₂BH (Scheme 3). Having in hand the mixture of lactones 8, the oxidation¹¹ of the vinyl group was performed with NaIO₄/RuCl₃ to afford almost quantitatively a mixture of acids 4. Gratifyingly the transformation of 4 into methyl esters 9 allowed us to improve the diastereomeric ratio to 10:1 trans/cis by heating the mixture with DBU in dry toluene. The compound trans-9 was then easily isolated chromatographically and then hydrolyzed to obtain >95% stereopure trans-4.

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**Table 1.** Hydroboration-addition of 6 to nonanal by "one-pot" protocol.

<table>
<thead>
<tr>
<th>Entry</th>
<th>RJB-H (1.2 equiv.)</th>
<th>Solvent</th>
<th>T</th>
<th>Overall yield (%)</th>
<th>syn-5/ trans-8 ratio⁶</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(Chx)₂BH</td>
<td>CH₂Cl₂</td>
<td>0 °C</td>
<td>rt</td>
<td>71</td>
</tr>
<tr>
<td>2</td>
<td>(Chx)₂BH</td>
<td>CH₂Cl₂</td>
<td>-20 °C</td>
<td>rt</td>
<td>54</td>
</tr>
<tr>
<td>3</td>
<td>(Chx)₂BH</td>
<td>THF</td>
<td>0 °C</td>
<td>rt</td>
<td>50</td>
</tr>
<tr>
<td>4</td>
<td>(Chx)₂BH</td>
<td>Et₂O</td>
<td>0 °C</td>
<td>rt</td>
<td>42</td>
</tr>
<tr>
<td>5°</td>
<td>(Chx)₂BH</td>
<td>CH₂Cl₂</td>
<td>0 °C</td>
<td>rt</td>
<td>68</td>
</tr>
<tr>
<td>6°</td>
<td>(Chx)₂BH</td>
<td>CH₂Cl₂</td>
<td>0 °C</td>
<td>rt</td>
<td>60</td>
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<tr>
<td>7</td>
<td>(-)-Ipc₂BH</td>
<td>CH₂Cl₂</td>
<td>0 °C</td>
<td>rt</td>
<td>45</td>
</tr>
<tr>
<td>8</td>
<td>disiamyl borane</td>
<td>THF-CH₂Cl₂</td>
<td>0 °C</td>
<td>rt</td>
<td>40</td>
</tr>
</tbody>
</table>

⁶ A minor amount (<4%) of cis-8 was detected in all the cases.

° Oxidative work-up (H₂O₂, pH 7) was used instead of triethanolamine.

° A 1:4:1:2:1 (Chx)₂BH/nonanal/6 ratio was used.
Scheme 4. Preparation of trans-4

The transformation of trans-4 into C75 was then quite straightforward (Scheme 5) and its methylenation by a known procedure\textsuperscript{12} completed the synthesis of C75 in a very respectable 29\% overall yield.

Although C75 can be stored for months at 0 °C with no loss of activity, it is prone to suffer facile isomerization to the more stable fully conjugate d-lactone 2 in solution or during chromatographic purifications on silica gel. We envisaged that a phenylseleno ether derivative should be an appropriate protecting group for such a delicate exocyclic double bond. After storage and/or purification, C75 could then be regenerated under mild oxidative conditions.\textsuperscript{13} This was confirmed by treating a sample of C75 with PhSeSePh and NaBH\textsubscript{4} in EtOH to afford the seleno derivative 3 in 90\% yield. It should be noted that 2 remains unchanged under these conditions.\textsuperscript{14} Derivative 3 could be easily purified by column chromatography\textsuperscript{15} and stored in a closed flask at rt for more than one year. Its treatment with 30\% H\textsubscript{2}O\textsubscript{2} in THF at rt then regenerated the desired C75.
Scheme 5. Preparation of C75 and its temporary transformation into the phenylseleno ether derivative 3.

In conclusion, we disclose a useful new method of preparation of C75 in 29% overall yield based on a hydroboration ethyl penta-3,4-dienoate/addition of nonanal tandem process. The unexpected chemical instability of the transient 2-alkenylboranes was mitigated by a recently reported one-pot strategy in which the allene was hydroborated in the presence of the aldehyde. The formation of a considerable amount of undesired syn stereoisomer was overcome by transformation of the adducts into methyl esters 9. These intermediates allowed us minimize and remove the undesired stereoisomer. Finally, we report the temporary transformation of C75 into a phenylseleno derivative as a practical method for its purification and storage. We envisage the application of such phenylseleno derivatives to the preparation of new analogues of C75 in the future.

Experimental

General information

All reactions involving moisture- or air-sensitive reagents were performed in oven-dried glassware under N₂. ¹H NMR and ¹³C NMR spectra were recorded on Mercury 400 or Varian Inova 300 instruments. Chemical shifts (δ) are quoted in parts per million and referenced to internal TMS for ¹H NMR and to CDCl₃ (δ 77.0 ppm) for ¹³C NMR. Column chromatography was performed on silica gel (Merck 230-400 mesh). HRMS analyses were recorded on an Agilent LC/MSD-TOF mass spectrometer. IR spectra (wave numbers in cm⁻¹) were recorded on a Nicolet 6700 FT-IR spectrometer. Ethyl penta-3,4-dienoate (6),¹⁶ Chx₂BH,⁸b (-)-Ipc₂BH,⁷ and disiamylborane⁸ were
prepared according to literature procedures. Samples of cis-4-methylene-2-octyl-5-oxotetrahydrofuran-3-carboxylic acid (1) and 4-methyl-2-octyl-5-oxo-2,5-dihydrofuran-3-carboxylic acid (2) were obtained by Kuhajda's protocol for comparative purposes.

cis-4-Methylene-2-octyl-5-oxotetrahydrofuran-3-carboxylic acid (1). White solid. Mp: 81-82 ºC (lit. 74-75.5 ºC); Rf (CH2Cl2/MeOH 9:1) = 0.27; 1H NMR (300 MHz, CDCl3) δ 0.88 (t, J = 6.7 Hz, 3H, CH3), 1.08–1.78 (m, 14H, CH2), 4.03 (dt, J = 7.6, 2.2 Hz, 1H, CHCOOH), 4.65 (td, J = 7.7, 5.3 Hz, 1H, CHO), 5.89 (d, J = 2.1 Hz, 1H, =CHH), 6.45 (d, J = 2.3 Hz, 1H, =CHCH2); 13C NMR: δ 14.2, 22.7, 25.7, 29.2, 29.3, 29.5, 31.5, 31.9, 48.9, 78.3, 125.8, 133.4, 169.1, 174.2; IR (KBr): 3000-3400, 2922, 2855.

4-Methyl-2-octyl-5-oxo-2,5-dihydrofuran-3-carboxylic acid (2). White solid. Mp: 113-114 ºC; Rf (CH2Cl2/MeOH 8:2) = 0.22; 1H NMR (CDCl3, 400 MHz) δ 0.81 (t, J = 6.8 Hz, 3H, CH3), 1.15–1.45 (m, 12H, CH2), 1.60 (m, 2H, CH2CO), 2.24 (s, 3H, CH3), 5.06 (m, 1H, CHO); 13C NMR (CDCl3, 101 MHz) δ 11.2, 14.2, 22.7, 24.9, 29.3, 29.4, 29.5, 32.0, 32.9, 81.6, 140.2, 146.8, 166.7, 172.8; IR (KBr): 3261, 2956–2854, 1744, 1700, 1215.

One-pot addition of ethyl penta-3,4-dienoate (6) to nonanal.

a) Using dicyclohexylborane

A solution of 6 (0.987 g, 7.79 mmol) and nonanal (1.61 mL, 9.386 mmol) in dry CH2Cl2 (3 mL) was added via cannula to a suspension of dicyclohexylborane (1.672 g, 9.386 mmol) in dry CH2Cl2 (4 mL) at 0 ºC under N2. The reaction mixture was allowed to warm to room temperature. After 20 hours, 2.6 mL (19.55 mmol) of triethanolamine was added and the mixture was stirred for further 15 min. The mixture was carefully concentrated under vacuum and the resulting crude was purified by flash column chromatography (hexanes/ EtOAc 9:1) affording ethyl syn-4-hydroxy-3-vinylidenedecanoate syn-5 (884 mg, 3.27 mmol, 42%) and 5-octyl-4-vinylidihydrofuran-2(3H)-one 8 (507 mg, 2.26 mmol, 29%) as a 20:1 mixture of trans/cis lactones.
Ethyl syn-4-hydroxy-3-vinyldecanoate (syn-5). Colorless oil; R_f (hexanes/EtOAc 8:2) = 0.38; 1H NMR (300 MHz, CDCl3): δ 0.87 (t, J = 6.7 Hz, 3H, CH3), 1.19–1.49 (m, 17H, 7x CH2 and CH3), 2.42 (dd, J = 14.8, 8.0 Hz, 1H, CHH), 2.56 (dd, J = 14.7, 6.1 Hz, 1H, CHH), 2.57–2.68 (m, 1H, CHCH=), 3.56 (m, 1H, CHOH), 4.11 (q, J = 7.1 Hz, 2H, CH2), 5.09–5.19 (m, 2H, CH=CH2), 5.77 (ddd, J = 17.3, 10.4, 8.4 Hz, 1H, CH=CH2); 13C NMR (101 MHz, CDCl3): δ 14.2, 14.4, 22.8, 26.0, 29.4, 29.7, 29.7, 32.0, 35.0, 36.6, 45.9, 60.5, 73.3, 118.0, 136.4, 172.9; IR (film): 2924, 2854, 1779, 1365; HRMS (ESI+) calculated for C14H31O3 [M+H]+: 271.2268; found: 271.2260.

trans-5-Octyl-4-vinylidihydrofuran-2(3H)-one (trans-8). Colorless oil; R_f (hexanes/EtOAc 9:1) = 0.28; 1H NMR (400 MHz, CDCl3): δ 0.88 (t, J = 6.9 Hz, 3H, CH3), 1.23–1.77 (m, 14H, 7xCH2), 2.44 (dd, J = 17.2, 10.5 Hz, 1H, CHH), 2.68 (dd, J = 17.2, 8.3 Hz, 1H, CHH), 2.73–2.82 (m, 1H, CHCH=), 4.14 (td, J = 8.3, 3.8 Hz, 1H, CHO), 5.13–5.23 (m, 2H, CH=CH2), 5.72 (ddd, J = 17.2, 10.2, 7.9 Hz, 1H, CH=CH2); 13C NMR (101 MHz, CDCl3): δ 14.0, 22.6, 25.7, 29.1, 29.3, 29.3, 31.8, 33.6, 35.4, 46.3, 84.8, 117.9, 135.7, 175.7; IR (film): 2924, 2854, 1779, 1365, 1216; HRMS (ESI+) calculated for C14H25O2 [M+H]+: 225.1849; found: 225.1845.

cis-5-Octyl-4-vinylidihydrofuran-2(3H)-one (cis-8)

A solution of syn-5 (135 mg, 0.499 mmol) in MeOH (4 mL) and 2M HCl (0.5 mL) was refluxed for 4 h. The solution was concentrated to ~1 mL and CH2Cl2 (10 mL) was added. The solution was washed with sat. NaHCO3, the organic layer dried (Na2SO4) and the volatiles removed to give almost pure cis-8 (110 mg, 100%). Colorless oil; R_f (hexanes/EtOAc 9:1) = 0.25; 1H NMR (400 MHz, CDCl3): δ 0.86 (t, J = 6.8 Hz, 3H, CH3), 1.18–1.63 (m, 14H, 7xCH2), 2.41 (dd, J = 17.3, 5.5 Hz, 1H, CHH), 2.68 (dd, J = 17.3, 8.1 Hz, 1H, CHH), 3.09–3.18 (m, 1H, CHCH=), 4.48 (ddd, J = 9.3, 6.4, 4.4 Hz, 1H, CHO), 5.20–5.10 (m, 2H, CH=CH2), 5.74 (ddd, J = 17.0, 10.3, 8.7 Hz, 1H, CH=CH2); 13C NMR (101 MHz, CDCl3): δ 14.2, 22.7, 25.8, 29.3, 29.4, 29.5, 31.0, 31.9, 34.8, 43.2, 83.4, 118.1, 134.1, 176.4; IR (film): 2923, 2854, 1775, 1365, 1160, 920; HRMS (ESI+) calculated for C14H25O2 [M+H]+: 225.1849; found: 225.1854.

b) Using disiamylborane

Borane dimethyl sulfide complex (0.2 mL, 1.902 mmol) were slowly added to a solution of 2-methyl-2-butene in dry THF (1.9 mL, 3.80 mmol) at 0 ºC under N2. The mixture was
warmed to room temperature and stirred for 1 hour. The solution was cooled to –78 °C and a solution of allene 6 (200 mg, 1.585 mmol) and nonanal (327 µL, 1.902 mmol) in dry CH₂Cl₂ (1 mL) was added. The mixture was stirred for further 15 minutes at –78 °C and 20 hours at room temperature. The reaction was quenched by addition of triethanolamine (0.5 mL, 3.963 mmol) and the resulting solution was stirred for 1 hour. After concentration under reduced pressure the crude was purified by flash column chromatography (hexanes/EtOAc 9:1) to afford syn-5 (18%) and trans-8 (22%).

c) Using diisopinocampheylborane

A solution of allene 6 (200 mg, 1.585 mmol) and nonanal (327 µL, 1.902 mmol) in dry CH₂Cl₂ (2 mL) was added to a cooled suspension of diisopinocampheylborane (0.720 g, 1.90 mmol) in dry CH₂Cl₂ (1 mL) at 0 °C under N₂. After 1.5 hours, the reaction was quenched by addition of triethanolamine (0.5 mL, 3.963 mmol) and the mixture was stirred at room temperature for 1 hour. The solvent was carefully removed under vacuum and the crude was purified by flash column chromatography (hexanes/EtOAc 95:5 and 9:1) giving syn-5 (28%) and trans-8 (17%). Analysis of a sample of trans-8 by GC using a chiral column (Supelco Alpha Dex 120, 30 m x 0.25 mm, 130 °C, tᵣ = 32.2 min and 32.4 min) showed a 55:45 enantiomeric ratio.

Stepwise addition of ethyl penta-3,4-dienoate (6) to nonanal.

A solution of 6 (0.494 g, 3.90 mmol) in dry CH₂Cl₂ (1 mL) was added via cannula to a suspension of dicyclohexylborane (0.836 g, 4.69 mmol) in dry CH₂Cl₂ (3 mL) at 0 °C under N₂. The reaction mixture was allowed to warm to room temperature. After 50 min, the solution was cooled again to –78 °C and nonanal (805 µL, 4.69 mmol) in dry CH₂Cl₂ (2 mL) was added. The reaction was allowed to warm to room temperature and after 1 h triethanolamine (1.3 mL, 9.78 mmol) was added and the mixture was stirred for further 15 min. The resulting mixture was carefully concentrated under vacuum to give a complex crude. Attempted purification by flash column chromatography (hexanes/EtOAc 95:5 and 9:1) afforded impure fractions in which hydroxy ester 5 and lactone 8 were detected in low yields (<15% overall yield).
Obtention of acid lactones 4 (cis/trans mixture)

A solution of allene 6 (0.307 g, 2.430 mmol) and nonanal (0.50 mL, 2.916 mmol) in 1.5 mL of anhydrous CH₂Cl₂ was added to a suspension of dicyclohexylborane (0.519 g, 2.916 mmol) in 1.5 mL of anhydrous CH₂Cl₂ under N₂ at 0 ºC. The resulting mixture was stirred for 10 min and then for 1 h at room temperature. 3M NaOH (1 mL) and H₂O₂ (30% in water, 1 mL) were added to the reaction. After 1 h at room temperature it was diluted with MeOH (2 mL) and acidified with aq 2M HCl to pH ~ 1 and was then heated at reflux for 3 hours. Water (30 mL) was added and the resulting aqueous layer was extracted with CH₂Cl₂ (3x30 mL). The organic layer was dried (MgSO₄) and the volatiles were removed. The resulting crude lactones 8 (381 mg) were used without further purification in the oxidation step.

NaIO₄ (2.62 g, 12.2 mmol) and RuCl₃.H₂O (9 mg, 0.042 mmol) were added to a stirred solution of lactones 8 in a 1:1:2 CCl₄/CH₃CN/water mixture (12 mL) at room temperature. After 20 h, water (40 mL) was added and the mixture was extracted with CH₂Cl₂ (3x40 mL). The organic extracts were dried (MgSO₄) and the volatiles were removed. The crude was filtered through a short pad of silica to obtain the corresponding mixture of acid lactones 4 (391 mg, 95%).

Preparation of compounds trans-9 and cis-9

Methyl iodide (100 µL, 1.59 mmol) was added to a mixture of acid lactones 4 (0.200 g, 0.826 mmol) and KHCO₃ (0.825 g, 8.25 mmol) in anhydrous DMF (3 mL) under N₂ at room temperature. The mixture was stirred overnight. Water (30 mL) was added and the mixture was extracted with Et₂O (3x40 mL). The combined organic extracts were washed with saturated aqueous NaHSO₃ (20 mL) and brine (100 mL). The organic layer was dried (MgSO₄) and the solvent was removed under vacuum to yield a 4:6 trans/cis mixture of esters 9 (0.211 g, 100%).

1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU, 120 µL, 0.80 mmol) was added to a solution of the mixture of esters 9 in toluene (10 mL) and the solution was heated at 100 ºC for 12 h. The solution was washed with 0.02M HCl (10 mL) and brine (10 mL). The organic layer was dried (MgSO₄) and the solvent was removed under vacuum. The residue was purified.
by flash column chromatography (CH₂Cl₂) to afford trans-9 (167 mg, 79%) and cis-9 (17 mg, 8%).

**Methyl trans-2-octyl-5-oxotetrahydrofuran-3-carboxylate (trans-9).** Colorless oil; Rᵣ (hexanes/EtOAc 7:3) = 0.46; ¹H NMR (CDCl₃, 300 MHz): δ 0.84–0.93 (m, 3H, CH₃), 1.18–1.59 (m, 12H, CH₂), 1.64–1.84 (m, 2H, CH₂), 2.77 (dd, J = 17.6, 9.5 Hz, 1H, CH/HCO), 2.92 (dd, J = 17.6, 8.7 Hz, 1H, CH/HCO), 3.04 (dd, J = 9.5, 7.1 Hz, 1H, CH/COOMe), 3.75 (s, 3H, CH₃), 4.57 (td, J = 7.3, 5.0 Hz, 1H, CHO); ¹³C NMR (CDCl₃, 101 MHz): δ 14.2, 22.7, 25.2, 29.2, 29.3, 29.4, 31.9, 32.3, 35.4, 45.7, 52.8, 82.0, 171.7, 174.5; IR (film), 2953, 2926, 2855, 1790, 1739, 1201; HRMS (ESI⁺) calculated for C₁₄H₂₅O₄ [M+H]⁺: 257.1747; found: 257.1746.

**Methyl cis-2-octyl-5-oxotetrahydrofuran-3-carboxylate (cis-9).** White solid. Mp: 43-44.5 °C; Rᵣ (hexanes/EtOAc, 7:3) = 0.41; ¹H NMR (CDCl₃, 300 MHz, CDCl₃): δ 0.84–0.93 (m, 3H, CH₃), 1.19–1.42 (m, 12H, CH₂), 1.43–1.65 (m, 2H, CH₂), 2.66 (dd, J = 17.6, 8.7 Hz, 1H, CH/HCO), 2.90 (dd, J = 17.6, 5.7 Hz, 1H, CH/HCO), 3.44 (dd, J = 8.7, 7.4, 5.7 Hz, 1H, CH/COOMe), 3.75 (s, 3H, CH₃), 4.62 (td, J = 7.4, 6.3 Hz, 1H, CHO); ¹³C NMR (CDCl₃, 101 MHz, CDCl₃): δ 14.2, 22.8, 25.9, 29.3, 29.3, 29.5, 31.5, 31.9, 44.4, 52.4, 80.5, 170.9, 175.0; IR (KBr) 2914, 2851, 1775, 1726, 1241; HRMS (ESI⁺) calculated for C₁₄H₂₅O₄ [M+H]⁺: 257.1747; found: 257.1750.

**trans-2-Octyl-5-oxotetrahydrofuran-3-carboxylic acid (trans-4)**

Aqueous NaOH (1M, 2 mL) was added to a solution of trans-9 (164 mg, 0.640 mmol) in THF (2 mL). The mixture was heated at 70 °C until of the starting material disappeared (1 h). The mixture was partitioned by adding CH₂Cl₂ (5 mL) and water (3 mL). The aqueous layer was extracted with CH₂Cl₂ (3 mL), decanted, acidified to pH ~1 with conc. HCl and heated to 70 °C for 1h. The aqueous phase was extracted with CH₂Cl₂ (4x4 mL) and the combined organic extracts were dried (MgSO₄). The solvent was removed under vacuum to give almost pure trans-4 as a white solid. Mp: 98-100 °C; Rᵣ (hexanes/EtOAc/HOAc 8:2:0.1) = 0.24; ¹H NMR (CDCl₃, 400 MHz): δ 0.88 (t, J = 6.7 Hz, 3H, CH₃), 1.28–1.56 (m, 12H, CH₂), 1.70–1.86 (m, 2 H, CH₂), 2.83 (dd, J = 9.6, 17.9 Hz, 1H, CH/HCO), 2.95 (dd, J = 8.4, 17.9 Hz, 1H, CH/HCO), 3.07–3.14 (m, 1H, CH/R/COOH), 4.60–4.65 (m, 1H, CHRO); ¹³C NMR (CDCl₃, 101 MHz): δ 14.2, 22.8, 25.3, 29.3, 29.3, 29.5, 31.9, 32.0, 35.5, 45.3,
trans-4-Methylene-2-octyl-5-oxotetrahydrofuran-3-carboxylic acid (C75)

A sample of trans-4 (85 mg, 0.35 mmol) was heated in a solution of MMC (magnesium methyl carbonate, 2M) in DMF (6 mL) at 130-135 °C under N2 for 45 h. 6M HCl (10 mL) and CH2Cl2 (15 mL) were added carefully. The aqueous layer was extracted with CH2Cl2 (2×10 mL), the combined organic extracts were dried (MgSO4) and the volatiles were removed to afford 100 mg of residue. This crude was stirred with 1.2 mL of a freshly prepared stock solution (1 mL AcOH, 0.75 mL formalin, 30 mg NaAcO and 0.26 mL N-methylaniline) for 1.45 h. To the resulting mixture, a 10:1 aq. NaCl/conc. HCl solution (5 mL) and CH2Cl2 (12 mL) were added. The aqueous layer was extracted with CH2Cl2 (5×10 mL). The combined organic extracts were washed with LiCl 5% (2×4 mL), HCl 0.02 M (2×4 mL) and H2O (3×5 mL). The organic layer was stirred with sat. NaHCO3 solution (5 mL) for 5 min and then the aqueous layer was acidified with concentrated HCl to pH 1-2 and was extracted with CH2Cl2 (4×10 mL). The combined organic extracts were washed with brine and dried (MgSO4) and the solvent was removed to give C75 as a white solid (54 mg, 0.21 mmol, 60%). Mp: 88-89 °C (lit.,3a 76-77 °C); Rf (CH2Cl2/MeOH 9:1) = 0.27; 1H NMR (400 MHz, CDCl3): δ 0.88 (t, J = 6.9 Hz, 3H, CH3), 1.20–1.53 (m, 12 H, CH2), 1.67–1.79 (m, 2H, CH2) 3.63 (dd, J = 5.6, 2.8 Hz, 1H, CHCOOH), 4.80 (td, J = 7.2, 5.6 Hz, 1H, CHRO), 6.00 (d, J = 2.7 Hz, 1H, =CHH), 6.46 (d, J = 2.7 Hz, 1H, =CHH); 13C NMR (101 MHz, CDCl3): δ 14.2, 22.7, 24.9, 29.2, 29.3, 29.5, 31.9, 35.8, 49.6, 79.1, 126.1, 132.5, 168.5, 174.7; IR (film): 3000–3400, 2924, 2852, 1743, 1717, 1660, 1621, 1460; HRMS (ESI+) calculated for C14H23O4: 255.1591[M+H]+; found: 255.1587.

trans,trans-2-Octyl-5-oxo-4-[(phenylselanylmethyl]tetrahydrofuran-3-carboxylic acid (3). A solution of C75 (0.200 g, 0.78 mmol) in EtOH (3 mL) was added dropwise via cannula to a mixture of Ph2Se2 (0.135 g, 0.43 mmol) and NaBH4 (0.035 g, 0.94 mmol) in EtOH (3 mL) under N2 at room temperature. The resulting yellow solution was stirred 3.5 h and then acidified with 2M HCl to pH = 1. Volatiles were evaporated and
the aqueous residue was extracted with CH₂Cl₂ (3x8 mL). The combined organic layers were washed with 20% NH₄Cl solution (2x5 mL) and brine (2x5 mL), dried (MgSO₄) and the solvent was removed under vacuum. The purification of the crude by flash chromatography (hexanes/EtOAc /HOAc 70:30:1) furnished the desired product (0.290 g, 0.70 mmol, 90 %) as a white solid. Mp: 116-118 °C; R_f (CH₂Cl₂/MeOH 9:1) = 0.44; ¹H NMR (CDCl₃, 400 MHz): δ 0.81 (t, J = 6.6 Hz, 3H, CH₃), 1.16–1.48 (m, 12H, CH₂), 1.61–1.70 (m, 1H, CHHCHO), 1.72–1.80 (m, 1H, CHHCHO), 3.03 (dd, J = 9.2, 10.2 Hz, 1H, CHCOOH), 3.09–3.15 (m, 1H, CHHSe), 3.32–3.38 (m, 2H, CHHSe and CH-Se), 4.47 (td, J = 8.8, 4.0 Hz, 1H, CHO), 7.17–7.19 (m, 3H, CH(Ar)), 7.43–7.45 (m, 2H, CH(Ar)); ¹³C NMR (CDCl₃, 101 MHz) δ 14.2, 22.8, 25.3, 27.1, 29.3, 29.4, 29.5, 29.8, 31.9, 35.1, 45.5, 51.4, 79.9, 127.8, 129.2, 129.4, 133.1, 174.8, 176.4; IR (KBr): 2951–2922, 1763, 1697, 1162; HRMS (ESI+) calculated for C₂₀H₂₈NaO₄Se [M+Na]⁺: 435.1045; found: 435.1039.

Preparation of C75 by oxidation of 3.

H₂O₂ 30% (48 µL, 0.428 mmol) was added to a stirred solution of 3 (0.044 g, 0.107 mmol) in THF (0.6 mL) at room temperature. After 2.5 h, the resulting mixture was diluted with CH₂Cl₂ (6 mL) and sat. NaHCO₃ (3 mL) was added. The layers were separated and the aqueous layer was washed with CH₂Cl₂ (3x3 mL) and acidified with 6M HCl until pH ~ 1. The aqueous layer was extracted with CH₂Cl₂ (4x3 mL) and the combined organic extracts were washed with brine (8 mL) and dried (MgSO₄). Solvent evaporation gave C75 (0.022 g, 0.087 mmol, 81%) as a white solid.

cis,trans-2-Octyl-5-oxo-4-[(phenylselanyl)methyl]tetrahydrofuran-3-carboxylic acid.

A solution of 1 (0.124 g, 0.49 mmol) in anh EtOH (2 mL) was added dropwise via cannula to a mixture of Ph₂Se₂ (0.084 g, 0.27 mmol) and NaBH₄ (0.018 g, 0.49 mmol) in EtOH (2.5 mL) under N₂ at room temperature. The resulting yellow solution was stirred 3.5 h and was acidified with 2M HCl to pH ~ 1. The volatiles were evaporated and the aqueous residue was extracted with CH₂Cl₂ (3x2 mL). The combined organic extracts were washed with 20% NH₄Cl (2x2 mL), brine (2 x 2 mL) and water (2 mL), dried (MgSO₄) and the solvent
was removed under vacuum. The resulting crude was purified by flash column chromatography (hexanes/EtOAc /HOAc 70:30:1) to give 0.166 g of the desired product (0.403 mmol, 83%) as a white solid. Mp: 87-88 °C; Rf (hexanes/EtOAc 8:2) = 0.23; \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 0.87 (t, \(J = 6.9\) Hz, 3H, CH\(_3\)), 1.13–1.69 (m, 14H, CH\(_2\)), 3.10–3.18 (m, 1H, CHCOOH), 3.34–3.41 (m, 2H, CH\(_2\)Se), 3.60 (t, \(J = 8.6\) Hz, 1H, CHCH\(_2\)Se), 4.70 (td, \(J = 8.6, 4.3\) Hz, 1H, CHO), 7.34–7.21 (m, 3H, CH(Ar)), 7.62–7.45 (m, 2H, CH(Ar)); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)): \(\delta\) 14.2, 22.8, 25.8, 26.8, 29.3, 29.5, 31.7, 31.9, 42.8, 49.2, 77.7, 125.5, 127.9, 129.5, 133.2, 174.5, 175.2. IR (KBr): 3198, 2920, 2853, 1746, 1653, 1407, 1143; HRMS (ESI+) calculated for C\(_{20}\)H\(_{38}\)NaO\(_4\)Se \([\text{M+Na}]^+\): 435.1045; found: 435.1039.

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Notes and references


10) Large amounts of the starting aldehyde could be detected in the crude product. A series of experiments using (–)-(Ipc)2BH, cathecolborane, cathecolborane in the presence of Wilkinson's catalyst or diisiamylborane did not improve these results.


14) Preliminary attempts using S instead of Se failed. Although the phenylthio ether derivative and its corresponding sulfoxide were easily obtained, the relatively high temperatures required to regenerate C75 caused the concomitant migration of the double bond leading to compound 2.

15) A sample of cis compound 1 obtained by Kuhajda's method\textsuperscript{3a,b} was transformed into its phenylseleno derivative. We then checked that this derivative could be separated chromatographically from 3 and from 2, demonstrating that cis compound 1 could be also removed from C75 by this method.