Synthesis and biological resolution of condensed bicyclic isoparaconic acid † derivatives

Sara Drioli, Fulvia Felluga, Cristina Forzato, Giuliana Pitacco * and Ennio Valentin

Dipartimento di Scienze Chimiche, Università degli Studi di Trieste, via L. Giorgieri 1, I-34127 Trieste, Italy

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Kinetic resolution of chiral racemic (1*R**,3a*S**,7a*S**)-hexahydro-2-oxobenzofuran-3-ylacetic acid ethyl ester was achieved by means of immobilized Lipozyme®. At low conversion values, the (−)-acid was isolated with 84% ee, while at high conversion values the (+)-ester was obtained with 98% ee. Their configurations were determined by transformation of the acid into the corresponding α-methylene derivative of known absolute configuration.

Introduction

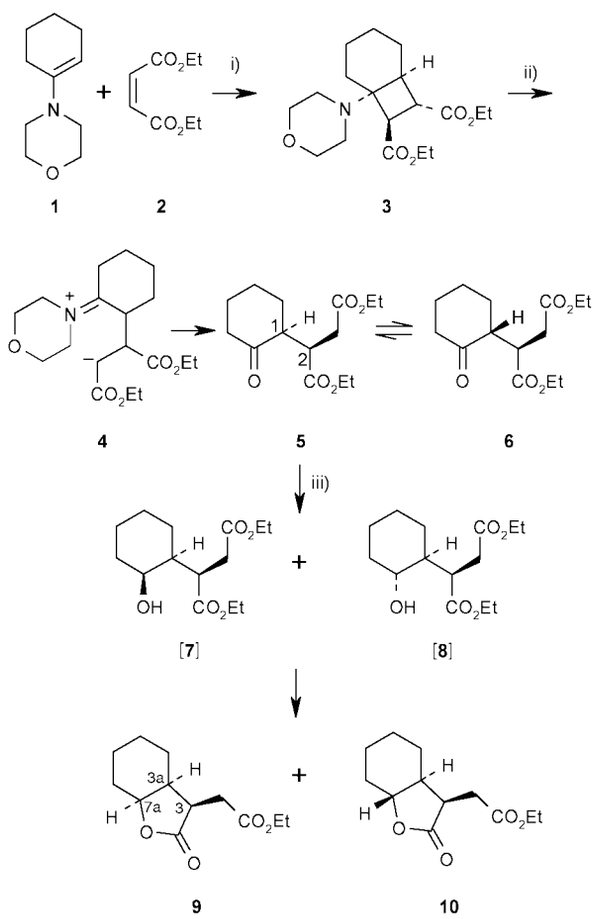
The availability of optically active γ-lactones is of particular interest because of the presence of the lactone ring in many natural products[1] and in pharmaceutically active compounds.[2] In particular α-methylene γ-butyrolactone derivatives represent a major class of natural products.[3] Recently we focused our attention on the synthesis of pure optically active condensed bicyclic γ-lactones[4] and paraconic acid derivatives[5] by means of biotransformations. In the present paper we describe the synthesis and kinetic resolution of optically active condensed isoparaconic acid derivatives[6] by means of hydrolases.

Results and discussion

The reaction of 1-(morpholin-4-yl)cyclohexene **1** and diethyl maleate **2** (or fumarate), run at 25 °C in dry acetonitrile for 3 days,[7] afforded the bicyclo[4.2.0]octane derivative **3**. X-Ray analysis[8] of the dimethyl analog of **3** revealed the *cis* fusion between the rings and the *trans* relationship between the two methoxycarbonyl groups. Since the NMR spectrum of the methyl diester was practically superimposable with that of the diethyl derivative **3**, the same stereochemistry was assigned also to **3**, as shown in Scheme 1.

Nucleophilic ring fission of **3** was carried out under hydrolytic conditions in phosphate buffer (pH 7.4) at room temperature. Under these mild conditions, the product of kinetic formation **5** in *anti* geometry was isolated in high diastereoselective purity (94% de). However, when the keto-diester **5** was kept in the reaction medium, a rapid equilibration at 1-C resulted in an approximately 1:1 mixture of *anti* and *syn* diastereoisomers **5** and **6**, respectively. Compound **5** was assigned the *anti* configuration on the basis of the mechanism of the nucleophilic ring fission, implying formation of the dipolar intermediate **4**[9] followed by hydrolysis,[7] as well as from a comparison of the values of J_{12} in the ^{1}H NMR spectra of the two diastereoisomers. In accordance with the Karplus equation, the average vicinal coupling constant in the *anti* (*erythro*) isomer **5** was larger (^3J 6.8 Hz) than that in the *syn* (*threo*) isomer **6** (^3J 4.4 Hz).[10]

Since the equilibration between the two diastereoisomers **5** and **6** was much faster than any enzymatic resolution, a kinetic resolution of racemic **5** was not possible. Moreover, the diastereomeric pair was inseparable on chiral HRGC, thus preventing the use of the mixture as a substrate for enzymatic hydrolyses. On the contrary, chemical reduction with sodium borohydride was fast enough to avoid the equilibration to take place. Therefore, when the ketodiester **5**, contaminated by 3% of the *syn* isomer **6**, was reduced with sodium borohydride in ethanol, a rapid cyclization of the resulting hydroxydiesters **7** and **8**, not isolated, occurred. Two isomeric bicyclic γ-lactones **9** and **10** in 85:15 ratio were obtained, as a consequence of a diastereoselective attack of hydride onto the carbonyl carbon atom.



Scheme 1 i) MeCN, 25 °C; ii) H_2O, pH 7.4; iii) $NaBH_4$, EtOH, 25 °C. Compounds in brackets were not isolated.

Since both lactones were derived from **5**, they differed in the stereochemistry of 7a-C. In the major component **9**, isolated

† The IUPAC name for paraconic acid is 5-oxotetrahydrofuran-3-carboxylic acid.

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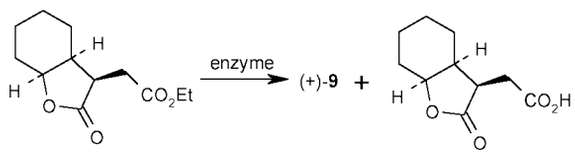
Table 1 Enzymatic hydrolyses of (±)-**9**



(±)-**9** (−)-**11**

			Ester (+)-**9**			Acid (−)-**11**		
Enzyme	Conv. (%)	*E*	Yield (%)[e]	ee[f] (%)	Configuration	Yield (%)[e]	ee[g] (%)	Configuration
Lipozyme®[a]	14	13	50	14	1*S*,3a*R*,7a*R*	11	84	1*R*,3a*S*,7a*S*
CAL-B[b] 9.2 U mg^{-1}	26	10	65	27	1*S*,3a*R*,7a*R*	11	76	1*R*,3a*S*,7a*S*
Lipozyme®[c]	64	—	30	98	1*S*,3a*R*,7a*R*	33	55	1*R*,3a*S*,7a*S*
CAL-B[d] 9.2 U mg^{-1}	64	—	34	96	1*S*,3a*R*,7a*R*	35	51	1*R*,3a*S*,7a*S*

[a] Conditions: 1.77 mmol of (±)-**9** and 318 mg of Lipozyme® in 8 cm^3 of 0.1 M phosphate buffer, pH 7.4, 25 °C. [b] Conditions: 1.77 mmol of (±)-**9** and 18 mg of CAL-B in 8 cm^3 of 0.1 M phosphate buffer, pH 7.4, 25 °C. [c] Conditions: 0.88 mmol of (±)-**9** (14% ee) and 150 mg of Lipozyme® in 8 cm^3 of 0.1 M phosphate buffer, pH 7.4, 25 °C. [d] Conditions: 1.15 mmol of (±)-**9** (27% ee) and 10 mg of CAL-B in 8 cm^3 of 0.1 M phosphate buffer, pH 7.4, 25 °C. [e] Chemical yield in isolated product. [f] Determined by chiral HRGC analysis. [g] Determined by chiral HRGC analysis of the ethyl ester derivative.

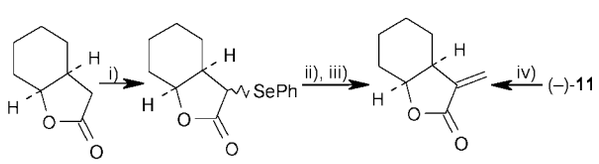
in 40% yield after purification by flash-chromatography, the fusion between the rings was *cis*, as proved by means of NOE difference experiments. In fact, irradiation of 3a-H enhanced the signals of both 3-H (7%) and 7a-H (7%), while the signals relative to 3a-H and 7a-H increased (7% and 6% respectively) upon irradiation of 3-H. The relative configuration of 3-C and 3a-C in both **9** and **10** was the same as in the parent ketodiester **5**, while the *trans* fusion in **10** was confirmed by the lack of enhancement of 7a-H from 3a-H.

Compound (±)-**9** was kinetically resolved by means of hydrolases. Several commercially available enzymatic systems were checked and the best results for low and high conversion values are presented in Table 1, which also details the absolute configuration of the enantiomers obtained. Although no enzymatic system was characterized by a high *E* value,[11] *Candida antarctica* lipase B (CAL-B), and immobilized Lipozyme® allowed the isolation of the corresponding optically active ester (+)-**9** and acid (−)-**11**, both with fairly good enantiomeric excesses.

Of the other enzymes checked, horse liver acetone powder (HLAP) showed an enantiocomplementary activity with respect to CAL-B and Lipozyme®, but only the lactonic ester (−)-**9** could be obtained in 85% ee, after 70% conversion, while the acid was a racemate. *Candida rugosa* lipase (CRL), porcine liver acetone powder (PLAP) and pig liver esterase (PLE) showed no enantioselectivity, while porcine pancreatic lipase (PPL) and α-chimotrypsin (α-CT) showed no activity.

The absolute configuration of the enantiomerically pure lactones **9** and **11** was determined by means of chemical correlation and by analysis of their CD spectra.

The acid (−)-**11** (84% ee) was transformed into the corresponding α-methylene γ-lactone (−)-**15**[12] (Scheme 2), by a



(−)-**12** 3*R*-(−)-**13** 3*S*-(−)-**14** (−)-**15**

Scheme 2 i) LDA, Ph_2Se_2; ii) LDA, CH_3I; iii) H_2O_2, AcOH; iv) $Pb(OAc)_4$, Cu^{2+}, py.

degradation reaction carried out under the conditions by Kochi,[13] *i.e.* with $Pb(OAc)_4$ in the presence of cupric ions. The same lactone (−)-**15** was also obtained starting from the already known lactone (−)-**12**, this latter compound was prepared *via* a biotransformation reaction.[4a,14] Lactone (−)-**12** was methylenated following the method by Grieco,[12b] *i.e.* by α-selenylation, methylation with MeI, oxidation and elimination. The α-selenylated intermediates (−)-**13** and (−)-**14**[15], obtained in the ratio of 3 : 2, were isolated and their configurations were assigned by means of DIFNOE measurements (see Experimental section). As a consequence, the absolute configuration of (−)-**9** is 1*R*,3a*S*,7a*S*.

The lactone (−)-**11** as well as its ethyl ester derivative (−)-**9** exhibited negative Cotton effects in their CD spectra, associated with the n→π* transition of the lactone group. A correlation between the sign of the Cotton effect and the absolute configuration of a series of condensed γ-lactones has recently been made.[4] The Okuda rule,[16] formulated for lactones having the hydroxy group at the α-position, was found to be valid also when a methyl or an ethyl group was the substituent.[17] In fact γ-lactones possessing the (1*R*,3a*S*,7a*S*) absolute configuration exhibited a negative Cotton effect, as a consequence of the orientation of the α-substituent. Since the absolute configuration of both (−)-**9** and (−)-**11** is (1*R*,3a*S*,7a*S*), this means that the Okuda rule still holds also when the substituent α to the carbonyl group is the CH_2CO_2R group.

As to the α-methylene γ-lactone (−)-**15**, it exhibited a weak positive Cotton effect at 256 nm, associated with the n→π* transition and an intense negative Cotton effect at 214 nm, associated with the π→π* transition. This is in accordance with that found for other analogous bicyclic α-methylene γ-lactones having the (3a*S*,7a*S*) absolute configuration.[4b,c]

Experimental

Materials

Lipase (EC 3.1.1.3) from porcine pancreas (type II, crude, No L-3126), from *Candida rugosa* (No. L-1754), esterase from pig liver (EC 3.1.1.1.) in 3.2 M $(NH_4)_2SO_4$ suspension (No. E-2884), porcine liver acetone powder (No. L-8251) and horse liver acetone powder (No. L-9627), were supplied from Sigma Chemicals Co.; Lipozyme® (immobilized lipase from *Mucor miehei*), lipase B recombinant from *Candida antarctica* (62288; 9.2 U mg^{-1}), α-chymotrypsin from bovine pancreas (27272; 53.1 U mg^{-1}) were supplied from Fluka Bio-Chemica.

General

IR spectra were recorded on a Jasco FT-IR 200 spectrophotometer. ^{1}H NMR and ^{13}C NMR were run on a JEOL

EX-400, at 400.0 and 100.4 MHz, respectively, using deuterochloroform as a solvent and tetramethylsilane as an internal standard; coupling constants are given in Hz. Optical rotations were determined on a Perkin-Elmer Model 241 polarimeter, at 25 °C with a 10 cm cell; [α] values are given as 10^{-1} deg cm^2 g^{-1}. CD spectra were obtained on a Jasco J-710A spectropolarimeter (with a 0.1 cm cell) in methanol; [Θ] values are given as deg cm^2 dmol^{-1}. Mass spectra (EI, positive ions) were run on a VG 7070 spectrometer at 70 eV. HRGC analyses were obtained on a Carlo Erba GC 8000 instrument using a Alltech type CARBOWAX column (30 m × 0.32 mm); chiral HRGC analyses were obtained on a Shimadzu 14B apparatus, using a Mega type DMePeBETACDX column (25 m × 0.32 mm) and Chiraldex™ type G-TA, trifluoroacetyl-γ-cyclodextrin column (40 m × 0.25 mm). Mps were determined on a Büchi SHP-20 apparatus and are uncorrected.

Diethyl [1*R**,6*S**,7*S**,8*R**]-1-(morpholin-4-yl)bicyclo[4.2.0]-octane-7,8-dicarboxylate 3

A solution of diethyl maleate **2** (2.1 g, 12 mmol) in dry acetonitrile (2 cm^3) was added dropwise to a solution of 1-(morpholin-4-yl)cyclohexene **1** (2.0 g, 12 mmol) in acetonitrile (50 cm^3), at 25 °C. After 3 days, the reaction mixture was worked up by the method of Brannock *et al.*[7] to give the cyclobutane derivative **3** (2.8 g, 70% yield), as a colourless oil; ν_{max} (film)/cm^{-1} 1724 (CO_2Et); δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.18 (6 H, 2 × t, *J* 7.1, 2 × OCH_2CH_3), 1.36–1.15 (3 H, m), 1.66–1.39 (4 H, m), 1.93 (1 H, m), 2.40 (1 H, m, 4-H), 2.52 (2 H, m, CH_2N), 2.62 (2 H, m, CH_2N), 2.92 (1 H, t, *J* 10.0, 7-H), 3.08 (1 H, d, *J* 10.0, 8-H), 3.60 (4 H, m, CH_2OCH_2), 4.07 (4 H, 2 × q, *J* 7.1, 2 × OCH_2CH_3); δ_C (100.4 MHz; $CDCl_3$) 14.1 (q), 20.8 (t), 22.1 (t), 23.8 (t), 24.8 (t), 35.7 (d), 40.0 (d), 47.0 (t), 47.5 (d), 60.4 (t), 61.6 (s), 67.4 (t), 171.2 (s), 173.5 (s).

u-2-(2-Oxocyclohexyl)butane-1,4-dioic acid diethyl ester 5

A suspension of **3** (1.0 g, mmol) in 5 cm^3 of 0.1 M KH_2PO_4–Na_2HPO_4 buffer (pH 7.4) was stirred at 25 °C, keeping the pH value within 7.4 and 7.8 by addition of 1 M HCl. After 24 h the aqueous phase was extracted with diethyl ether (3 × 10 cm^3), the organic phase dried (Na_2SO_4), and evaporated to give **5** (0.67 g, 85% yield), as an oil; R_t 26.17 min (CARBOWAX, 200 °C isotherm); ν_{max} (film)/cm^{-1} 1735 (CO_2Et), 1711 (C=O); δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.25 (6 H, 2 × t, *J* 7.1, 2 × OCH_2CH_3), 1.56 (1 H, m, 3-H), 1.66 (2 H, m, 4-H, 5-H), 1.91 (1 H, m, 4-H), 2.02 (1 H, m, 3-H), 2.07 (1 H, m, 5-H), 2.32 (1 H, m, 6_{ax}-H), 2.40 (1 H, m, 6_{eq}-H), 2.48 (1 H, dd, *J* 4.4 and 16.6, CH_2CO_2Et), 2.78 (1 H, m, $CHCO$), 2.81 (1 H, dd, *J* 9.3 and 16.6, CH_2CO_2Et), 3.16 (1 H, ddd, *J* 4.4, 6.8 and 9.3, $CHCO_2Et$), 4.14 (4 H, 2 × q, *J* 7.1, 2 × OCH_2CH_3); δ_C (100.4 MHz; $CDCl_3$) 14.0 (q), 14.1 (q), 24.8 (t), 27.3 (t), 31.1 (t), 33.7 (t), 41.1 (d), 41.9 (t), 51.6 (d), 60.4 (t), 60.5 (t), 172.0 (s), 173.5 (s), 210.0 (s).

l-2-(2-Oxocyclohexyl)butane-1,4-dioic acid diethyl ester 6

ν_{max} (film)/cm^{-1} 1735 (CO_2Et), 1711 (C=O); δ_H (400 MHz; $CDCl_3$; Me_4Si) 2.50 (1 H, dd, *J* 4.4 and 16.6, CH_2CO_2Et), 2.68 (1 H, dd, *J* 9.0 and 16.6, CH_2CO_2Et), 2.82 (1 H, m, $CHCO$), 3.28 (1 H, dd, *J* 4.4 and 9.0, $CHCO_2Et$), 4.14 (4 H, 2 × q, *J* 7.1, 2 × OCH_2CH_3).

(1*R**,3a*S**,7a*S**)-2-Oxooctahydrobenzofuran-3-ylacetic acid ethyl ester 9

Sodium borohydride (0.13 g, 3.5 mmol) was added portionwise at 25 °C to a stirred solution of the substrate **5** (1.88 g, 7.0 mmol) in ethanol (4 cm^3). After 4 h, water was added and the aqueous phase was extracted with ether (3 × 10 cm^3). The organic phase was washed with brine and dried on Na_2SO_4. Removal of the solvent left an oily residue (1.28 g, 81% yield) which was purified by flash chromatography (eluant: ethyl acetate–light petroleum (40–70 °C); gradient from 0% to 20%) affording the lactone **9** (0.6 g; 40% yield), as an oil; R_t 30.64 min (CARBOWAX, 200 °C isotherm); ν_{max} (film)/cm^{-1} 1776 (O–C=O), 1734 (CO_2Et); δ_H (400 MHz; $CDCl_3$; Me_4Si) 0.94 (1 H, m, 7_{ax}-H), 1.16 (1 H, m, 6_{ax}-H), 1.23 (3 H, t, *J* 7.1, CH_3), 1.33 (1 H, m, 5_{ax}-H), 1.55 (3 H, m, 7_{eq}-H, 4_{ax}-H, 5_{eq}-H), 1.70 (1 H, m, 6_{eq}-H), 2.20 (1 H, m, 4_{eq}-H), 2.40 (1 H, dd, *J* 10.3 and 17.0, CH_2CO_2Et), 2.45 (1 H, m, 7a-H), 2.76 (1 H, dd, *J* 4.9 and 17.1, CH_2CO_2Et), 3.15 (1 H, ddd, *J* 4.9, 5.9 and 10.3, $CHCO$), 4.13 (2 H, q, *J* 7.1, OCH_2CH_3), 4.46 (1 H, m, CHO); δ_C (100.4 MHz; $CDCl_3$) 14.1 (q), 19.5 (t), 22.9 (t), 23.0 (t), 27.3 (t), 29.3 (t), 37.9 (d), 44.3 (d), 60.8 (t), 77.6 (d), 171.5 (s), 177.7 (s); *m*/*z* (EI, 70 eV) 226 ($M^{+\bullet}$, 11%), 208 (13), 181 (64), 163 (28), 152 (20), 146 (34), 136 (100), 128 (17), 118 (13), 109 (33), 108 (48), 96 (92), 94 (94), 88 (41), 81 (98), 79 (68), 70 (27), 67 (91).

General procedure for enzymatic hydrolyses of the lactonic ester (±)-9

To a suspension of (±)-**9** in 0.1 M KH_2PO_4–Na_2HPO_4 buffer at pH 7.4, enzyme was added at 25 °C under vigorous stirring. The pH value was kept within 7.4 and 7.8 by adding 1 M NaOH. The course of the reaction was monitored by chiral HRGC. At 20% conversion diethyl ether was added, the mixture was centrifuged and the ethereal phase separated. This procedure was repeated 4 times, then the organic phase was dried over Na_2SO_4. Removal of the solvent gave the unreacted compound (+)-**9**. The neutral mother liquors were acidified to pH 2 with 1 M HCl and extracted with diethyl ether. The organic phase was washed with water and dried on Na_2SO_4. Evaporation of the solvent gave the acid (−)-**11**. The recovered ester, with a low enantiomeric excess, was subsequently hydrolyzed with the same enzyme at high conversion, followed by the usual work-up.

(−)-(1*R*,3a*S*,7a*S*)-2-Oxooctahydrobenzofuran-3-ylacetic acid 11. Hydrolysis of (±)-**9** (0.4 g, 1.77 mmol) by Lipozyme® was run using 318 mg of the immobilized enzyme (180 mg mmol^{-1}). After 6 h and addition of 0.25 eq. of NaOH, the hydrolysis was stopped. The workup gave the acid (−)-**11** in 11% yield; mp 84 °C (from light petroleum (40–70 °C) and ethyl acetate) (Found: C, 60.3, H, 7.1; $C_{10}H_{14}O_4$ requires: C, 60.6, H, 7.1%); ν_{max}($CHCl_3$)/cm^{-1} 1761 (CO_2H), 1714 (C=O); δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.00 (1 H, m), 1.19 (1 H, m), 1.38 (1 H, m), 1.61 (3 H, m), 1.76 (1 H, m), 2.26 (1 H, m), 2.48 (1 H, m, 7a-H), 2.51 (1 H, dd, *J* 9.3 and 17.6, CH_2CO_2Et), 2.88 (1 H, dd, *J* 4.9 and 17.6, CH_2CO_2Et), 3.18 (1 H, dt, *J* 5.6 and 9.8, CHCO), 4.51 (1 H, m, CHO), 10.40 (1 H, br s, OH); δ_C (100.4 MHz; $CDCl_3$) 19.5 (t), 22.9 (t), 23.0 (t), 27.3 (t), 29.2 (t), 37.9 (d), 44.2 (d), 77.9 (d), 176.9 (s), 177.8 (s); *m*/*z* (EI, 70 eV) 180 (M − H_2O, 7%), 152 (9), 136 (26), 119 (8), 108 (12), 98 (7), 95 (38), 94 (100), 93 (10), 91 (9), 82 (12), 81 (62), 79 (51), 67 (53); 84% ee (by chiral HRGC of its ethyl ester derivative); $[\alpha]_D^{25}$ −69.6 (*c* 0.1 in MeOH); $[\Theta]_{216}$ −2079.

(+)-(1*S*,3a*R*,7a*R*)-2-Oxooctahydrobenzofuran-3-ylacetic acid ethyl ester 9. Hydrolysis of (+)-**9** (14% ee) (200 mg, 0.88 mmol), carried out with 150 mg of Lipozyme® for a further 72 h, afforded, after the usual workup, the unreacted ketoester (+)-**9** in 30% yield; 98% ee (by chiral HRGC); $[\alpha]_D^{25}$ + 41.0 (*c* 0.36 in MeOH); $[\Theta]_{215}$ +1518.

α-Methylenation of (−)-12

The lactone (−)-**12** (99% ee)[14] (180 mg, 1.28 mmol) was α-phenylselenated with Ph_2Se_2 according to the literature.[12b] Compounds (−)-**13** and (−)-**14**[15] were obtained in the ratio of 3:2. The products were separated by flash chromatography (eluant: light petroleum (40–70 °C)–ethyl acetate 99.5:0.5).

(−)-(3*R*,3a*R*,7a*S*)-3-Phenylselanylhexahydrobenzofuran-2-(3*H*)-one 13.[15] (40% yield) δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.17 (3 H, m), 1.40 (2 H, m), 1.54 (1 H, m), 1.68 (1 H, m), 2.00 (1 H, m), 2.22 (1 H, m, H-3a), 3.57 (1 H, d, *J* 2.2, C*H*-SePh), 4.60 (1 H, dt, $J_1 = J_2$ 4.2, J_3 8.1 C*H*O), 7.24 (3 H, m, Ar-*H*), 7.56 (2 H, m, Ar-*H*); DIFNOE measurements: irradiation at 4.60 ppm enhanced the signal at 2.22 ppm (6%); irradiation at 3.57 ppm enhanced the signal at 2.22 ppm (3%); 99% ee, $[\alpha]_D^{25}$ −40.0 (*c* 0.1 in MeOH); $[\Theta]_{304}$ −1032, $[\Theta]_{275}$ +1070, $[\Theta]_{252}$ −1633, $[\Theta]_{218}$ −12573.

(−)-(3*S*,3a*R*,7a*S*)-3-Phenylselanylhexahydrobenzofuran-2-(3*H*)-one 14.[15] (21% yield) δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.38–1.05 (3 H, m), 1.49 (2 H, m), 1.68 (1 H, m), 1.84 (1 H, m), 2.15 (1 H, m), 2.39 (1 H, sext., H-7a), 4.23 (1H, d, *J* 6.2, C*H*-SePh), 4.42 (1 H, q, *J* 3.3, C*H*O), 7.18 (3 H, m, Ar-*H*), 7.58 (2H, m, Ar-*H*); DIFNOE measurements: irradiation at 4.42 ppm enhanced the signal at 4.23 ppm (6%) and at 2.39 ppm (5%); 99% ee, $[\alpha]_D^{25}$ −90.9 (*c* 0.1 in MeOH), $[\Theta]_{285}$ −7524, $[\Theta]_{230}$ +17061.

(−)-(3a*S*,7a*S*)-3-Methylenehexahydrobenzofuran-2(3*H*)-one 15.[12] Methylation of the mixture of (−)-**13** and (−)-**14**, followed by oxidation–elimination by the method of Grieco,[12b] afforded the lactone (−)-**15**. The IR and ^1H NMR data were identical with those reported in the literature.[12] δ_C (100.4 MHz; $CDCl_3$) 20.5 (t), 21.1 (t), 26.2 (t), 28.8 (t), 39.5 (d), 76.7 (d), 119.8 (t), 139.8 (s), 171.0 (s); 99% ee $[\alpha]_D^{25}$ −46.4 (*c* 0.07 in MeOH); $[\Theta]_{256}$ +516, $[\Theta]_{214}$ −6904.

The acid (−)-**11** having 84% ee was decarboxylated with $Pb(OAc)_4$ according to the literature[13] to give (−)-**15**, 84% ee (determined by chiral HRGC, γ-CDX, 120 °C for 20 min, 3 °C min^{-1} up to 150 °C).

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