Free-Radical Cyclization of Petroselinic Acid

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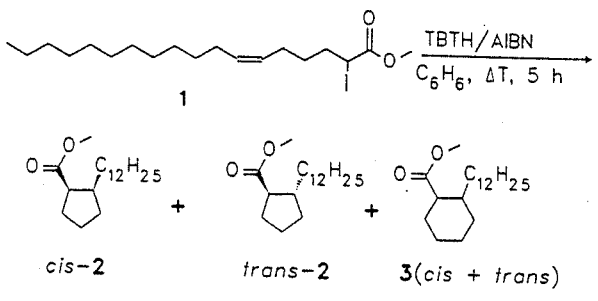
Petroselinic acid was cyclized via methyl 2-iodopetroselinate (**1**) with tributyltin hydride to give methyl *trans*- and *cis*-2-dodecyl-1-cyclopentanecarboxylate (**2**). The atom-transfer method with hexabutylditin resulted in the formation of bicyclic γ-lactones **4** and methyl *trans*-2-(1'-iodododecyl)-1-cyclopentanecarboxylate (*trans*-**5**). The same products were obtained with the new initiator system $SnCl_2$/AgOAc. This method showed, if compared with the other methods, the shortest reaction time, the highest yield and stereoselectivity combined with a very simple workup procedure and the use of less toxic chemicals.

Petroselinic acid (*cis*-6-octadecenoic acid) is a new fatty compound with a content of up to 80% in the seed oil of *coriandrum sativum*[1] and is of interest as a renewable raw material[2]. Intermolecular free-radical additions to unsaturated fatty compounds were investigated by Metzger and Linker[3,4]. Selective formation of a radical center at C-2 of petroselinic acid and the subsequent intramolecular cyclization should give interesting 1,2-disubstituted cyclopentane derivatives.

Therefore we treated methyl 2-iodopetroselinate (**1**), prepared by treatment of methyl petroselinate with lithium diisopropyl amide (LDA) and iodine[5], in the presence of catalytic amounts of AIBN with tributyltin hydride (TBTH). A mixture of the cyclized products *cis*-**2** and *trans*-**2** could be isolated in 35% yield by DBU workup procedure, bulb-to-bulb distillation and urea crystallization to remove linear fatty compounds. Cyclohexane derivatives **3** could be detected by GC/MS as minor products (Scheme 1). The ratio of the products *cis*-**2**/*trans*-**2**/**3** (*cis*/*trans*) was 49:45:6 (3:3) as detected by GC analysis. Compounds **2** were characterized by ^{1}H-NMR, ^{13}C-NMR spectra, mass spectra, and elementary analysis.

Scheme 1



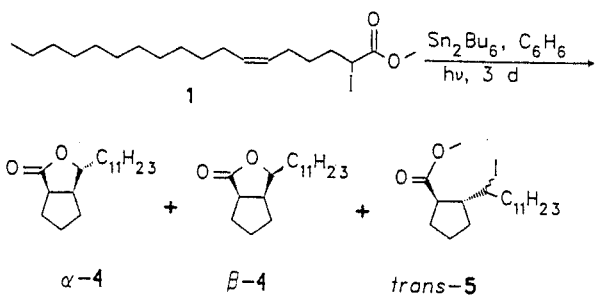
Atom-transfer cyclization of **1** could be achieved by the method of Curran and Chang[6]. Irradiation of **1** with a 300-W sun lamp in C_6H_6 in the presence of 10% hexabutylditin for three days yielded products **4** and *trans*-**5**. The ratio of the products α-**4**/β-**4**/*trans*-**5** was 33:28:39, as detected by GC analysis (Scheme 2).

Lactones α-**4** and β-**4** could be separated by DBU workup procedure and flash chromatography. Iodides **5** could be concentrated by urea crystallization. The overall yield of cyclized products was 50%.

TBTH[7] and hexabutylditin[8] are convenient and often-used reagents to perform such cyclizations[9]. However, there are several problems associated with the use of organotin compounds. For example:

- difficult workup and isolation of the products;
- frequent contamination of the desired products by traces of organotin compounds;
- toxicity of organotin compounds and hence disposal problems[10].

Scheme 2



Thus, methods which avoid the use of organotin compounds in free-radical ractions are increasingly of interest.

Therefore, the system $SnCl_2$/AgOAc[11] was used to add perfluoroalkyl iodides via perfluoroalkyl radicals to the C–C double bond of fatty compounds[4]. We have now applied this initiator system for the first time to the generation of free radicals from α-iodocarboxylates.

The reaction of **1** with $SnCl_2$ and AgOAc in methanol at room temperature gave the same products as the atom-transfer method (Scheme 2). The reaction time was only four hours. The ratio of the products α-**4**/β-**4**/*trans*-**5** was 35:31:34. The workup procedure is very simple. The initiator system can be removed from the products by silica-gel filtration. Lactones **4** could be separated by flash chromatography. Fractions containing *trans*-**5** were reduced with TBTH to *trans*-**2** which was converted into the free acid **6** with methanolic KOH (Scheme 3). The total yield of cyclized products was 68%.

We propose that the reation is initiated by electron transfer from silver to the iodide **1** (Scheme 4). Cyclization of the formed radical and iodine-atom transfer from **1** gives the stereoisomeric products *cis*-**5** and *trans*-**5**. The reaction seems to have a very short chain length because $SnCl_2$/AgOAc has to be applied in stoichiometric amounts. *cis*-**5** could not be detected in the reaction mixture by GC

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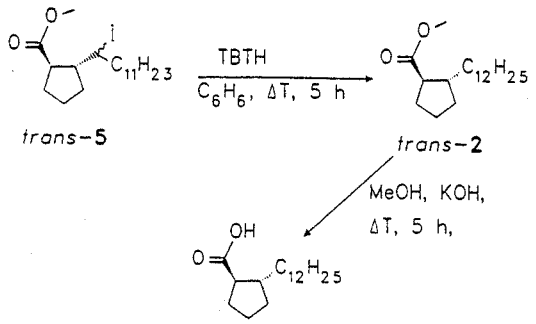
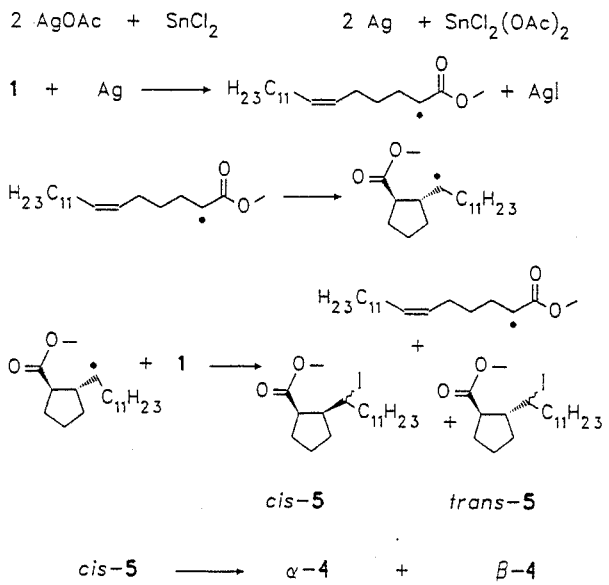
analysis. The reason is a rapid ionic lactonization of *cis*-5 to give the lactones 4.

Scheme 3



Scheme 4



A comparison of the three methods shows that the *cis/trans* ratio (as detected by GC analysis) of the cyclized products decreases with increasing reaction temperature (Table 1).

Table 1. Product ratios of the cyclization reactions of 1

Initiator system	Reaction temperature [°C]	*cis/trans*
TBTH/AIBN	80	52:48[a]
$Sn_2Bu_6/h\nu$	80	53:47[b]
$Sn_2Bu_6/h\nu$	45	61:39[b]
$SnCl_2$/AgOAc	25	66:34[b]

[a] *cis*-2/*trans*-2. — [b] 4/*trans*-5.

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Experimental

Melting points (uncorrected): Leitz Laborlux 12. — n_D: Zeiss-Abbé-Refraktometer. — Elemental analyses: Fa. Beller, Göttingen. — ^1H and ^{13}C NMR: Bruker AM 300 (300 MHz); solvent $CDCl_3$; internal standard tetramethylsilane (TMS). — MS: Finnigan MAT 212 (for GC/MS coupled with Varian 3700). — Analytical GC: Carlo Erba GC 6000 Vega Series 2 with FID detector and Spectra Physics Data Jet Integrator, fused silica capillary column DB 1 30 m. — Medium-pressure liquid chromatography (MPLC): Merck silica gel 60, 0.04–0.063 mm. — Thin-layer chromatography (TLC): Merck plates, silica gel 60 F; detection by treatment with a solution of 15% H_2SO_4, followed by heating at 200°C. — Irradiation: Technolight P 500; 300 W. — Solvents were purified and dried in the usual way. — Petroselinic acid (81.3% petroselinic acid, 3.3% palmitic acid, 0.4% stearic acid, 13.5% $C_{18:2}$), Henkel KGaA, was used without further purification.

Methyl rac-2-Iodopetroselinate (1): 0.81 g (8.00 mmol) of diisopropylamine in 20 ml of dry tetrahydrofuran was cooled under N_2 to −40°C. Then 5.00 ml (8.00 mmol) of *n*-butyllithium in hexane (1.6 M solution, Merck) was added dropwise. After 15 min, the mixture was cooled to −78°C, and 2.08 g (5.70 mmol) of methyl petroselinate was added slowly, and the mixture was stirred for 1 h. It was then added slowly to a solution of 2.45 g (9.60 mmol) of iodine in 20 ml of dry tetrahydrofuran at −78°C. After stirring for 15 min, 2 ml of concentrated HCl was added. The mixture was extracted with a satd. $Na_2S_2O_3$ solution and water, dried with magnesium sulfate and concentrated. The residue was dissolved in petroleum ether/ethyl acetate (1:1). Filtration of the solution through silica gel and concentration of the filtrate yielded 2.95 g of the crude product. GC analysis indicated 9% of methyl petroselinate and 70% of 1. Further purification failed. This mixture was used as starting material in the following reactions. The yield of 1 was 87% based on methyl petroselinate. — ^1H NMR ($CDCl_3$): δ = 5.3–5.4 (m, 2H, 6-, 7-H), 4.31 (t, 1H, 2-H), 3.75 (s, 3H, OCH_3), 1.9–2.1 (m, 6H, 3-, 5-, 8-H), 1.2–1.3 (m, 20H, CH_2), 0.88 (t, 3H, 18-H); $J_{2,3}$ = 7.6 Hz; $J_{17,18}$ = 6.6 Hz. — ^{13}C NMR ($CDCl_3$): δ = 131.0 [C-7(6)], 128.2 [C-6(7)], 52.6 (OCH_3), 35.6 (C-2), 31.8 (C-16), 29.6–28.8 (CH_2), 27.1, 27.1, 26.1, 22.6 (C-17), 20.2, 14.0 (C-18). — CI MS (isobutane): *m/z* = 423 [MH^+]. — MS (70 eV): *m/z* (%) = 295 (5.4) [M^+ − I], 263 (5.8), 235 (5.2), 109 (18), 95 (36), 87 (100), 81 (42), 74 (15).

Methyl rac-2-Dodecyl-1-cyclopentanecarboxylate (*cis*-2 and *trans*-2): Under N_2 (1 bar) 2.00 g (3.20 mmol) of 1 and 0.01 g of AIBN were dissolved in 500 ml of benzene, and the solution was heated to reflux. Then a solution of 1.80 g (6.20 mmol) of TBTH in 50 ml of benzene was added during 2 h. After the addition of 0.01 g of AIBN, the mixture was heated for further 3 h. It was then concentrated to afford a residue which was dissolved in diethyl ether, and DBU was added to the solution. A yellow precipitate formed. DBU was added until no new precipitate was observed. The mixture was titrated with a solution of iodine in diethyl ether until the iodine color persisted. Silica-gel filtration, bulb-to-bulb distillation and threefold urea crystallization to remove linear fatty compounds (product mixture/urea/methanol = 1:10:80) yielded 0.33 g (35%) of a mixture of the cyclized products *cis*-2 and *trans*-2.

rac-cis-2: ^1H NMR ($CDCl_3$): δ = 3.65 (s, 3H, OCH_3), 2.81 (td, *J* = 5.4, 7.7 Hz, 1H, 1-H), 2.0–2.2 (m, 1H, 2-H), 1.4–1.9 (m, 6H, 3-, 4-, 5-H), 1.1–1.3 (m, 22H, CH_2), 0.86 (t, 12′-H); $J_{12',11'}$ = 6.7 Hz. — ^{13}C NMR ($CDCl_3$): δ = 175.9 (CO_2CH_3), 50.8 (OCH_3), 47.5 (C-1), 43.8 (C-2), 31.9 (C-10′), 31.1, 31.0, 29.8–29.3, 28.6, 28.2, 23.8, 22.7 (C-11′), 14.0 (C-12′). — CI MS (isobutane): *m/z* = 297 [MH^+].

– MS (70 eV): *m/z* (%) = 296 (1.2) [M^+], 264 (3), 227 (18), 141 (17), 127 (37) [$M^+ - C_{12}H_{25}$], 87 (100), 67 (28), 55 (45).

rac-trans-2: ^{1}H NMR ($CDCl_3$): δ = 3.62 (s, 3H, OCH_3), 2.30 (q, *J* = 8.3 Hz, 1H, 1-H), 2.0–2.2 (m, 1H, 2-H), 1.4–2.0 (m, 6H, 3-, 4-, 5-H), 1.2–1.4 (m, 22H, CH_2), 0.86 (t, 3H, 12′); $J_{11',12'}$ = 6.7 Hz. – ^{13}C NMR ($CDCl_3$): δ = 177.1 (CO_2CH_3), 51.3 (OCH_3), 50.3 (C-1), 44.4 (C-2), 35.3, 32.5, 31.9 (C-10′), 30.3, 29.7–29.3, 28.3, 24.9, 22.7 (C-11′), 14.1 (C-12′). – CI MS (isobutane): *m/z* = 297 [MH^+]. – MS (70 eV): *m/z* (%) = 296 (1.3) [M^+], 264 (1.4), 141 (1.5), 127 (100) [$M^+ - C_{12}H_{25}$], 87 (32), 67 (16), 55 (18), 43 (9).

$C_{19}H_{36}O_2$ (296.49) Calcd. C 76.97 H 12.24
cis/trans mixture: Found C 76.88 H 12.19

rac-(3α,3aα,6aα)- and rac-(3α,3aβ,6aβ)-Hexahydro-3-undecyl-1H-cyclopenta[c]furan-1-one (α-4 and β-4) and *Methyl rac-trans-2-(1′-Iododecyl)-1-cyclopentanecarboxylate* (*trans*-5): Under N_2 2.00 g (3.20 mmol) of 1 and 0.20 g (0.30 mmol) of Sn_2Bu_6 were dissolved in 500 ml of benzene. The solution was irradiated for 72 h. After 36 h, another 0.10 g (0.15 mmol) of Sn_2Bu_6 was added. After concentration of the mixture and DBU-workup procedure, a flash chromatography [petroleum ether/ethyl acetate (8:2)] yielded fractions containing 4. 0.13 g (14%) of β-4 and 0.15 g (17%) of α-4 could be separated by MPLC [petroleum ether/ethyl acetate (92:8)]. Fractions containing *trans*-5 were concentrated by urea crystallization to afford 0.49 g (19%) of *trans*-5. The total yield of cyclized products was 50%.

rac-α-4: Colorless oil. – n_D^{20} = 1.4704. – IR (neat): $\tilde{\nu}$ = 2980 cm^{-1}, 2950, 2880, 1780, 1470. – ^{1}H NMR ($CDCl_3$): δ = 4.09 (ddd, 1H, 3-H), 3.05 (ddd, 1H, 6a-H), 2.56 (dddd, 1H, 3a-H), 1.4–2.2 (m, 8H, 4-, 5-, 6-, 1′-H), 1.2–1.4 (m, 18H, CH_2), 0.88 (t, 3H, 11′-H); $J_{3a,6a}$ = 9.4 Hz, $J_{6,6a}$ = 2.7, 9.4 Hz, $J_{3,3a}$ = 3.7 Hz, $J_{4,3a}$ = 8.0, 3.0 Hz, $J_{3,1'}$ = 5.9, 7.1 Hz, $J_{10',11'}$ = 6.7 Hz. – ^{13}C NMR ($CDCl_3$): δ = 180.6 (CO_2), 86.4 (C-3), 45.0 (C-3a), 45.0 (C-6a), 36.6, 33.6, 31.9 (C-9′), 30.8, 29.6–29.3 (6-C), 25.4, 25.0, 22.6 (C-10′), 14.1 (C-11′). – CI MS (isobutane): *m/z*: 281 [MH^+]. – MS (70 eV): *m/z* (%) = 280 (1.3) [M^+], 262 (1.0), 168 (3.5), 125 (100) [$M^+ - C_{11}H_{23}$], 82 (14), 79 (20), 68 (18), 67 (35).

$C_{18}H_{32}O_2$ (280.45) Calcd. C 77.09 H 11.50
Found C 77.20 H 11.42

rac-β-4: M.p. 55°C (petroleum ether). – IR (KBr): $\tilde{\nu}$ = 2970 cm^{-1}, 2930, 2860, 1700, 1470. – ^{1}H NMR ($CDCl_3$): δ = 4.50 (dt, 1H, 3-H), 3.09 (ddd, 1H, 6a-H), 2.76 (dddd, 1H, 3a-H), 1.4–2.1 (m, 8H, 4-, 5-, 6-, 1′-H), 1.2–1.4 (m, 18H, CH_2), 0.88 (t, 3H, 11′-H); $J_{3a,6a}$ = 8.7 Hz, $J_{6,6a}$ = 3.7, 8.6 Hz, $J_{3,3a}$ = 8.3 Hz, $J_{4,3a}$ = 8.5, 3.7 Hz, $J_{3,1'}$ = 5.6 Hz, $J_{10',11'}$ = 6.7 Hz. – ^{13}C NMR ($CDCl_3$): δ = 180.7 (C-1), 81.3 (C-3), 46.8 (C-6a), 44.1 (C-3a), 31.9 (C–9′), 31.1, 29.6–28.8 (7 C), 26.2, 26.1, 26.1, 22.6 (C-10′), 14.1 (C-11′). – CI MS (isobutane): *m/z*: 281 [MH^+]. – MS (70 eV): *m/z* (%) = 280 (10) [M^+], 262 (4.0), 236 (1.5), 125 (100) [$M^+ - C_{11}H_{23}$], 82 (70), 79 (30), 68 (61), 67 (94).

$C_{18}H_{32}O_2$ (280.45) Calcd. C 77.09 H 11.50
Found C 77.07 H 11.63

rac-(3α,3aα,6aα)- and rac-(3α,3aβ,6aβ)-Hexahydro-3-undecyl-1H-cyclopenta[c]furan-1-one (α-4 and β-4) and *rac-trans-2-Dodecyl-1-cyclopentanecarboxylic Acid* (6): Under N_2 2.00 g (3.20 mmol) of 1 was added to a mixture of 2.00 g (10.6 mmol) of $SnCl_2$ and 0.20 g (1.10 mmol) of AgOAc in 500 ml of methanol. After 1 h and after 3 h again, 0.20 g (1.10 mmol) of AgOAc was added. After 4 h, the reaction mixture was filtered, concentrated, the residue dissolved in petroleum ether/ethyl acetate (1:1) and the solution filtered through silica gel. After flash chromatography of the filtrate [petroleum ether/ethyl acetate (8:2 and 94:6)], 0.21 g (23%) of α-4 and 0.18 g (20%) of β-4 were obtained. Fractions containing *trans*-5 were treated as usual with TBTH to give *trans*-2, which gave on treatment with methanolic KOH and workup as usual the free acid 6. Recrystallization and MPLC [petroleum ether/ethyl acetate (96:4)] gave 0.22 g (24%) of 6. The yield of cyclized products was 68%.

rac-trans-2-Dodecyl-1-cyclopentanecarboxylic Acid (6): M.p. 61°C (petroleum ether). – IR (KBr): $\tilde{\nu}$ = 2980 cm^{-1}, 2940, 2880, 1710, 1480, 930. – ^{1}H NMR ($CDCl_3$): δ = 2.35 (q, *J* = 8.2 Hz, 1H, 1-H), 2.0–2.2 (m, 1H, 2-H), 1.4–2.0 (m, 6H, 3-, 4-, 5-H), 1.2–1.4 (m, 22H, CH_2), 0.88 (t, 3H, 12′-H); $J_{11',12'}$ = 6.6 Hz. – ^{13}C NMR ($CDCl_3$): δ = 183.4 (CO_2H), 50.3 (C-1), 44.5 (C-2), 35.4, 32.6, 31.9 (C-10′), 31.0, 30.4–29.7 (6-C), 29.4, 28.2, 24.9, 22.7 (C-11′), 14.1 (C-12′). – CI MS (isobutane): *m/z* = 283 [MH^+]. – MS (70 eV): *m/z* (%) = 282 (1.8) [M^+], 264 (0.8), 127 (3), 113 (100) [$M^+ - C_{12}H_{25}$], 95 (7), 81 (8), 73 (12), 67 (13).

$C_{18}H_{34}O_2$ (282.47) Calcd. C 76.54 H 12.13
Found C 76.54 H 12.11

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