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A Highly Stereoselective Divergent Synthesis of Bicyclic Models of Photoreactive Sesquiterpene Lactones

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Sesquiterpene lactones are natural stereochemically pure compounds, which show a number of biological activities. In order to study the reactivity of sesquiterpene lactones in biological systems, we describe herein the asymmetric synthesis of a simple model, the α-methylene-hexahydrobenzofuranone **1**, which includes the α-methylene-γ-butyrolactone moiety and presents all the different possible ring junctions. Enantioselectivity was obtained by asymmetric palladium-catalyzed allylic substitution, and diastereoselectivity was achieved by iodolactonization. This strategy afforded the different lactones with an enantiomeric excess of >98 %.

Introduction

The α-methylene-γ-butyrolactone ring system is of great interest and significance since this cyclic template is found in many highly bioactive molecules and especially in sesquiterpene lactones (Figure 1). Sesquiterpene lactones are natural products, reported to have considerable biological activities as allergenic agents,[1] growth inhibitors[2] and antibacterial,[3] antiinflammatory[4] and antitumor agents.[5] Previous work has shown that α,β-unsaturated carbonyl systems such as an α-methylene-γ-butyrolactone, an α,β-unsaturated cyclopentenone or a conjugated ester was required for significant activity. Indeed these structures have been shown to react with nucleophiles, especially cysteine sulfhydryl groups, by a Michael-type addition.[6] While the cyclopentenone moiety reacts readily with glutathion (GSH) and plays an important role in detoxification, the α-methylene-γ-lactone seems to be very important in pharmacological activity.[1,5,6] More recently, we have shown that α-methylene-γ-butyrolactones have an interesting photoreactivity potential and can form intramolecular photoadducts with psoralens[7] and intra or intermolecular photoadducts with thymine.[8] The intermolecular photochemical reaction gives [2+2] photocycloadducts involving the 5,6-double bond of the thymine and the exomethylenic unsaturated bond of the lactone. This high photoreactivity of sesquiterpene lactones towards thymine could explane observed phototoxic reactions such as chronic actinic dermatitis, one of the most extreme forms of photosensitivity, which may develop after sensitization to sesquiterpene lactones.[9]

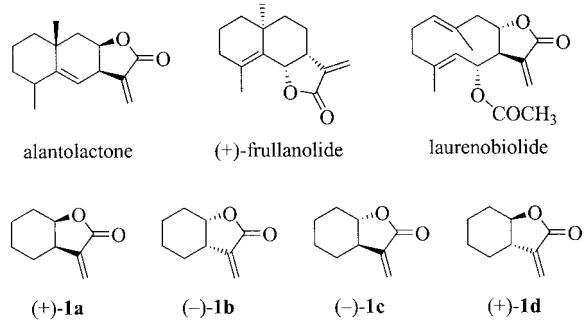

Figure 1. Example of natural sesquiterpene lactones and structures of the 4 models **1**.

Sesquiterpene lactones are stereochemically pure compounds, which present a *cis* or *trans* ring junction at the α-methylene-γ-butyrolactone ring (Figure 1). The importance of the ring junction has already been demonstrated for allergic contact dermatitis[10] and is suspected in the photoreactivity of these molecules with DNA. In order to study the reactivity of sesquiterpene lactones in biological systems, we have developed a simple model, the α-methylene-hexahydro-benzofuranone **1**, which includes the α-methylene-γ-butyrolactone moiety and represents all the different possible ring junctions (Figure 1). There are a number of synthetic approaches to α-methylene-γ-butyrolactones, but few of them are asymmetric.[11] A simple approach, used for many years for the synthesis of α-methylene-γ-butyrolactones, has been the synthesis of pure optically active lactones followed

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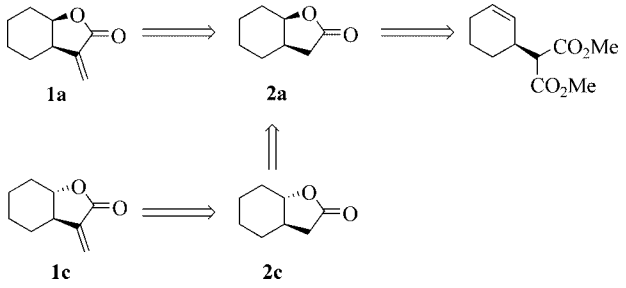
by the introduction of the α-methylene moiety. Among the different reports regarding the synthesis of optically active lactones **2**, the most efficient strategies are: i) the asymmetric Baeyer–Villiger oxidation of cyclic ketones, which results in a mixture of normal and abnormal lactones,[12] ii) the biological reduction of γ- and δ-keto acids and their esters[13] and iii) the enantioselective C–H bond insertion catalyzed by rhodium(II).[14] Unfortunately, even if these strategies led to lactone **2** with the desired enantioselectivity and diastereoselectivity, none of them gave access to the four enantiomers in their pure form.

We describe herein an efficient divergent synthesis of the four stereoisomers of **1** with high enantiomeric excess. The key step of this strategy is based on a palladium-catalyzed allylic asymmetric alkylation, followed by a directed iodolactonization.

Results and Discussion

For the synthesis of **1**, we used a divergent strategy as described in the retrosynthetic analysis (Scheme 1). The *trans* ring junction at the γ-butyrolactone ring is therefore obtained from the *cis* one. The α-methylenation of the lactone ring was performed in the last steps.

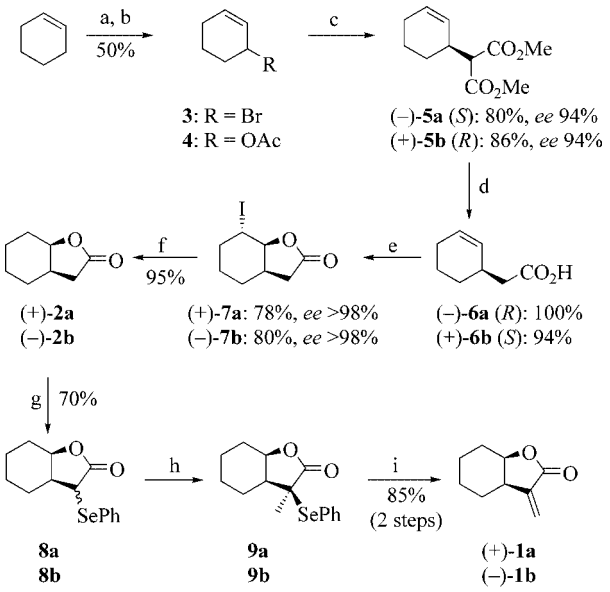


Scheme 1. Retrosynthetic scheme.

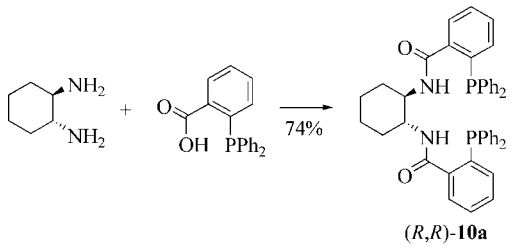
Obtention of the *cis* Ring-Junction γ-Butyrolactone

Enantioselectivity was obtained by the asymmetric palladium-catalyzed allylic substitution of acetate **4** with dimethyl malonate, and diastereoselectivity was achieved by iodolactonization. The precursor of the palladium-catalyzed reaction was synthesized from cyclohexene in two steps: a Wohl–Ziegler allylic bromination according to a known procedure[15] followed by a substitution of the bromide by acetate (Scheme 2).

Recently, efficient systems have been developed to perform allylic alkylations.[16] The flow of new ligands has never stopped, and a dramatic enhancement of enantioselectivity has been observed as a result. We chose Trost's bidentate ligand, because its C_2-symmetry gives a rigid complex resulting in good enantioselectivities on cyclic substrates. This ligand is commercially available, but it can also be easily synthesized by a peptidic coupling reaction between *o*-diphenylphosphinylbenzoic acid and chiral diaminocyclohexanes. Different ways of obtaining this ligand have been described with dicyclohexylcarbodiimide (DCC) or 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide (EDCI) as the coupling reagent. The literature reports highly variable yields ranging from 30–90%, and a purification by column chromatography on silica is generally necessary. In our hands, when the reaction was conducted under the conditions described by Trost and coworkers,[17] with DCC as the coupling reagent and catalytic amounts of 4-(dimethylamino)pyridine (DMAP), only poor yields were obtained (41%), and a purification by column chromatography on silica was necessary. More recently, Lloyd-Jones and Stephen[18] described a modification of the Trost procedure with EDCI, a water-soluble carbodiimide, instead of DCC in the presence of a catalytic amount of DMAP to afford the expected ligand in 55% yield. This methodology applied on the 2 chiral diamines in the presence of catalytic or stoichiometric amounts of DMAP resulted in the formation of ligand (*R*,*R*)-**10a** and ligand (*S*,*S*)-**10b** in similar yields (55%). However, we observed that the order of addition of the reagents also had much influence. In the procedure described by Trost and coworkers, the coupling agent DCC or EDCI was added to the reaction mixture last. Indeed, if the EDCI is added to the mixture of acid and DMAP before the addition of the amine, the reaction resulted in the formation of ligand (*R*,*R*)-**10a** and ligand (*S*,*S*)-**10b** in 74% and 64% yield, respectively, after recrystallisation, and no further purification by chromatography was necessary (Scheme 3).



Scheme 2. Synthesis of the *cis* ring-junction models **1a** and **1b**. Reagents and conditions: (a) NBS, AIBN, CCl_4, Δ, 3 h; (b) CH_3COOH, NEt_3, acetone, room temp., 14 h; (c) $(C_3H_5PdCl)_2$, (*R*,*R*)-**10a** or (*S*,*S*)-**10b**, CH_2Cl_2, $NaCH(COOCH_3)_2$, THAB, room temp., 6 d; (d) NaCN, DMSO, Δ, overnight; (e) I_2, KI, $NaHCO_3$, H_2O, room temp., overnight; (f) $n$$Bu_3SnH$, AIBN, THF, Δ, 40 min. (g)[11a] LDA, $(SePh)_2$, HMPA, THF, –78 °C, 1 h, then –40 °C, 3 h; (h)[11a] LDA, MeI, HMPA, THF, ether, –78–0 °C, 12 h; (i)[11a] H_2O_2, CH_3COOH, 0 °C, 40 min.



Scheme 3. Synthesis of ligand (*R*,*R*)-**10a**. Reagents and conditions: EDCI, DMAP, CH_2Cl_2, room temp., overnight.

The allylic acetate **4** was transformed into the diester (*S*)-**5a** by treatment with $NaCH(CO_2Me)_2$ in the presence of a catalytic amount of (π-allylPdCl)$_2$ and ligand (*R*,*R*)-**10a** with high enantioselectivity. The limited solubility of the sodium salt of dimethyl malonate led to the use of tetraalkylammonium salts (THAB).[19] As shown in Table 1, conversion and enantiomeric excess are highly dependent on the number of equiv. and the addition mode of the reagents. Upon decreasing the amount of sodium dimethyl malonate and THAB, the *ee* varied from 82% to 88% (Table 1, Entry 2). The enantioselectivity was improved by reversing the addition order of the two solutions, but the conversion was low (Table 1, Entry 3). Finally, by doubling the quantities of ligand and catalyst, while maintaining the number of equiv. of dimethyl malonate, we succeeded in substantially improving the conversion to 86%, while preserving good enantioselectivity (Table 1, Entry 4). A similar study in the presence of ligand (*S*,*S*)-**10b** afforded the enantiomer (*R*)-**5b** with the same results. Enantioselectivities were determined by NMR spectroscopy with the Eu(hfc)$_3$ shift reagent, and absolute configurations were determined by comparison to optical rotations reported in the literature.[20]

Table 1. Asymmetric allylic alkylation of acetate **4** with dimethyl malonate (DMM) afforded (*S*)-**5a**.[a]

Entry	Molar equiv. of				Yield	*ee*[b]
	(π-allylPdCl)$_2$	ligand **10a**	DMM	THAB	[%]	[%]
1[c]	0.025	0.05	2	2	50–60	82
2[c]	0.025	0.05	1	1	50–60	88
3[d]	0.025	0.05	1.3	1.3	10–50	94
4[d]	0.05	0.1	1.3	1.3	86	94

[a] All reactions were performed at room temperature for 1 week. [b] The enantioselectivity was determined by integration of the NMR signals of the vinylic proton, upon titration with europium chiral shift reagent (+)-Eu(hfc)$_3$. [c] A solution of palladium, ligand (*R*,*R*)-**10a** and acetate **4** was added dropwise to the nucleophile, generated from dimethyl malonate, sodium hydride and THAB in CH_2Cl_2. [d] Reversed addition: a solution of the nucleophile was added dropwise to the reaction mixture.

Decarboxylation of the alkyl malonate (*S*)-**5a** under conditions described by Krapcho (2 equiv. of NaCN, wet DMSO, 160 °C)[21] followed by a saponification step afforded the monoacid (*R*)-**6a** in good yields. A modification of this reaction, with 2.3 equiv. instead of 2 equiv. of NaCN in the presence of wet DMSO at 190 °C gave quantitatively the monoacid (*R*)-**6a** in one step. An iodolactonization, directed by the first stereogenic centre, afforded quantitatively the iodolactone **7a** with a perfect diastereospecificity (94% *ee*). The enantiomeric purity of this compound could be raised to *ee* > 98% by recrystallisation, as described previously.[22] A hydrodeiodination of **7a** in the presence of Bu_3SnH led to the enantiomerically pure lactone (3a*R*,7a*R*)-**2a** in quantitative yield. The enantiomeric purity was supported by $[\alpha]_D^{20}$ values and by the absence of the signal due to the undesired enantiomer in the 300 MHz ^{1}H NMR spectrum in the presence of a europium chiral shift reagent. The major drawback of this reaction is the excess of hydride needed to increase both the rate and the yield of the reaction, resulting in a more difficult separation of the product from tin residues. A solution to this problem was the use of the simple work-up procedure described by Berge and Roberts.[23] We thus obtained the lactone (3a*R*,7a*R*)-**2a** in 95% yield, and no further purification was necessary.

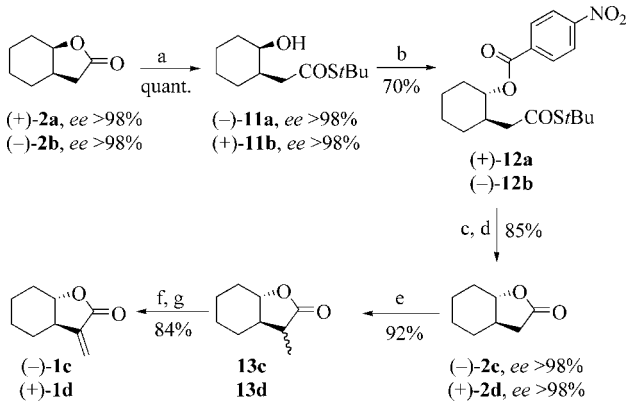
With the same procedure, the *cis* ring-junction γ-butyrolactone (3a*S*,7a*S*)-**2b** was obtained with the same enantioselectivity and similar yields with the (*S*,*S*)-**10b** enantiomer as the chiral ligand in the allylic alkylation catalyzed by palladium.

Lactones (3a*R*,7a*R*)-**2a** and (3a*S*,7a*S*)-**2b** were then converted into their corresponding α-methylene-γ-butyrolactones **1a** and **1b**, according to the procedure described by Grieco and coworkers,[11a] (i.e. by α-selenylation, methylation with MeI and oxidation leading to a β-*syn* elimination). The α-selenylation step gave a mixture of 2 diastereomers in a 8:2 ratio, which was used without separation to give the α-methylene-γ-butyrolactone **1a** or **1b** in good yields.

Obtention of the γ-Butyrolactone with *trans* Ring Junction

In order to benefit from the good enantioselectivities obtained in the synthesis of the *cis*-configured lactones, we decided to convert lactones (3a*R*,7a*R*)-**2a** and (3a*S*,7a*S*)-**2b** into the *trans*-configured lactones (3a*R*,7a*S*)-**2c** and (3a*S*,7a*R*)-**2d**, respectively. This could be done by ring opening of the *cis*-configured lactone, followed by inversion of the oxygenated stereogenic centre and recyclisation. While the isomerization of lactone **2** with a *trans* ring junction into a lactone with a *cis* ring junction is well known in the literature,[24] the opposite isomerization (i.e. obtention of the *trans* lactone starting from the *cis* lactone) was never reported. This is probably due to the great stability of lactones with a *cis* ring junction, compared to their open-ring α-hydroxyester or α-hydroxy acid forms. We solved this problem as described in Scheme 4.

cis-Configured lactones (3a*R*,7a*R*)-**2a** and (3a*S*,7a*S*)-**2b** were opened into their relatively stable hydroxy thioesters **11a** and **11b**, respectively, in good yields with a sulfur nucleophile prepared from *tert*-butyl mercaptan and trimethylaluminium.[25] A Mitsunobu reaction was then applied to the hydroxy thioester in the presence of 4-nitrobenzoic acid (2 equiv.), PPh_3 (2.25 equiv.) and diisopropyl azodicarboxylate (AIBN, 2.25 equiv.)[26] to afford the corresponding diesters **12a** and **12b**, respectively, in good yields. Enantio-



Scheme 4. Synthesis of *trans* ring-junction models **1c** and **1d**. Reagents and conditions: (a) $AlMe_3$, *t*BuSH, CH_2Cl_2, room temp., overnight; (b) DIAD, PPh_3, *p*-$NO_2C_6H_4COOH$, THF, room temp., overnight; (c) NaOH, MeOH, room temp., overnight; (d) toluene, Δ, 30 min. (e)[11a] LDA, MeI, HMPA, THF, diethyl ether, –40 °C, 3 h; (f)[11a] LDA, $(SePh)_2$, HMPA, THF, –78 °C, 1 h, then –40 °C, 1.5 h; (g)[11a] H_2O_2, CH_3COOH, 0 °C, 40 min.

selectivities were determined by NMR spectroscopy with the Eu(hfc)$_3$ shift reagent. The *trans* ring-junction lactones (3a*R*,7a*S*)-**2c** and (3a*S*,7a*R*)-**2d** were obtained by saponification (NaOH and MeOH), followed by an azeotropic distillation in toluene. In this step, the 4-nitrobenzoic acid obtained from the saponification is used as an acid catalyst for lactone formation.

Lactones (3a*R*,7a*S*)-**2c** and (3a*S*,7a*R*)-**2d** were then converted into their corresponding α-methylene-γ-butyrolactones **1c** and **1d**, respectively, according to the procedure described by Grieco and coworkers.[11a] In the case of *trans* ring-junction lactones, methylation with MeI is first realised, followed by an α-selenylation in order to obtain exclusively the exocyclic α-methylene group. Yields of these 2 reactions could be increased from 60% to 90% with a mixture of THF and diethyl ether instead of THF alone.

Conclusions

We have prepared the four isomers of **1** according to a highly efficient procedure. The first stereogenic centre was generated by a palladium-catalyzed asymmetric allylic alkylation with good enantioselectivity. The enantioselectivity of the lactone has been increased to >98% by recrystallisation after iodolactonization. Studies on the reactivity of these models towards DNA are in progress.

Experimental Section

All air- or moisture-sensitive reactions were conducted in flame-dried glassware under an atmosphere of dry argon. All solvents were reagent grade. Dried solvents were freshly distilled before use. Tetrahydrofuran and diethyl ether were distilled from sodium benzophenone. CH_2Cl_2 was dried with P_2O_5 before distillation. Diisopropylamine was refluxed 30 min over potassium hydroxide and then distilled. Chromatographic purifications were conducted on silica gel columns (Merck 60, 0.040–0.063 mm) according to the flash chromatography technique. Analytical TLC was performed on pre-coated silica gel plates (Merck 60 F_{254}). Melting points were determined in capillary tubes with a Büchi Tottoli 510 apparatus and are uncorrected. Elemental analyses were performed with a Perkin–Elmer 240B instrument and were within ±0.4% of calculated values in all cases. Optical rotations were determined with a Perkin–Elmer 241 or a Perkin–Elmer 341 polarimeter at the sodium D line (589 nm) and are reported as follows: $[a]_D^{20}$ (*c* given in g/100 mL, solvent). Infrared spectra were obtained with a Perkin–Elmer FT-IR 1600 spectrometer; peaks are reported in reciprocal centimetres. ^1H and ^{13}C NMR spectra were recorded with Bruker AC200 [200.13 MHz (^1H) and 50.32 MHz (^{13}C)] or Avance 300 [300.13 MHz (^1H) and 75.46 MHz (^{13}C)] spectrometers in $CDCl_3$, unless otherwise specified. Chemical shifts are reported in ppm (δ) with respect to TMS, and $CHCl_3$ was used as the internal standard (δ = 7.27 ppm). Multiplicities are indicated by s (singlet), d (doublet), t (triplet) and m (multiplet). ^{31}P NMR spectra were recorded with a Bruker AM-400 (162 MHz) spectrometer at ambient temperature in $CDCl_3$. All enantiomeric purities were determined by ^1H NMR on a Bruker Avance 300, with the chiral shift reagent europium tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorate] [(+)-Eu(hfc)$_3$] in C_6D_6.

3-Bromocyclohexene (3): To a suspension of AIBN (cat.) and *N*-bromosuccinimide (NBS, 46.3 g, 0.26 mol) in tetrachloromethane (150 mL), was added under argon, freshly distilled cyclohexene (40 mL, 0.4 mol). The mixture was refluxed until the disappearance of NBS. The mixture was then filtered, concentrated and distilled under vacuum (63–64 °C, 15 mbar). The colourless liquid was stored in the absence of light (30.1 g, 72% yield). ^1H NMR (200 MHz, $CDCl_3$): δ = 5.95–5.76 (m, 2 H, 1-H, 2-H), 4.87–4.81 (m, 1 H, 3-H), 2.22–1.54 (m, 6 H, 3×CH_2) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 131.1 (C-2), 129.0 (C-1), 49.0 (C-3), 32.8 (CH_2), 24.7 (CH_2), 18.9 (CH_2) ppm.

(±)-2-Cyclohexen-1-yl Acetate (4): To a solution of 3-bromocyclohexene (**3**, 9.6 mL, 83 mmol) in acetone (150 mL), was added under argon, acetic acid (95 mL, 1.7 mol, 20 equiv.) and then, cautiously, triethylamine (160 mL, 1.2 mol). The mixture was stirred for 14 h at room temperature, and saturated aqueous $NaHCO_3$ (140 mL) was added. After concentration, the aqueous residue was extracted with diethyl ether (4×70 mL). The combined organic layers were washed with water (2×70 mL) and then brine (1×70 mL), dried with $MgSO_4$ and concentrated. Purification by distillation under vacuum (71–73 °C, 15 mbar) afforded a pale yellow oil (8.15 g, 70% yield). ^1H NMR (200 MHz, $CDCl_3$): δ = 6.0–5.92 (m, 1 H, 2′-H), 5.75–5.66 (m, 1 H, 3′-H), 5.31–5.22 (m, 1 H, 1′-H), 2.06 (s, 3 H, 2-H), 2.02–1.59 (m, 6 H, 3×CH_2) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 170.7 (C=O), 132.6 (C-2′), 125.7 (C-3′), 68.1 (C-1′), 28.3 (CH_2), 24.9 (CH_2), 21.4 (C-2), 18.9 (CH_2) ppm. IR (film): $\tilde{\nu}$ = 3032, 2940, 2867, 2835, 1700, 1240 cm^{-1}.

General Procedure for Palladium-Catalyzed Asymmetric Allylic Alkylation: (±)-2-Cyclohexen-1-yl acetate (**4**, 1.68 g, 12 mmol) was added to a solution of allylpalladium chloride dimer [$(C_3H_5PdCl)_2$, 0.22 g, 0.6 mmol, 0.05 equiv.] and chiral ligand **10** (0.83 g, 1.2 mmol, 0.1 equiv.) in dry CH_2Cl_2 (20 mL). This clear yellow solution was stirred at room temperature for 30 min. In another flask, sodium hydride (60% dispersion, 0.60 g, 14.9 mmol, 1.24 equiv.) and tetra-*n*-hexylammonium bromide (THAB, 6.48 g, 14.9 mmol, 1.24 equiv.) were suspended in dry CH_2Cl_2 (70 mL), and freshly distilled dimethyl malonate (1.8 mL, 15.6 mmol, 1.3 equiv.) was added dropwise at room temperature. The resulting viscous mixture was then added dropwise to the yellow solution and stirred at room temperature for 6 d. The reaction mixture was

concentrated in vacuo. Water (100 mL) was added, and the resulting solution was extracted with diethyl ether (3 × 100 mL). The organic layer was washed with water (2 × 50 mL), brine (50 mL), dried with $MgSO_4$ and concentrated in vacuo. Purification was carried out by flash chromatography over silica gel (hexane/ethyl acetate, 95:5).

Dimethyl (–)-(*S*)-2-(Cyclohex-2-enyl)malonate (5a): The general conditions with ligand (*R*,*R*)-**10a** gave (–)-**5a** as a colourless oil (2.05 g, 80% yield). $[a]_D^{20}$ = –43.5 (*c* = 1.9, $CHCl_3$), ref.[20] $[a]_D^{23}$ = –43.2 (*c* = 1.75, $CHCl_3$, 99% *ee*), ref.[27] $[a]_D^{22}$ = –15.6 (*c* = 2.6, $CHCl_3$, 50% *ee*); *ee* = 94% was determined by NMR spectroscopy with (–)-**5a** (17 mg) with (+)-Eu(hfc)$_3$ (70 mg, 0.7 equiv.) in C_6D_6. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 5.83–5.73 (m, 1 H, 2′-H), 5.56–5.49 (m, 1 H, 3′-H), 3.74 (s, 6 H, 2 × OCH_3), 3.29 (d, *J* = 9.5 Hz, 1 H, 2-H), 2.98–2.84 (m, 1 H, 1′-H), 2.05–1.98 (m, 2 H, 4′-H), 1.84–1.26 (m, 4 H, 5′H and 6′-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 168.9 (2 × C=O), 129.7 (C-2′), 127.4 (C-3′), 56.9 (C-2), 52.4 (2 × Me), 35.4 (C-1′), 26.7 (CH_2), 24.9 (CH_2), 20.9 (CH_2) ppm. IR (film): $\tilde{\nu}$ = 3024, 2951, 2840, 1735, 1250, 1150 cm^{-1}.

Dimethyl (+)-(*R*)-2-(Cyclohex-2-enyl)malonate (5b): The general conditions with ligand (*S*,*S*)-**10b** gave (+)-**5a** as a colourless oil (2.20 g, 86% yield). $[a]_D^{20}$ = +43.1 (*c* = 1.9, $CHCl_3$), ref.[28] $[a]_D^{20}$ = +38.5 (*c* = 3.4, $CHCl_3$, 82% *ee*); *ee* = 94% was determined by NMR spectroscopy with (+)-**5b** (32 mg) with (+)-Eu(hfc)$_3$ (128 mg, 0.7 equiv.) in C_6D_6.

(–)-(*R*)-Cyclohex-2-enylacetic Acid (6a): To wet DMSO (75 mL) were added sodium cyanide (95%, 9 g, 175 mmol, 2.3 equiv.) and the diester (–)-**5a** (16.1 g, 76 mmol). The mixture was refluxed overnight and then cooled to room temp., diluted with water (300 mL), washed with pentane (1 × 40 mL) and acidified to pH = 4 with acetic acid. This aqueous phase was extracted with ethyl acetate (3 × 400 mL). The organic layer was washed with water (200 mL), dried with $MgSO_4$ and concentrated in vacuo to afford a brown oil. Purification was accomplished by filtration through silica gel (hexane/ethyl acetate, 65:35) to yield (–)-**6a** as a colourless oil (10.60 g, 99% yield). $[a]_D^{20}$ = –59.5 (*c* = 2.6, $CHCl_3$), ref.[29] $[a]_D$ = –46.9 (*c* = 0.9, $CHCl_3$, 86% *ee*). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 11.23 (sl, 1 H, COOH), 5.75–5.65 (m, 1 H, 3′-H), 5.53 (dd, J_1 = 10.1 Hz, J_2 = 2.3 Hz, 1 H, 2′-H), 2.65–2.48 (m, 1 H, 1′-H), 2.35 (B part of an ABX system, J_{AB} = 15.2 Hz, J_{BX} = 6.5 Hz, 1 H, 2-H), 2.29 (A part of an ABX system, J_{AB} = 15.2 Hz, J_{AX} = 8.5 Hz, 1 H, 2-H), 2.00–1.20 (m, 6 H, 3 × CH_2) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 179.6 (C=O), 129.8 (C=C), 128.4 (C=C), 40.7 (C-2), 32.1 (C-3′), 28.8 (CH_2), 25.0 (CH_2), 21.0 (CH_2) ppm. IR (film): $\tilde{\nu}$ = 3000, 3019, 2929, 1707, 1291 cm^{-1}.

(+)-(*S*)-Cyclohex-2-enylacetic Acid (6b): The same procedure as for (–)-**6a** starting from (+)-**5b** (3.14 g, 14.8 mmol) gave (+)-**6b** as a colourless oil (1.94 g, 94% yield). $[a]_D^{20}$ = +59.4 (*c* = 2.6, $CHCl_3$), ref.[28] $[a]_D^{27}$ = +54.2 (*c* = 2.9, $CHCl_3$, 82% *ee*).

(+)-(3a*R*,7*S*,7a*S*)-Hexahydro-7-iodobenzofuran-2-one (7a): To aqueous $NaHCO_3$ (0.2 M, 80 mL, 16.9 mmol, 1.2 equiv.) containing the acid (–)-**6a** (1.98 g, 14.1 mmol), were added a solution of I_2 (3.94 g, 15.5 mmol, 1.1 equiv.) and KI (4.69 g, 28.2 mmol, 2 equiv.) in water (20 mL). The mixture was stirred at room temperature overnight, and then saturated aqueous $Na_2S_2O_3$ (20 mL) was added. The aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL). The organic layer was washed with water (15 mL), dried with $MgSO_4$ and concentrated. The clear orange solid (+)-**7a** was obtained with good purity in a quantitative yield (3.70 g), which after recrystallisation from ethyl acetate/hexane, gave enantiomerically pure (+)-**5** as colourless crystals (2.93 g, 78% yield). M.p. 95–96 °C. $[a]_D^{20}$ = +55.7 (*c* = 1.2, MeOH); *ee* ≥ 98% was determined by NMR spectroscopy with (+)-**7a** (15 mg) with (+)-Eu(hfc)$_3$ (80 mg, 1.2 equiv.) in C_6D_6; the (–)-enantiomer could not be detected. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 4.68 (dd, J_1 = J_2 = 4.4 Hz, 1 H, 7a-H), 4.58 (ddd, J_1 = J_2 = J_3 = 4.3 Hz, 1 H, 7-H), 2.83–2.67 (m, 1 H, 3a-H), 2.53 (B part of an ABX system, J_{AB} = 16.8 Hz, J_{BX} = 6.8 Hz, 1 H, 3-H), 2.24 (A of an ABX system, J_{AB} = 16.8 Hz, J_{AX} = 3.6 Hz, 1 H, 3-H), 1.96–1.18 (m, 6 H, 3 × CH_2) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 176.0 (C=O), 83.0 (C-7a), 36.9 (C-3), 32.6 (C-3a or C-7), 30.7 (CH_2), 27.7 (C-3a or C-7), 26.4 (CH_2), 20.5 (CH_2) ppm. IR (nujol): $\tilde{\nu}$ = 2940, 2862, 1784, 1175 cm^{-1}.

(–)-(3a*S*,7*R*,7a*R*)-Hexahydro-7-iodobenzofuran-2-one (7b): The same procedure as for (+)-**7a** starting from (+)-**6b** (0.32 g, 2.29 mmol) gave (–)-**7b**, after recrystallisation, as colourless crystals (0.49 g, 80% yield). M.p. 94–95 °C. $[a]_D^{20}$ = –56.0 (*c* = 1.5, MeOH), ref.[28] $[a]_D^{20}$ = –53.4 (*c* = 3.6, MeOH, 99.9% *ee*); *ee* ≥ 98% was determined by NMR spectroscopy with (–)-**7b** (15 mg) with (+)-Eu(hfc)$_3$ (80 mg, 1.2 equiv.) in C_6D_6; the (+)-enantiomer could not be detected.

(+)-(3a*R*,7a*R*)-Hexahydrobenzofuran-2-one (2a): Tributyltin hydride (Bu_3SnH, 3.2 mL, 12 mmol, 1.6 equiv.) was added under argon to a solution of iodolactone (+)-**7a** (2.0 g, 7.52 mmol) and AIBN (cat.) in THF (20 mL). The mixture was allowed to reflux for 40 min and then concentrated. The residue was dissolved in MeCN (40 mL) and washed with small fractions of hexane (8 × 10 mL). Evaporation of MeCN afforded a colourless oil (1.0 g, 95% yield) free of tin residues. $[a]_D^{20}$ = +50.6 (*c* = 1.4, $CHCl_3$), ref.[30] $[a]_D^{20}$ = +50.3 (*c* = 0.1, $CHCl_3$, 100% *ee*); *ee* ≥ 98% was determined by NMR spectroscopy with (+)-**2a** (14 mg) with (+)-Eu(hfc)$_3$ (80 mg, 0.7 equiv.) in C_6D_6; the (–)-enantiomer could not be detected. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 4.51 (ddd, J_1 = J_2 = J_3 = 4.1 Hz, 1 H, 7a-H), 2.60 (B part of an ABX system, J_{AB} = 16.5 Hz, J_{BX} = 6.8 Hz, 1 H, 3-H), 2.46–2.30 (m, 1 H, 3a-H), 2.24 (A part of an ABX system, J_{AB} = 16.5 Hz, J_{AX} = 2.6 Hz, 1 H, 3-H), 1.96–1.18 (m, 8 H, 4 × CH_2) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 177.5 (C=O), 79.1 (C-7a), 37.4 (C-3), 34.8 (C-3a), 27.8 (CH_2), 27.1 (CH_2), 22.8 (CH_2), 19.9 (CH_2) ppm. IR (film): $\tilde{\nu}$ = 2934, 2858, 1777, 1174 cm^{-1}.

(–)-(3a*S*,7a*S*)-Hexahydrobenzofuran-2-one (2b): The same procedure as for (+)-**2a** starting from (–)-**7b** (2.57 g, 9.64 mmol) gave (–)-**2b** as a colourless oil (1.30 g, 96% yield). $[a]_D^{20}$ = –51.7 (*c* = 0.5, $CHCl_3$), ref.[13b] $[a]_D^{20}$ = –52.0 (*c* = 2.074, $CHCl_3$, 97.2% *ee*, ref.[31] $[a]_D^{20}$ = –45.5 (*c* = 0.548, $CHCl_3$, 100% *ee*); *ee* ≥ 98% was determined by NMR spectroscopy with (–)-**2b** (5 mg) with (+)-Eu(hfc)$_3$ (40 mg, 1 equiv.) in C_6D_6; the (+)-enantiomer could not be detected.

***α*-Methylenation of Lactones with a *cis* Ring Junction [(+)-2a and [(–)-2b]:** Lactones (+)-**2a** and (–)-**2b** (≥98%) were transformed into the corresponding α-methylene-γ-butyrolactones (+)-**1a** and (–)-**1b** according to the procedure described by Grieco and coworkers:[11a] an α-selenylation (purification by flash chromatography over silica gel, pentane/diethyl ether (95:5), 70% yield), followed by methylation and oxidation (purification by flash chromatography over silica gel, hexane/ethyl acetate (85:15), 85% yield for the 2 steps).

(3a*S*,7a*R*)-3-(Phenylselenyl)hexahydrobenzofuran-2-one (8a) and (3a*R*,7a*S*)-3-(Phenylselenyl)hexahydrobenzofuran-2-one (8b): Yellow oil. (major isomer): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.66–7.62 (m, 2 H, SePh), 7.31–7.25 (m, 3 H, SePh), 4.67 (ddd, J_1 = J_2 = J_3 = 4.1 Hz, 1 H, 7a-H), 3.63 (d, *J* = 2.4 Hz, 1 H, 3-H), 2.34–2.24 (m, 1 H, 3a-H), 2.11–2.04 (m, 1 H), 1.79–1.14 (m, 7 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 175.8 (C=O), 135.1, 129.4, 128.8 and 127.2 (SePh), 77.5 (7a-C), 44.7 (3-C or 3a-C), 42.1 (3-C or 3a-C), 27.6 (CH_2), 27.3 (CH_2), 22.8 (CH_2), 19.8 (CH_2) ppm. (minor isomer):

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.66–7.62 (m, 2 H, SePh), 7.31–7.25 (m, 3 H, SePh), 4.48 (m, 1 H, 7a-H), 4.30 (d, J = 6.2 Hz, 1 H, 3-H), 2.51–2.41 (m, 1 H, 3a-H), 1.95–1.87 (m, 1 H), 1.79–1.14 (m, 7 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 134.0, 129.3 and 128.0 (SePh), 78.2 (C-7a), 49.7 (C-3 or C-3a), 39.6 (C-3 or C-3a), 27.7 (CH_2), 25.3 (CH_2), 23.4 (CH_2), 19.4 (CH_2) ppm (signals of quaternary C atoms were not visible).

(3*S*,3a*S*,7a*R*)-3-Methyl-3-(phenylselenyl)hexahydrobenzofuran-2-one (9a) and (3*R*,3a*R*,7a*S*)-3-Methyl-3-(phenylselenyl)hexahydrobenzofuran-2-one (9b): Orange oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.71–7.53 (m, 2 H, SePh), 7.37–7.20 (m, 3 H, SePh), 4.56 (ddd, J_1 = J_2 = J_3 = 5.8 Hz, 1 H, 7a-H), 2.43–2.29 (m, 1 H, 3a-H), 2.10–0.77 (m, 8 H), 1.45 (s, 3 H, CH_3) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 178.7 (C=O), 138.0, 129.3, 128.9 and 126.2 (SePh), 76.6 (C-7a), 52.0 (C-3), 48.0 (C-3a), 28.5 (CH_2), 25.9 (CH_2), 23.8 (Me), 23.7 (CH_2), 20.6 (CH_2) ppm.

(+)-(3a*R*,7a*R*)-3-Methylene-*cis*-hexahydrobenzofuran-2(*3H*)-one (1a): Colourless oil, *ee* ≥ 98%. $[\alpha]_D^{20}$ = +71.9 (c = 1.8, $CHCl_3$), ref.[32] $[\alpha]_D^{25}$ = +63.3 ($CHCl_3$, 90% *ee*). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 6.16 (d, J = 2.5 Hz, 1 H, 8-H), 5.49 (d, J = 2.5 Hz, 1 H, 8-H), 4.52 (ddd, J_1 = J_2 = J_3 = 6.0 Hz, 1 H, 7a-H), 3.02–2.98 (m, 1 H, 3a-H), 1.92–1.19 (m, 8 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 170.3 (C=O), 139.2 (C-3), 119.0 (C-8), 76.2 (C-7a), 38.9 (C-3a), 28.2 (CH_2), 25.6 (CH_2), 20.5 (CH_2), 19.8 (CH_2) ppm. $C_9H_{12}O_2$ (152.19): calcd. C 71.03, H 7.95; found C 71.42, H 8.12.

(–)-(3a*S*,7a*S*)-3-Methylene-*cis*-hexahydrobenzofuran-2(*3H*)-one (1b): Colourless oil, *ee* ≥ 98%. $[\alpha]_D^{20}$ = –69.6 (c = 1.9, $CHCl_3$), ref.[33] $[\alpha]_D^{25}$ = –46.4 (c = 0.07, $CHCl_3$, 99% *ee*). $C_9H_{12}O_2$ (152.19): calcd. C 71.03, H 7.95; found C 71.06, H 8.12.

(+)-(1*R*,2*R*)-1,2-Bis[*o*-(diphenylphosphanyl)benzoylamino]cyclohexane (10a): To a solution of 2-(diphenylphosphanyl)benzoic acid (4.83 g, 15.78 mmol, 2.2 equiv.), DMAP (cat.) and EDCI (3.30 g, 17.19 mmol, 2.4 equiv.) in dry CH_2Cl_2 (50 mL), was added (1*R*,2*R*)-*trans*-1,2-diaminocyclohexane (0.82 g, 7.17 mmol). The mixture was stirred at room temperature overnight. Diethyl ether (100 mL) was added, and the organic layer was washed with 10% hydrochloric acid (3 × 100 mL), water (1 × 100 mL), saturated aqueous $NaHCO_3$ (3 × 100 mL), water (1 × 100 mL) and brine (1 × 100 mL), dried with $MgSO_4$ and concentrated in vacuo. The slightly brown solid (4.5 g, 92% yield) was recrystallized from MeCN to yield (1*R*,2*R*)-**10a** as a white solid (3.66 g, 74% yield). M.p. 136–139 °C. $[\alpha]_D^{24}$ = +55.6 (c = 2.3, CH_2Cl_2), ref.[34] $[\alpha]_D$ = +55.1 (c = 2.85, CH_2Cl_2), ref.[18] $[\alpha]_D$ = +61 (c = 2.3, CH_2Cl_2). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.58–7.48 (m, 2 H, 13-H and 13′-H), 7.26–7.16 [m, 24 H, $P(C_6H_5)_2$ and 11-H, 11′-H, 12-H, 12′-H], 6.94–6.88 (m, 2 H, 10-H and 10′-H), 6.45 (bd, J = 7.3 Hz, 2 H, NH), 3.87–3.70 (m, 2 H, 1-H and 2-H), 1.90–1.78 (m, 2 H, CH_2), 1.70–1.58 (m, 2 H, CH_2), 1.30–0.90 (m, 4 H, 2 × CH_2) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 169.2 (2 × C=O), 140.7 (d, J = 24.6 Hz, C-8 and C-8′), 137.7 (d, J = 13.1 Hz, C-9 and C-9′), 136.6 (d, J = 21.3 Hz, C), 134.2 (CH), 133.8 (d, J = 19.7 Hz, C-10 and C-10′), 130.1 (CH) 128.7 (CH), 128.5 (CH), 128.4 (CH), 127.5 (CH), 53.8 (C-1 and C-2), 31.9 (C-3 and C-6), 24.6 (C-4 and C-5) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): –8.3 (s).

(–)-(1*S*,2*S*)-1,2-Bis[*o*-(diphenylphosphanyl)benzoylamino]cyclohexane (10b): The same procedure as for (+)-(1*R*,2*R*)-**10a** starting from (1*S*,2*S*)-*trans*-1,2-diaminocyclohexane (0.80 g, 7.00 mmol) gave the product as a white solid (3.09 g, 64% after recrystallisation from MeCN). M.p. 134–136 °C.

General Procedure for the Opening of *cis*-Configured Lactones: To a solution of trimethylaluminium (2 M in toluene, 7.4 mL, 14.9 mmol, 2.5 equiv.) in dry CH_2Cl_2 (30 mL), was carefully added *tert*-butyl mercaptan (1.7 mL, 14.9 mmol, 2.5 equiv.) at 0 °C under argon. The mixture was stirred at 0 °C for 5 min and then warmed to room temperature for 10 min. The *cis*-configured lactone **2** (0.84 g, 6.0 mmol) in CH_2Cl_2 (6 mL) was then added, and the mixture was stirred at room temperature overnight. Quenching of the reaction was performed by the addition of diethyl ether (50 mL), followed by the careful addition of 10% hydrochloric acid (35 mL). The aqueous phase was extracted with diethyl ether (2 × 20 mL), and the organic layer was washed with saturated aqueous $NaHCO_3$ (15 mL), water (15 mL) and brine (15 mL). Purification was performed by flash chromatography over silica gel (pentane/diethyl ether, 7:3) to yield the relatively stable hydroxy thioester **11** as a white solid (1.24 g, 91% yield).

***S*-*tert*-Butyl (–)-(1′*R*,2′*R*)-2-(2′-Hydroxycyclohexyl)thioacetate (11a):** M.p. 46 °C. $[\alpha]_D^{20}$ = –6.7 (c = 1.6, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.87–3.84 (m, 1 H, 2′-H), 2.58 (B part of an ABX system, J_{AB} = 14.6 Hz, J_{BX} = 7.5 Hz, 1 H, 2-H), 2.40 (A part of an ABX system, J_{AB} = 14.6 Hz, J_{AX} = 6.8 Hz, 1 H, 2-H), 2.06–1.95 (m, 1 H, 1′-H), 1.84 (br. s, 1 H, OH), 1.75–1.20 (m, 8 H, 4 × CH_2), 1.44 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 200.8 (C=O), 68.7 (C-2′), 48.0 [*C*(CH_3)$_3$], 47.0 (C-2), 39.2 (C-1′), 32.6 (CH_2), 29.7 [C(*C*H_3)$_3$], 26.7 (CH_2), 24.7 (CH_2), 20.3 (CH_2) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3600–3300 (O-H), 2933, 2862, 1673 cm^{-1}. $C_{12}H_{22}O_2S$ (230.37): calcd. C 62.57, H 9.62; found C 62.88, H 9.67.

***S*-*tert*-Butyl (+)-(1′*S*,2′*S*)-2-(2′-Hydroxycyclohexyl)thioacetate (11b):** $[\alpha]_D^{20}$ = +6.4 (c = 1.5, $CHCl_3$). $C_{12}H_{22}O_2S$ (230.37): calcd. C 62.57, H 9.62; found C 62.79, H 9.67.

General Procedure for the Mitsunobu Reaction: DIAD (2.6 mL, 12.1 mmol, 2.25 equiv.) was added under argon to a solution of **11** (1.24 g, 5.38 mmol), PPh_3 (3.18 g, 12.1 mmol, 2.25 equiv.) and *p*-nitrobenzoic acid (1.8 g, 10.76 mmol, 2 equiv.) in THF (30 mL) at –12 °C. The mixture was stirred at room temperature overnight, and then silica gel was added. The crude was carefully concentrated and the orange solid obtained was purified by flash chromatography over silica gel (pentane/diethyl ether, 95:5) to yield **12** (1.43 g, 70% yield) as a white solid.

(+)-(1*S*,2*R*)-2-(*tert*-Butylthiocarbonylmethyl)cyclohexyl *p*-Nitrobenzoate [(+)-12a]: M.p. 79–81 °C. $[\alpha]_D^{20}$ = +58.8 (c = 3.0, $CHCl_3$). ^{1}H NMR (300 MHz, C_6D_6): δ = 7.72–7.68 (m, 4 H Ar), 4.69 (ddd, J_1 = J_2 = 10.2 Hz, J_3 = 4.2 Hz, 1 H, 1-H), 2.59 (B part of an ABX, J_{AB} = 14.5 Hz, J_{BX} = 4.0 Hz, 1 H, 7-H), 2.32–2.12 (m, 1 H, 2-H), 2.16 (A part of an ABX system, J_{AB} = 14.5 Hz, J_{AX} = 8.3 Hz, 1 H, 7-H), 2.02–1.97 (m, 1 H), 1.81–1.77 (m, 1 H), 1.44–0.80 (m, 6 H), 1.26 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (75 MHz, C_6D_6): δ = 197.9 (SCO), 163.7 (OCO), 150.0 (CNO_2), 135.3 (*C*ArCO), 130.3 (2 × CH), 123.1 (2 × CH), 77.4 (C-1), 47.6 [*C*(CH_3)$_3$], 47.5 (C-7), 39.3 (C-2), 31.5 (CH_2), 30.5 (CH_2), 29.3 [C(CH_3)$_3$], 24.7 (CH_2), 24.0 (CH_2) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3030, 2939, 2863, 1720, 1676, 1530, 1365, 1275 cm^{-1}. $C_{19}H_{25}NO_5S$ (379.47): calcd. C 60.14, H 6.64, N 3.69; found C 60.07, H 6.65, N 3.63.

(–)-(1*R*,2*S*)-2-(*tert*-Butylthiocarbonylmethyl)cyclohexyl *p*-Nitrobenzoate [(–)-12b]: $[\alpha]_D^{20}$ = –57.7 (c = 1.3, $CHCl_3$). $C_{19}H_{25}NO_5S$ (379.47): calcd. C 60.14, H 6.64, N 3.69; found C 60.03, H 6.70, N 3.53.

(–)-(3a*R*,7a*S*)-Hexahydro-benzofuran-2-one (2c): To a solution of (+)-**12a** (1.34 g, 3.52 mmol) in MeOH (100 mL) was added dropwise aqueous sodium hydroxide (1 M, 14 mL, 14 mmol, 4 equiv.), and the mixture was stirred overnight at room temperature. The crude was concentrated, acidified with 10% hydrochloric acid, and the aqueous layer was extracted several times with diethyl ether

(15 × 8 mL). After concentration of the combined organic layers, the white solid was dissolved in toluene (400 mL). After 30 min of azeotropic distillation, the mixture was cooled to room temperature, washed with saturated aqueous $NaHCO_3$ (2 × 50 mL) and brine (2 × 20 mL), dried with $MgSO_4$ and concentrated in vacuo. The white solid (–)-**2c** was obtained with good purity (469 mg, 95% yield) or could be further purified by flash chromatography over silica gel (pentane/diethyl ether, 7:3, 82% yield). M.p. 30–32 °C. $[\alpha]_D^{20}$ = –83.3 (*c* = 0.5, $CHCl_3$), ref.[13b] $[\alpha]_D^{18}$ = –93 (*c* = 2.034, $CHCl_3$, 98.4% *ee*), ref.[24b] $[\alpha]_D^{23}$ = –77.6 (*c* = 4.6, $CHCl_3$, pure). The diastereomer could not be detected by NMR spectroscopy. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.78 (ddd, $J_1 = J_2$ = 11 Hz, J_3 = 3.8 Hz, 1 H, 7a-H), 2.50 (B part of an ABX system, J_{AB} = 16.2 Hz, J_{BX} = 6.2 Hz, 1 H, 3-H), 2.22 (A part of an ABX system, J_{AB} = 16.2 Hz, J_{AX} = 13.0 Hz, 1 H, 3-H), 2.00–1.20 (m, 9 H, 3a-H and 8 H cyclohexane) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 177.6 (C=O), 85.2 (C-7a), 44.8 (C-3a), 35.9 (C-3), 30.3 (CH_2), 28.3 (CH_2), 25.3 (CH_2), 24.1 (CH_2) ppm.

(+)-(3a*S*,7a*R*)-Hexahydro-benzofuran-2-one (2d): The same procedure as for (–)-**2c** starting from (–)-**12b** (1.36 g, 3.58 mmol) gave (+)-**2d** as a white solid (409 mg, 82% yield after purification). $[\alpha]_D^{20}$ = +84.3 (*c* = 1.8, $CHCl_3$), ref.[13b] $[\alpha]_D^{18}$ = +88 (*c* = 2.044, $CHCl_3$, 96.8% *ee*), ref.[24b] $[\alpha]_D^{23}$ = +78.5 (*c* = 2.9, $CHCl_3$, pure). The diastereomer could not be detected by NMR spectroscopy.

α-Methylenation of Lactones with a *trans* Ring Junction [(–)-2c and (+)-2d]: The lactones (–)-**2c** and (+)-**2d** (*ee* ≥ 98%) were converted into the corresponding α-methylene-γ-butyrolactones (–)-**1c** and (+)-**1d**, respectively, according to the procedure described by Grieco and coworkers:[11a] methylation [purification by flash chromatography over silica gel, pentane/diethyl ether (90:10), 92% yield], followed by an α-selenylation and direct oxidation [purification by flash chromatography over silica gel, hexane/ethyl acetate (85:15), 70% yield for the 2 steps].

(3a*R*,7a*S*)-3-Methyl-hexahydrobenzofuran-2-one (13c) and (3a*S*,7a*R*)-3-Methyl-hexahydrobenzofuran-2-one (13d): Colourless oil. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.96 (ddd, $J_1 = J_2$ = 11 Hz, J_3 = 3.8 Hz, 1 H, 7a-H), 2.62 (qd, $J_1 = J_2$ = 7.6 Hz, 1 H, 3-H), 2.26–2.22 (m, 1 H, 3a-H), 2.00–1.70 (m, 4 H, CH_2 cyclohexane), 1.60–1.16 (m, 4 H, CH_2 cyclohexane), 1.15 (d, *J* = 7.6 Hz, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 180.1 (C=O), 81.8 (C-7a), 47.3 (C-3a), 38.8 (C-3), 30.6 (CH_2), 25.2 (CH_2), 24.6 (CH_2), 24.0 (CH_2), 9.6 (C-8) ppm.

(–)-(3a*R*,7a*S*)-3-Methylene-*trans*-hexahydrobenzofuran-2(3*H*)-one (1c): White solid. M.p. 60 °C, *ee* ≥ 98%. $[\alpha]_D^{20}$ = –60.0 (*c* = 1.7, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 6.04 (d, *J* = 3.2 Hz, 1 H, 8-H), 5.36 (d, *J* = 3.2 Hz, 1 H, 8-H), 3.69 (ddd, $J_1 = J_2$ = 11.1 Hz, J_3 = 3.5 Hz, 1 H, 7a-H), 2.44–2.34 (m, 1 H, 3a-H), 2.28–2.21 (m, 1 H), 2.15–2.09 (m, 1 H), 1.98–1.82 (m, 2 H), 1.67–1.54 (m, 1 H), 1.44–1.29 (m, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.6 (C=O), 139.6 (C-3), 117.1 (C-8), 83.1 (C-7a), 48.9 (C-3a), 30.5 (CH_2), 25.8 (CH_2), 24.9 (CH_2), 24.0 (CH_2). $C_9H_{12}O_2$ (152.19): calcd. C 71.03, H 7.95; found C 70.92, H 8.03.

(+)-(3a*S*,7a*R*)-3-Methylene-*trans*-hexahydrobenzofuran-2(3*H*)-one (1d): White solid. M.p. 61 °C, *ee* ≥ 98%. $[\alpha]_D^{20}$ = +59.5 (*c* = 1.9, $CHCl_3$). $C_9H_{12}O_2$ (152.19): calcd. C 71.03, H 7.95; found C 70.90, H 8.15.

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