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Oxazaborolidine catalysed enantioselective reduction of cyclic *meso*-imides

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Abstract: Full details of the enantioselective reduction of cyclic *meso*-imides catalysed by an enantiopure oxazaborolidine derived from (*S*)-α,α-diphenylprolinol are reported. Treatment of the imides with borane in the presence of the catalyst led to a mixture of *cis*- and *trans*-hydroxylactams and, after subsequent ethanolysis, to the corresponding diastereomerically pure *trans*-ethoxylactams. The enantiomeric excesses were shown to be 68–94% by HPLC-determination. One example, in which the ethoxylactam was converted into the benzenesulfonyllactam, could be crystallized to >99% enantiomeric purity. © 1997 Elsevier Science Ltd

Introduction

Desymmetrisation of *meso*-compounds is one of the most powerful transformations in asymmetric synthesis. Differentiation between two enantiotopic groups in such compounds leads to two or more stereocentres in only one step. In this respect, a useful class of starting materials are cyclic *meso*-imides **1** (Scheme 1). Stereoselective reduction of one of the carbonyls would lead to a product with three contiguous stereocentres. Although the products of this reduction form an interesting class of starting materials in the synthesis of natural products, especially in enantiopure form, only a few studies have been published on this subject. A few research groups have reported diastereoselective reductions of *meso*-imides using a chiral substituent on nitrogen as an auxiliary.[1] The group of Matsuki reported the first example of an enantioselective reduction method.[2] They achieved e.e.'s up to 91% using stoichiometric amounts of the (*R*)-BINAL–H complex. Kang *et al.* have reported a mixture of a thiazazincolidine complex (20% of catalyst) and bis(2,6-dimethylphenoxy)borane which reduced *meso*-imides in 70–99% e.e.[3] However, the excellent results of these groups were only obtained for *N*-aryl-substituted imides. Very recently Seebach and co-workers published their results on the nonreductive enantioselective ring opening of *N*-methylsulfonyl-substituted imides by using stoichiometric amounts of the diisopropoxytitanium-tetraaryl-1,3-dioxalane-4,5-dimethanolate complex, reaching e.e.'s between 73% and 95%.[4]

The seminal work of the groups of Itsuno and Corey has resulted in a variety of new oxazaborolidines which have been applied in numerous enantioselective reductions and other stereoselective transformations.[5] The most widely used oxazaborolidine to date is derived from (*S*)-α,α-diphenylprolinol (**2**, Scheme 1). We have embarked on a study of the use of a combination of this catalyst and borane for the enantioselective reductions of *meso*-imides. The reduction of imides has been a research interest of our group since the early seventies[6] as they form the key starting materials for *N*-acyliminium ion chemistry. Our preliminary results on the enantioselective imide reduction were recently disclosed.[7] Herein, full details of this research are described.

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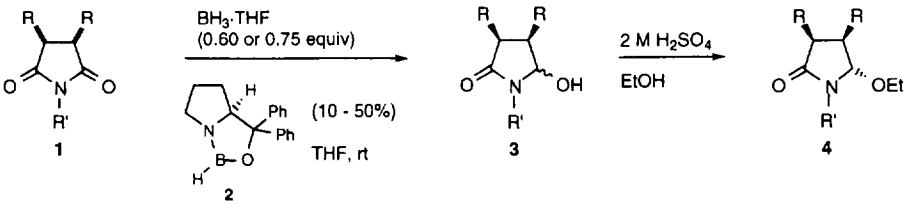


Scheme 1.

Results and discussion

Table 1 shows the various imides which were used in the reduction experiments. The imides were synthesized from the corresponding anhydrides. For entries 1, 8, 9 and 10 *cis*-1,2-cyclohexanedicarboxylic anhydride was condensed (neat, 200°C, 30 min) with benzylamine, aniline, cyclohexylamine and 3-aminopropionitrile, respectively. For entry 4 benzylamine was condensed by using the same method with *cis*-1,2-cyclopropanedicarboxylic anhydride, which was synthesized using a literature procedure.[8] For entry 2 *cis*-1,2-cyclopentanedicarboxylic anhydride was synthesized using a literature procedure,[9] condensed with ammonia and *N*-alkylated using sodium methoxide and benzyl bromide. For entry 3 *cis*-1,2-cyclobutanedicarboxylic anhydride was condensed with ammonia and *N*-alkylated using sodium methoxide and benzyl bromide. For entries 5, 6 and 7 the dicarboxylic acids were treated with acetyl chloride, benzylamine and again acetyl chloride to give the imides. *exo*-7-Oxabicyclo[2.2.1]-5-heptane-2,3-dicarboxylic acid[10] and cyclopentane-1,3-dicarboxylic acid[11] were synthesized according to literature procedures. Exact details of the synthesis of these *meso*-imides are found in the Experimental.

When the cyclic imides **1** were treated with borane in the presence of varying catalytic amounts of oxazaborolidine **2**, a mixture of optically active *cis*- and *trans*-5-hydroxy-2-pyrrolidinones **3** was obtained (Scheme 1). The catalyst **2** was generated by condensing $BH_3 \cdot THF$ (3 equiv) with (*S*)-α,α-diphenylprolinol in refluxing THF for 17 h.[5b] After removal of the volatiles *in vacuo*, the residue was dissolved in THF. This catalyst solution (ca. 0.3 M) was added to a solution of the imide in THF (0.2 M) at 0°C. The reaction was started at 0°C by adding the optimised amount of $BH_3 \cdot THF$. The reaction was monitored by TLC until the starting material had disappeared. The reaction mixture was quenched by using an aqueous 5% HCl solution and submitted to the usual work-up procedure (see Experimental). The ratio of the two diastereomeric hydroxylactams **3** depended on the reaction time and the work-up method and the isomers were difficult to separate with flash chromatography. However, when this mixture was treated with 2 M H_2SO_4 in EtOH, the *trans*-ethoxylactams **4** were obtained as single diastereomers in moderate to good overall yields. For the majority of the *meso*-imides, the optimum conditions for the reduction reaction involved 50% of catalyst and 0.75 equiv of BH_3. In a number of cases the use of less catalyst and borane appeared equally effective.

HPLC analysis was successful for most of the ethoxylactams which unambiguously established the e.e. For some compounds (entries 2, 3 and 9) the optical purities were determined by using the two-step procedure of Mukaiyama *et al.*[1a] To this end, the mixture of hydroxylactams was reductively ring-opened to the hydroxyamide and subsequently converted into the lactone of which the maximum rotation is known[12] (Table 2). Both methods were compared for the reduction of imide **5** (Table 2, entry 1). The acceptable agreement of the results (HPLC: 75% e.e., enantiomeric excess 80%) confirmed the validity of the latter method.

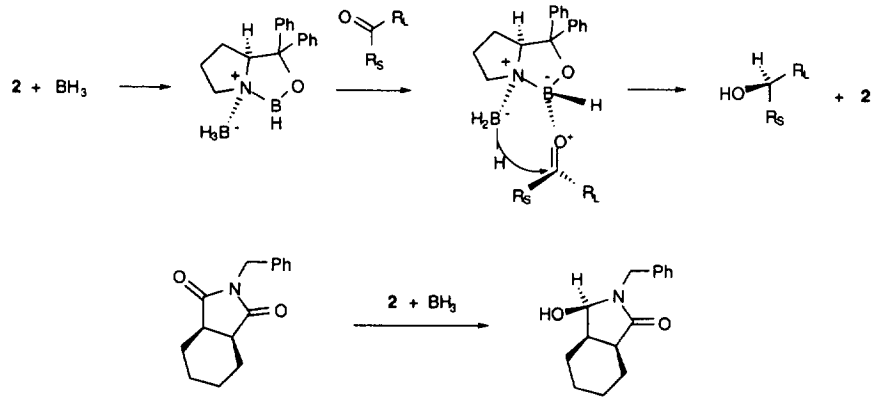
By comparing the signs of the specific rotations of the lactones formed from the hydroxylactams with those known in literature,[12] the absolute configuration of the reduction products was determined. In view of the structural similarities of the imides in Table 2 compared with those in Table 1, we assume that the other substrates are reduced in the same stereochemical sense.

As shown in Table 1, most of the reductions proceeded in good yields. Some slight modifications

of the general procedure were sometimes used to enhance the enantioselectivities. The ethoxylactam in entry 1 for example, was formed in 80% e.e. at 0°C, while reaction at rt proceeded with an e.e. of 75%. In one case (entry 4) $BH_3 \cdot Me_2S$ was used instead of $BH_3 \cdot THF$, because the former gave more reproducible results. In entries 2, 3 and 7 the hydroxylactam was not purified, but immediately converted into the ethoxylactam, which greatly enhanced the overall yield. In entry 5, it was not possible to convert the hydroxylactam derived from *meso*-tartaric acid diacetate into the ethoxylactam. The kinetic product of the reduction reaction was immediately transformed into the triacetate under standard conditions (excess acetic anhydride, catalytic DMAP in pyridine).

In most cases reduction of the amount of catalyst resulted in a significant drop of the e.e. This is most probably due to competitive, uncatalysed reduction by borane. It is well known that borane is able to reduce imides.[13] The 50% hydride excess (0.75 equiv BH_3, assuming that each borane molecule donates two hydrides) was necessary for the reactions to reach completion. The optimised conditions for most of the reductions were thus found to be 50% of catalyst and 0.75 equiv BH_3. However, entries 8, 9 and 10 show exceptions. The *N*-phenyl-substituted imide (entry 8) was reduced much faster than the other substrates. Only 10% of catalyst and 0.60 equiv BH_3 were sufficient to reduce the imide in 72% yield and 68% e.e. The use of 5% of catalyst resulted in a longer reaction time (6 h) and a lower e.e. (54%). Entry 9 shows that 0.60 equiv BH_3 was sufficient to drive the reduction reaction of the *N*-cyclohexyl-substituted imide to completion, giving the ethoxylactam in an enantiomeric excess of 94%. For the *N*-propionitrile substituted imide (entry 10) 0.60 equiv of borane proved also to be sufficient. For this compound the use of 20% of catalyst gave the same optical rotation and reaction time as 50% of catalyst. Our enantioselective reduction method is well suited for scale-up as compound **14** was reduced several times on a 10 gram scale with a reproducible yield and e.e.

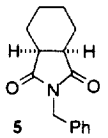
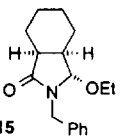
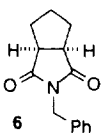
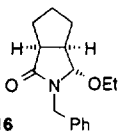
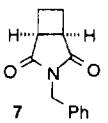
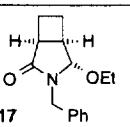
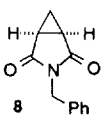
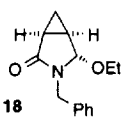
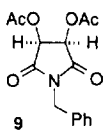
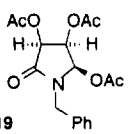
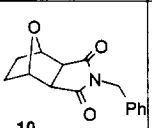
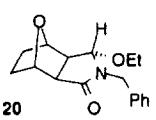
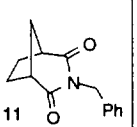
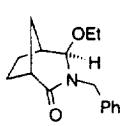
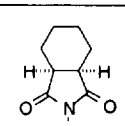
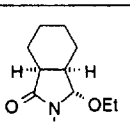
In Scheme 2 the general reduction of a ketone is shown. The stereochemical outcome of such reductions has been explained by using the transition state model shown.[5b] When acetophenone (R_L=phenyl, R_S=methyl) is reduced by using the borane complex of catalyst **2**, the (*R*)-alcohol is obtained. This result is explained by assuming a six-membered cyclic transition state in which the borane and the ketone complex at the same convex side of the oxazaborolidine. The R_L is positioned at the least hindered convex side of the bicycle, so that the *Si*-face of the ketone is attacked by hydride.

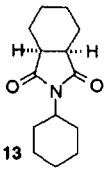
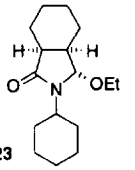
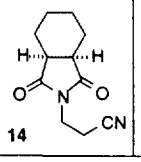
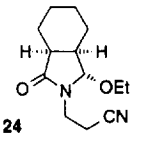


Scheme 2.

This model can also be applied to the cyclic imide system. It is assumed that the *cis*-hydroxylactam is the kinetic product as a result of hydride attack from the least hindered face of the carbonyl group. When the mechanistic picture of the ketone reduction is now applied to the cyclic *meso*-imides, the nitrogen moiety is the large substituent (R_L), and the fused ring moiety is the small substituent (R_S). Because the enantioselectivity of the reduction is higher if the difference in size between R_L and R_S is larger, a decrease of the size of R_S should give a higher enantioselectivity. This was borne out

Table 1. Reduction of *meso*-imides using chiral oxazaborolidine **2** (see Scheme 1)

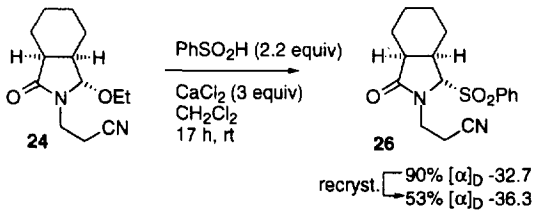
entry	imide	reduction to hydroxylactam				ethoxylactam	ethanolysis of hydroxylactam		
		catalyst (equiv)	borane (equiv)	time (h)	yield		yield	e.e. / o.p.[1]	$[\alpha]_D$[2]
1	 **5**	0.50	0.75	2[3]	95%	 **15**	87%	80% (e.e.)	-53.7 (*c* 1.2)
2	 **6**	0.50	0.75	1	n.d.[4]	 **16**	85%[5]	77% (o.p.)	-37.9 (*c* 1.6)
3	 **7**	0.50	0.75	2	n.d.[4]	 **17**	68%[5]	89% (o.p.)	-18.9 (*c* 1.5)
4	 **8**	0.50	0.75[6]	3	74%[7]	 **18**	94%	88% (e.e.)	-36.3 (*c* 1.0)
5	 **9**	0.50	0.75	2	63%	 **19**	69%[8]	87% (e.e.)	+43.7 (*c* 0.60)
6	 **10**	0.50	0.75	2	n.d.[4]	 **20**	68%[5]	76% (e.e.[9])	+23.8 (*c* 0.58)
7	 **11**	0.50	0.75	5	55%	 **21**	53%[10]	86% (e.e.)	-28.5 (*c* 1.0)
8	 **12**	0.10	0.60	0.5	72%	 **22**	100%	68% (e.e.)	+18.8 (*c* 1.0)

entry	imide	reduction to hydroxylactam				ethoxylactam	ethanolysis of hydroxylactam		
		catalyst (equiv)	borane (equiv)	time (h)	yield		yield	e.e. / o.p.[1]	$[\alpha]_D$[2]
9	 13	0.50	0.60	0.5	47%	 23	70%	94% (o.p.)	+24.9 (*c* 1.0)
10	 14	0.20	0.60	1.2[11]	90%[12]	 24	70%	90% (e.e.)	-17.9 (*c* 1.0)

[1]Enantiomeric excess (e.e.) determined by HPLC or optical purity (o.p.) determined according to Table 2. [2]Determined at rt in $CHCl_3$. [3]Reaction at 0°C. [4]The unpurified reaction products were ethanolysed. [5]Overall yield starting from the imide. [6]$BH_3 \cdot Me_2S$. [7]Corrected for 14% starting material. [8]After treatment of the hydroxylactam with Ac_2O (5 equiv) and DMAP (cat) in pyridine. [9]Determined by HPLC-analysis of the allyl derivative **28**. [10]Mixture of diastereomers (82:18). [11]Slow addition of $BH_3 \cdot THF$ over 1 h. [12]Corrected for 14% starting material.

by experiment as can be seen from Table 1: in case of entries 3 and 4, in which somewhat smaller substituents R_S are present, slightly higher e.e.'s are found. A bulky substituent on the nitrogen atom gives higher selectivity as well, shown in entry 9, where the *N*-cyclohexyl substituted imide gives an e.e. of 94%.

Most of the enantioselective reductions in Table 1 proceeded in enantioselectivities around 85%. However, for application to total synthesis enantiopure compounds are required. The most practical way of obtaining enantiopure compounds starting from enantio-enriched compounds, is recrystallisation. However, none of the ethoxylactams were crystalline. In our search for crystalline lactam derivatives, we came across the work of Ley and co-workers who converted ethoxylactams into benzenesulfonyllactams.[14] We applied their conditions for the formation of benzenesulfonyllactams to the ethoxylactam **24** (Scheme 3). When this compound was treated with 2.2 equiv of benzenesulfinic acid in the presence of calcium chloride, the crystalline sulfone **26** was formed in 90% yield.

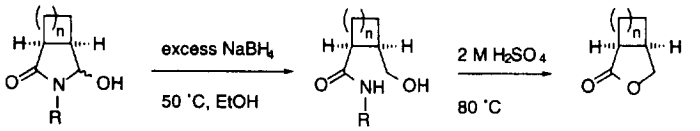


Scheme 3.

We were very pleased to be able to raise the e.e. of **26** to >99% (according to HPLC) by only a single recrystallisation from a pentane/ethyl acetate mixture. This compound is a useful intermediate in our studies towards the synthesis and applications of enantiopure DBN analogues.[15]

As already mentioned, 5-ethoxypyrrolidinones as well as their 5-benzenesulfonyl derivatives are versatile building blocks for synthetic purposes. Their synthetic utility mainly rests upon the possibility to effect C–C bond formation *via* *N*-acyliminium chemistry. Two examples of such reactions are given in Scheme 4. When compound **26** was treated with 2 equiv of both trimethylallylsilane and $BF_3 \cdot OEt_2$ at low temperature, the allyl-substituted lactam **27** was obtained in a quantitative yield. Under the same

Table 2. Determination of enantiomeric excess and absolute configuration of selected reduction products

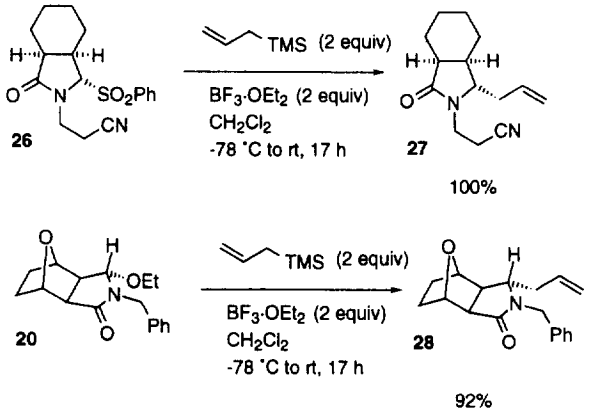


25a-d

		lactone				
entry	hydroxylactam	yield from **25**	$[\alpha]_D$	$[\alpha]_D$ max[1]	o.p.	e.e.
1	**25a** (n = 3, R = Bn)	95%	+38.9	+48.8	80%[2]	75%[2]
2	**25b** (n = 2, R = Bn)	59%	+74.7	+96.6	77%	n.d.
3	**25c** (n = 1, R = Bn)	71%	+106	+119	89%	n.d.
4	**25d** (n = 3, R = cHex)	62%	+40.2	+48.8	82%[3]	n.d.

[1]See ref.[12]. [2]The ethoxylactam from **25a** has $[\alpha]_D$ −51.7 (*cf* entry 1, Table 1). [3]The ethoxylactam from **25d** has $[\alpha]_d$ +21.8 (*cf* entry 9, Table 1).

conditions lactam **20** was allylated in 92% yield. Compound **28** was used for the e.e. determination of the reduction of imide **10**.



Scheme 4.

In conclusion, we have shown that several *meso*-imides are reduced in high enantioselectivities (up to 94%) and moderate to good yields by using oxazaborolidine **2**. By conversion to a benzenesulfonyl-lactam, it proved possible to raise the e.e. to >99% after a single recrystallisation. The enantiomerically pure lactams obtained in this way are useful starting materials for various synthetic purposes.

Experimental

General information

All reactions were carried out under an inert atmosphere of dry nitrogen, unless described otherwise. Standard syringe techniques were applied for transfer of dry solvents and air or moisture sensitive reagents. Infrared (IR) spectra were obtained from $CHCl_3$ solutions using a Perkin Elmer 1310 or a Bruker IFS 28 spectrophotometer and absorptions are reported in cm^{-1}. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were determined in $CDCl_3$ using a Bruker AC 200 (200 MHz), a Bruker WM 250 (250 MHz) or a Bruker ARX 400 (400 MHz) spectrometer. Carbon nuclear magnetic resonance (^{13}C-NMR) spectra were also obtained from a $CDCl_3$ solution using the same instruments

(50, 63 or 100 MHz, respectively). Chemical shifts are reported on the δ scale in ppm relative to an internal standard of residual chloroform (7.27 ppm for ^{1}H-NMR and 77.0 ppm for ^{13}C-NMR). Mass spectra and accurate mass determinations were performed on a JEOL JMS SX/SX102A four-sector mass spectrometer, coupled to a JEOL MS-MP7000 data system. Elemental analyses were performed on a Vario EL in the Inorganic Laboratory of this university. Optical rotations were measured on a Perkin–Elmer 241 in $CHCl_3$ at rt. Flash chromatography was performed by using Acros Chimica silica gel (0.030–0.075 mm). Melting points are uncorrected. High pressure liquid chromatography (HPLC) was performed using a Chiralpak AS column obtained from Daicel Chemical Industries Ltd. The column was attached to a L-6200 Intelligent Pump, samples were monitored using a 655A Variable Wavelength UV Monitor, and the chromatograms were run on a D-2500 Chromato-Integrator, all from Merck Hitachi. Ethyl acetate (EtOAc) and petroleum ether 60–80 (PE) were distilled before use. Tetrahydrofuran (THF) was freshly distilled from sodium benzophenone ketyl prior to use. (*S*)-α,α-Diphenylprolinol was obtained from Fluka. $BH_3 \cdot THF$ (1.0 M solution in THF) and $BH_3 \cdot Me_2S$ (neat) were obtained from Aldrich.

General procedure A for the synthesis of meso-*imides* ***5***, ***8***, ***12–14***

In the absence of solvent, equimolar amounts of the anhydride and the amine were mixed. This mixture was heated to 200°C and water was allowed to evaporate. After 30–60 min at this temperature, the mixture was cooled and dissolved in ethanol. Charcoal was added and the mixture was refluxed for 1 h. Charcoal was then removed by filtration and the imide was allowed to crystallise from the solution.

cis-*2-Benzyl-octahydroisoindole-1,3-dione* ***5***

According to general procedure A, starting from *cis*-1,2-cyclohexanedicarboxylic anhydride (50 g, 324 mmol) and benzylamine (35 mL, 324 mmol) and using a reaction time of 30 min, the imide (73 g, 299 mmol, 92%) was obtained as white crystals, mp 71–72°C. IR: 1770, 1700. ^{1}H-NMR (250 MHz): 7.37–7.27 (m, 5 H, *Ph*CH_2N), 4.64 (s, 2 H, PhCH_2), 2.88–2.79 (m, 2 H, C(O)C*H*C*H*C(O)), 1.89–1.31 (m, 8 H, –$(CH_2)_4$). ^{13}C-NMR (100 MHz): 179.2 (*C*O), 136.0, 128.5, 128.4, 127.7 (*Ph*), 42.0 (CH_2Ph), 39.6 (C(O)*C*H), 23.5 (C(O)CHCH_2), 21.4 (C(O)CHCH_2CH_2). Anal. Calcd for $C_{15}H_{17}NO_2$: C, 74.05; H, 7.04; N, 5.76. Found: C, 73.93; H, 6.93; N, 5.68.

cis-*3-Benzyl-3-aza-bicyclo[3.1.0]hexane-2,4-dione* ***8***

According to general procedure A, starting from the corresponding anhydride[8] (1.89 g, 16.9 mmol) and benzylamine (2.02 mL, 16.9 mmol), and using a reaction time of 1 h, the imide (2.45 g, 12.2 mmol, 72%) was obtained as white crystals, mp 90–91°C. IR: 1773, 1709. ^{1}H-NMR (200 MHz): 7.29 (m, 5 H, *Ph*), 4.50 (s, 2 H, PhCH_2N), 2.50–2.44 (dd, 2 H, *J*=8.1, 3.1 Hz, C*H*CH_2CH), 1.54–1.44 (dt, 1 H, *J*=8.0, 4.8 Hz, CHC*H*HCH), 1.33–1.27 (dt, 1 H, *J*=4.6, 3.6 Hz CHCH*H*CH). ^{13}C-NMR (100 MHz): 174.8 (CO), 136.0, 128.6, 128.4, 127.8 (*Ph*), 41.5 (CH_2Ph), 20.4 (CHCH_2CH), 20.2 (*C*H). Anal. Calcd for $C_{12}H_{11}NO_2$: C, 71.63; H, 5.51; N, 6.96. Found: C, 72.18; H, 5.63; N, 7.32.

cis-*2-Phenyl-octahydroisoindole-1,3-dione* ***12***

According to general procedure A, starting from *cis*-1,2-cyclohexanedicarboxylic anhydride (52 g, 334 mmol) and aniline (31 mL, 334 mmol) and using a reaction time of 2 h, the imide (27 g, 119 mmol, 36%) was obtained as slightly yellow crystals, mp 70.5–72.5°C. IR: 1767, 1693. ^{1}H-NMR (400 MHz): 7.44 (t, 2 H, *J*=7.3 Hz, *Ph*), 7.35 (t, 1 H, *J*=7.5 Hz, *Ph*), 7.27 (d, 2 H, *J*=7.2 Hz, *Ph*), 3.02–2.96 (quintet, 2 H, *J*=1.9 Hz, C(O)C*H*C*H*C(O)), 1.93–1.82 (m, 4 H, 2×C(O)CHCH_2), 1.50–1.47 (m, 4 H, –$(CH_2)_2$–). ^{13}C-NMR (100 MHz): 178.4 (CO), 132.0, 128.9, 128.1, 126.1 (*Ph*), 39.9 (C(O)*C*H*C*H*C*(O)), 23.8 (C(O)CHCH_2), 21.7 (–$(CH_2)_2$–). Anal. Calcd for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.11%. Found: C, 73.09; H, 6.34; N, 6.01.

cis-*2-Cyclohexyl-octahydroisoindole-1,3-dione* ***13***

According to general procedure A, starting from *cis*-1,2-cyclohexanedicarboxylic anhydride (50 g, 324 mmol) and cyclohexylamine (37 mL, 324 mmol) and using a reaction time of 45 min, the imide (43.9 g, 201 mmol, 62%) was obtained as slightly yellow crystals, mp 72–73°C. IR: 1708. ^{1}H-NMR (400 MHz): 3.94–3.82 (tt, 1 H, *J*=12.3, 3.8 Hz, NC*H*), 2.78–2.69 (quint, 2 H, *J*=4.2 Hz, C(O)C*H*C*H*C(O)), 2.13–2.00 (dq, 2 H, *J*=12.5, 3.2 Hz, NCHC*H*H(C*H*H)), 1.80–1.07 (m, 16 H, –$(CH_2)_4$– and NCHCH*H*–$(CH_2)_3$–CHH). ^{13}C-NMR (100 MHz): 179.7 (CO), 51.1 (N*C*H), 39.5 (C(O)*C*H*C*HC(O)), 28.7, 25.8, 23.7 and 21.5 (–$(CH_2)_4$– and NCH–$(CH_2)_2$–CH_2–$(CH_2)_2$–), 25.0 (NCH–$(CH_2)_2$–CH_2–$(CH_2)_2$–). Anal. Calcd for $C_{14}H_{21}NO_2$: C, 71.46; H, 8.99; N, 5.95. Found: C, 71.08; H, 8.76; N, 5.91.

3-Amino-propionitrile

To a solution of 3-amino-propionitrile fumarate (52 g, 406 mmol) in THF (150 mL) was added KOH (46 mL, 812 mmol, 18 M solution in H_2O) in 10 min at 0°C. After stirring for 30 min at rt, the salts were filtered off and washed (3×, 1:1 THF/Et_2O). The combined solvents were dried ($MgSO_4$) and concentrated *in vacuo*. The amine was obtained as a slightly yellow oil (28.4 g, 406 mmol, 100%) and was used without further purification. ^{1}H-NMR (250 MHz): 2.96–2.91 (t, 2 H, *J*=6.4 Hz, C$H_2$$NH_2$), 2.44–2.39 (t, 2 H, *J*=6.4 Hz, CH_2CN), 1.31 (m, 2 H, *N*H_2).

3-(1,3-Dioxo-octahydroisoindol-2-yl)-propionitrile ***14***

According to general procedure A, starting from *cis*-1,2-cyclohexanedicarboxylic anhydride (56 g, 364 mmol) and 3-amino-propionitrile (25.5 g, 364 mmol) and using a reaction time of 30 min, the imide (71 g, 346 mmol, 95%) was obtained as white crystals, mp: 61–61.5°C. IR: 2250, 1779, 1711. ^{1}H-NMR (200 MHz): 3.74–3.71 (t, 2 H, *J*=6.8 Hz, NCH_2), 2.89–2.83 (m, 2 H, C(O)C*H*C*H*C(O)), 2.70–2.66 (t, 2 H, *J*=6.7 Hz, CH_2CN), 1.86–1.67 (m, 4 H, CHCH_2–$(CH_2)_2$–CH_2), 1.45–1.34 (m, 4 H, –$(CH_2)_2$–). ^{13}C-NMR (100 MHz): 175.0 (CO), 116.8 (CN), 39.7 (C(O)*C*H*C*HC(O)), 33.7 (N*C*H_2), 23.7 (CH*C*H_2–$(CH_2)_2$–CH_2), 21.5 (–$(CH_2)_2$–), 16.2 (CH_2CN). Anal. Calcd for $C_{11}H_{14}N_2O_2$: C, 64.06; H, 6.84; N, 13.58. Found: C, 64.07; H, 6.79; N, 13.52.

General procedure B for the preparation of the N*-benzylimides* ***6*** *and* ***7***

A solution of the NH compound in methanol was added dropwise at 0°C to a solution of sodium (1 equiv) in methanol. After stirring for 1 h at 0°C, benzyl bromide (1.4 equiv) was added dropwise. The reaction mixture was stirred at rt for 72 h and then concentrated *in vacuo*. The residue was purified by flash chromatograpy.

cis-*2-Benzyl-tetrahydrocyclopenta[c]pyrrole-1,3-dione* ***6***

According to general procedure B, starting from the corresponding NH compound[9] (9.0 g, 64.8 mmol), sodium (1.5 g, 64.7 mmol), MeOH (80 mL) and benzyl bromide (9.8 mL, 90.6 mmol), the imide (12.7 g, 55.5 mmol, 86%) was obtained as a white solid after flash chromatography (EtOAc/PE 1:1), mp 49–50°C. IR: 1770, 1695. ^{1}H-NMR (400 MHz): 7.32–7.21 (m, 5 H, *Ph*CH_2N), 4.59 (s, 2 H, PhCH_2), 3.14–3.10 (m, 2 H, C(O)C*H*C*H*C(O)), 2.11–2.06 (m, 2 H, C*H*HCHCHC*H*H), 1.87–1.77 (m, 2 H, CH*H*CHCHCH*H*), 1.72–1.66 (m, 1 H, CH_2C*H*HCH_2), 1.21–1.14 (m, 1 H, CH_2CH*H*CH_2). ^{13}C-NMR (100 MHz): 179.9 (CO), 135.9, 128.5, 128.3, 127.7 (*Ph*), 45.1 (C(O)*C*H), 42.3 (*C*H_2Ph), 30.4 (C(O)CH*C*H_2), 24.7 (CHCH_2CH_2).). Anal. Calcd for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.11. Found: C, 73.38; H, 6.71; N, 6.10.

cis-*3-Benzyl-3-azabicyclo[3.2.0]heptane-1,3-dione* ***7***

According to general procedure B, starting from the corresponding NH compound[16] (6.25 g, 50.0 mmol), sodium (1.15 g, 50.0 mmol), MeOH (75 mL) and benzyl bromide (8.35 mL, 70.0 mmol), the imide (8.07 g, 40.5 mmol, 81%) was obtained as a white solid after flash chromatography (EtOAc/PE

1:1), mp 50–52°C. IR: 1770, 1695. ^{1}H-NMR (400 MHz): 7.38–7.23 (m, 5 H, *Ph*CH_2N), 4.68 (s, 2 H, PhCH_2), 3.26–3.23 (m, 2 H, C(O)C*H*C*H*C(O)), 2.65–2.57 and 2.12–2.06 (m, 4 H, –$(CH_2)_2$–). ^{13}C-NMR (100 MHz): 179.4 (CO), 135.9, 128.5, 128.4, 127.7 (*Ph*), 42.3 (*C*H_2Ph), 38.3 (C(O)*C*H), 22.8 (CH_2CH_2). Anal. Calcd for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09; N, 6.51. Found: C, 73.07; H, 6.24; N, 6.82.

General procedure C for the synthesis of ***9*** *and* ***10***

A mixture of the corresponding dicarboxylic acid (30 mmol) and acetyl chloride (20 mL, 280 mmol) was heated at reflux for 1.5 h and then concentrated *in vacuo*. The resulting crude anhydride was dissolved in THF (20 mL) and benzylamine (3.6 mL, 33 mmol) was slowly added. After stirring for 4 h the mixture was concentrated *in vacuo*, and the residue was heated at reflux in acetyl chloride (20 mL, 280 mmol) for 17 h. After concentration of the reaction mixture *in vacuo*, the residue was purified by flash chromatography and subsequent recrystallization.

cis-*1-Benzyl-3,4-diacetoxypyrrolidin-2,5-dione* ***9***

Following general procedure C, the imide (4.4 g, 17 mmol, 57%) was obtained as a white solid after flash chromatography (EtOAc/PE 1:1) and recrystallisation (EtOH). IR: 1760, 1720. ^{1}H-NMR (200 MHz): 7.37–7.26 (m, 5 H, *Ph*CH_2N), 5.85 (s, 2 H, C(O)C*H*C*H*C(O)), 4.75 (s, 2 H, PhCH_2), 2.43 (s, 6 H, 2×CH_3C(O)O).

cis-*4-Benzyl-10-oxa-4-azatricyclo[5.2.1.0]decane-3,5-dione* ***10***

Following general procedure C, the imide (5.4 g, 18.6 mmol, 62%) was obtained as a white solid after flash chromatography (EtOAc/PE 1:1) and recrystallization (EtOAc), mp 68–70°C. IR: 1780, 1700. ^{1}H-NMR (250 MHz): 7.30–7.24 (m, 5 H, *Ph*CH_2N), 4.88 (m, 2 H, CH_2C*H*OC*H*CH_2), 4.62 (s, 2 H, PhCH_2), 2.87 (s, 2 H, C(O)C*H*C*H*C(O)), 1.87–1.54 (m, 4 H, –$(CH_2)_2$). ^{13}C-NMR (100 MHz): 176.7 (CO), 135.4, 128.8, 128.5, 128.0 (*Ph*), 79.0 (*C*HOCH), 49.9 (C(O)*C*HCHC(O)), 42.4 (CH_2Ph), 28.5 (CH_2CH_2).

cis-*3-Benzyl-3-aza-bicyclo[3.2.1]octane-2,4-dione* ***11***

To a solution of the corresponding anhydride[11] (3.0 g, 21.4 mmol) in THF (12 mL) was slowly added a solution of benzylamine (2.82 mL, 23.5 mmol) in THF (8 mL). After stirring for 2 h at rt, the solvent was removed *in vacuo* and AcCl (15.2 mL, 214 mmol) was added. The mixture was refluxed for 6 h. The excess of AcCl was removed under a stream of N_2. Flash chromatography (EtOAc:PE 1:2) and distillation afforded the imide as a yellow oil (3.63 g, 15.8 mmol, 74%). IR: 1730, 1689. ^{1}H-NMR (400 MHz): 7.24–7.16 (m, 5 H, *Ph*), 4.77 (s, 2 H, CH_2Ph), 3.11 (dd, 2 H, *J*=6.6, 4.1 Hz, C*H*C(O)), 2.1–1.8 (m, 5 H, (–CH_2)$_2$– and CHCH*H*CH), 1.56 (dt, 1 H, *J*=12.1, 4.1 Hz, CHC*H*HCH). ^{13}C-NMR (100 MHz): 176.3 (CO), 137.3, 128.4, 128.0, 127.2 (*Ph*), 44.7 (*C*HCH$_2$CH), 41.9 (*C*H_2Ph), 32.3 (*C*HCH$_2$CH), 27.1 (CH_2CH_2).

General procedure D for the enantioselective reduction and ethanolysis

(*S*)-α,α-Diphenylprolinol was dissolved in THF (0.2 M) under an Argon atmosphere. After the addition of BH_3 (3 equiv of a 1.0 M solution in THF) the reaction mixture was refluxed for 17 h (bath temperature 74°C). The clear solution was concentrated by using an oil pump (0.1 mm Hg, 30 min, rt) and the white solid (the oxazaborolidine) was taken up in THF (0.3 M) and used without further purification.

At 0°C, the solution of the catalyst was added to a solution of the imide in THF (0.2 M). After addition of the optimised amount of BH_3 (0.60–0.75 equiv of a 1.0 M solution in THF) the reaction mixture was allowed to warm to rt and stirring was continued. After 0.5–5 h the reaction was carefully quenched with an aqueous solution of 5% HCl. After extraction of the water layer by using CH_2Cl_2 (5×), the combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. The hydroxylactam was purified by flash chromatography.

The purified hydroxypyrrolidinone was dissolved in ethanol and the solution was acidified (to pH ca. 2) with H_2SO_4 (2 M solution in ethanol). After being stirred for 1–3 h at rt the reaction mixture was carefully quenched with an aqueous saturated $NaHCO_3$ solution. After extraction of the water layer using CH_2Cl_2 (5×), the combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. The ethoxylactam was purified by flash chromatography.

(3S,3aR,7aS)-2-Benzyl-3-ethoxy-octahydroisoindol-1-one ***15***

According to general procedure D, starting from (*S*)-α,α-diphenylprolinol (40.2 mg, 0.16 mmol), $BH_3 \cdot THF$ (1.0 mL, 1.0 mmol, 1.0 M in THF) and THF (1 mL)(for the catalyst) and imide **5** (77.2 mg, 0.32 mmol) in THF (2 mL) and $BH_3 \cdot THF$ (0.24 mL, 0.24 mmol, 1.0 M in THF) and using a reaction time of 2 h at 0°C, there was obtained after flash chromatography (EtOAc/PE 1:5) 72.9 mg (0.30 mmol, 95%) of hydroxylactams as white crystals. In another experiment the diastereomers were separated using flash chromatography (CH_2Cl_2/acetone 9.5:0.5). **2-Benzyl-3β-hydroxy-octahydroisoindol-1-one**. IR: 3380, 1670, 1450. ^{1}H-NMR (400 MHz): 7.33–7.24 (m, 5 H, *Ph*CH_2N), 5.00 (ABX dd, 1 H, *J*=5.4, 9.4 Hz, C*H*(OH)CH), 4.78 (AB d, 1 H, *J*=14.8 Hz, PhC*H*HN), 4.23 (AB d, 1 H, *J*=14.8 Hz, PhCH*H*N), 2.47–2.34 (m, 2 H, C(OH)C*HCH*C(O)), 2.01–1.95 (m, 1 H, O*H*), 1.69–1.25 (m, 8 H, –$(CH_2)_4$–). $[\alpha]_{578}$ +39 (*c* 1.0; $CHCl_3$). **2-Benzyl-3α-hydroxy-octahydroisoindol-1-one**. ^{1}H-NMR (250 MHz): 7.35–7.17 (m, 5 H, *Ph*CH_2N), 4.79 (AB d, 1 H, *J*=14.7 Hz, PhC*H*HN), 4.54 (d, 1 H, *J*=5.3 Hz, C*H*(OH)N), 4.22 (AB d, 1 H, *J*=14.7 Hz, PhCH*H*N), 2.81–2.77 (m, 1 H, –O*H*), 2.21–2.04 (m, 2 H, C(OH)C*HCH*C(O)), 1.69–0.88 (m, 8 H, –$(CH_2)_4$–). $[\alpha]_{578}$ −54 (*c* 0.65; $CHCl_3$). The above mixture of hydroxylactams (73 mg, 0.30 mmol) was solvolysed in EtOH (2 mL) for 1 h to the ethoxylactam, which was purified by using flash chromatography (EtOAc/PE 1:10) to give a yellow oil (75.1 mg, 0.26 mmol, 87%). IR: 1690, 1440. ^{1}H-NMR (400 MHz): 7.35–7.25 (m, 5 H, *Ph*CH_2N), 4.99 (AB d, 1 H, *J*=14.7 Hz, PhC*H*HN), 4.10 (s, 1 H, C*H*OEt), 4.01 (AB d, 1 H, *J*=14.7 Hz, PhCH*H*N), 3.48–3.38 (m, 2 H, OCH_2CH_3), 2.88–2.79 (m, 1 H, C*H*C(O)), 2.24–2.18 (m, 2 H, C*H*HCHC(O) and C*H*CHOEt), 1.64–0.74 (m, 7 H, (C(O)CHCH*H*$(CH_2)_3$), 1.18 (t, 3 H, *J*=7.0 Hz, OCH_2CH_3). ^{13}C-NMR (50 MHz): 176.1 (*C*(O)N), 136.8, 128.5, 128.4, 127.3 (*Ph*), 92.2 (*C*HOEt), 63.2 (OCH_2CH_3), 44.3 (CH_2Ph), 38.6 (*C*HC(O)), 37.6 (*C*HCHOEt), 26.7, 23.4, 22.8 and 22.7 ($(CH_2)_4$), 15.2 (OCH_2CH_3). HRMS calcd for $C_{17}H_{23}NO_2$ 273.1729, found 273.1736. $[\alpha]_D$ −53.7 (*c* 1.2; $CHCl_3$). e.e. (HPLC, eluent *n*-heptane/ethanol 97:3) 80%.

(3S,3aR,6aS)-2-Benzyl-3-ethoxy-hexahydrocyclopenta[c]pyrrol-1-one ***16***

According to general procedure D, starting from (*S*)-α,α-diphenylprolinol (127 mg, 0.50 mmol), $BH_3 \cdot THF$ (2.0 mL, 2.0 mmol, 1.0 M in THF) and THF (2 mL)(for the catalyst) and imide **6** (229 mg, 1.0 mmol) in THF (5 mL) and $BH_3 \cdot THF$ (0.75 mL, 0.75 mmol, 1.0 M in THF) and using a reaction time of 1 h, the crude product was transformed into the ethoxylactam using EtOH (3 mL) and a reaction time of 1 h. After flash chromatography (CH_2Cl_2/acetone 9.5:0.5) **16** (220 mg, 0.85 mmol, 85%) was obtained as a yellow oil. IR: 1660, 1440. ^{1}H-NMR (200 MHz): 7.40–7.19 (m, 5 H, *Ph*CH_2N), 4.69 (AB d, 1 H, *J*=14.7 Hz, PhC*H*HN), 4.32 (s, 1 H, C*H*OEt), 3.69 (AB d, 1 H, *J*=14.7 Hz, PhCH*H*N), 3.44–3.27 (m, 2 H, OCH_2CH_3), 3.10–2.95 (m, 1 H, C*H*C(O)), 2.57–2.47 (m, 1 H, C*H*CHOEt), 2.11–1.24 (m, 6 H, $(CH_2)_3$), 1.19 (t, 3 H, *J*=7.0 Hz, OCH_2CH_3). ^{13}C-NMR (50 MHz): 177.0 (*C*(O)N), 136.7, 128.5, 128.2 and 127.4 (*Ph*), 93.6 (*C*HOEt), 61.2 (OCH_2CH_3), 46.2 (*C*HC(O)), 43.8 (CH_2Ph), 42.4 (*C*HCHOEt), 32.1, 30.1, and 25.4 ($(CH_2)_3$), 15.2 (OCH_2CH_3). HRMS calcd for $C_{16}H_{21}NO_2$ 259.1713, found 259.1561. $[\alpha]_D$ −37.9 (*c* 1.6; $CHCl_3$). Enantiomeric excess 77%.

(1S,4S,5R)-3-Benzyl-4-ethoxy-3-azabicyclo[3.2.0]heptan-2-one ***17***

According to general procedure D, starting from (*S*)-α,α-diphenylprolinol (127 mg, 0.50 mmol), $BH_3 \cdot THF$ (2.0 mL, 2.0 mmol, 1.0 M in THF) and THF (2 mL)(for the catalyst) and imide **7** (215 mg, 1.0 mmol) in THF (5 mL) and $BH_3 \cdot THF$ (0.75 mL, 0.75 mmol, 1.0 M in THF) and using a reaction

time of 2 h, the crude product was transformed into the ethoxylactam using 3 mL EtOH and a reaction time of 1 h. After flash chromatography (CH_2Cl_2/acetone 9.5:0.5) **17** (165 mg, 0.68 mmol, 68%) was obtained as a yellow oil. IR: 1670, 1420. ^{1}H-NMR (250 MHz): 7.41–7.24 (m, 5 H, *Ph*CH_2N), 5.01 (AB d, 1 H, *J*=14.7 Hz, PhC*H*HN), 4.44 (s, 1 H, C*H*OEt), 4.04 (AB d, 1 H, *J*=14.7 Hz, PhCH*H*N), 3.34–3.21 (m, 2 H, OCH_2CH_3), 3.08–3.04 (m, 1 H, C*H*C(O)), 2.86–2.75 (m, 2 H, C*H*CH(OEt) and C*H*HCHC(O)), 2.53–1.59 (m, 3 H,C*H*HCH_2), 1.19 (t, 3 H, *J*=7.0 Hz, OCH_2CH_3). ^{13}C-NMR (50 MHz): 177.5 (C(O)N), 136.9, 128.1, 127.8 and 127.5 (*Ph*), 92.5 (*C*HOEt), 60.5 (OCH_2CH_3), 43.9 (CH_2Ph), 40.2 (CHC(O)), 35.9 (*C*HCHOEt), 23.4, 22.5 ((CH_2)$_2$), 15.2 (OCH_2CH_3). HRMS calcd for $C_{15}H_{19}NO_2$ 245.1572, found 245.1415. $[\alpha]_D$ −18.9 (*c* 1.5; $CHCl_3$). Enantiomeric excess 89%.

(1S,4S,5R)-3-Benzyl-4-ethoxy-3-azabicyclo[3.1.0]hexan-2-one ***18***

According to general procedure D, starting from (*S*)-α,α-diphenylprolinol (127 mg, 0.50 mmol), BH_3·Me_2S (1.0 mL, 2.0 mmol, 2.0 M in toluene) and THF (10 mL)(for the catalyst) and imide **8** (200 mg, 1.0 mmol) in THF (2 mL) and BH_3·Me_2S (0.38 mL, 0.75 mmol, 2.0 M in toluene), and using a reaction time of 3 h, the hydroxylactam (128 mg, 0.64 mmol, 64%) was obtained after flash chromatography (EtOAc/PE 1:3) as a colourless oil together with starting material **8** (26 mg, 0.13 mmol, 13%). **3-Benzyl-4-hydroxy-3-azabicyclo[3.1.0]hexane-2-one**. IR: 3600, 1698. ^{1}H-NMR (250 MHz): 7.35–7.21 (m, 5 H, *Ph*), 5.1 (d, 1 H, *J*=5.2 Hz, C*H*OH), 4.6 (AB d, 1 H, *J*=14.8 Hz, CH*H*Ph), 3.9 (AB d, 1 H, *J*=14.8 Hz, C*H*HPh), 1.99–1.96 (m, 2 H, 2×CH), 1.04–0.97 (m, 2 H, CH_2). The above mixture of hydroxylactams (128 mg, 0.64 mmol) was solvolysed in EtOH (2 mL) for 1 h to the ethoxylactam, which was purified by using flash chromatography (EtOAc/PE 1:1) to give a yellow oil (141 mg, 0.60 mmol, 94%). IR: 1670. ^{1}H-NMR (200 MHz): 7.3–7.0 (m, 5 H, *Ph*),), 4.7 (AB d, 1 H, *J*=14.7 Hz, CH*H*Ph), 4.5 (d, 1 H, *J*=1.7 Hz, C*H*OEt), 3.9 (AB d, 1 H, *J*=14.7 Hz, C*H*HPh), 3.54–3.29 (m, 2H, OCH_2CH_3), 2.02–1.90 (m, 1 H, CHCHHC*H*), 1.89–1.77 (m, 1 H, C*H*CHHCH), 1.15–1.08 (t, 3 H, *J*=7.0 Hz, CH_2CH_3), 1.05–0.93 (m, 1 H, CHC*H*HCH), 0.43–0.37 (m, 1 H, CHCH*H*CH). ^{13}C-NMR (100 MHz): 174.6 (*C*(O)), 137.0, 128.6, 128.2, 127.4 (*Ph*), 87.5 (*C*HOEt), 59.7 (CH_3CH_2O), 43.0 (CH_2Ph), 19.0 (*C*HC(O)), 17.7 (*C*HCHOEt), 15.2 (CH_3CH_2O), 12.4 (CH*C*H_2CH). HRMS calcd for $C_{14}H_{17}NO_2$ 231.1259, found 231.1243. $[\alpha]_D$ −36.3 (*c* 1.0; $CHCl_3$). e.e. (HPLC, eluent *n*-heptane/*i*-PrOH 80:20) 88%.

(3S,4R,5R)-1-Benzyl-3,4,5-triacetoxypyrrolidin-2-one ***19***

According to general procedure D, starting from (*S*)-α,α-diphenylprolinol (253 mg, 1.00 mmol), BH_3·THF (3.0 mL, 3.0 mmol, 1.0 M in THF) and THF (3 mL)(for the catalyst) and imide **9** (584 mg, 2.00 mmol) in THF (10 mL) and BH_3·THF (1.5 mL, 1.5 mmol, 1.0 M in THF) and using a reaction time of 2 h, the hydroxylactam (431 mg, 1.26 mmol, 63%) was obtained after flash chromatography (CH_2Cl_2/acetone 9:1) as white crystals. **1-Benzyl-3,4-diacetoxy-5β-hydroxypyrrolidin-2-one**. mp 159–161°C. IR: 3400, 1760, 1700, 1420. ^{1}H-NMR (200 MHz): 7.34–7.26 (m, 5 H, *Ph*CH_2N), 5.38–5.26 (dd and d superimposed, 2 H, C*H*C(O)CH_3C*H*C(O)CH_3), 5.08 (dd, 1 H, *J*=4.8, 11.9 Hz, C*H*(OH)), 4.93 (AB d, 1 H, *J*=14.6 Hz, PhC*H*HN), 4.25 (AB d, 1 H, *J*=14.6 Hz, PhC*H*HN), 3.08 (d, 1 H, *J*=11.9 Hz, –O*H*), 2.17 (s, 6 H, 2× OC(O)CH_3). A mixture of diacetoxyhydroxylactam (190 mg, 0.65 mmol), acetic anhydride (0.30 mL, 3.25 mmol), pyridine (2.9 mL) and a catalytic amount of DMAP was stirred at rt for 36 h. To the solution was added 3 mL of toluene and the mixture was concentrated *in vacuo* (this was repeated 2 times). The residue was dissolved in CH_2Cl_2 (5 mL) and poured out into aq saturated NH_4Cl (2 mL). Extraction of the water layer with CH_2Cl_2 (3×5 mL), drying of the combined organic layers (Na_2SO_4), evaporation of the solvent and purification of the residue by flash chromatography (CH_2Cl_2/acetone 9.5:0.5) afforded **19** (150 mg, 0.45 mmol, 69%) as a colourless oil. IR: 1760, 1720, 1440, 1420. ^{1}H-NMR (400 MHz): 7.39–7.21 (m, 5 H, *Ph*CH_2N), 6.24–6.20 (m, 1 H, NC*H*OC(O)CH_3), 5.46–5.30 (two dd superimposed, 2 H, 2×C*H*OC(O)CH_3), 4.79 (AB d, 1 H, *J*=14.8 Hz, PhC*H*HN), 4.28 (AB d, 1 H, *J*=14.8 Hz, PhCH*H*N), 2.18, 2.03, 1.97 (3×s, 9

H, 3×OC(O)CH_3). ^{13}C-NMR (50 MHz): 169.3, 169.0, 168.7 (3×O*C*(O)CH_3), 167.8 (*C*(O)N), 135.0, 128.4, 128.0 and 127.7 (*Ph*), 79.6 (N*C*HOAc), 66.9 (C(O)*C*HOAc), 64.8 (CHOAc*C*HOAcCHOAc), 44.6 (CH_2Ph), 20.0, 19.9, 19.8 (3×CH_3C(O)). HRMS calcd for $C_{15}H_{15}NO_5$ (M−OAc) 289.0950, found 289.0944. $[\alpha]_D$ +43.7 (*c* 0.6; $CHCl_3$). e.e. (HPLC, eluent *n*-hexane/ethanol 90:10) 87%.

(1S,2R,5S,6S,7R)-4-Benzyl-5-ethoxy-10-oxa-4-azatricyclo[5.2.1.0]decan-3-one ***20***

According to general procedure D, starting from (*S*)-α,α-diphenylprolinol (127 mg, 0.50 mmol), BH_3·THF (3.0 mL, 3.0 mmol, 1.0 M in THF) and THF (2 mL)(for the catalyst) and imide **10** (257 mg, 1.00 mmol) in THF (6 mL) and BH_3·THF (0.75 mL, 0.75 mmol, 1.0 M in THF) and using a reaction time of 2 h, the crude product was transformed into the ethoxylactam using EtOH (3 mL) and a reaction time of 1 h. After flash chromatography (CH_2Cl_2/acetone 9.0:1.0) **20** (195 mg, 0.68 mmol, 68%) was obtained as a colourless oil. IR: 1680, 1450. ^{1}H-NMR (250 MHz): 7.33–7.20 (m, 5 H, *Ph*CH_2N), 4.93 (AB d, 1 H, *J*=15.1 Hz, PhC*H*HN), 4.82 (d, 1 H, *J*=4.3 Hz, C*H*OCHC(O)), 4.53 (s, 1 H, C*H*OEt), 4.45 (d, 1 H, *J*=4.5 Hz, C*H*OCHOEt), 4.00 (AB d, 1 H, *J*=15.1 Hz, PhCH*H*N), 3.40–3.32 (m, 2 H, OCH_2CH_3), 2.84 (d, 1 H, *J*=7.7 Hz, C*H*C(O)), 2.26 (d, 1 H, *J*=7.7 Hz, C*H*CHOEt), 1.79–1.25 (m, 4 H, $(CH_2)_2$), 1.15 (t, 3 H, *J*=7.0 Hz, OCH_2CH_3). ^{13}C-NMR (63 MHz): 173.4 (*C*(O)N), 135.8, 128.4, 127.6, 127.1 (*Ph*), 91.1 (*C*HOEt), 80.6 (*C*HOCHC(O)), 78.8 (*C*HOCHOEt), 61.3 (OCH_2CH_3), 51.9 (*C*HC(O)), 47.2 (*C*HCHOEt), 43.6 (CH_2Ph), 28.6, 28.3 ($(CH_2)_2$), 15.1 (OCH_2CH_3). HRMS calcd for $C_{17}H_{21}NO_3$ 287.1521, found 287.1524. $[\alpha]_D$ +23.8 (*c* 0.58; $CHCl_3$). e.e. 76%.

(1R,4R,5S)-3-Benzyl-4-ethoxy-3-azabicyclo[3.2.1]octan-2-one ***21***

According to general procedure D, starting from (*S*)-α,α-diphenylprolinol (127 mg, 0.50 mmol), BH_3·THF (2.0 mL, 2.0 mmol, 1.0 M in THF) and THF (10 mL)(for the catalyst) and imide **11** (233 mg, 1.0 mmol) and BH_3·THF (0.75 mL, 0.75 mmol, 1.0 M in THF), and using a reaction time of 5 h, the hydroxylactam (129 mg, 0.55 mmol, 55%) was obtained after flash chromatography (EtOAc/PE 1:1) as a yellow oil. **3-Benzyl-4-hydroxy-3-aza-bicyclo-[3.2.1]octan-2-one**. ^{1}H-NMR (400 MHz): 7.32–7.15 (m, 5 H, *Ph*), 4.95–4.91 (AB d, 1 H, *J*=14.9 Hz, NC*H*HPh), 4.78 (bt, 1 H, C*H*OH), 4.22–4.18 (AB d, 1 H, *J*=14.9 Hz, NCH*H*Ph), 4.18–4.15 (bs, 1 H, –O*H*), 2.74 (m, 1 H, C(O)C*H*), 2.45–2.41 (q, 1 H, *J*=5.2 Hz, C*H*C(OH)), 2.17–2.02 (m, 1 H, CHC*H*HCH), 1.88–1.50 (m, 5 H, –$(CH_2)_2$–, CHCH*H*CH). ^{13}C-NMR (100 MHz): 175.5 (*C*(O)), 137.4, 128.3, 127.9, 126.9 (*Ph*), 81.7 (*C*HOH), 43.5 (NCH_2Ph), 43.0 (C(O)*C*H), 40.6 (C(OH)*C*H), 31.4, 28.5 (–$(CH_2)_2$–), 20.5 (CHCH_2CH). The above mixture of hydroxylactams (129 mg, 0.55 mmol) was solvolysed in EtOH (2 mL) for 1 h to the ethoxylactams, which were purified and separated by using flash chromatography (EtOAc/PE 1:1) to give a yellow oil (76 mg, 0.29 mmol, 53%) which consisted of a 82:18 mixture of the *endo* and *exo* diastereomers. ***exo*-(1*R*,4*S*,5*S*)-3-Benzyl-4-ethoxy-3-azabicyclo[3.2.1]octan-2-one**. IR: 1670. ^{1}H-NMR (400 MHz): 7.23–7.08 (m, 5 H, *Ph*), 5.22 (AB d, 1 H, *J*=14.9 Hz, CH*H*Ph), 3.85 (d, 1 H, *J*=2.0 Hz, C*H*OEt), 3.80 (AB d, 1 H, *J*=14.9 Hz, C*H*HPh), 3.47–3.23 (m, 2 H, OCH_2CH_3), 2.75 (s, 1 H, C*H*CO), 2.42 (s, 1 H, C*H*CHOEt), 2.17 (d, 1 H, *J*=11.7 Hz, CHC*H*HCH), 1.81–1.68 (m, 4 H, CH_2CH_2), 1.30 (dt, 1 H, *J*=4.4 Hz, *J*=11.7 Hz, CHCH*H*CH), 1.14 (t, 3 H, *J*=7.0 Hz, CH_3CH_2O). ^{13}C-NMR (100 MHz): 174.1 (C(O)), 137.7, 128.5, 127.9, 127.1 (*Ph*), 89.8 (*C*HOEt), 63.56 (OCH_2CH_3), 44.9 (CH_2Ph), 44.1 (*C*HC(0)), 36.3 (*C*HCOEt), 28.4 and 29.9 (CH_2CH_2), 24.3 (CHCH_2CH), 15.3 (CH_3). ***endo*-(1*R*,4*R*,5*S*)-3-Benzyl-4-ethoxy-3-azabicyclo[3.2.1]octan-2-one**. IR: 1670. ^{1}H-NMR (400 MHz): 7.25–7.10 (m, 5 H, *Ph*), 5.10 (AB d, 1H, NCH*H*Ph), 4.25 (d, 1 H, C*H*OEt), 3.98 (AB d, 1 H, C*H*HPh), 3.40–3.30 (m, 1 H, OCH*H*CH_3), 3.21–3.10 (m, 1 H, OC*H*HCH_3), 2.75 (s, 1 H, C*H*CO), 2.60–2.45 (m, 1 H, C*H*CHOEt), 2.15–2.05 (m, 1 H, CHCH*H*CH), 1.81–1.60 (m, 4 H, CH_2CH_2), 1.60–1.41 (m, 1 H, CHC*H*HCH), 1.16–1.12 (m, 3 H, CH_2CH_3). ^{13}C-NMR (100 MHz): 174.1 (*C*(O)), 137.1, 128.4, 128.2, 127.9 (*Ph*), 88.0 (*C*HOEt), 62.8 (OCH_2CH_3), 43.2 (CH_2Ph), 43.2 (*C*HC(0)), 37.1 (*C*HCOEt), 28.5 and 31.0 (CH_2CH_2), 20.7 (CHCH_2CH), 15.2 (CH_2CH_3). HRMS

calcd for $C_{16}H_{21}NO_2$ 259.1572, found 259.1566. $[\alpha]_D$ −28.5 (*c* 1.0; $CHCl_3$). e.e. (HPLC, eluent *n*-heptane/*i*-PrOH 90:10) 86%.

(3S,3aR,7aS)-2-Phenyl-3-ethoxy-octahydroisoindol-1-one **22**

According to general procedure D, with addition at rt, starting from (*S*)-α,α-diphenylprolinol (100 mg, 0.39 mmol), BH_3·THF (2.0 mL, 2.0 mmol, 1.0 M in THF) and THF (5 mL)(for the catalyst) and imide **12** (905 mg, 3.95 mmol) in THF (10 mL) and BH_3·THF (2.4 mL, 2.4 mmol, 1.0 M in THF) and using a reaction time of 30 min, the hydroxylactam (662 mg, 2.86 mmol, 72%) was obtained after flash chromatography (EtOAc/PE 1:5) as a yellow oil. **2-Phenyl-3β-hydroxy-octahydroisoindol-1-one**. ^{1}H-NMR (250 MHz): 7.5–7.1 (m, 5 H, *Ph*), 5.61 (bd, 1 H, C*H*OH), 2.50 (m, 2 H, C(O)C*H*C*H*H), 1.5–2.1 (m, 8 H, CH(OH)C*H*–(C*H*$_2$)$_3$–CHH). ^{13}C-NMR (63 MHz): 175.7 (CO), 137.0, 128.8, 125.8, 123.9 (*Ph*), 85.5 (N*C*H), 41.6 (C(O)*C*H), 36.8 (C(OH)*C*H), 24.5, 23.2, 23.1, 22.1 (–(*C*H$_2$)$_4$–). The above mixture of hydroxylactams (662 mg, 2.9 mmol) was solvolysed in EtOH (10 mL) for 1 h to the ethoxylactam, which was purified by using flash chromatography (EtOAc/PE 1:7) to give yellow crystals (777 mg, 2.9 mmol, 100%). mp: 80–80.5°C. IR: 1680. ^{1}H-NMR (400 MHz): 7.53 (d, 2 H, *J*=7.3 Hz, *Ph*), 7.34 (t, 2 H, *J*=7.5 Hz, *Ph*), 7.16 (t, 2 H, *J*=7.2 Hz, *Ph*), 4.78 (s, 1 H, C*H*OEt), 3.47 (q, 2 H, *J*=7.0 Hz, OC*H*$_2$CH$_3$), 2.99 (bt, 1 H, *J*=5.8 Hz, C(O)C*H*), 2.37 (quint, 1 H, *J*=5.9 Hz, C(O)CHC*H*H), 2.25 (bd, 1 H, *J*=13.9, C(O)CHCH*H*), 1.60 (m, 1 H, CH(OEt)C*H*), 2.7–1.0 (m, 6 H, –(C*H*$_2$)$_3$–), 1.17 (t, 3 H, *J*=7.0 Hz, OCH$_2$C*H*$_3$). ^{13}C-NMR (100 MHz): 175.5 (CO), 139.1, 128.9, 125.4, 122.4 (*Ph*), 94.8 (*C*HOEt), 63.4 (O*C*H$_2$CH$_3$), 39.9 and 38.1 (C(O)*C*HCHC(OEt)), 26.9, 23.6, 22.8, 22.7 (–(*C*–H$_2$)$_4$–), 15.3 (OCH$_2$CH$_3$). HRMS calcd for $C_{16}H_{21}NO_2$ 259.1572, found 259.1578. $[\alpha]_D$ +18.8 (*c* 1.0, $CHCl_3$). e.e. (HPLC, eluent *n*-heptane/*i*-PrOH 99:1) 68%.

(3S,3aR,7aS)-2-Cyclohexyl-3-ethoxy-octahydroisoindol-1-one **23**

According to general procedure D, starting from (*S*)-α,α-diphenylprolinol (304 mg, 1.20 mmol), BH_3·THF (6.0 mL, 6.0 mmol, 1.0 M in THF) and THF (8 mL)(for the catalyst) and imide **13** (562 mg, 2.24 mmol) in THF (5 mL) and BH_3·THF (1.4 mL, 1.4 mmol, 1.0 M in THF) and using a reaction time of 30 min, the hydroxylactam (251 mg, 1.06 mmol, 47%) was obtained after flash chromatography (EtOAc/PE 1:5) as a yellow oil. **2-Cyclohexyl-3β-hydroxy-octahydroisoindol-1-one**. ^{1}H-NMR (400 MHz): 4.6 (bd, 1 H, C*H*OH), 3.65 (m, 1 H, NC*H*), 2.6 (bd, 1 H, C(O)C*H*), 2.2 (m, 3 H, C(O)CHC*H*H and NCHC*H*H(C*H*H)), 2.0–0.5 (m, 16 H, CH(OH)C*H*–(C*H*$_2$)$_3$–CH*H* and NCHCH*H*–(C*H*$_2$)$_3$–CH*H*). The above mixture of hydroxylactams (52 mg, 0.22 mmol) was solvolysed in EtOH (2 mL) for 1 h to the ethoxylactam, which was purified by using flash chromatography (EtOAc/PE 1:8) to give a yellow oil (40 mg, 0.15 mmol, 70%). IR: 1680. ^{1}H-NMR (400 MHz): 4.23 (s, 1 H, C*H*OEt), 3.75–3.85 (m, 1 H, NC*H*), 3.51–3.41 (m, 2 H, OC*H*$_2$CH$_3$) 2.78–2.75 (t, 1 H, *J*=6.0 Hz, C(O)C*H*), 2.24–2.17 (m, 2 H, C(O)CHC*H*H and NCHC*H*H), 1.92–1.82 (m, 1 H, CH(OEt)C*H*), 1.80–0.81 (m, 16 H, –(C*H*$_2$)$_3$–CH*H* and NCH–(C*H*$_2$)$_4$–CHH), 1.21–1.18 (t, 3 H, *J*=7.0 Hz, OCH$_2$CH$_3$). ^{13}C-NMR (100 MHz): 175.7 (CO), 91.6 (NCH), 51.2 (*C*HOEt), 38.7 and 37.4 (C(O)*C*HCHC(OEt)), 31.6, 30.5, 27.1, 25.8, 25.6, 25.5, 23.5, 22.7 and 22.5 (–(*C*H$_2$)$_4$– and NCH–(*C*H$_2$)$_5$), 15.4 (OCH$_2$*C*H$_3$). HRMS calcd for $C_{16}H_{27}NO_2$ 265.2042, found 265.2047. $[\alpha]_D$ +24.9 (*c* 1.0; $CHCl_3$). Enantiomeric excess 94%.

3-((1S,3aS,7aR)-1-Ethoxy-3-oxo-octahydroisoindol-2-yl)-propionitrile **24**

According to general procedure D, starting from (*S*)-α,α-diphenylprolinol (2.61 g, 10.3 mmol), BH_3·THF (50 mL, 50 mmol, 1.0 M in THF) and THF (50 mL)(for the catalyst) and imide **14** (10.6 g, 51.5 mmol) in THF (50 mL) and BH_3·THF (30.9 mL, 30.9 mmol, 1.0 M in THF) (added in 60 min at 0°C), and using a reaction time of 10 min, the hydroxylactams (8.3 g, 39.8 mmol, 77%) were obtained after flash chromatography (EtOAc/PE 2:1) as a yellow oil, along with starting material **14** (1.5 g, 7.3 mmol, 14%). **3-(1-Hydroxy-3-oxo-octahydroisoindol-2-yl)-propionitrile**. IR: 3369, 2252, 1689. ^{1}H-NMR (400 MHz, two diastereomers): 5.25–5.22 (m, 1 H, C*H*OH), 4.83 (s, 1 H, C*H*OH), 4.31 (d,

1 H, *J*=7.6 Hz, –O*H*), 4.03 (d, 1 H, *J*=7.7 Hz, –OH), 3.68–3.50 (m, 2 H, NCH_2), 2.79–2.73 (m, 2 H, NCH_2), 2.69 (t, 2 H, *J*=6.7 Hz, CH_2CN), 2.61 (t, 2 H, *J*=6.1 Hz, CH_2CN), 2.47–2.39 (m, 2 H, C(O)C*H*C*H*), 2.25–2.05 (m, 2 H, C(O)C*H*C*H*), 1.96–1.93 (m, 1 H, C(O)CHC*H*H), 1.82–1.79 (m, 1 H, C(O)CHC*H*H),1.68–1.12 (m, 14 H, 2×(–(CH_2)$_3$–CH*H*). ^{13}C-NMR (100 MHz, one diastereomer): 176.3 (*C*O), 118.5 (CH$_2$*C*N), 87.1 (*C*HOH), 41.2 and 36.7 (C(O)C*H*C*H*), 35.8 (N*C*H$_2$), 26.0, 23.5, 23.1 and 23.0 (–*C*H$_2$)$_4$–), 18.2 (*C*H$_2$CN). The above mixture of hydroxylactams (8.30 g, 39.8 mmol) was solvolysed in EtOH (100 mL) for 2 h to the ethoxylactam, which was purified by using flash chromatography (EtOAc/PE 1:2) to give a yellow oil (6.60 g, 27.9 mmol, 70%). IR: 2250, 1702. ^{1}H-NMR (400 MHz): 4.39 (s, 1 H, C*H*OEt), 3.55 (ddd, 1 H, *J*=14.1, 7.0, 5.6 Hz, NC*H*HCH$_2$), 3.49–3.39 (m, 3 H, NCH*H*CH$_2$ and OCH_2CH$_3$), 2.71–2.63 (m, 2 H, C(O)C*H* and C*H*HCN), 2.24–2.16 (m, 1 H, CH(OEt)C*H*), 2.06–2.02 (m, 1 H, C(O)CHC*H*H), 1.74–1.70 (m, 1 H, C(O)CHCH*H*), 1.55–0.89 (m, 6 H, C(O)CH$_2$–(CH_2)$_3$–), 1.13 (t, 3 H, *J*=7.0 Hz, OCH$_2$CH$_3$). ^{13}C-NMR (100 MHz): 176.6 (*C*(O)), 118.1 (*C*N), 94.1 (*C*HOEt), 63.1 (OCH_2CH$_3$), 38.2 (C(O)*C*H), 37.5 (N*C*H$_2$), 37.4 (CH(OEt)*C*H), 26.9, 23.4, 22.7. 22.6 (–(*C*H$_2$)$_4$–), 20.0 (*C*H$_2$CN), 15.2 (OCH$_2$*C*H$_3$). HRMS calcd for $C_{13}H_{20}N_2O_2$ 236.1525, found 236.1518. $[\alpha]_D$ −17.9 (*c* 1.0; $CHCl_3$).

3-((1S,3aS,7aR)-1-Benzenesulfonyl-3-oxo-octahydroisoindol-2-yl)-propionitrile **26**

To a solution of the ethoxylactam (6.60 g, 27.9 mmol) in CH_2Cl_2 (100 mL) was added benzenesulfinic acid (8.8 g, 62.4 mmol) (obtained by dissolving the sodium salt in water, acidifying with conc H_2SO_4 to pH=1, extraction of the water layer (CH_2Cl_2, 3×), drying of the organic layers (Na_2SO_4) and concentration *in vacuo*) and $CaCl_2$ (9.30 g, 83.3 mmol). After stirring for 24 h at rt, the reaction mixture was quenched with H_2O. After extraction of the water layer (CH_2Cl_2, 5×), drying of the organic layers (Na_2SO_4) and concentration *in vacuo* the sulfone was obtained after flash chromatography (EtOAc/PE 1:2) as white crystals (8.07 g, 25.1 mmol, 90%). $[\alpha]_D$ −32.2 (*c* 1; $CHCl_3$). e.e. (HPLC, eluent *n*-heptane/ethanol 90:10) 90%. After one recrystallisation from a 1:1 mixture of pentane and ethyl acetate enantiopure, colourless crystals were obtained (4.79 g, 14.9 mmol, 53%). mp: 95.0–96.5°C. IR: 2250, 1708, 1585. ^{1}H-NMR (400 MHz): 7.78 (d, 2 H, *J*=8.3 Hz, *Ph*), 7.73 (t, 1 H, *J*=8.2 Hz, *Ph*), 7.61 (t, 2 H, *J*=8.3 Hz, *Ph*), 4.34 (s, 1 H, C*H*SO$_2$Ph), 4.00–3.93 (m, 1 H, NC*H*H), 3.63–3.56 (m, 1 H, NCH*H*), 2.92–2.84 (m, 1 H, C*H*HCN), 2.73–2.67 (m, 1 H, CH*H*CN), 2.65–2.58 (m, 1 H, CH(SO$_2$Ph)C*H*), 2.32–2.29 (t, 1 H, *J*=6.7 Hz, C(O)C*H*)), 2.09–2.04 (m, 1 H, CH(SO$_2$Ph)CHC*H*H), 1.89–1.83 (m, 1 H, C(O)CHC*H*H), 1.60–0.97 (m, 6 H, C(O)CHCH*H*–(CH_2)$_2$–CHH). ^{13}C-NMR (100 MHz): 176.6 (CO), 136.1, 134.9, 129.8, 128.9 (*Ph*), 117.8 (*C*N), 83.3 (*C*HSO$_2$Ph), 39.1 (N*C*H$_2$), 37.9 and 35.4 (C(O)*C*HCH), 29.0 (C(O)CH*C*H$_2$), 23.3, 22.3 (–(*C*H$_2$)$_2$–), 22.1 (NCHCH*C*H$_2$), 15.9 (*C*H$_2$CN). Anal. Calcd for $C_{17}H_{20}N_2O_3S$: C, 61.42; H, 6.06; N, 8.43; S, 9.64. Found: C, 61.57; H, 5.90; N, 8.31; S, 9.38. $[\alpha]_D$ −36.3 (*c* 1; $CHCl_3$). e.e. (HPLC, eluent *n*-heptane/ethanol 90:10) >99%.

General procedure E for the reduction of the hydroxylactams and the conversion into the lactones

To a solution of the hydroxylactams in 60% aqueous EtOH was added $NaBH_4$ (2 equiv). After stirring at 50°C for 4 h the reaction mixture was poured into EtOAc. To this mixture was added slowly, at 0°C, a 5% aqueous solution of HCl. The separated organic layer was dried (Na_2SO_4) and concentrated *in vacuo*. The residue was chromatographed to give the corresponding hydroxyamide. A suspension of this hydroxyamide in 2 M H_2SO_4 was stirred at 80°C for 2 h. After cooling to rt, the reaction mixture was extracted (CH_2Cl_2, 3 times). The combined organic layers were dried ($NaSO_4$) and concentrated *in vacuo*. The lactone was purified by bulb-to-bulb distillation.

(3aR,7aS)-Hexahydroisobenzofuran-1-one from **25a**

According to general procedure E, starting from hydroxylactam **25a** (760 mg, 3.12 mmol), 60% aqueous EtOH (8 mL) and $NaBH_4$ (236 mg, 6.24 mmol), the hydroxyamide (760 mg, 3.08 mmol, 99%) was obtained after flash chromatography (EtOAc) as a white solid. ^{1}H-NMR (200 MHz): 7.3 (m, 5 H, *Ph*), 6.14 (bs, 1 H, N*H*), 4.43 (s, 2 H, NCH_2Ph), 3.87–3.77 (m, 1 H, C*H*HOH), 3.57–3.55

(m, 1 H, CH*H*OH), 3.19–3.01 (m, 1 H, –O*H*), 2.54–2.49 (m, 1 H, C(O)C*H*), 2.21–2.05 (m, 9 H, C(O)CH–(CH_2)$_4$–C*H*). According to general procedure B, starting from this hydroxyamide (750 mg, 3.46 mmol) and 2 M H_2SO_4 (10.5 mL), the lactone (368 mg, 2.63 mmol, 76%) was obtained after distillation (125–130°C, 1 mm Hg) as a colourless oil. IR: 1760, 1450. ^{1}H-NMR (200 MHz): 4.17 (ABX dd, 1 H, *J*=8.7, 6.1 Hz, C*H*HO), 3.93 (ABX d, 1 H, *J*=8.7 Hz, CH*H*O), 2.62 (m, 1 H, C*H*C(O)), 2.45 (m, 1 H, *J*=8.7, 6.1, C*H*CHO), 2.18–2.12 (m, 8 H, –(CH_2)$_4$–). $[\alpha]_D$ +38.9 (*c* 0.65; $CHCl_3$); lit[12] $[\alpha]_D$ +48.8 (*c* 0.5; $CHCl_3$). Optical purity 80% for an ethoxylactam with $[\alpha]_D$ −51.7 (*c* 1; $CHCl_3$).

*(3a*R*,6a*S*)-Hexahydrocyclopenta[c]furan-1-one from* ***25b***

According to general procedure E, starting from hydroxylactam **25b** (720 mg, 3.12 mmol), 60% aqueous EtOH (10 mL) and $NaBH_4$ (236 mg, 6.24 mmol), the hydroxyamide (501 mg, 2.14 mmol, 69%) was obtained after flash chromatography (CH_2Cl_2/acetone 4:1) as a white solid. IR: 3420, 1640, 1500, 1450. ^{1}H-NMR (200 MHz): 7.39–7.20 (m, 5 H, *Ph*), 6.25 (bs, 1 H, N*H*), 4.44 (d, 2 H, *J*=5.7 Hz, NCH_2Ph), 3.66–3.38 (m, 2 H, CH_2OH), 2.74–2.63 (m, 1 H, –O*H*), 2.49–2.30 (m, 1 H, C(O)C*H*), 2.05–1.19 (m, 7 H, C(O)CH–(CH_2)$_3$–CH). According to general procedure B, starting from this hydroxyamide (590 mg, 2.53 mmol) and 2 M H_2SO_4 (7.6 mL), the lactone (271 mg, 2.15 mmol, 85%) was obtained after distillation (60°C, 0.25 mm Hg) as a colourless oil. IR: 1760. ^{1}H-NMR (200 MHz): 4.44 (ABX dd, 1 H, *J*=7.7, 9.3 Hz, C*H*HO), 3.95 (ABX d, 1 H, *J*=9.3, 2.9 Hz, CH*H*O), 3.03–2.83 (m, 2 H, CH$_2$C*H*C*H*C(O)), 2.10–1.40 (m, 6 H, –(CH_2)$_3$–). $[\alpha]_D$ +74.7 (*c* 2.2; $CHCl_3$); lit[12] $[\alpha]_D$ +96.9 (*c* 1.0; $CHCl_3$). Optical purity 77% for an ethoxylactam with $[\alpha]_D$ −37.9 (*c* 1.6; $CHCl_3$).

*(1*S*,5*R*)-3-oxabicyclo[3.2.0]heptan-2-one from* ***25c***

According to general procedure E, starting from hydroxylactam **25c** (360 mg, 1.66 mmol), 60% aqueous EtOH (5 mL) and $NaBH_4$ (126 mg, 3.32 mmol), the hydroxyamide (260 mg, 3.08 mmol, 72%) was obtained after flash chromatography (CH_2Cl_2/acetone 7:3) as a white solid. IR: 3420, 1640, 1500, 1450. ^{1}H-NMR (200 MHz): 7.40–7.26 (m, 5 H, *Ph*), 5.93 (bs, 1 H, N*H*), 4.45 (d, 2 H, *J*=5.8 Hz, NCH_2Ph), 3.89–3.59 (m, 2 H, CH_2OH), 3.34–3.21 (dd, 1 H, *J*=17, 8.8 Hz, –O*H*), 2.84–2.74 (m, 1 H, C(O)C*H*), 2.62–1.37 (m, 5 H, C(O)CH–(CH_2)$_2$–C*H*). According to general procedure B, starting from this hydroxyamide (250 mg, 1.15 mmol) and 2 M H_2SO_4 (4.5 mL), the lactone (110 mg, 1.14 mmol, 99%) was obtained after distillation (100°C, 10 mm Hg) as a colourless oil. IR: 1760. ^{1}H-NMR (250 MHz): 4.34 (ABX dd, 1 H, *J*=9.4, 6.2 Hz, C*H*HO), 4.21 (ABX d, 1 H, *J*=9.4, 1.3 Hz, CH*H*O), 3.22–3.04 (m, 2 H, CH$_2$C*H*C*H*C(O)), 2.62–1.22 (m, 4 H, –(CH_2)$_2$–). $[\alpha]_D$ +106 (*c* 5.3; $CHCl_3$); lit[12] $[\alpha]_D$ +119 (*c* 10; $CHCl_3$). Optical purity 89% for an ethoxylactam with $[\alpha]_D$ −18.9 (*c* 1.5; $CHCl_3$).

*(3a*R*,7a*S*)-Hexahydroisobenzofuran-1-one from* ***25d***

According to general procedure E, starting from hydroxylactam **25d** (340 mg, 1.4 mmol), 60% aqueous EtOH (5 mL) and $NaBH_4$ (108 mg, 2.8 mmol), the hydroxyamide (312 mg, 1.3 mmol, 93%) was obtained after flash chromatography (EtOAc/PE 1:2) as a yellow oil. ^{1}H-NMR (400 MHz): 5.73 (bs, 1 H, N*H*), 3.85–3.80 (dd, 1 H, *J*=11.3, 8.8 Hz, C*H*HOH), 3.82–3.72 (bm, 1 H, –O*H*), 3.57–3.53 (dd, 1 H, *J*=11.4, 4.4 Hz, CH*H*OH), 2.46–2.43 (m, 1 H, C(O)C*H*), 1.95–0.95 (m, 20 H, C(O)CH–(CH_2)$_4$–C*H*) and –C*H*(CH_2)$_5$–). According to general procedure B, starting from this hydroxyamide (312 mg, 1.3 mmol) and 2 M H_2SO_4 (5 mL), the lactone (122 mg, 0.87 mmol, 67%) was obtained after distillation (125–130°C, 1 mm Hg) as a colourless oil. IR: 1760, 1450. ^{1}H-NMR (200 MHz): 4.17 (ABX dd, 1 H, *J*=8.7, 6.1 Hz, C*H*HO), 3.93 (ABX d, 1 H, *J*=8.7 Hz, CH*H*O), 2.62 (m, 1 H, C*H*C(O)), 2.45 (m, 1 H, *J*=8.7, 6.1, C*H*CHO), 2.12–2.18 (m, 8 H, –(CH$_2$)$_4$–). $[\alpha]_D$ +40.2 (*c* 1; $CHCl_3$); lit[12] $[\alpha]_D$ +48.8 (*c* 0.5; $CHCl_3$). Optical purity 82% for an ethoxylactam with $[\alpha]_D$ +21.8 (*c* 1; $CHCl_3$).

General procedure F for the $BF_3 \cdot OEt_2$ mediated coupling with allyltrimethylsilane

To a solution of the lactam in CH_2Cl_2 were slowly added, at −78°C, $BF_3 \cdot OEt_2$ (2 equiv) and allyltrimethylsilane (2 equiv). After being stirred for 1 h, the reaction mixture was allowed to warm to rt and stirred for another 17 h. The reaction mixture was then poured out ice-cold aq saturated $NaHCO_3$ and extracted with CH_2Cl_2 (5×). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was chromatographed.

3-((1R,3aS,7aR)-1-Allyl-3-oxo-octahydroisoindol-2-yl)-propionitrile **27**

According to general procedure F, starting from lactam **26** (8.50 g, 25.6 mmol), CH_2Cl_2 (50 mL), $BF_3 \cdot OEt_2$ (6.7 mL, 53 mmol) and allyltrimethylsilane (8.5 mL, 53 mmol), **27** (5.9 g, 25.6 mmol, 100%) was obtained as a white solid after flash chromatography (EtOAc/PE 1:1). An analytic sample was recrystallised from a Et_2O/cyclohexane mixture to give colourless crystals, mp 97.0–98.5°C. IR: 2252, 1683. ^{1}H-NMR (400 MHz): 5.68–5.60 (m, 1 H, C*H*=CH_2), 5.05–5.01 (m, 2 H, CH=C*H*$_2$), 3.77–3.70 (m, 1 H, NC*H*HCH$_2$), 3.17–3.10 (m, 2 H, NC*H* and NCH*H*CH$_2$), 2.68–2.60 (m, 1 H, NCH$_2$C*H*H), 2.52–2.44 (m, 2 H, C*H*C(O) and NCH$_2$CH*H*), 2.26–2.21 (m, 1 H, C*H*HCH=CH$_2$), 2.14–2.10 (m, 1 H, CH*H*CH=CH$_2$), 2.08–2.04 (m, 1 H, NCHC*H*), 1.95–1.91 (m, 1 H, C(O)CHC*H*H), 1.66–1.63 (m, 1 H, C(O)CHCH*H*), 1.47–1.03 (m, 6 H, (C*H*$_2$)$_3$). ^{13}C-NMR (100 MHz): 175.8 (*C*(O)), 133.3 (*C*H=CH$_2$), 118.1 (CH=*C*H$_2$), 117.8 (*C*N), 62.6 (N*C*H), 38.8 (C(O)*C*H), 37.0 (N*C*H$_2$), 36.3 (NCH*C*H), 35.0 (*C*H$_2$CH=CH$_2$), 28.4, 23.3, 22.8, 22.5, ((*C*H$_2$)$_4$), 15.9 (*C*H$_2$CN). Anal. Calcd for $C_{14}H_{20}N_2O$: C, 72.38; H, 8.68; N, 12.06. Found: C, 72.10; H, 8.68; N, 11.82. $[\alpha]_D$ −44.3 (*c* 1.0; $CHCl_3$).

(1S,2R,5R,6S,7R)-5-Allyl-4-benzyl-10-oxa-4-azatricyclo[5.2.1.0]decan-3-one **28**

According to general procedure F, starting from lactam **20** (100 mg, 0.35 mmol), CH_2Cl_2 (3.0 mL), $BF_3 \cdot OEt_2$ (86 µL, 0.70 mmol) and allyltrimethylsilane (0.11 mL, 0.70 mmol), **28** (95 mg, 0.32 mmol, 92%) was obtained as a colourless oil after flash chromatography (CH_2Cl_2/acetone 9:1). IR: 1660, 1440. ^{1}H-NMR (250 MHz): 7.36–7.20 (m, 5 H, *Ph*CH$_2$), 5.68–5.48 (m, 1 H, C*H*=CH$_2$), 5.14–4.96 (m, 3 H, CH=C*H*$_2$ and PhC*H*H), 4.88 (d, 1 H, *J*=4.7 Hz, C*H*OCHC(O)), 4.31 (d, 1 H, *J*=4.4 Hz, C*H*OCHN), 3.90 (AB d, 1 H, *J*=15.4 Hz, PhCH*H*), 3.34–3.28 (m, 1 H, C*H*C(O)), 2.74 (d, 1 H, *J*=8.2 Hz, NC*H*CH$_2$CH=CH$_2$), 2.43–2.01 (m, 3 H, C*H*CHC(O) and C*H*$_2$CH=CH$_2$), 1.85–1.44 (m, 4 H, (C*H*$_2$)$_2$). ^{13}C-NMR (50 MHz): 174.1 (*C*(O)), 135.7 (*Ph*), 132.1 (*C*H=CH$_2$), 128.5, 127.5, 127.2 (*Ph*), 119.1 (CH=*C*H$_2$), 82.4, 79.3 (CH$_2$*C*HO*C*HCH$_2$), 60.9 (N*C*H), 52.4 (*C*HC(O)), 44.9 (*C*HCHC(O)), 44.1 (N*C*H$_2$Ph), 37.2 (*C*H$_2$CH=CH$_2$), 28.2, 28.1 ((*C*H$_2$)$_2$). $[\alpha]_D$ +33.3 (*c* 1.34; $CHCl_3$). e.e. (HPLC, eluent *n*-hexane/ethanol 90:10) 76%.

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References

1. (a) Mukaiyama, T.; Yamashita, H.; Asami, M. *Chem. Lett.* **1983**, 385. (b) Miller, S. A.; Chamberlin, A. R. *J. Org. Chem.* **1989**, *54*, 2502.
2. (a) Matsuki, K.; Inoue, H.; Ishida, A.; Takeda, M. *Heterocycles* **1993**, *36*, 937. (b) Matsuki, K.; Inoue, H.; Ishida, A.; Takeda, M.; Nakagawa, M.; Hino, T. *Chem. Pharm. Bull.* **1994**, *42*, 9.
3. Kang, J.; Lee, J. W.; Kim, J. I.; Pyun, C. *Tetrahedron Lett.* **1995**, *36*, 4265.
4. Ramón, D. J.; Guillena, G.; Seebach, D. *Helv. Chim. Act.* **1996**, *79*, 875.
5. (a) Hirao, A.; Itsuno, S.; Nakahama, S.; Yamazaki, N. J. *J. Chem. Soc., Chem. Commun.* **1981**, 315. (b) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551. (c) Mathre, E. J.; Jones, T. K.; Xavier, L. C.; Blacklock, T. J.; Reamer, R. A.; Mohan, J. J.; Turner Jones, E. T.;

Hoogsteen, K.; Baum, M. W.; Grabowski, E. J. J. *J. Org. Chem.* **1991**, *56*, 751. (d) Jones, T. K.; Mohan, J. J.; Xavier, L. C.; Blacklock, T. J.; Mathre, E. J.; Sohar, P.; Turner Jones, E. T.; Reamer, R. A.; Roberts, F.; Grabowski, E. J. J. *J. Org. Chem.* **1991**, *56*, 763. (e) Xavier, L. C.; Mohan, J. J.; Mathre, D. J.; Thompson, A. S.; Carroll, J. D.; Corly, E. G.; Desmond, R. *Org. Synth.* **1996**, *74*, 50. Reviews: (f) Wallbaum, S.; Martens, J. *Tetrahedron: Asymm.* **1992**, *3*, 1475. (f) Deloux, L.; Srebnik, M. *Chem. Rev.* **1993**, *93*, 763.

6. Hubert, J. C.; Steege, W.; Speckamp, W. N.; Huisman, H. O. *Synth. Commun.* **1971**, *1*, 103.
7. Romagnoli, R.; Roos, E. C.; Hiemstra, H.; Moolenaar, M. J.; Speckamp, W. N.; Kaptein, B.; Schoemaker, H. E. *Tetrahedron Lett.* **1994**, *35*, 1087.
8. Layton, L.; McCoy, L. *J. Am. Chem. Soc.* **1958**, *80*, 6568.
9. (a) Rice, L. M.; Grogan, C. H. *J. Org. Chem.* **1959**, *24*, 7. (b) Crockett, G. C.; Koch, T. H. *J. Org.Chem.* **1977**, *42*, 2721.
10. Kwart, H.; Burchuk, I. *J. Am. Chem. Soc.* **1952**, *74*, 3094.
11. Roberts, J. D.; Lee, C. C.; Saunders, W. H. *J. Am. Chem. Soc.* **1954**, *76*, 4501.
12. Jakovac, I. J.; Goodbrand, H. B.; Lok, K. P.; Jones, J. B. *J. Am. Chem. Soc.* **1982**, *104*, 4659.
13. Süess, R. *Helv. Chim. Act.* **1977**, *60*, 1650.
14. Brown, D. S.; Charreau, P.; Hansson, T.; Ley, S. V. *Tetrahedron* **1991**, *47*, 1311.
15. Dijkink, J.; Goubitz, K.; Van Zanden, M. N. A.; Hiemstra, H. *Tetrahedron: Asymm.* **1996**, *7*, 515.
16. Rice, L. M.; Grocan, C. H. *J. Org. Chem.* **1957**, *22*, 1100.

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