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A New Synthesis of (±)-Frullanolide: Application of 2-Phenylselenopropanoic Acid

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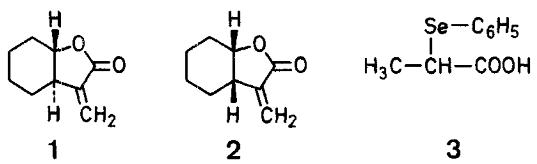
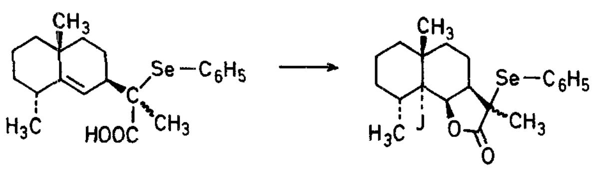
As a part of our efforts to explore the utility of selenium-containing reagents in organic synthesis, we have been interested in the introduction of a masked acrylate unit to suitable substrates resulting in the construction of an α-methylene-γ-butyrolactone moiety. In an earlier report[1], we described the stereoselective synthesis of both *trans*- and *cis*- fused α-methylenelactones **1** and **2**, employing 2-phenylselenopropanoic acid (**3**) as a common synthon.

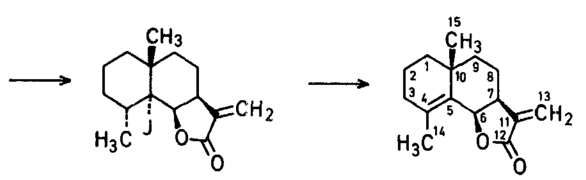


1 **2** **3**

We now report a new total synthesis of (±)-Frullanolide[2-5] (**7**) - an allergenically active lactone sesquiterpene first isolated by Ourisson and coworkers[6] - and thereby demonstrate another application of the synthon **3** as a precursor of the exocyclic double bond. The strategy of our route consists in the construction of the key-intermediate **4a**, which possesses all the necessary functionality for subsequent conversion into the desired product **7**.



4a **5**

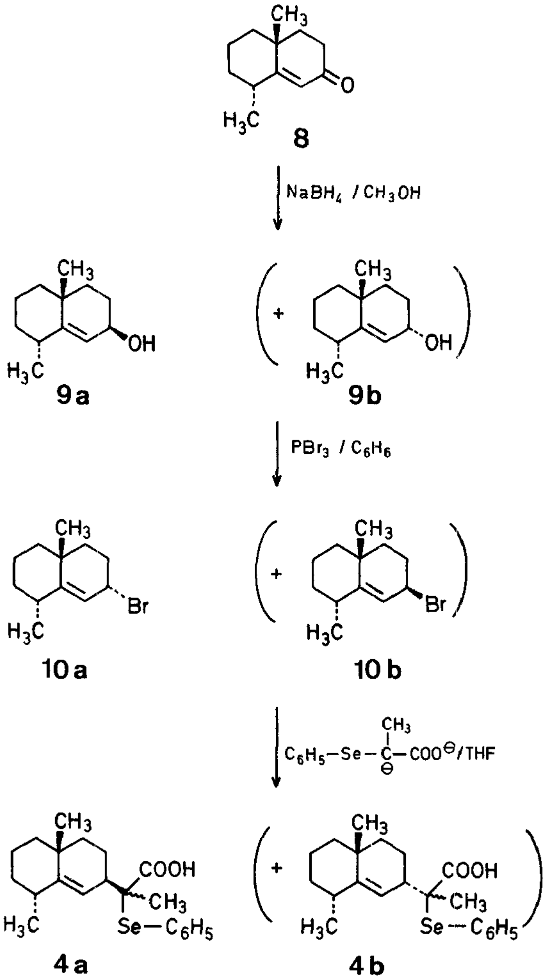


6 **7**

The α-phenylseleno-α-methyl-γ,δ-unsaturated acid **4** can be iodolactonized to **5** (the stereochemistry of this reaction is well known[7,8], giving the *cis*-fused lactone as only product).

Oxidation-elimination[9] of **5** should furnish the product **6** with the exocyclic double bond. As we have demonstrated before[1], the presence of iodine promotes the methyl-proton abstraction, independent of the relative configuration at C-11. Thus, the formation of the undesirable endocyclic double bond isomer is avoided. The iodolactone **6** is the same one synthesized by Still and coworkers[3] and readily undergoes an *anti*-elimination of hydriodic acid to form (±)-Frullanolide (**7**).

In order to obtain **4** with the appropriate stereochemistry at C-7 (an equatorial substituent), we need a precursor with an axial leaving group, which can be substituted in an S_N2 reaction by the dianion of the acid **3**. The allylic bromide **10a** can be such a precursor. Thus, starting from the known octalone **8**[10], the intermediate **4** was obtained in three steps as shown below.



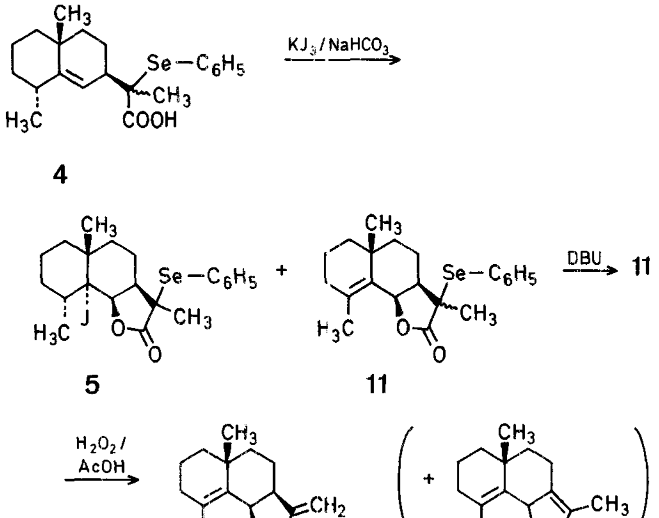
Octalone **8** was prepared via the convenient procedure given in Ref.[11]. Reduction of **8** with sodium borohydride in methanol[12] gave preferentially the expected[13] pseudo-equatorial alcohol **9a** in 88% yield (**9a**:**9b** = 4:1, by G.L.C. analysis).

Reaction of **9** with phosphorus tribromide in benzene furnished the desired allyl bromide **10**, an unstable compound which undergoes spontaneous elimination. Therefore the product **10** was treated without further purification with the dilithio derivative of **3**, giving the acid **4** in 54% overall yield (as a 4:1 mixture of **4a** and **4b**, by ^{1}H-N.M.R. analysis).

Surprisingly, iodoactonization of **4** with potassium triiodide and sodium hydrogen carbonate[4] afforded a mixture containing the expected iodolactone **5** and the dehydroiodination product **11**. This result can be attributed to the presence of iodide ions in excess, which acting as a base, convert the previously formed compound **5** into **11**, probably in an equilibrium reaction. Therefore we were unable to obtain exclusively **11** from **4**; the best results were the formation of a 1:1 mixture of **5** and **11**.

It must be pointed out that, of the two isomers **4a** and **4b**, only **4a** possesses the stereoelectronic requirements to undergo iodolactionization via a diaxial opening of the intermediate iodonium ion. Accordingly, the minor component **4b** was recovered unchanged.

In view of the unexpected formation of lactone **11**, we decided to invert the order of the reactions: the alternative sequence of hydriodic acid elimintion from **5** before its deselenation was then effected.



Treatment of the mixture **5**+**11** with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) furnished pure **11** in 76% yield. The α-phenylseleno-α-methyllactone **11**, when treated with hydrogen peroxide gave (±)-Frullanolide (**7**) in 65% yield. In contrast to our previous report[1], the formation of the endocyclic double bond isomer **12** was not observed. The regioselective exo-elimination is therefore not dependent on the presence of the iodine atom.

2-Hydroxy-8,10-dimethyl-1(9)-octalin (9):

To a solution of octalone **8** (2.85 g, 16 mmol) in methanol (40 ml) at 0°C is added sodium borohydride (0.63 g, 16 mmol). After stirring for 3 h, the mixture is poured into water (60 ml) and extracted with ether (3 × 20 ml). The organic layer is washed with saturated aqueous sodium chloride (20 ml), dried with magnesium sulfate, and the solvent evaporated. The crude product (4:1 mixture of **9a** and **9b** by G.L.C. analysis; conditions: OV-17, 180°C, N_2) is distilled; yield: 2.55 g (88%); b.p. 80–81°C/0.2 torr.

$C_{12}H_{22}O$	calc.	C 79.94	H 11.28
(182.3)	found	80.30	11.65

I.R. (film): ν = 3330, 1658, 1055 cm^{-1}.

^{1}H-N.M.R. (CCl_4): δ = 1.0 (d, J = 6 Hz, 3H); 1.1 (s, 3H); 1.2–2.4 (m, 11H); 3.0 (br. s, 1H); 3.9–4.2 (m, 1H); 5.2 ppm (m, 1H).

2-Bromo-8,10-dimethyl-1(9)-octalin (10):

To a solution of phosphorus tribromide (0.35 g, 1.3 mmol) in anhydrous benzene (2 ml) at 0°C under nitrogen atmosphere, is added **9** (0.45 g, 2.5 mmol). After stirring for 45 min, the mixture is poured into cold water (5 ml) and extracted with petroleum ether (2 × 5 ml). The organic layer is washed with cold saturated aqueous sodium chloride (5 ml) and dried with magnesium sulfate. The solvent is evaporated and the unstable product is used in the next step without purification.

2-Phenylseleno-2-[8,10-dimethyl-1(9)-octal-2-yl]-propanoic Acid (4):

Lithium diisopropylamide (4.4 mmol) is prepared from diisopropylamine and n-butyllithium in tetrahydrofuran (0°C, 15 min, nitrogen atmosphere). To this solution is added the acid **3** (0.46 g, 2 mmol) in tetrahydrofuran (2 ml). After stirring for 15 min at 0°C and 30 min at 40°C, the mixture is recooled to 0°C and a solution of **10** (0.52 g, 2.1 mmol) in tetrahydrofuran (2 ml) is added. After stirring for 15 min at 0°C, the mixture is treated with cold dilute hydrochloric acid (3 ml), extracted with ether (3 × 5 ml), washed with saturated aqueous sodium chloride (5 ml), dried with magnesium sulfate, and the solvent evaporated. The crude product recrystallizes poorly and is purified by chromatography over silica gel, using 15% ether in hexane as eluent; yield: 0.45 g (54% from the alcohol **9**).

$C_{21}H_{28}O_2Se$	calc.	C 64.45	H 7.21
(391.4)	found	64.17	6.84

I.R. (Nujol): ν = 1690, 1580, 1270 cm^{-1}.

^{1}H-N.M.R. (CCl_4): δ = 0.9–3.0 (m, 21H); 4.9 (br. s, 0.2H); 5.7 (br. s, 0.8H); 7.2–7.8 (m, 5H); 10.6 ppm (Br. s, 1H).

5-Iodo-11-phenylseleno-4,5,11,13-tetrahydrofrullanolide (5):

To a solution of **4** (0.39 g, 1 mmol) in tetrahydrofuran (5 ml) are added a 0.5 normal solution of sodium hydrogen carbonate (4 ml) and a solution of iodine (0.25 g, 1 mmol) and potassium iodide (0.49 g, 3 mmol) in water (2 ml). After stirring for 24 h at room temperature, the mixture is extracted with ether (3 × 5 ml). The organic layer is washed with dilute aqueous sodium hydrogen sulfite (5 ml), saturated aqueous sodium chloride (5 ml), dried with magnesium sulfate, and the solvent evaporated; the crude product (0.28 g; 1:1 mixture of **5** and **11** by N.M.R. analysis) is not purified further.

11-Phenylseleno-11,13-dihydrofrullanolide (11):

Following a described procedure[3], a solution of compounds **5** and **11** (0.28 g) in tetrahydrofuran (1 ml) is treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (0.1 g, 0.6 mmol) at room temperature for 1.5 h, then poured into water (3 ml), extracted with ether (3 × 5 ml), washed with saturated aqueous sodium chloride (5 ml), and dried with magnesium sulfate. The solvent is evaporated and the product was purified by chromatography on silica gel (15% ether in petroleum ether as eluent), giving pure compound **11**; yield: 0.16 g (68% from the acid **4**, based on the unrecovered starting material); m.p. 134–135°C.

$C_{12}H_{26}O_2Se$	calc.	C 64.78	H 6.73
(281.3)	found	64.96	6.72

I.R. (Nujol): ν = 1765, 1755, 1640, 1570 cm^{-1}.

^{1}H-N.M.R. (CCl_4): δ = 1.0–2.4 (m, 20H); 5.6 (d, J = 4 Hz, 1H); 7.2–7.7 ppm (m, 5H).

(±)-Frullanolide (7):

A solution of compound **11** (0.16 g, 0.4 mmol) in tetrahydrofuran (2 ml), containing acetic acid (0.06 ml), is treated with 30% hydrogen peroxide (0.3 ml) at 0°C for 30 min, then poured into cold saturated sodium hydrogen carbonate solution (3 ml), and extracted with ether (3 × 5 ml). The organic layer is washed with saturated aqueous sodium chloride (3 ml) and dried with magnesium sulfate. The solvent is evaporated and the crude, racemic product recrystallized from hexane; yield: 0.06 g (65%); m.p. 93.0–93.5°C (Lit.[6], m.p. 92.0–92.5 °C; the pure enantiomer has m.p. 76–77 °C). Spectral data (I.R. and N.M.R.) are identical to those reported in literature[6].

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