

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

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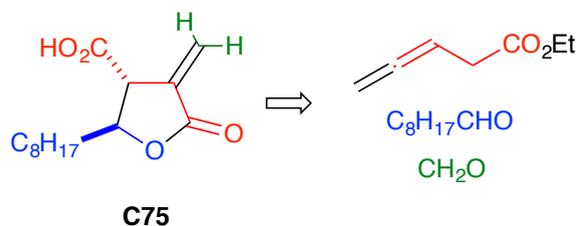
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A new approach to the enzyme inhibitor C75 and its temporary transformation into a phenylseleno ether derivative is disclosed. This procedure facilitates the purification, manipulation and storage of C75.



## Abstract

C75 is a synthetic racemic  $\alpha$ -methylene- $\gamma$ -butyrolactone exhibiting antitumoural properties *in vitro* and *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 *cis* and *trans* isomers, in good yield. The DBU-catalyzed isomerization of the methyl esters **9** arising from **8** gave a 10:1 *trans/cis* mixture from which the *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 *in vivo*. Over the last few years, C75 as a racemic mixture of its *trans* diastereoisomers has been used extensively in the study of fatty acid synthesis in metabolic disorders and cancer.<sup>1</sup>

In the course of our ongoing search for potential new drugs against obesity and type 2 diabetes,<sup>2</sup> we required multigram quantities of racemic *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 *et al.*<sup>3</sup> This procedure was based on previous work<sup>4</sup> by Carlson *et al.* that uses itaconic anhydride and *p*-methoxybenzyl alcohol as starting materials. Under these conditions C75 is obtained as a separable mixture of C75 and its *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**.

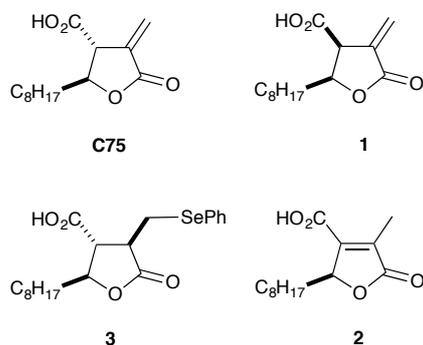
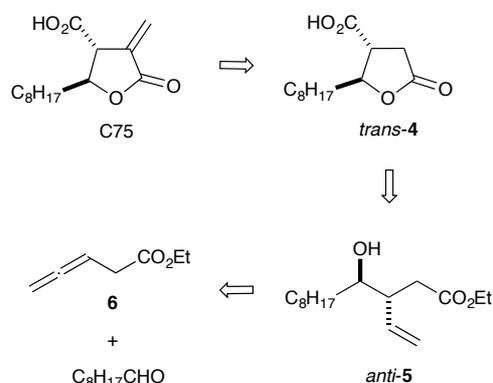


Figure 1. Structures of **C75** and compounds **1–3**.

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  $\gamma$ -hydroxyester *anti*-**5** (Scheme 1). Taking advantage of our recent studies on the stereoselective addition of allenes to aldehydes,<sup>5</sup> 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**.<sup>6</sup> Herein, we report our findings in this respect.

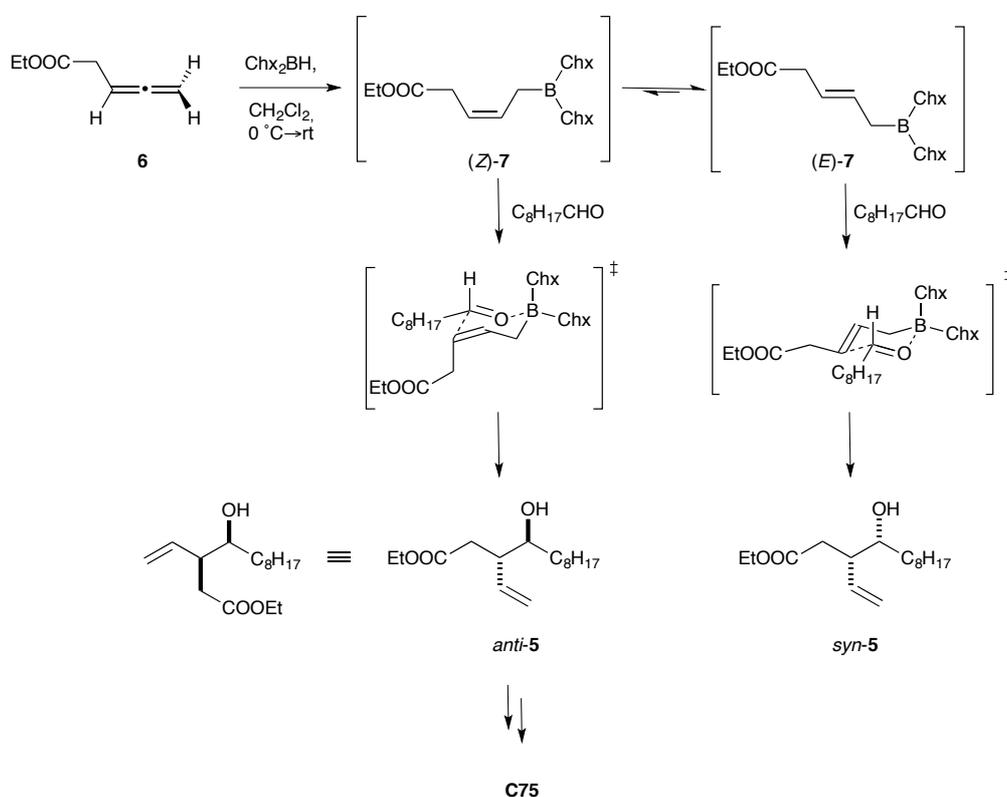


Scheme 1. Retrosynthetic analysis of **C75**.

## 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

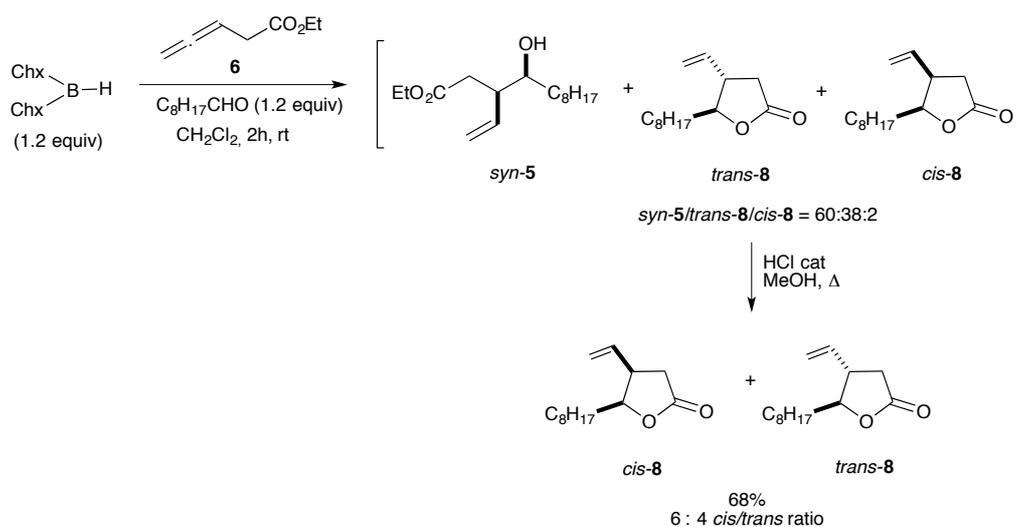
form a transient (*Z*)-2-alkenylborane. However, this kinetically formed borane reagent suffers fast isomerization to the thermodynamically more stable (*E*)-2-alkenylborane at room temperature. The addition of an aldehyde to this then affords a *syn* homoallylic alcohol as the major product, through a 6-membered transition state. Recently, we demonstrated that the hydroboration of the allene is also possible in the presence of the aldehyde.<sup>5b</sup> In such conditions, the (*Z*)-borane reagent can be trapped immediately by the aldehyde leading to *anti* adducts. Accordingly, we expected that the treatment of a mixture of ethyl penta-3,4-dienoate **6** and nonanal with  $\text{Chx}_2\text{BH}$  would lead to *anti*-**5** by trapping the transient (*Z*)-2-alkenylborane, (*Z*)-**7** (Scheme 2). In contrast, the hydroboration of **6** with dicyclohexylborane ( $\text{Chx}_2\text{BH}$ ) followed by the addition of nonanal would afford selectively the  $\gamma$ -hydroxyester *syn*-**5**.



*Scheme 2.* Mechanism of hydroboration of **6** followed by nonanal addition.

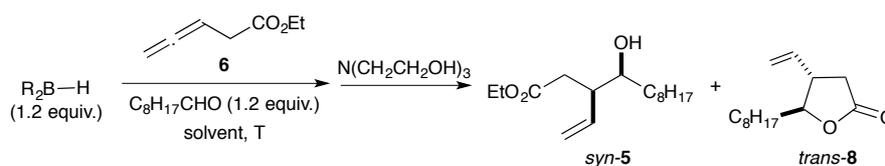
In practice, the addition of allene **6** to a mixture of  $\text{Chx}_2\text{BH}$  (1.2 equiv) and nonanal (1.2 equiv) in  $\text{CH}_2\text{Cl}_2$  gave, after work-up (triethanolamine) and chromatographic separation, a separable mixture of hydroxyester *syn*-**5** and the lactone *trans*-**8** arising from *anti*-**5** but in a disappointing 6:4 ratio (Scheme 3). Apparently, the minor *anti*-**5** isomer formed suffers a selective lactonization during the work-up and/or chromatographic processes to give *trans*-

**8.** 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 crotylboranes 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.<sup>5b</sup> 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.



*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<sub>2</sub>O), or work-up (triethanolamine or H<sub>2</sub>O<sub>2</sub>) nor a fine tuning of the allene/aldehyde/Chx<sub>2</sub>BH ratio were satisfactory. Consequently, we considered the use of more hindered hydroborating agents. Both (–)-Ipc<sub>2</sub>BH<sup>7</sup> (Ipc = isopinocampheyl), and disiamylborane<sup>8</sup> 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<sub>2</sub>BH revealed low enantioselectivities (55:44 ratio).



entry	R <sub>2</sub> BH	Solvent	T	Overall yield (%)	syn-5/trans-8 ratio <sup>a</sup>
1	(Chx) <sub>2</sub> BH	CH <sub>2</sub> Cl <sub>2</sub>	0 °C → rt	71	60:40
2	(Chx) <sub>2</sub> BH	CH <sub>2</sub> Cl <sub>2</sub>	-20 °C → rt	54	45:55
3	(Chx) <sub>2</sub> BH	THF	0 °C → rt	50	65:35
4	(Chx) <sub>2</sub> BH	Et <sub>2</sub> O	0 °C → rt	42	65:35
5 <sup>b</sup>	(Chx) <sub>2</sub> BH	CH <sub>2</sub> Cl <sub>2</sub>	0 °C → rt	68	58:42
6 <sup>c</sup>	(Chx) <sub>2</sub> BH	CH <sub>2</sub> Cl <sub>2</sub>	0 °C → rt	60	60:40
7	(-)-Ipc <sub>2</sub> BH	CH <sub>2</sub> Cl <sub>2</sub>	0 °C → rt	45	62:38
8	disiamyl borane	THF-CH <sub>2</sub> Cl <sub>2</sub>	0 °C → rt	40	45:55

<sup>a</sup> A minor amount (<4%) of *cis*-8 was detected in all the cases.

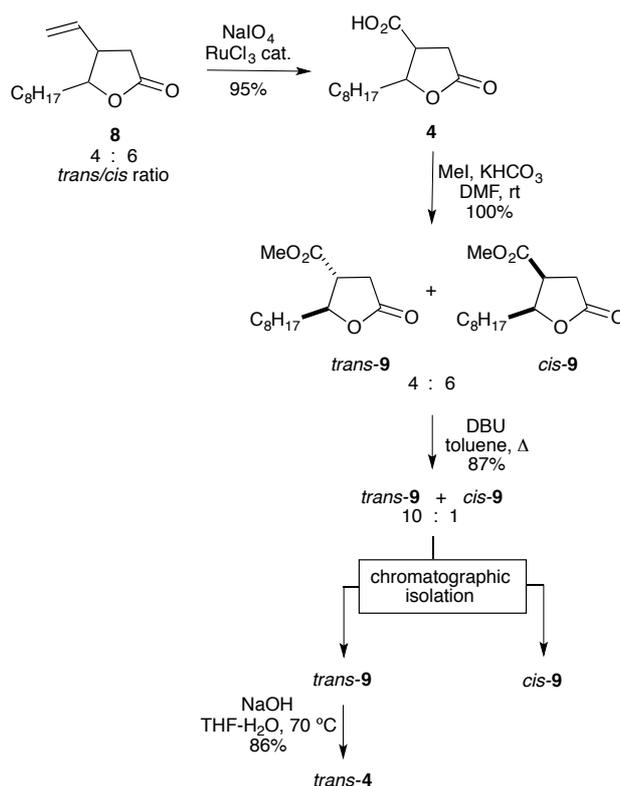
<sup>b</sup> Oxidative work-up (H<sub>2</sub>O<sub>2</sub>, pH 7) was used instead of triethanolamine.

<sup>c</sup> A 1.4:1.2:1 (Chx)<sub>2</sub>BH/nonanal/6 ratio was used.

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

On the other hand, when we performed the alternative stepwise process for comparative purposes, *i.e.* hydroboration of **6** (CH<sub>2</sub>Cl<sub>2</sub> or THF) with (Chx)<sub>2</sub>BH (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 laboratory<sup>5</sup> and others<sup>9</sup> 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.<sup>10</sup>

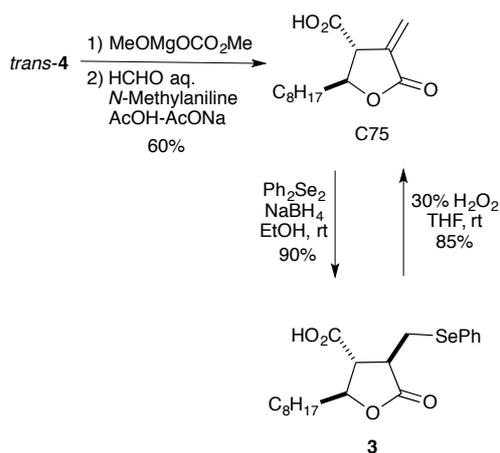
Consequently, we turned our attention to the former one-pot hydroboration with Chx<sub>2</sub>BH (Scheme 3). Having in hand the mixture of lactones **8**, the oxidation<sup>11</sup> of the vinyl group was performed with NaIO<sub>4</sub>/RuCl<sub>3</sub> to afford almost quantitatively a mixture of acids **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**.



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<sup>12</sup> 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 conjugated 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.<sup>13</sup> This was confirmed by treating a sample of C75 with PhSeSePh and NaBH<sub>4</sub> in EtOH to afford the seleno derivative **3** in 90% yield. It should be noted that **2** remains unchanged under these conditions.<sup>14</sup> Derivative **3** could be easily purified by column chromatography<sup>15</sup> and stored in a closed flask at rt for more than one year. Its treatment with 30% H<sub>2</sub>O<sub>2</sub> 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  $\text{N}_2$ .  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectra were recorded on Mercury 400 or Varian Inova 300 instruments. Chemical shifts ( $\delta$ ) are quoted in parts per million and referenced to internal TMS for  $^1\text{H}$  NMR and to  $\text{CDCl}_3$  ( $\delta$  77.0 ppm) for  $^{13}\text{C}$  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  $\text{cm}^{-1}$ ) were recorded on a Nicolet 6700 FT-IR spectrometer. Ethyl penta-3,4-dienoate (**6**),<sup>16</sup>  $\text{ChX}_2\text{BH}$ ,<sup>8b</sup>  $(-)\text{-Ipc}_2\text{BH}$ ,<sup>7</sup> and disiamylborane<sup>8</sup> 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<sup>3a</sup> for comparative purposes.

***cis*-4-Methylene-2-octyl-5-oxotetrahydrofuran-3-carboxylic acid (1).** White solid. Mp: 81-82 °C (lit.<sup>3a</sup> 74-75.5 °C);  $R_f$ (CH<sub>2</sub>Cl<sub>2</sub>/MeOH 9:1) = 0.27; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.88 (t,  $J$  = 6.7 Hz, 3H, CH<sub>3</sub>), 1.08–1.78 (m, 14H, CH<sub>2</sub>), 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, =CHH); <sup>13</sup>C 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, 1748, 1713, 1663.

**4-Methyl-2-octyl-5-oxo-2,5-dihydrofuran-3-carboxylic acid (2).** White solid. Mp: 113-114 °C;  $R_f$ (CH<sub>2</sub>Cl<sub>2</sub>/MeOH 8:2) = 0.22; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ 0.81 (t,  $J$  = 6.8 Hz, 3H, CH<sub>3</sub>CH<sub>2</sub>), 1.15–1.45 (m, 12H, CH<sub>2</sub>), 1.60 (m, 2H, CH<sub>2</sub>CO), 2.24 (s, 3H, CH<sub>3</sub>), 5.06 (m, 1H, CHO); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 101 MHz) δ 11.2, 14.2, 22.8, 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 CH<sub>2</sub>Cl<sub>2</sub> (3 mL) was added *via* cannula to a suspension of dicyclohexylborane (1.672 g, 9.386 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (4 mL) at 0 °C under N<sub>2</sub>. 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-vinyldodecanoate *syn*-**5** (884 mg, 3.27 mmol, 42%) and 5-octyl-4-vinyldihydrofuran-2(3*H*)-one **8** (507 mg, 2.26 mmol, 29%) as a 20:1 mixture of *trans/cis* lactones.

**Ethyl *syn*-4-hydroxy-3-vinyldodecanoate (*syn*-5).** Colorless oil;  $R_f$  (hexanes/EtOAc 8:2) = 0.38;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  0.87 (t,  $J = 6.7$  Hz, 3H,  $\text{CH}_3$ ), 1.19–1.49 (m, 17H, 7x  $\text{CH}_2$  and  $\text{CH}_3$ ), 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,  $\text{CHCH=}$ ), 3.56 (m, 1H,  $\text{CHOH}$ ), 4.11 (q,  $J = 7.1$  Hz, 2H,  $\text{CH}_2$ ), 5.09–5.19 (m, 2H,  $\text{CH=CH}_2$ ), 5.77 (ddd,  $J = 17.3, 10.4, 8.4$  Hz, 1H,  $\text{CH=CH}_2$ );  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ ):  $\delta$  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, 1781, 1167; HRMS (ESI+) calculated for  $\text{C}_{16}\text{H}_{31}\text{O}_3$   $[\text{M}+\text{H}]^+$ : 271.2268; found: 271.2260.

***trans*-5-Octyl-4-vinyldihydrofuran-2(3H)-one (*trans*-8).** Colorless oil;  $R_f$  (hexanes/EtOAc 9:1) = 0.28;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  0.88 (t,  $J = 6.9$  Hz, 3H,  $\text{CH}_3$ ), 1.23–1.77 (m, 14H, 7x $\text{CH}_2$ ), 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,  $\text{CHCH=}$ ), 4.14 (td,  $J = 8.3, 3.8$  Hz, 1H,  $\text{CHO}$ ), 5.13–5.23 (m, 2H,  $\text{CH=CH}_2$ ), 5.72 (ddd,  $J = 17.2, 10.2, 7.9$  Hz, 1H,  $\text{CH=CH}_2$ );  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  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  $\text{C}_{14}\text{H}_{25}\text{O}_2$   $[\text{M}+\text{H}]^+$ : 225.1849; found: 225.1845.

#### ***cis*-5-Octyl-4-vinyldihydrofuran-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  $\text{CH}_2\text{Cl}_2$  (10 mL) was added. The solution was washed with sat.  $\text{NaHCO}_3$ , the organic layer dried ( $\text{Na}_2\text{SO}_4$ ) and the volatiles removed to give almost pure *cis*-8 (110 mg, 100%). Colorless oil;  $R_f$  (hexanes/EtOAc 9:1) = 0.25;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  0.86 (t,  $J = 6.8$  Hz, 3H,  $\text{CH}_3$ ), 1.18–1.63 (m, 14H, 7x $\text{CH}_2$ ), 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,  $\text{CHCH=}$ ), 4.48 (ddd,  $J = 9.3, 6.4, 4.4$  Hz, 1H,  $\text{CHO}$ ), 5.20–5.10 (m, 2H,  $\text{CH=CH}_2$ ), 5.74 (ddd,  $J = 17.0, 10.3, 8.7$  Hz, 1H,  $\text{CH=CH}_2$ );  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  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  $\text{C}_{14}\text{H}_{25}\text{O}_2$   $[\text{M}+\text{H}]^+$ : 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 °C under  $\text{N}_2$ . The mixture was

warmed to room temperature and stirred for 1 hour. The solution was cooled to  $-78\text{ }^{\circ}\text{C}$  and a solution of allene **6** (200 mg, 1.585 mmol) and nonanal (327  $\mu\text{L}$ , 1.902 mmol) in dry  $\text{CH}_2\text{Cl}_2$  (1 mL) was added. The mixture was stirred for further 15 minutes at  $-78\text{ }^{\circ}\text{C}$  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  $\mu\text{L}$ , 1.902 mmol) in dry  $\text{CH}_2\text{Cl}_2$  (2 mL) was added to a cooled suspension of diisopinocampheylborane (0.720 g, 1.90 mmol) in dry  $\text{CH}_2\text{Cl}_2$  (1 mL) at  $0\text{ }^{\circ}\text{C}$  under  $\text{N}_2$ . 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,  $130\text{ }^{\circ}\text{C}$ ,  $t_{\text{R}} = 32.2\text{ min}$  and  $32.4\text{ min}$ ) 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  $\text{CH}_2\text{Cl}_2$  (1 mL) was added *via* cannula to a suspension of dicyclohexylborane (0.836 g, 4.69 mmol) in dry  $\text{CH}_2\text{Cl}_2$  (3 mL) at  $0\text{ }^{\circ}\text{C}$  under  $\text{N}_2$ . The reaction mixture was allowed to warm to room temperature. After 50 min, the solution was cooled again to  $-78\text{ }^{\circ}\text{C}$  and nonanal (805  $\mu\text{L}$ , 4.69 mmol) in dry  $\text{CH}_2\text{Cl}_2$  (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 CH<sub>2</sub>Cl<sub>2</sub> was added to a suspension of dicyclohexylborane (0.519 g, 2.916 mmol) in 1.5 mL of anhydrous CH<sub>2</sub>Cl<sub>2</sub> under N<sub>2</sub> at 0 °C. The resulting mixture was stirred for 10 min and then for 1 h at room temperature. 3M NaOH (1 mL) and H<sub>2</sub>O<sub>2</sub> (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 CH<sub>2</sub>Cl<sub>2</sub> (3x30 mL). The organic layer was dried (MgSO<sub>4</sub>) and the volatiles were removed. The resulting crude lactones **8** (381 mg) were used without further purification in the oxidation step.

NaIO<sub>4</sub> (2.62 g, 12.2 mmol) and RuCl<sub>3</sub>·H<sub>2</sub>O (9 mg, 0.042 mmol) were added to a stirred solution of lactones **8** in a 1:1:2 CCl<sub>4</sub>/CH<sub>3</sub>CN/water mixture (12 mL) at room temperature. After 20 h, water (40 mL) was added and the mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3x40 mL). The organic extracts were dried (MgSO<sub>4</sub>) 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 KHCO<sub>3</sub> (0.825 g, 8.25 mmol) in anhydrous DMF (3 mL) under N<sub>2</sub> at room temperature. The mixture was stirred overnight. Water (30 mL) was added and the mixture was extracted with Et<sub>2</sub>O (3x40 mL). The combined organic extracts were washed with saturated aqueous NaHSO<sub>3</sub> (20 mL) and brine (100 mL). The organic layer was dried (MgSO<sub>4</sub>) 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 °C for 12 h. The solution was washed with 0.02M HCl (10 mL) and brine (10 mL). The organic layer was dried (MgSO<sub>4</sub>) and the solvent was removed under vacuum. The residue was purified

by *flash* column chromatography (CH<sub>2</sub>Cl<sub>2</sub>) 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; R<sub>f</sub> (hexanes/EtOAc 7:3) = 0.46; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): δ 0.84–0.93 (m, 3H, CH<sub>3</sub>), 1.18–1.59 (m, 12H, CH<sub>2</sub>), 1.64–1.84 (m, 2H, CH<sub>2</sub>), 2.77 (dd, *J* = 17.6, 9.5 Hz, 1H, CHHCO), 2.92 (dd, *J* = 17.6, 8.7 Hz, 1H, CHHCO), 3.04 (ddd, *J* = 9.5, 8.7, 7.1 Hz, 1H, CHCOOMe), 3.75 (s, 3H, CH<sub>3</sub>), 4.57 (td, *J* = 7.3, 5.0 Hz, 1H, CHO); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 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 C<sub>14</sub>H<sub>25</sub>O<sub>4</sub> [M+H]<sup>+</sup>: 257.1747; found: 257.1746.

**Methyl *cis*-2-octyl-5-oxotetrahydrofuran-3-carboxylate (*cis*-**9**).** White solid. Mp: 43–44.5 °C; R<sub>f</sub> (hexanes/EtOAc, 7:3) = 0.41; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 0.84–0.93 (m, 3H, CH<sub>3</sub>), 1.19–1.42 (m, 12H, CH<sub>2</sub>), 1.43–1.65 (m, 2H, CH<sub>2</sub>), 2.66 (dd, *J* = 17.6, 8.7 Hz, 1H, CHHCO), 2.90 (dd, *J* = 17.6, 5.7 Hz, 1H, CHHCO), 3.44 (ddd, *J* = 8.7, 7.4, 5.7 Hz, 1H, CHCOOMe), 3.75 (s, 3H, CH<sub>3</sub>), 4.62 (td, *J* = 7.4, 6.3 Hz, 1H, CHO); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>): 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 C<sub>14</sub>H<sub>25</sub>O<sub>4</sub> [M+H]<sup>+</sup>: 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 CH<sub>2</sub>Cl<sub>2</sub> (5 mL) and water (3 mL). The aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 mL), decanted, acidified to pH ~1 with conc. HCl and heated to 70 °C for 1h. The aqueous phase was extracted with CH<sub>2</sub>Cl<sub>2</sub> (4x4 mL) and the combined organic extracts were dried (MgSO<sub>4</sub>). The solvent was removed under vacuum to give almost pure *trans*-**4** as a white solid. Mp: 98–100 °C; R<sub>f</sub> (hexanes/EtOAc/HOAc 8:2:0.1) = 0.24; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz): δ 0.88 (t, *J* = 6.7 Hz, 3H, CH<sub>3</sub>), 1.28–1.56 (m, 12H, CH<sub>2</sub>), 1.70–1.86 (m, 2 H, CH<sub>2</sub>), 2.83 (dd, *J* = 9.6, 17.9 Hz, 1H, CHHCO), 2.95 (dd, *J* = 8.4, 17.9 Hz, 1H, CHHCO), 3.07–3.14 (m, 1H, CHR<sub>2</sub>COOH), 4.60–4.65 (m, 1H, CHRO); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 101 MHz): δ 14.2, 22.8, 25.3, 29.3, 29.3, 29.5, 31.9, 32.0, 35.5, 45.3,

82.0, 174.7, 176.7; IR (ATR): 3000–3300, 2925, 2853, 1749, 1718, 1393, 1243, 1215, 1195, 759, 669; HRMS (ESI+) calculated for C<sub>13</sub>H<sub>22</sub>NaO<sub>4</sub> [M+Na]<sup>+</sup>: 265.1410; found: 265.1410.

***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 N<sub>2</sub> for 45 h. 6M HCl (10 mL) and CH<sub>2</sub>Cl<sub>2</sub> (15 mL) were added carefully. The aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (2×10 mL), the combined organic extracts were dried (MgSO<sub>4</sub>) 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 CH<sub>2</sub>Cl<sub>2</sub> (12 mL) were added. The aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (5×10 mL). The combined organic extracts were washed with LiCl 5% (2×4 mL), HCl 0.02 M (2×4 mL) and H<sub>2</sub>O (3×5 mL). The organic layer was stirred with sat. NaHCO<sub>3</sub> solution (5 mL) for 5 min and then the aqueous layer was acidified with concentrated HCl to pH 1–2 and was extracted with CH<sub>2</sub>Cl<sub>2</sub> (4×10 mL). The combined organic extracts were washed with brine and dried (MgSO<sub>4</sub>) and the solvent was removed to give C75 as a white solid (54 mg, 0.21 mmol, 60%). Mp: 88–89 °C (lit.,<sup>3a</sup> 76–77 °C); R<sub>f</sub> (CH<sub>2</sub>Cl<sub>2</sub>/MeOH 9:1) = 0.27; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 0.88 (t, *J* = 6.9 Hz, 3H, CH<sub>3</sub>), 1.20–1.53 (m, 12 H, CH<sub>2</sub>), 1.67–1.79 (m, 2H, CH<sub>2</sub>) 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); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>): 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 C<sub>14</sub>H<sub>23</sub>O<sub>4</sub>: 255.1591[M+H]<sup>+</sup>; found: 255.1587.

***trans,trans*-2-Octyl-5-oxo-4-[(phenylselanyl)methyl]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 Ph<sub>2</sub>Se<sub>2</sub> (0.135 g, 0.43 mmol) and NaBH<sub>4</sub> (0.035 g, 0.94 mmol) in EtOH (3 mL) under N<sub>2</sub> 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 CH<sub>2</sub>Cl<sub>2</sub> (3x8 mL). The combined organic layers were washed with 20% NH<sub>4</sub>Cl solution (2x5 mL) and brine (2x5 mL), dried (MgSO<sub>4</sub>) 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<sub>f</sub> (CH<sub>2</sub>Cl<sub>2</sub>/MeOH 9:1) = 0.44; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz): δ 0.81 (t, *J* = 6.6 Hz, 3H, CH<sub>3</sub>), 1.16–1.48 (m, 12H, CH<sub>2</sub>), 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-CH<sub>2</sub>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)); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 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 C<sub>20</sub>H<sub>28</sub>NaO<sub>4</sub>Se [M+Na]<sup>+</sup>: 435.1045; found: 435.1039.

### **Preparation of C75 by oxidation of 3.**

H<sub>2</sub>O<sub>2</sub> 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 CH<sub>2</sub>Cl<sub>2</sub> (6 mL) and sat. NaHCO<sub>3</sub> (3 mL) was added. The layers were separated and the aqueous layer was washed with CH<sub>2</sub>Cl<sub>2</sub> (3x3 mL) and acidified with 6M HCl until *pH* ~ 1. The aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (4x3 mL) and the combined organic extracts were washed with brine (8 mL) and dried (MgSO<sub>4</sub>). 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 Ph<sub>2</sub>Se<sub>2</sub> (0.084 g, 0.27 mmol) and NaBH<sub>4</sub> (0.018 g, 0.49 mmol) in EtOH (2.5 mL) under N<sub>2</sub> 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 CH<sub>2</sub>Cl<sub>2</sub> (3x2 mL). The combined organic extracts were washed with 20% NH<sub>4</sub>Cl (2x2 mL), brine (2 x 2 mL) and water (2 mL), dried (MgSO<sub>4</sub>) 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;  $R_f$  (hexanes/EtOAc 8:2) = 0.23;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  0.87 (t,  $J$  = 6.9 Hz, 3H,  $\text{CH}_3$ ), 1.13–1.69 (m, 14H,  $\text{CH}_2$ ), 3.10–3.18 (m, 1H,  $\text{CHCOOH}$ ), 3.34–3.41 (m, 2H,  $\text{CH}_2\text{Se}$ ), 3.60 (t,  $J$  = 8.6 Hz, 1H,  $\text{CHCH}_2\text{Se}$ ), 4.70 (td,  $J$  = 8.6, 4.3 Hz, 1H,  $\text{CHO}$ ), 7.34–7.21 (m, 3H,  $\text{CH}(\text{Ar})$ ), 7.62 – 7.45 (m, 2H,  $\text{CH}(\text{Ar})$ );  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ ):  $\delta$  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  $\text{C}_{20}\text{H}_{28}\text{NaO}_4\text{Se}$   $[\text{M}+\text{Na}]^+$ : 435.1045; found: 435.1039.

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## Notes and references

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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<sup>3a,b</sup> 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.

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