Asymmetric Alkylation of N-Acylisoindolin-1-ones via α-Bromoimides: A Novel Route to 1-Substituted Isoindolines

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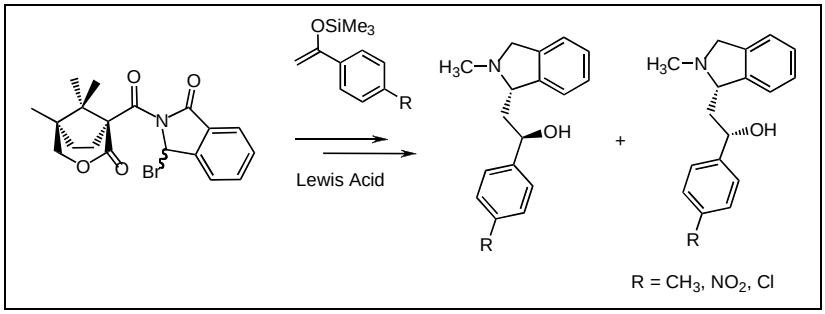

Key intermediate in the synthesis of the title compounds **9a-c** and **10a-c** was the chiral α-bromoimide **1** which has been prepared by radical bromination of the corresponding *N*-acylisoindolin-1-one **13**. **1** was alkylated with silyl enol ethers under Lewis acid catalysis using α-amidoalkylation methodology. *N,N*-diacyliminium ion **14** is presumably the intermediate in this reaction. Further transformations of the alkylated compounds yielded 1-substituted isoindolines as target compounds.

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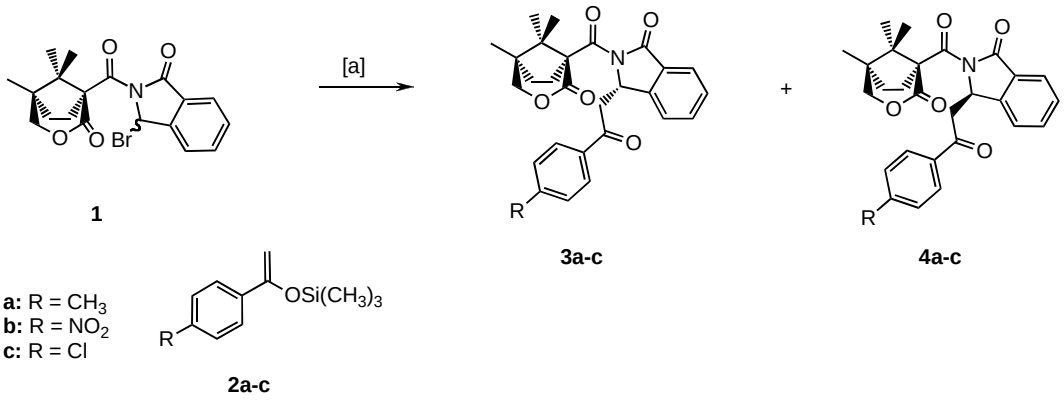
INTRODUCTION

α-Amidoalkylation is a well-established method for the nucleophilic substitution of amino derivatives in the α-position [1]. In recent years we have demonstrated that α-amidoalkylation reactions can be carried out efficiently in an asymmetric manner by using α-amidoalkylation reagents provided with a camphoric acid derivative as a chiral auxiliary [2]. With this approach it was possible to prepare several α-substituted heterocycles, including tetrahydroisoquinolines, piperidines and pyrrolidines in high diastereoselectivity. Based on the results obtained so far it seemed highly rewarding to apply this synthetic concept also to the stereoselective synthesis of 1-substituted isoindoline derivatives. As main targets we selected isoindoline derivatives substituted with a 2-hydroxyethyl group in the α-position of the ring nitrogen as the 1,3-aminoalcohol moiety represents a common motif in many pharmacologically active compounds, [2a,3]. As stereoisomers are known to quite often display signicantly different biological activities their preparation in diastereomerically and enantiomerically pure form seemed especially advisable.

For the preparation of the desired isoindoline derivatives exhibiting a 1,3-aminoalcohol moiety we followed the synthetic concept that can be found in Schemes 1 and 2.

The key step of this sequence is an asymmetric electrophilic α-amidoalkylation reaction based on the α-bromoimide **1**. As preliminary amidoalkylation

Scheme 1



[a] Lewis acid (0.1 or 1.1 equiv.), **2a-c** (1.5 equiv.), CH_2Cl_2

reactions with the corresponding *N*-acylisoindoline derivative had met with no success, compound **1** representing an *N*-acylisoindolinone was selected for this reaction. Interestingly, to the best of our knowledge no amidoalkylation reactions based on imide derivatives with *N*,*N*-diacyliminium ions as presumable intermediates have been reported so far.

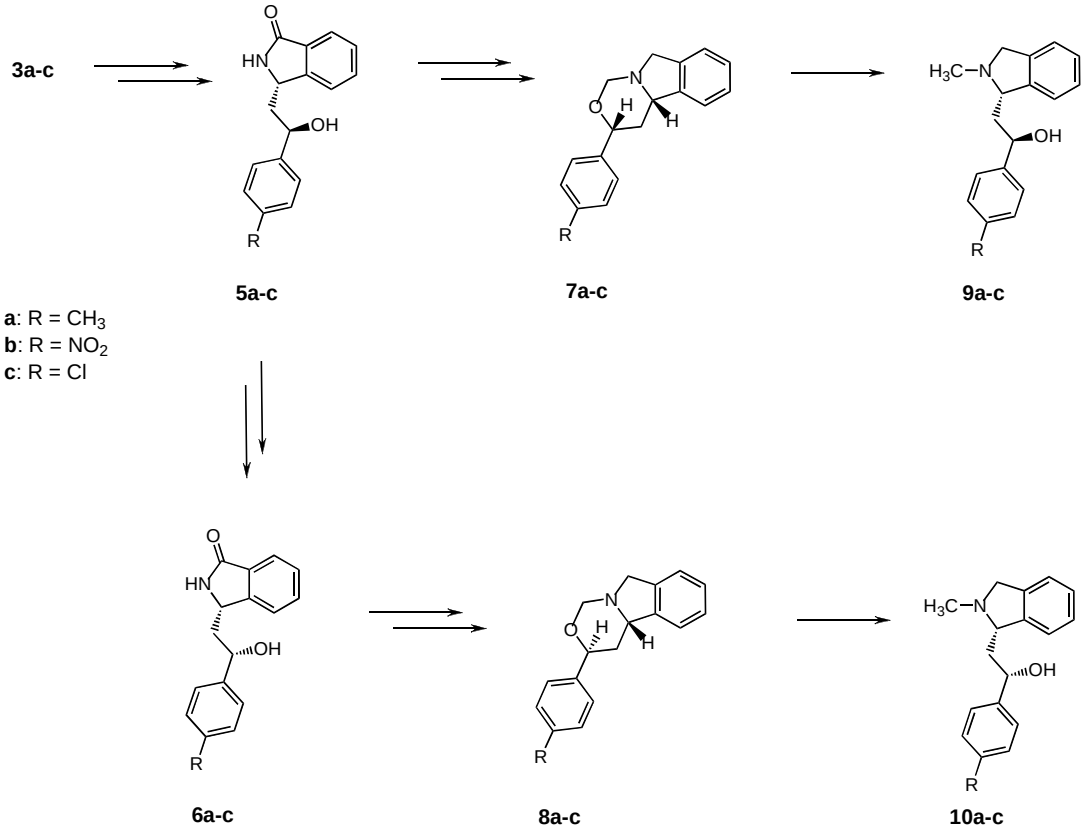
The synthesis of the phenacyl substituted isoindole derivative **3a-c/4a-c** should be easy to accomplish by simply employing the silyl enol ethers **2a-c** in the amidoalkylation reactions with **1** (Scheme 1). A few subsequent group transformations, including the reduction of the keto function to an alcohol and of the lactam carbonyl group to a methylene unit, should, after the removal of the chiral auxiliary, finally lead to the desired isoindoline derivatives (see Scheme 2).

A positive aspect of the approach described above is that it can give access to the final compounds in stereochemically pure form even if the asymmetric induction in the amidoalkylation reaction with **1** is incomplete. In this case the mixture of diasteromers formed during the amidoalkylation process has simply to be purified to a single diastereomer, a task that can be accomplished by conventional methods. Furthermore, by controlling the configuration of the stereocenter in the side chain both diastereomers of the individual compounds should become accessible, too (**9a-c** and **10a-c,** repectively).

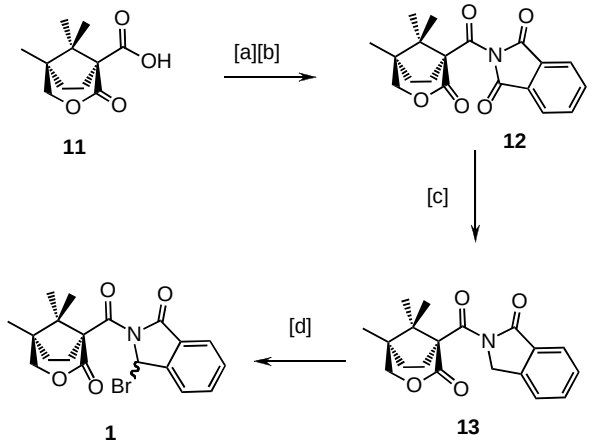
Synthesis of α-bromoimide 1. The preparation of α-bromoimide **1**, representing a key compound in our synthetic project, was accomplished according to the synthetic sequence outlined in Scheme 3. Treating phthalimide with the acid chloride derived from the chiral auxiliary **11** provided the *N*-acylphthalimide **12** in a 96 % yield. Subsequent catalytic hydrogenation of **12** in the presence of palladium on charcoal and trifluoro acetic acid yielded the *N*-acylisoindolinone **13** in 99 % [3]. Radical bromination of **13** with *N*-bromosuccinimide and AIBN in CCl_4 finally led to the desired α-bromoimide **1**. Though compound **1** was found to be labile and prone to hydrolysis we were eventually able to obtain it in pure form by crystallization and in yields of up to 80 %.

Synthesis of amidoketones 3a-c/4a-c. With the α-bromoimide **1** in our hand we were prepared for the critical step of the synthetic sequence: the asymmetric α-amidoalkylation reaction (Scheme 4). Various Lewis acids were tested for their suitability as catalyst for the reaction of the α-bromoimide **1** with different silyl enol ethers **2a-c** which should lead to the stereoisomeric amidoketones **3** and **4** [4]. The reactions were carried out in dichloromethane at 0 °C or room temperature with catalytic (0.1 equiv.) or stochiometric (1.1 equiv.) amounts of Lewis acid. The best diastereomeric ratios

Scheme 2



Scheme 3



[a] $(COCl)_2$, $DMF_{cat.}$, CH_2Cl_2; [b] phthalimide, NEt_3, DMAP, CH_2Cl_2; [c] H_2, Pd/C, TFA, EtOAc; [d] NBS, AIBN, CCl_4, reflux

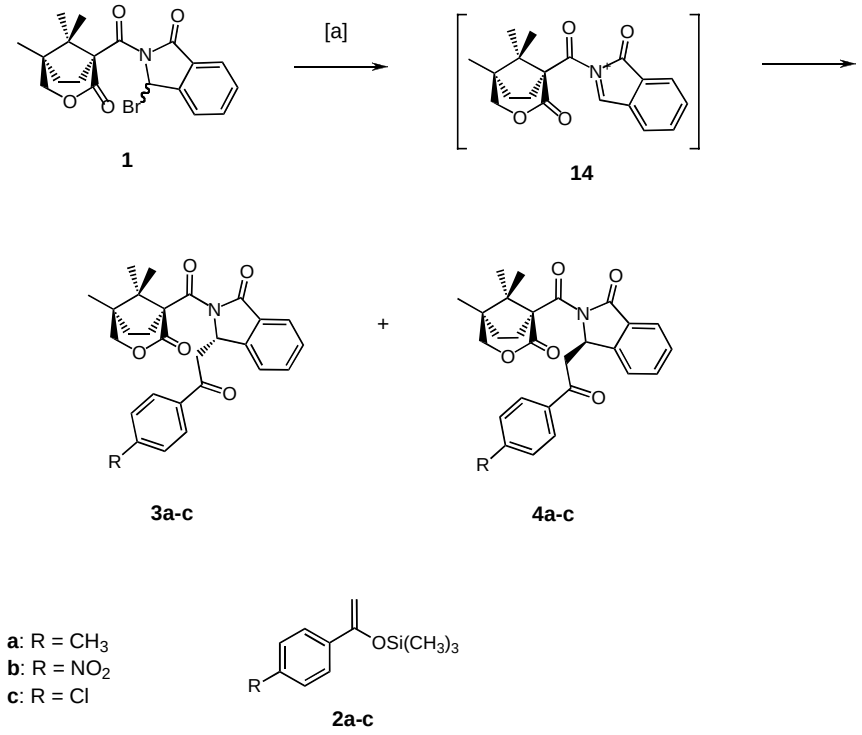
were obtained using mercury(II) iodide as lewis acid (80/20, Table 1, entries 1-3). When tin(II) triflate was employed the diastereoselectivities sank slightly (75/25, Table 1, entries 4-6). In both series the diastereomers **3a-c** exhibiting (*S*)-configuration at the newly created stereo center predominated. In contrast to the results described above the diastereoselectivity became almost insignificant when tin(IV) chloride was used as Lewis acid (Table 1, entries 7-9). In general, the yields of these reactions were satisfactory considering that HgI_2 and $SnCl_4$ gave somewhat better results (total yield of **3** and **4** ~ 50 %) than $Sn(OTf)_2$. Interestingly, no conversion of α-bromoimide **1** was observed with titan(IV) chloride, trimethylsilyl triflate or boron trifluoride etherate.

It was expected that the diastereoselectivity of the amidoalkylation step could be improved by lowering the reaction temperature. But experiments with HgI_2 and $Sn(OTf)_2$ as Lewis acids produced no better results.

So far it remains unclear why the stereoselectivity is highest in the addition reaction with mercury(II) iodide as catalyst. Possibly mercury(II) iodide forms a π-complex with the silyl enol ethers prior to their addition reactions. The increased steric demand of the incoming nucleophile alone or together with a putative coordination of this complex to the amidoalkylation reagent **1** or the reactive intermediate delineated from the former could account for the improved stereoselectivity [5].

Amidoalkylation reactions with **1** proceed probably *via* *N*,*N*-bisacyliminium ion **14** (Scheme 4). Though nmr experiments to identify the intermediate remained unsuccessful, this assumption is supported by the stereochemical outcome of the amidoalkylation reactions.

Scheme 4



[a] Lewis acid (0.1 or 1.1 equiv.), **2a-c** (1.5 equiv.), CH_2Cl_2

Table 1

Alkylation of α-bromoimide **1** [a]

Entry	Nucleophile (R)	Lewis Acid (equiv)	Products	Temp.	dr (3 : 4)	Yield (3+4) %
1	**2a** (-CH_3)	HgI_2 (0.1)	**3a**, **4a**	rt	84 : 16	- [b]
2	**2b** (-NO_2)	- " -	**3b**, **4b**	rt	80 : 20	53
3	**2c** (-Cl)	- " -	**3c**, **4c**	rt	79 : 21	55
4	**2a** (-CH_3)	$Sn(OTf)_2$ (0.1)	**3a**, **4a**	rt	77 : 23	32
5	**2b** (-NO_2)	- " -	**3b**, **4b**	rt	75 : 25	40
6	**2c** (-Cl)	- " -	**3c**, **4c**	rt	77 : 23	47
7	**2a** (-CH_3)	$SnCl_4$ (1.1)	**3a**, **4a**	0 °C	53 : 47	48
8	**2b** (-NO_2)	- " -	**3b**, **4b**	0 °C	54 : 46	56
9	**2c** (-Cl)	- " -	**3c**, **4c**	0 °C	50 : 50	55

[a] CH_2Cl_2, 1.5 equiv. **2a-c**; [b] not isolated

As a 1:1 mixture of the diastereomeric α-bromoimides **1** was used as starting material, no diastereoselection should occurr if the reaction followed an S_N2-pathway. The fact that at least some of our experiments resulted in significant diastereoselectivities (Table 1) points to an S_N1-like mechanism with the of *N*,*N*-bisacyliminium ion **14** as the reactive intermediate.

Reduction of the keto group in the side chain. Next the keto function present in the phenacyl side chain had to be reduced to a hydroxyl group. Lithium tris-*tert*-butoxyaluminum hydride proved to be the most suitable reducing agent for this purpose. When the reaction was carried out in THF at 0 °C (Scheme 5) the (2'*R*,3*S*)-configurated alcohols **15a-c** were obtained in good to excellent yields and with high stereoselectivities (Table 2, entries 1-3). In contrast, when using $NaBH_4$, KBH_4 and tBuNH$_2$·BH$_3$ as reducing agents the diastereoselectivities (*dr*) became distinctly lower. In addition, the yields were reduced slightly but the major isomers remained the same in all cases (Table 2, entries 4-7).

Scheme 5

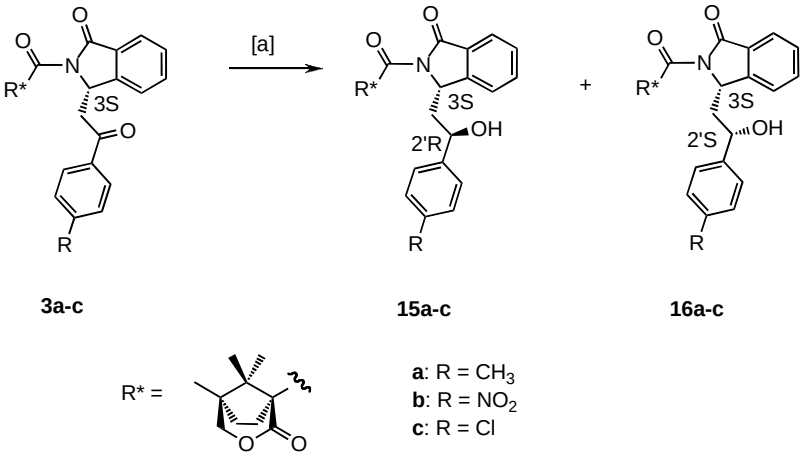


Table 2

Reduction of the keto group in the side chain

Entry	Educt (R)	Reagent (equiv.)	Products	Solvent	Temp.	dr (15 : 16)	Yield (15) %
1	**3a** (-CH_3)	Li[Al(tBuO)$_3$H] (5)	**15a**, **16a**	THF	0 °C	94:6	90
2	**3b** (-NO_2)	Li[Al(tBuO)$_3$H] (5)	**15b**, **16b**	THF	0 °C	97:3	90
3	**3c** (-Cl)	Li[Al(tBuO)$_3$H] (5)	**15c**, **16c**	THF	0 °C	95:5	76
4	**3a** (-CH_3)	$NaBH_4$ (2.5)	**15a**, **16a**	EtOH	0 °C	78:22	57
5	**3b** (-NO_2)	KBH_4 (5)	**15b**, **16b**	MeOH	rt	82:18	23
6	**3c** (-Cl)	KBH_4 (5)	**15c**, **16c**	MeOH	rt	81:19	48
7	**3a** (-CH_3)	t BuNH$_2$ · BH$_3$ (2)	**15a**, **16a**	THF	0 °C	76:24	96

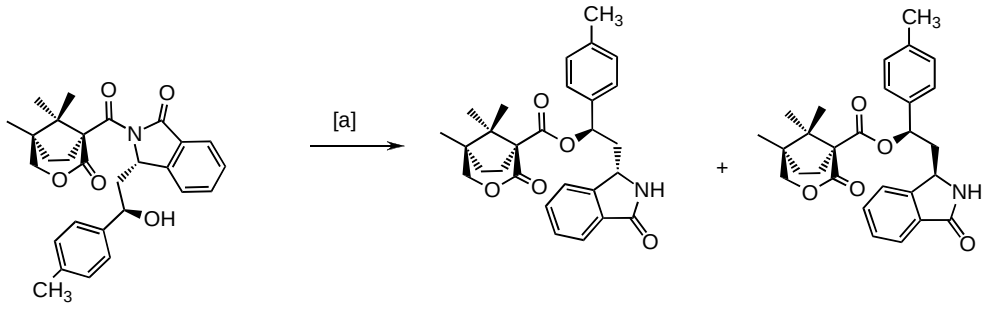
Removal of the chiral auxiliary. While imides generally can be easily transformed into the corresponding amides by alkaline hydrolysis, treatment of the imidoalcohol **15a** with dilute sodium or potassium hydroxide solution (in MeOH or EtOH) did not lead to the corresponding isoindolinone **5a**. Instead a mixture of compounds **17a** and **18a** arising from a rearrangement reaction was obtained. Spectroscopic data made the diastereomeric nature of the two compounds, **17a** and **18a**, immediately evident, but not their stereochemistry. The latter could be assigned based on the results of a deutaration experiment. When the rearrangement reaction was performed with 0.9 *M* of $NaOCD_3$ in $DOCD_3$ no incorporation of deuterium was observed for **17a** whereas in case of **18a** exactly one proton, the proton at C-3 of the isoindolinone ring was exchanged by deuterium (Scheme 6). The configuration of compound **17a** therefore can not have changed and must be the same as the configuration of the starting compound **15a**. Compound **18a** which is a diastereomer of **17a** can differ from the latter only with respect to the configuration at C-3 of the isoindoline system. Consequently, the compound must exhibit the stereochemical configuration depicted in Scheme 6.

Likewise, the chiral auxiliary could not be removed when a protocol for the cleavage of imides with lithium hydroperoxide according to *Evans et al*. was applied [6]. Again we observed predominat formation of amidoester **17a** while only small amounts of the desired isoindolinone **5a** were obtained.

Finally, we discovered that the removal of the chiral auxiliary could be best effected by a reductive procedure employing $LiBH_4$ as reducing agent. This led to the isoindolinones **5a-c** in moderate to good yields (66 – 90 %) without any rearranged or epimerized products being observed (Scheme 7).

Inversion of configuration at the asymmetric center in the side chain. To gain access to the isomers **6a-c** with (2'*S*,3*S*)-configuration, the stereocenter in 2'-position of the side chain of the isoindoline moiety had to be inverted. This was accomplished by subjecting the amidoalcohols **5a-c** to a Mitsunobu reaction which is known to proceed with inversion of the affected carbon [7]. This way, the benzoates **19a-c** were obtained from **5a-c** by treatment with DIAD and PPh_3. Upon reductive cleavage of the newly created ester function this finally afforded the desired (2'*S*,3*S*)-amidoalcohols **6a-c** in satisfactory yields (Scheme 8).

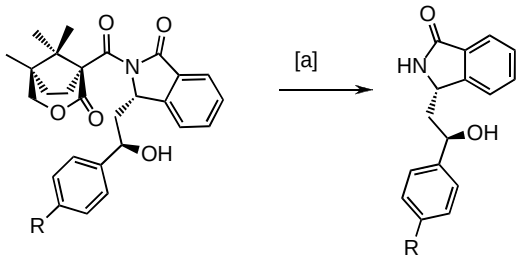
Scheme 6



15a **17a** **18a**

[a] NaOH, MeOH

Scheme 7



15a-c **5a-c**

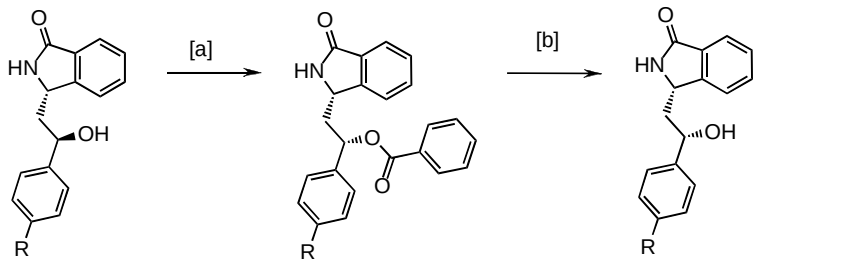
a: R = CH_3
b: R = NO_2
c: R = Cl

[a] $LiBH_4$, THF

Transformation of the isoindolinone into an isoindoline moiety. The reduction of amides to the corresponding amines is commonly effected by using either borane, borane·THF or borane·dimethylsulfide (BMS). Since BMS is the most stable of those reagents, we regarded it as the most suitable for our purposes even though the removal of dimethyl sulfide can be difficult in some cases [8].

When the isoindolinones **5a-c** and **6a-c** were treated with BMS in refluxing tetrahydrofurane the starting material was completely consumed within several hours. Unfortunately, we did not succeed in isolating compounds **20a-c** and **21a-c**, neither in reasonable yields nor in pure form even though there was clear evidence that the desired aminoalcohols **20a-c** and **21a-c**, respectively, had formed. To ease the isolation we therefore decided to transform **20a-c** and **21a-c** directly to the corresponding oxazinanes **7a-c** and **8a-c**. This was easily accomplished by treating the crude reaction product resulting from the reduction of **5a-c** and **6a-c** with BMS for 16 hours with formaldehyde (15 equiv.). The desired oxazinanes **7a-c** and **8a-c** could then be isolated in moderate yields (Scheme 9).

Scheme 8

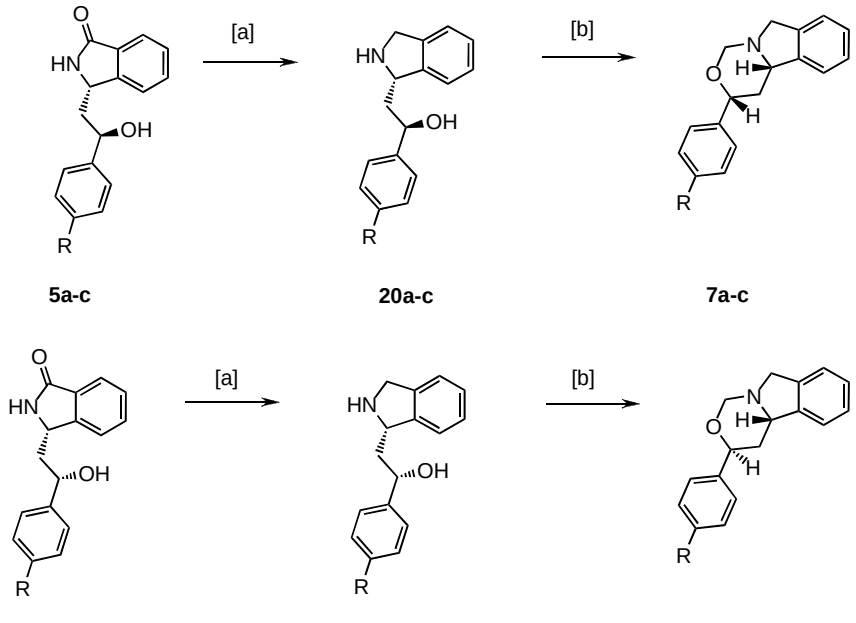


5a-c **19a-c** **6a-c**

a: R = CH_3
b: R = NO_2
c: R = Cl

[a] DIAD, PPh_3, benzoic acid, THF; [b] $Li[AlH_2(OMe)_2]$, THF, 0 °C or $LiBH_4$, THF

Scheme 9



5a-c **20a-c** **7a-c**

6a-c **21a-c** **8a-c**

a: R = CH_3
b: R = NO_2
c: R = Cl

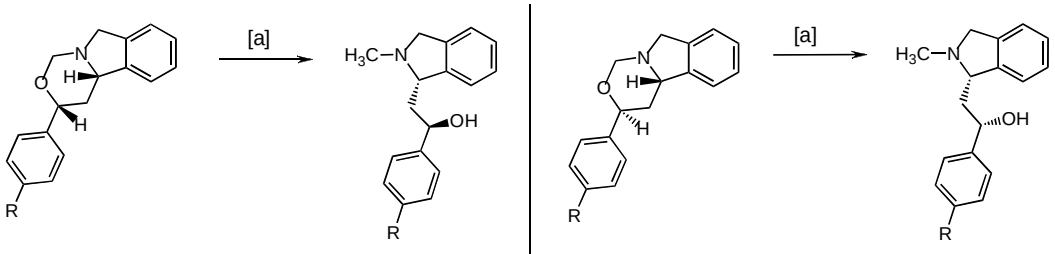
[a] BMS, THF, reflux; [b] HCHO, THF

Formation of the N-Methylisoindolines 9a-c and 10a-c. The last step of our synthetic sequence involved the reduction of the oxazinanes **7a-c** and **8a-c** to give the

N-methylisoindolines **9a-c** and **10a-c**, respectively. This step was efficiently accomplished by treating the oxazinanes **7a-c** and **8a-c** with sodium cyanoborohydride in methanol at pH 4-5 providing the target compounds **9a-c** and **10a-c** in good yields (Scheme 10).

(*R*)-Configuration at C-3 could be confirmed for **4b** and **4c**, too, by comparison of both nmr- and chromatographical data obtained for these compounds. Consequently, compounds **3a-c** as diastereomers of **4a-c** must have (*S*)-configuration at C-3 of the isoindoline ring.

Scheme 10



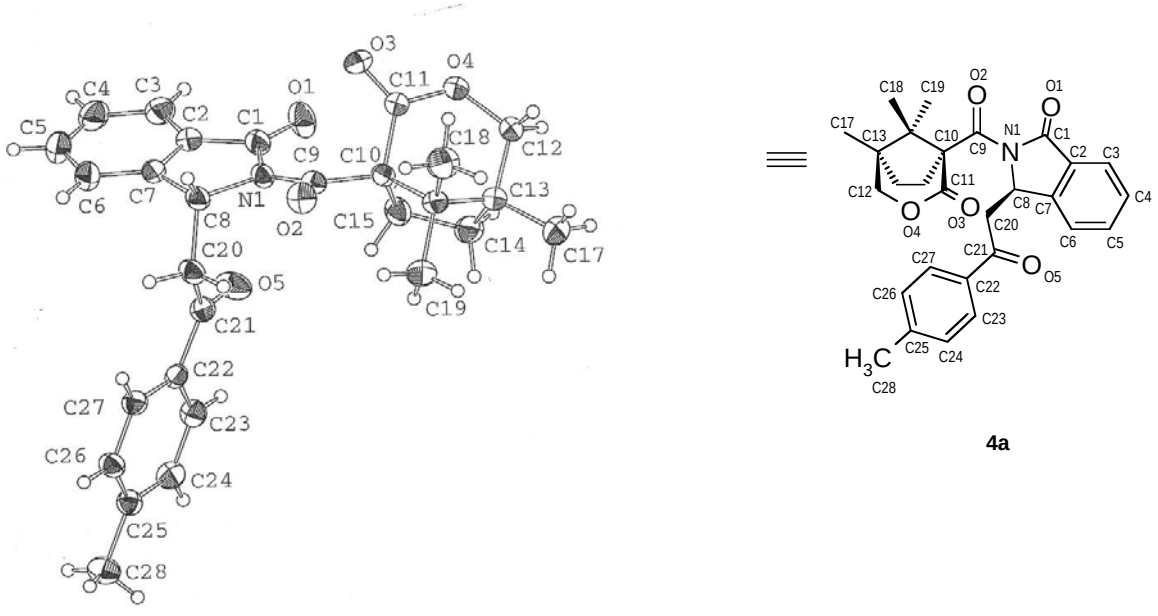
a: R = CH_3
b: R = NO_2
c: R = Cl

[a] Na[BH_3CN], MeOH, HOAc

Stereochemistry. In order to determine the configuration of the stereocenter generated in the course of the amidoalkylation reaction of the bromoimide **1** and the silylenolether **2a**, an X-ray analysis of minor isomer **4a**, which had given suitable crystals, was perfomed. By taking the stereochemistry of the chiral auxiliary into account the results of the X-ray analysis revealed (*R*)-configuration at C-3 of the isoindolinone ring (Scheme 11).

To determine the configuration of the stereocenter in the side chain (C-2') it was necessary to prepare the oxazinanone **22**, as nmr spectra of the oxazinanes **7a-c** did not allow conclusive analysis, even though the nmr data for **7a-c** were very similar to each other indicating that all compounds possessed the same relative configuration.

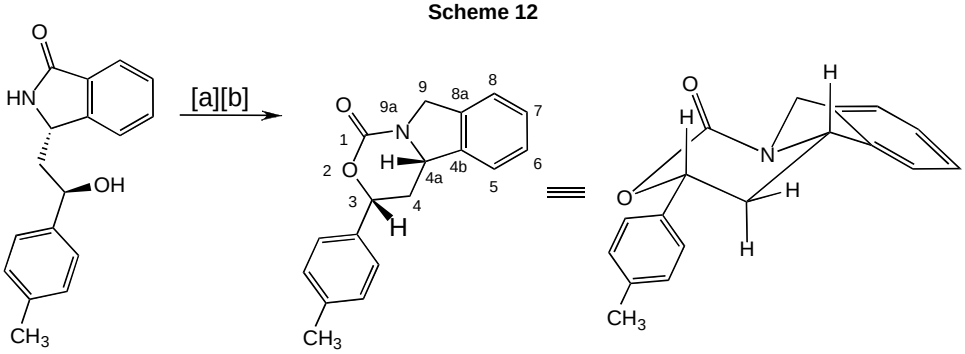
Scheme 11



4a

Compound **22** was prepared by BMS reduction of isoindolinone **5a** followed by treatment with carbonyldiimidazole (Scheme 12).

Scheme 12



5a **22**

[a] BMS, THF, reflux; [b] CDI, THF

NOE-DIF nmr experiments as well as the analysis of the coupling constants in the ^{1}H nmr spectrum of **22** indicated *cis*-configuration of the methin protons at C-3 and C-4a (Scheme 12). As we already had conclusively assigned the absolute configuration of C-4a (= C-3 in compound **4a**), we could ascribe (3*R*,4a*S*)-configuration to **22**.

Since the preparation of oxazinanes **7a-c** was very similar to that of oxazinanone **22** and none of the stereogenic centres was affected during all other reaction steps, the configuration of 22 must also apply to the oxazinanes **7a-c**, the isoindolinones **5a-c**, the imido-alkohols **15a-c** and the target isoindolines **9a-c**. Consequently, the diastereomeres of these compounds, the oxazinanes **8a-c**, the isoindolinones **6a-c**, the imidoalcohols **16a-c** as well as the final compounds **10a-c** must possess (*S*,*S*)-configuration [(3*S*,4a*S*) for **8a-c**, (2'*S*,3*S*) for **6a-c** and **16a-c** and (1*S*,2'*S*) for **10a-c**], as they differ from the aforementioned compounds only with respect to the configuration of the stereocenter located outside the isoindoline moiety.

Finally, in each case the (*R*,*S*)-configured compounds **5a-c**, **15a-c**, **9a-c** and **7a-c** showed nmr data which significantly differed from that of the corresponding (*S*,*S*)-isomers **6a-c**, **16a-c**, **10a-c** and **8a-c**. It was therefore possible to verify the stereochemical purity of these compounds simply by analyzing their nmr spectra.

Conclusion. The α-bromoimide **1** was successfully employed in asymmetric α-amidoalkylation reactions with silyl enol ethers **2a-c** providing the phenacyl substituted isoindolinone derivatives **3a-c** as major diastereomers. *N*,*N*-bisacyliminium ion **14** is thought to be the intermediate in these reactions. The addition products **3a-c** proved to be valuable starting materials for the construction of the *N*-methylisoindoline derivatives **9a-c** and **10a-c**.

EXPERIMENTAL

All reactions were carried out in vacuum dried glassware under nitrogen atmosphere. All reagents were used as commercially available. Silyl enol ethers were prepared as described in literature [2a,4]. Solvents were dried prior to use. THF was freshly distilled from sodium metal/benzophenone ketyl, CH_2Cl_2 from CaH_2 and CH_3OH from Mg prior to use. Melting points were determined on a Büchi melting point apparatus no. 510 (Dr. Tottoli) and are uncorrected. Infrared spectra were recorded with a Perkin Elmer FT-IR spectrometer Paragon 1600. Solids were measured as KBr pellets, liquids as films between NaCl plates. Nmr spectra were obtained with JEOL JNMR-GX 400 (400MHz), JNM-ECP 400 (400 MHz) or JNM-ECP 500 (500 MHz) spectrometers, respectively. Tetramethylsilane was used as internal standard. The nmr spectra were recalculated with NUTS, 2D version 2002. Mass spectra were recorded on a Hewlett Packard 5989 A mass spectrometer with 59980 B particle beam LC/MS interface. Hrms spectra were obtained with a JEOL JMS 700 and a JEOL JMS GC-Mate II mass spectrometer. CHN-analyses were determined an HERAEUS Rapid or an ELEMENTAR Vario EL elemental analysator. Tlc: Merck 60 F-254. Column chromatrography (CC) was performed as flash chromatography with silica gel 60 (Merck, 0.040- 0.063 mm) Analytical hplc: L-6200, L-7100 or L7100 pump, L-4000 or L-7400 UV/Vis detector, D-7000 HPLC-System-Manager (Merck-Hitachi) LiChroCart® with LiChroSpher® 100 RP-18 cartridge (5 μm, 250x4 mm with precolumn 4x4 mm), (Merck). Preparative hplc: L-6000 pump, L-4000 UV/Vis detector, D-2000 Chromato Integrator (Merck Hitachi), column #1: Hibar RT LiChrosorb® Si 60 (7 μm, 250x25 mm) (Merck); column #2: Hibar RT Lichrosorb® RP-18 (7μm, 250x25 mm) (Merck).

General Procedures.

General Procedure for the Alkylation of 1 with $SnCl_4$ and Silyl Enol Ethers 2a-c - GP1. A 0.2 *M* solution of **1** in CH_2Cl_2 was cooled to 0 °C. After dropwise addition of 1.1 equivalents of $SnCl_4$ the solution was stirred for 1 hour. Then 1.5 equivalents of the appropriate silyl enol ether **2a-c** were added. After 16 hours the reaction was terminated by addition of saturated NH_4Cl-solution and warmed to room temperature. The aqueous layer was extracted with CH_2Cl_2 (4x) and the combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. Diastereoselectivity was determined by hplc from the crude product.

General Procedure for the Alkylation of 1 with $Sn(OTf)_2$ and Silyl Enol Ethers 2a-c - GP2. A 0.05 *M* solution of **1** in CH_2Cl_2 was treated with 1.5 equivalents of the appropriate silyl

enol ethers **2a-c** and stirred for 15 minutes at room temperature. Then 0.1 equivalents of $Sn(OTf)_2$ were added and the mixture was stirred for 5 hours. After addition of saturated NH_4Cl-solution, the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*.

General Procedure for the Alkylation of 1 with HgI_2 and Silyl Enol Ethers 2a-c - GP3. Like GP2 using HgI_2 instead of $Sn(OTf)_2$.

General Procedure for the Preparation of Imidoalcohols 15a-c and 16a-c by Li[Al(*t*BuO)$_3$H] Reduction of Imidoketones 3a-c - GP4. A 0.05 *M* solution of the appropriate imidoketone **3a-c** in THF was cooled to 0 °C and treated with 5 equivalents of Li[Al(*t*BuO)$_3$H]. After stirring for 16 hours, KH_2PO_4-solution (10%) was added to terminate the reaction. The mixture then was allowed to warm to room temperature. The aqueous layer was extracted with Et_2O (4x). The combined organic layers were washed with brine (2x), dried over $MgSO_4$ and concentrated *in vacuo*.

General Procedure for the Removal of the Chiral Auxiliary by Reductive Cleavage of Imidoalcohols 15a-c with $LiBH_4$ - GP5. A 0.044 *M* solution of the appropriate imidoalcohol **15a-c** was added to a 0.21 *M* solution of 5 equivalents of $LiBH_4$ at 0 °C. The mixture was allowed to warm to room temperature and stirred for 24 hours. After addition of 2 *N* HCl and after the evolution of gas had ceased, the mixture was saturated with NaCl and extracted with Et_2O (5x). The combined extracts were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*.

General Procedure for the Mitsunobu Esterification of the Amidoalcohols 5a-c - GP6. 2.05 equivalents of PPh_3 were dissolved in THF and cooled to 0 °C (ice bath) before 2.0 equivalents of DIAD were added. The mixture was stirred for 15 minutes, then 2.1 equivalents of benzoic acid were added. After 30 minutes a 0.15 *M* solution of the appropriate educt (**5a-c**) in THF was added dropwise. Then the ice bath was removed and the mixture was stirred for 30 minutes. The solvent was removed *in vacuo* and the crude product was purified by CC.

General Procedure for the Cleavage of the Benzoates 19b-c - GP7. A 0.1 *M* solution of the benzoate 19b-c in THF was cooled to 0 °C and added to an ice cold 0.23 *M* solution of 5 equivalents of $LiBH_4$ in THF. The mixture was allowed to warm to room temperature and stirred for 16-24 hours. Excessive $LiBH_4$ was destroyed by addition of 2 *N* HCl (ice bath). The ice bath was removed. When gas formation had stopped, Et_2O was added and the organic layer was separated. The aqueous layer was saturated with NaCl and extracted with Et_2O (5x). The combined organic layers were dried with $MgSO_4$ and concentrated *in vacuo*.

General Procedure for the Preparation of the Oxazinanes 7a-c and 8a-c - GP8. A 0.025 *M* solution of the appropriate amidoalcohol **5a-c**, **6a-c** was cooled with an ice bath and treated with 5 equivalents of borane dimethylsulfide (BMS, 2 *M* in THF) The mixture was allowed to warm to room temperature before it was refluxed for 6 hours. After addition of CH_3OH (ice bath) the solvent was removed *in vacuo*. To remove decomposition products of BMS the residue was repeatedly dissolved in 5 ml CH_3OH and the solvent was removed *in vacuo*. Next, the residue was dissolved in THF (~0.05 *M*) and 15 equivalents of HCHO (35% in H_2O) were added. The resulting mixture was stirred for 16 hours and then concentrated *in vacuo*.

General Procedure for the Conversion of the Oxazinanes 7a-c and 8a-c into the *N*-methylaminoalcohols 9a-c and 10a-c - GP9. A 0.025 *M* solution of the appropriate oxazinane **7a-c**, **8a-c** in CH_3OH was treated with 5 equivalents of $Na[BH_3CN]$. By dropwise addition of glacial acetic acid the solution was adjusted to pH 4-5. After stirring for 2.5 hours the solvent was removed *in vacuo* and the residue was dissolved in 1 *N* HCl. This solution was washed with Et_2O (3x) and the organic layers were discarded. The aqueous layer was alkalized with KOH, saturated with NaCl and extracted with Et_2O (5x). The combined organic layers were dried over $MgSO_4$. To obtain the hydrochlorides of the desired *N*-methylaminoalkohols the solution and was concentrated treated with HCl (1 *M* in Et_2O) and the resulting precipitate was isolated by centrifugation. To obtain the free bases of the *N*-methylaminoalcohols the dried organic layers were concentrated *in vacuo*.

2-[(1*S*,5*R*)-5,8,8-Trimethyl-2-oxo-3-oxabicyclo[3.2.1]-octane-1-carbonyl]isoindol-1,3-dione (12). 209 mg (0.99 mmol) **11** [2e] were dissolved in 2 ml of CH_2Cl_2. The solution was cooled in an ice bath and mixed with 89 μl (1.04 mmol) of oxalyl chloride and 4 μl (0.05 mmol) of DMF. After 10 minutes the ice bath was removed and the mixture was stirred at room temperature until gas formation had ceased. The solvent was removed *in vacuo* and the residue was dissolved in 1.2 ml of CH_2Cl_2. This solution was cooled in an ice bath and transferred to an ice cold mixture of 231 mg (1.57 mmol) of phthalimide, 6 mg (0.05 mmol) of DMAP, 280 μl (2.01 mmol) of NEt_3 and 0.5 ml of CH_2Cl_2. The resulting mixture was stirred for 16 hours at room temperature. Then it was washed with 5 ml of 2 *N* NaOH (2x), 5 ml of 2 *N* HCl (2x) and 5 ml of H_2O and dried over $MgSO_4$. After the solvent had been removed *in vacuo*, 326 mg (96%) of **12** were obtained as a yellowish solid, mp 188 °C; tlc: R_f = 0.16 (*n*-heptane/EtOAc = 60/40); $[\alpha]_D^{20}$ = +96.0 (c = 1.10 in CH_2Cl_2); ir: 2973, 1800, 1740, 1469, 1285, 1213, 1052, 1021, 721 cm^{-1}; ^1H nmr ($CDCl_3$, rt): δ = 0.93 (s, 3H, CH_3), 1.05 (s, 3H, CH_3), 1.35 (s, 3H, CH_3), 1.85-1.98 (m, 2H, CH_2CH_2), 2.38 (ddd, J = 14.5/11.5/5.5 Hz, 1H, CH_2CH_2), 2.75 (ddd, J = 14.5/9.5/5.5 Hz, 1H, CH_2CH_2), 4.00 (d, J = 11 Hz, 1H, OCH_2), 4.20 (dd, J = 11/2 Hz, 1H, OCH_2), 7.80-7.84 (m, 2H, $H_{arom.}$), 7.91-7.95 (m, 2H, $H_{arom.}$);ms (CI, CH_5^+): 342 (34) $[M+H]^+$, 227 (40), 212 (6), 195 (100), 85 (12). *Anal.* Calcd. for $C_{19}H_{19}NO_5$ (341.37): C, 66.85; H, 5.61; N, 4.10. Found: C, 66.57; H, 5.79; N 4.29.

2-[(1*S*,5*R*)-5,8,8-Trimethyl-2-oxo-3-oxabicyclo[3.2.1]-octane-1-carbonyl]-2,3-dihydroisoindol-1-one (13). 7.016 g (20.55 mmol) of **12** were dissolved in 700 ml of EtOAc. 1.404 g of Pd/C (10% palladium) and 35 ml of trifluoroacetic acid were added. The mixture was stirred for 4 days under hydrogen at normal pressure and room temparature. The catalyst was filtered off and the filtrate was concentrated *in vacuo* to give 6.647 g (99%) of **13** as white solid, mp 218-221 °C; tlc: R_f = 0.27 (*n*-heptane/EtOAc = 60/40); ir: = 3428, 2961, 1725, 1685, 1325, 1295, 1274, 1120, 1020, 854, 736 cm^{-1}; $[\alpha]_D^{20}$ = +53.5 (c = 1.03 in CH_2Cl_2); ^1H nmr ($C_5D_5NO_2$, 140 °C): δ = 1.03 (s, 3H, CH_3), 1.25 (s, 3H, CH_3), 1.50 (s, 3H, CH_3), 1.96-2.10 (m, 2H, CH_2CH_2), 2.63-2.72 (m, 1H, CH_2CH_2), 3.12-3.21 (m, 1H, CH_2CH_2), 4.12 (d, J = 11 Hz, 1H, OCH_2), 4.37 (d, J = 11 Hz, 1H, OCH_2), 4.86 (d, J = 17.5 Hz, 1H, NCH_2), 5.05 (d, J = 17.5 Hz, 1H, NCH_2), 7.50-7.56 (m, 2H, $H_{arom.}$), 7.67 (t, J = 8 Hz, 1H, $H_{arom.}$), 7.89 (d, J = 8 Hz, 1H, $H_{arom.}$); ms (CI, CH_5^+): 328 (100) $[M+H]^+$, 227 (10), 195 (45), 167 (8). *Anal.* Calcd. for $C_{19}H_{21}NO_4$ (327.38): C, 69.71; H, 6.47; N, 4.28. Found: C, 69.52; H, 6.78; N, 4.25.

3-Bromo-2-[(1*S*,5*R*)-5,8,8-trimethyl-2-oxo-3-oxabicyclo-[3.2.1]octane-1-carbonyl]-2,3-dihydroisoindol-1-one (1). 50 mg (0.28 mmol) of NBS and a catalytic amount AIBN were added to a suspension of 80 mg of **13** in 2.4 ml of CCl_4. The mixture was refluxed for 5.5 hours and then cooled to room temperature. Floating succinimide was filtered off. The filtrate was washed with aqueous $NaHSO_3$ solution (20%, 3x5 ml) and water (2x5 ml). The organic layer was concentrated, mixed with 1 ml of pentane and stored at 4 °C over night. The precipitate was isolated by filtration and washed with pentane (5x2 ml). This yielded 81 mg (80 %) of **1** as white to yellow solid, mp 206 °C; tlc: diastereomer **1**: R_f = 0.64, diastereomer **2**: R_f = 0.44 (CH_2Cl_2/EtOAc = 96/4); ir: 2975, 1754, 1723, 1686, 1607, 1467, 1455, 1410, 1393, 1372, 1312, 1288, 1274, 1245, 1213, 1193, 1167, 1151, 1128, 1097 cm^{-1} ^{1}H nmr (CD_2Cl_2): δ = 0.92 (s, 0.5 x 3 H,CH_3), 0.93 (s, 0.5 x 3H, CH_3), 0.97 (s, 0.5 x 3H, CH_3), 1.14 (s, 0.5 x 3H, CH_3), 1.26 (s, 0.5 x 3H, CH_3), 1.30 (s, 0.5 x 3H, CH_3), 1.81-1.99 (m, 2H, CH_2-CH_2), 2.06-2.27 (m, 1H, CH_2CH_2), 2.91-3.05 (m, 0.5 x 1H, CH_2CH_2), 3.20-3.35 (m, 0.5 x 1H, CH_2CH_2), 3.95 (d, J = 10.5 Hz, 0.5 x 1H, OCH_2), 4.04 (d, J = 10.5 Hz, 0.5 x 1H, OCH_2), 4.14 (d, J = 10.5Hz, 0.5 x 1H, OCH_2), 4.36 (d, J = 10.5Hz, 0.5 x 1H, OCH_2), 7.29 (s, 0.5 x 1H, NCH), 7.35 (s, 0.5 x 1H, NCH), 7.60 (t, J = 7.5 Hz, 1H, $H_{arom.}$), 7.67 (d, J = 7.5 Hz, 1H, $H_{arom.}$), 7.77 (m, 1H, $H_{arom.}$), 7.84 (d, J = 7.5 Hz, 1 H, $H_{arom.}$); (diastereomeric ratio = 50:50); ^{13}C nmr ($CDCl_3$, rt): δ = 15.20 (0.5 x 1 C, CH_3), 15.28 (0.5 x 1 C, CH_3), 18.63 (0.5 x 1 C, CH_3), 18.95 (0.5 x 1 C, CH_3), 19.83 (0.5 x 1 C, CH_3), 20.35 (0.5 x 1 C, CH_3), 27.83 (0.5 x 1 C, CH_2), 31.79 (0.5 x 1 C, CH_2), 33.05 (0.5 x 1 C, CH_2), 34.19 (0.5 x 1 C, CH_2), 44.10 (0.5 x 1 C, C_q), 44.23 (0.5 x 1 C, C_q), 46.81 (0.5 x 1 C, C_q), 46.88 (0.5 x 1 C, C_q), 57.38 (0.5 x 1 C, CH), 57.64 (0.5 x 1 C, CH), 66.49 (0.5 x 1 C, C_q), 66.84 (0.5 x 1 C, C_q), 78.34 (0.5 x 1 C, OCH_2), 79.89 (0.5 x 1 C, OCH_2), 124.37 (0.5 x 1 C, $C_{arom.}$), 124.52 (0.5 x 1 C, $C_{arom.}$), 125.40 (0.5 x 1 C, $C_{arom.}$), 125.66 (0.5 x 1 C, $C_{arom.}$), 128.90 (0.5 x 1 C, C_q), 129.20 (0.5 x 1 C, C_q), 130.60 (0.5 x 1 C, $C_{arom.}$), 130.62 (0.5 x 1 C, $C_{arom.}$), 134.89 (0.5 x 1 C, $C_{arom.}$), 135.16 (0.5 x 1 C, $C_{arom.}$), 143.23 (0.5 x 1 C, C_q), 143.56 (0.5 x 1 C, C_q), 163.45 (0.5 x 1 C, C=O), 164.06 (0.5 x 1 C, C=O), 166.44 (0.5 x 1 C, C=O), 166.74 (0.5 x 1 C, C=O), 170.89 (0.5 x 1 C, C=O), 171.08 (0.5 x 1 C, C=O); (diastereomeric ratio = 50:50); ms (CI, CH_5^+): 406 $[M+H]^+$ (1), 326 (100), 227 (14), 216 (7), 195 (23); hrms (FAB$^+$): Calcd. ($C_{19}H_{21}BrNO_4$, $[M+H]^+$): 406.0654, found: 406.0661; *Anal.* Calcd. for $C_{19}H_{20}BrNO_4$ (406.28): C, 56.17; H, 4.96; N, 3.45. Found: C, 55.47; H, 5.05; N, 3.42.

(3*S*)-3-[2-(4-Methylphenyl)-2-oxoethyl]-2-[(1*S*,5*R*)-5,8,8-trimethyl-2-oxo-3-oxabicyclo[3.2.1]octane-1-carbonyl]-2,3-dihydroisoindol-1-one (3a) and (3*R*)-3-[2-(4-Methylphenyl)-2-oxoethyl]-2-[(1*S*,5*R*)-5,8,8-trimethyl-2-oxo-3-oxabicyclo-[3.2.1]octane-1-carbonyl]-2,3-dihydroisoindol-1-one (4a)

Method A: The synthesis was performed according to GP1 employing 1421 mg (3.5 mmol) of **1** and 1.5 equivalents of **2a**. hplc (CH_3CN/H_2O = 60/40; 1 ml/min): **3a**: t_R = 14.7 minutes, 53%; **4a**: t_R = 17.3 minutes, 47%. Repeated CC (isohexane/ EtOAc/CH_2Cl_2 = 70/20/10) gave the crude diastereomers. Prep. hplc (column #2, CH_3OH /H2O = 75/25) then yielded 412 mg (26%) **3a** and crystallization (*n*-heptane/EtOAc = 80/20) gave 357 mg (22%) **4a**.

Method B: 116 mg (0.29 mmol) of **1** were reacted with **2a** according to GP2. The diastereomeric ratio was determined in the ^{1}H nmr spectrum of the crude product: **3a**:**4a** = 77:23. Purification by CC (isohexane/EtOAc/CH_2Cl_2 = 70/20/10) and prep. hplc (column #1, isohexane/EtOAc/CH_2Cl_2 = 70:20:10) yielded 34 mg (26%) **3a** and 8 mg (6%) **4a**.

3a: The compound was obtained as white solid, mp 103 °C.; tlc: R_f = 0.21 (isohexane/EtOAc/CH_2Cl_2 = 70:20:10); $[\alpha]_D^{20}$ = +200.8 (c = 0.500 in CH_2Cl_2); ir: 2923, 1740, 1680, 1606, 1325, 1295, 1250, 1213, 1123, 753, 703 cm^{-1}; ^{1}H nmr ($C_6D_5NO_2$, 130 °C): δ = 0.93 (s, 3H, CH_3), 1.08 (s, 3H, CH_3), 1.47 (s, 3H, CH_3), 1.83-1.99 (m, 2H, CH_2CH_2), 2.35 (s, 3H, $C_6H_4CH_3$), 2.58-2.72 (m, 1H, CH_2CH_2), 2.79-2.92 (m, 1H, CH_2CH_2), 3.45 (dd, J = 17/8 Hz, 1H, CH_2), 4.00 (d, J = 10.5 Hz, 1H, OCH_2), 4.14 (d, J = 17 Hz, 1H, CH_2), 4.37 (d, J = 10.5 Hz, 1H, OCH_2), 5.84-5.93 (m, 1H, NCH), 7.20 (d, J = 7.5 Hz, 2H, $C_6H_4CH_3$), 7.39-7.48 (m, 1H, $H_{isoindol.}$), 7.52-7.60 (m, 2H, $H_{isoindol.}$), 7.77-7.88 (m, 1H, $H_{isoindol.}$ and 2H, $C_6H_4CH_3$); ms (CI, CH_5^+): 460 $[M+H]^+$ (36), 325 (8), 293 (18), 279 (14), 233 (100), 212 (13), 195 (13). *Anal.* Calcd. for $C_{28}H_{29}NO_5$ (459.55): C, 73.18; H, 6.36; N, 3.05. Found: C, 72.93; H, 6.75; N, 2.76.

4a: The compound was obtained as white solid, mp 223 °C; tlc: R_f = 0.26 (isohexane/EtOAc/CH_2Cl_2 = 70:20:10); $[\alpha]_D^{20}$ = -104.6 (c = 0.545 in CH_2Cl_2); ir: 2956, 1731, 1684, 1605, 1323, 1297, 1270, 1228, 1123 cm^{-1}; ^{1}H nmr ($C_6D_5NO_2$, 130 °C): δ = 0.91 (s, 3H, CH_3), 1.16 (s, 3H, CH_3), 1.42 (s, 3H, CH_3), 1.85-2.02 (m, 2H, CH_2CH_2), 2.35 (s, 3H, $C_6H_4CH_3$), 2.42-2.59 (m, 1H, CH_2CH_2), 3.29-3.34 (m, 1H, CH_2CH_2), 3.48 (dd, J = 17/7 Hz, 1H, CH_2), 3.91 (d, J = 17 Hz, 1H, CH_2), 4.06 (d, J = 10.5 Hz, 1H, OCH_2), 4.23 (d, J = 10.5 Hz, 1H, OCH_2), 5.98 (d, J = 7 Hz, 1H, NCH), 7.20 (d, J = 7.5 Hz, 2H, $C_6H_4CH_3$), 7.38-7.48 (m, 1H, $H_{isoindol.}$), 7.52-7.60 (m, 2H, $H_{isoindol.}$), 7.78-7.89 (m, 1H, $H_{isoindol.}$ and 2H, $C_6H_4CH_3$); ms (CI, CH_5^+): 460 $[M+H]^+$ (100), 264 (12), 227 (16), 212 (10), 195 (36), 167 (10), 134 (30), 132 (25). *Anal.* Calcd. for $C_{28}H_{29}NO_5$ (459.55): C, 73.18; H, 6.36; N, 3.05. Found: C, 73.08; H, 6.31; N, 3.02.

(3*S*)-3-[2-(4-Nitrophenyl)-2-oxoethyl]-2-[(1*S*,5*R*)-5,8,8-trimethyl-2-oxo-3-oxabicyclo[3.2.1]octane-1-carbonyl]-2,3-dihydroisoindol-1-one (3b) and (3*R*)-3-[2-(4-Nitrophenyl)-2-oxoethyl]-2-[(1S,5R)-5,8,8-trimethyl-2-oxo-3-oxabicyclo-[3.2.1]octane-1-carbonyl]-2,3-dihydroisoindol-1-one (4b).

Method A: 4282 mg (10.54 mmol) of **1** were reacted with **2b** according to GP1. hplc (CH_3CN/H_2O = 65/35, 1 ml/min): **3b**: t_R = 8.0 minutes, 54%; **4b**: t_R = 9.1 minutes, 46%. Repeated CC (isohexane/EtOAc/CH_2Cl_2 = 65/25/10) yielded 1534 mg (30%) **3b** and 1360 mg (26%) **4b**.

Method B: 116 mg (0.29 mmol) of **1** were reacted with **2b** according to GP2. hplc (CH_3CN/H_2O = 65/35, 1 ml/min): **3b**: t_R = 8.1 minutes, 75%; **4b**: t_R = 9.1 minutes, 25%. Purification by CC (isohexane/EtOAc/CH_2Cl_2 = 65/25/10) and prep. hplc (column #1, isohexane/EtOAc/CH_2Cl_2 = 70/20/10) yielded 38 mg (27%) **3b** and 18 mg (13%) **4b**.

Method C: 117 mg (0.29 mmol) of **1** were reacted with **2b** according to GP3. hplc (CH_3CN/H_2O = 65/35, 1 ml/min): **3b**: t_R = 8.1 minutes, 80%; **4b**: t_R = 9.1 minutes, 20%. Purification by CC (isohexane/EtOAc/CH_2Cl_2 = 65/25/10) and prep. hplc (column #1, isohexane/EtOAc/CH_2Cl_2 = 70/20/10) yielded 57 mg (40%) **3b** and 19 mg (13%) **4b**.

3b: The compound was obtained as white solid, mp 203 °C; tlc: R_f = 0.16 (isohexane/EtOAc/CH_2Cl_2 = 65/25/10); $[\alpha]_D^{20}$ = +173.0 (c = 0.52 in CH_2Cl_2); ir: 2969, 1741, 1691, 1526, 1346, 1321, 1295, 1250, 1213, 1124 cm^{-1}; ^{1}H nmr ($C_6D_5NO_2$, 130 °C): δ = 0.91 (s, 3H, CH_3), 1.07 (s, 3H, CH_3), 1.42 (s, 3H, CH_3), 1.82-1.98 (m, 2H, CH_2CH_2), 2.63-2.84 (m, 2H, CH_2CH_2), 3.56 (dd, J = 17/7 Hz, 1H, CH_2), 3.98 (d, J = 11 Hz, 1H, OCH_2), 4.15 (dd, J = 17/2 Hz, 1H, CH_2), 4.33 (d, J = 11 Hz, 1H, OCH_2), 5.82-5.88 (m, 1H, NCH), 7.42-7.49 (m, 1H, $H_{isoindol.}$), 7.54-7.62 (m, 2H, $H_{isoindol.}$), 7.83 (d, J = 7.5 Hz, 1H, $H_{isoindol.}$), 8.06-8.11 (m, 2H,

$C_4H_6NO_2$), 8.17-8.22 (m, 2H, $C_4H_6NO_2$); ms (CI, CH_5^+): 491 $[M+H]^+$ (5), 461 (10), 212 (48), 195 (9), 132 (100). *Anal.* Calcd. for $C_{27}H_{26}N_2O_7$ (490.52): C, 66.11; H, 5.34; N, 5.71. Found: C, 66.03; H, 5.60; N, 5.48.

4b: The compound was obtained as white solid, mp 230 °C; tlc: R_f = 0.23 (isohexane/EtOAc/CH_2Cl_2 = 65/25/10); $[\alpha]_D^{20}$ = -93.0 (c = 1.02 in CH_2Cl_2); ir: 2970, 1734, 1690, 1526, 1346, 1321, 1296, 1271, 1213 cm^{-1}; ^1H nmr ($C_6D_5NO_2$, 130 °C): δ = 0.88 (s, 3H, CH_3), 1.12 (s, 3H, CH_3), 1.37 (s, 3H, CH_3), 1.82-1.99 (m, 2H, CH_2CH_2), 2.42-2.56 (m, 1H, CH_2CH_2), 3.21-3.44 (m, 1H, CH_2CH_2), 3.60 (dd, J = 17/7.5 Hz, 1H, CH_2), 3.95 (dd, J = 7.5/3.5 Hz, 1H, CH_2), 4.03 (d, J = 11 Hz, 1H, OCH_2), 4.21 (d, J = 11 Hz, 1H, OCH_2), 5.90-5.96 (m, 1H, NCH), 7.40-7.49 (m, 1H, $H_{isoindol.}$), 7.54-7.64 (m, 2H, $H_{isoindol.}$), 7.81 (d, J = 7.5 Hz, 1H, $H_{isoindol.}$), 8.06-8.13 (m, 2H, $C_6H_4NO_2$), 8.17-8.23 (m, 2H, $C_6H_4NO_2$); ms (CI, CH_5^+): 491 $[M+H]^+$ (5), 461 (4), 212 (13), 195 (10), 132 (100). *Anal.* Calcd. for $C_{27}H_{26}N_2O_7$ (490.52): C, 66.11; H, 5.34; N, 5.71. Found: C, 65.88; H, 5.33; N, 5.65.

(3*S*)-3-[2-(4-Chlorophenyl)-2-oxoethyl]-2-[(1*S*,5*R*)-5,8,8-trimethyl-2-oxo-3-oxabicyclo[3.2.1]octane-1-carbonyl]-2,3-dihydroisoindol-1-one (3c) and (3*R*)-3-[2-(4-Chlorophenyl)-2-oxoethyl]-2-[(1*S*,5*R*)-5,8,8-trimethyl-2-oxo-3-oxabicyclo-[3.2.1] octane-1-carbonyl]-2,3-dihydroisoindol-1-one (4c).

Method A: 1148 mg (28.26 mmol) of **1** were reacted with **2c** according to GP1. hplc (CH_3CN/H_2O, 1 ml/min): **3c**: t_R = 12.8 minutes, 50%; **4c**: t_R = 14.5 minutes, 50%. Repeated CC (isohexane/EtOAc/CH_2Cl_2 = 75/15/10) yielded 3733 mg (28%) of **3c** and 3725 mg (27%) of **4c**.

Method B: 116 mg (0.29 mmol) of **1** were reacted with **2c** according to GP2. hplc (CH_3CN/H_2O, 1 ml/min): **3c**: t_R = 12.7 minutes, 77%; **4c**: t_R = 14.5 minutes, 23%. Purification by CC (isohexane/EtOAc/CH_2Cl_2 = 70/20/10) and prep. hplc (column #1, isohexane/EtOAc/CH_2Cl_2 = 70/20/10) yielded 52 mg (37%) of **3c** and 14 mg (10%) of **4c**.

Method C: 117 mg (0.29 mmol) of **1** were reacted with **2c** according to GP3. hplc (CH_3CN/H_2O, 1 ml/min): **3c**: t_R = 12.8 minutes, 79%; **4c**: t_R = 14.5 minutes, 21%. Purification by CC (isohexane/EtOAc/CH_2Cl_2 = 70/20/10) and prep. hplc (column #1, isohexane/EtOAc/CH_2Cl_2 = 70/20/10) yielded 64 mg (46%) of **3c** and 13 mg (9%) of **4c**.

3c: The compound was obtained as white solid, mp 114 °C; tlc: R_f = 0.24 (isohexane/EtOAc/CH_2Cl_2 = 75/15/10); $[\alpha]_D^{20}$ = +196.5 (c = 0.592 in CH_2Cl_2);ir: 2966, 1739, 1683, 1589, 1325, 1295, 1250, 1213, 1123 cm^{-1}; ^1H nmr ($C_6D_5NO_2$, 130 °C): δ = 0.91 (s, 3H, CH_3), 1.06 (s, 3H, CH_3), 1.43 (s, 3H, CH_3), 1.81-1.99 (m, 2H, CH_2CH_2), 2.62-2.72 (m, 1H, CH_2CH_2), 2.82 (ddd, J = 14.5/11.5/6.5 Hz, 1H, CH_2CH_2), 3.46 (dd, J = 17/7.5 Hz, 1H, CH_2), 3.98 (d, J = 11 Hz, 1H, OCH_2), 4.11 (ddd, J = 17/3/1.5 Hz, 1H, CH_2), 4.33 (d, J = 11 Hz, 1H, OCH_2), 5.86 (br d, J = 7.5 Hz, 1H, NCH), 7.33-7.37 (m, 2H, C_6H_4Cl), 7.44 (t, J = 7.5 Hz, 1H, $H_{isoindol.}$), 7.53-7.60 (m, 2H, $H_{isoindol.}$), 7.81 (d, J = 7.5 Hz, 1H, $H_{isoindol.}$), 7.85-7.89 (m, 2H, C_6H_4Cl); ms (CI, CH_5^+): 480 $[M+H]^+$ (100), 284 (11), 227 (46), 212 (20), 195 (94), 167 (22), 132 (72). *Anal.* Calcd. for $C_{27}H_{26}ClNO_5$ (479.96): C, 67.57; H, 5.46; N, 2.92. Found: C, 67.37; H, 5.83; N, 2.78.

4c: The compound was obtained as white solid, mp 245 °C; tlc: R_f = 0.29 (isohexane/EtOAc/CH_2Cl_2 = 75:15:10); $[\alpha]_D^{20}$ = -86.5 (c = 0.200 in $CHCl_3$).ir: 2955, 1729, 1685, 1588, 1320, 1293, 1269, 1216, 1123 cm^{-1}. ^1H nmr ($C_6D_5NO_2$, 130 °C): δ = 0.89 (s, 3H, CH_3), 1.13 (s, 3H, CH_3), 1.38 (s, 3H, CH_3), 1.80-1.99 (m, 2H, CH_2CH_2), 2.40-2.56 (m, 1H, CH_2CH_2), 3.25-3.42 (m, 1H, CH_2CH_2), 3.49 (dd, J = 17/7.5 Hz, 1H, CH_2), 3.88 (dd, J = 17/3 Hz, 1H, CH_2), 4.03 (d, J = 11 Hz, 1H, OCH_2), 4.21 (d, J = 11 Hz, 1H, OCH_2), 5.94 (dd, J = 7.5/3 Hz, 1H, NCH), 7.34-7.38 (m, 2H, C_6H_4Cl), 7.43 (t, J = 7.5 Hz, 1H, $H_{isoindol.}$), 7.53-7.60 (m, 2H, $H_{isoindol.}$), 7.81 (d, J = 7.5 Hz, 1H, $H_{isoindol.}$), 7.87-7.91 (m, 2H, C_6H_4Cl); ms (CI, CH_5^+): 480 $[M+H]^+$ (95), 284 (10), 227 (55), 212 (21), 195 (100), 167 (23), 132 (48). *Anal.* Calcd. for $C_{27}H_{26}ClNO_5$ (479.96): C, 67.57; H, 5.46; N 2.92. Found: C, 67.21; H, 5.28; N, 2.83.

(3*S*)-3-[(2*R*)-2-Hydroxy-2-(4-methylphenyl)ethyl)-2-[(1*S*,5*R*)-5,8,8-trimethyl-2-oxo-3-oxabicyclo[3.2.1]octane-1-carbonyl]-2,3-dihydroisoindol-1-one (15a) and (3*S*)-3-[(2*S*)-2-Hydroxy-2-(4-methylphenyl)ethyl)-2-[(1*S*,5*R*)-5,8,8-trimethyl-2-oxo-3-oxabicyclo[3.2.1]octane-1-carbonyl]-2,3-dihydroisoindol-1-one (16a). 638 mg (1.39 mmol) of **3a** were reacted with Li[Al(*t*BuO)$_3$H] according to GP4. hplc (CH_3CN/H_2O = 55/45, 1 ml/min): **15a**: t_R = 15.1 minutes, 94%; **16a**: t_R = 16.7 minutes; 6%. Purification by CC (isohexane/EtOAc = 70/30) yielded 576 mg (90%) of **15a** and 54 mg (8%) of **16a**.

15a: The compound was obtained as white solid, mp 175 °C; tlc: R_f = 0.13 (isohexane/EtOAc = 70/30); $[\alpha]_D^{20}$ = +104.9 (c = 0.710 in CH_2Cl_2); ir: 3546, 2956, 1734, 1677, 1468, 1295, 1248,1213, 1123 cm^{-1}; ^1H nmr ($C_2Cl_4D_2$, 130 °C): δ = 0.89 (s, 3H, CH_3), 1.00 (s, 3H, CH_3), 1.27 (s, 3H, CH_3), 1.79-1.90 (m, 2H, CH_2), 2.25 (ddd, J = 14.5/7.5/3.5 Hz, 1H, CH_2), 2.30 (s, 3H, $C_6H_4CH_3$), 2.58-2.69 (m, 3H, CH_2), 3.88 (d, J = 11 Hz, 1H, OCH_2), 4.24 (d, J = 11 Hz, 1H, OCH_2), 4.93 (dd, J = 10/3.5 Hz, 1H, OCH), 5.51 (dd, J = 7.5/3.0 Hz, 1H, NCH), 7.09 (d, J = 8 Hz, 2H, $C_6H_4CH_3$), 7.17 (d, J = 8 Hz, 2H, $C_6H_4CH_3$), 7.41-7.48 (m, 2H, $H_{isoindol.}$), 7.60 (td, J = 7.5/1 Hz, 1H, $H_{isoindol.}$), 7.81 (d, J = 7.5 Hz, 1H, $H_{isoindol.}$); ms (CI, CH_5^+): 462 $[M+H]^+$ (13), 444 (4), 344 (6), 266 (53), 250 (33), 227 (11), 213 (23), 197 (100), 169 (23). *Anal.* Calcd. for $C_{28}H_{31}NO_5$ (461.56): C, 72.86; H, 6.77; N, 3.03. Found: C, 72.96; H, 7.06; N, 2.88.

16a: The compound was obtained as white solid, mp 210 °C; tlc: R_f = 0.17 (isohexane/EtOAc = 70/30); ir: 3561, 2968, 1749, 1234, 1659, 1467, 1357, 1297, 1257, 1211, 1124 cm^{-1}; ^1H nmr ($C_2Cl_4D_2$, 130 °C): δ = 0.91 (s, 3H, CH_3), 1.06 (s, 3H, CH_3), 1.32 (s, 3H, CH_3), 1.77-1.89 (m, 2H, CH_2), 2.20-2.31 (m, 1H, CH_2), 2.28 (s, 3H, $C_6H_4CH_3$), 2.46-2.76 (m, 3H, CH_2), 3.89 (d, J = 11 Hz, 1H, OCH_2), 4.26 (d, J = 11 Hz, 1H, OCH_2), 4.72 (dd, J = 9/3.5 Hz, 1H, OCH), 5.50 (t, J = 4.5 Hz, 1H, NCH), 7.06 (d, J = 8 Hz, 2H, $C_6H_4CH_3$), 7.13 (d, J = 8 Hz,2 H, $C_6H_4CH_3$), 7.33 (d, J = 7.5 Hz, 1H, $H_{isoindol.}$), 7.40 (t, J = 7.5 Hz, 1H, $H_{isoindol.}$), 7.55 (td, J = 7.5/1 Hz, 1H, $H_{isoindol.}$), 7.78 (d, J = 7.5 Hz, 1H, $H_{isoindol.}$); ms (CI, CH_5^+): 462 $[M+H]^+$ (37), 444 (20), 344 (16), 327 (3), 266 (13), 251 (18), 233 (12), 212 (32), 199 (20), 132 (100).

(3*S*)-3-[(2*R*)-2-Hydroxy-2-(4-nitrophenyl)ethyl]-2-[(1*S*,5*R*)-5,8,8-trimethyl-2-oxo-3-oxabicyclo[3.2.1]octane-1-carbonyl]-2,3-dihydroisoindol-1-one (15b) and (3*S*)-3-[(2*S*)-2-Hydroxy-2-(4-nitrophenyl)ethyl]-2-[(1*S*,5*R*)-5,8,8-trimethyl-2-oxo-3-oxabicyclo[3.2.1]octane-1-carbonyl]-2,3-dihydroisoindol-1-one (16b). 1524 mg (3.11 mmol) of **3b** were reacted with Li[Al(*t*BuO$_3$)H] according to GP4. hplc (CH_3CN/H_2O = 50/50, 1.5 ml/min) **15b**: t_R = 19.5 minutes, 97%; **16b**: t_R = 20.3 minutes; 3%. Purification by CC (isohexane/EtOAc = 60:40) yielded 1384 mg (90%) of **15b**.

15b: The compound was obtained as white solid, mp 210 °C; tlc: R_f = 0.1 (isohexane/EtOAc = 60/40); $[\alpha]_D^{20}$ = +93.2 (c = 0.325 in CH_3OH); ir: 3523, 3370, 2923, 1738, 1719, 1701, 1686, 1597, 1521, 1468, 1413, 1344, 1295, 1270 cm^{-1}; ^1H nmr ($C_2Cl_4D_2$, 130 °C): δ = 0.97 (s, 3H, CH_3), 1.13 (s, 3H, CH_3), 1.34 (s, 3H, CH_3), 1.85-2.00 (m, 2H, CH_2), 2.28 (d, J = 4 Hz, 1H, OH), 2.45-2.65 (m, 3H, CH_2), 2.83-2.97 (m, 1H, CH_2), 3.99 (d, J = 11 Hz, 1H,

OCH_2), 4.26 (d, J = 11 Hz, 1H, OCH_2), 5.10-5.18 (m, 1H, OCH), 5.51-5.57 (m, 1H, NCH), 7.47-7.57 (m, 2H, $H_{isoindol.}$ and 2H, $C_6H_4NO_2$), 7.69 (t, J = 7.5 Hz, 1H, $H_{isoindol.}$), 7.89 (d, J = 7.5 Hz, 1H, $H_{isoindol.}$), 8.16 (d, J = 8.5 Hz, 2H, $C_6H_4NO_2$); ms (CI, CH_5^+): 493 $[M+H]^+$ (1), 475 (0), 447 (1), 283 (50), 253 (14), 212 (29), 197 (8), 150 (100), 134 (28), 132 (40). *Anal*. Calcd. for $C_{27}H_{28}N_2O_7$ (492.53): C, 65.84; H, 5.73; N, 5.69. Found: C, 65.80; H, 5.67; N, 5.67.

16b: tlc: R_f = 0.04 (CH_2Cl_2/EtOAc = 95/5); ir: 3441, 2968, 2818, 1739, 1671, 1599, 1520, 1468, 1455, 1408, 1346, 1325, 1293, 1250 cm^{-1}; ^1H nmr ($C_2Cl_4D_2$. 130 °C): δ = 0.91 (s, 3H, CH_3), 1.10 (s, 3H, CH_3), 1.31 (s, 3H, CH_3), 1.78-1.91 (m, 2H, CH_2), 2.15-2.24 (m, 1H, CH_2), 2.46-2.58 (m, 1H, CH_2), 2.63 (ddd, *J* = 15/9/4 Hz, 1H, CH_2), 2.71-2.83 (m, 1H, CH_2), 3.19 (br s, 1H, OH), 3.93 (d, J = 11 Hz, 1H, OCH_2), 4.23 (d, J = 11 Hz, 1H, OCH_2), 4.79-4.85 (m, 1H, OCH), 5.52 (t, J = 4.5 Hz, 1H, NCH), 7.35 (d, J = 7.5 Hz, 1H, $H_{isoindol.}$), 7.39 (d, J = 8.5 Hz, 2H, $C_6H_4NO_2$), 7.44 (t, J = 7.5 Hz, 1H, $H_{isoindol.}$), 7.59 (td, J = 7.5/1.0 Hz, 1H, $H_{isoindol.}$), 7.80 (d, J = 7.5 Hz, 1H, $H_{isoindol.}$), 8.06 (d, J = 8.5 Hz, 2H, $C_6H_4NO_2$); ms (CI, CH_5^+): 493 $[M+H]^+$ (10), 475 (2), 445 (0), 283 (19), 251 (12), 227 (6), 213 (11), 195 (8), 150 (34), 132 (36).

(3*S*)-3-[(2*R*)-2-Hydroxy-2-(4-chlorophenyl)ethyl]-2-[(1*S*,5*R*)-5,8,8-trimethyl-2-oxo-3-oxabicyclo[3.2.1]octane-1-carbonyl]-2,3-dihydroisoindol-1-one (15c) and (3*S*)-3-[(2*S*)-2-Hydroxy-2-(4-chlorophenyl)ethyl]-2-[(1*S*,5*R*)-5,8,8-trimethyl-2-oxo-3-oxabicyclo[3.2.1]octane-1-carbonyl]-2,3-dihydroisoindol-1-one (16c). 1602 mg (3.34 mmol) of **3c** were reacted with Li[Al(*t*BuO)$_3$H] according to GP4. hplc (CH_3CN/H_2O = 45/55, 1.5 ml/min): **15c**: t_R = 35.7 minutes, 95%; **16c**: t_R = 39.2 minutes; 5%. Purification by CC (isohexane/EtOAc = 65/35) yielded 1215 mg (76%) of **15c**.

15c: The compound was obtained as white solid, mp 212 °C; tlc: R_f = 0.1 (isohexane/EtOAc = 65/35); $[\alpha]_D^{20}$ = +5.8 (c = 0.775 in CH_2Cl_2); ir: 3536, 2918, 1736, 1722, 1680, 1614, 1469, 1368, 1294, 1266 cm^{-1}; ^1H nmr ($C_2Cl_4D_2$, 130 °C): δ = 0.96 (s, 3H, CH_3), 1.08 (s, 3H, CH_3), 1.33 (s, 3H, CH_3), 1.85-1.97 (m, 2H, CH_2), 2.12 (br s , 1H, OH), 2.40 (ddd, J = 14.5/7/3.5 Hz, 1H, CH_2), 2.55-2.79 (m, 3H, CH_2), 3.96 (d, J = 11 Hz, 1H, OCH_2), 4.28 (d, J = 11 Hz, 1H, OCH_2), 5.01 (dd, J = 11/3 Hz, 1H, OCH), 5.55 (dd, J = 7.5/2.5 Hz, 1 H, NCH), 7.28 (d, J = 8.5 Hz, 2H, C_6H_4Cl), 7.32 (d, J = 8.5 Hz, 2H, C_6H_4Cl), 7.48-7.56 (m, 2H, $H_{isoindol.}$), 7.67 (t, J = 7.5 Hz, 1H, $H_{isoindol.}$), 7.87 (d, J = 7.5 Hz, 1H, $H_{isoindol.}$); ms (CI, CH_5^+): 482 $[M+H]^+$ (6), 461 (7), 272 (47), 270 (66), 197 (58), 146 (25), 139 (84), 134 (100). *Anal*. Calcd. for $C_{27}H_{28}NO_5Cl$ (481.98): C, 67.29; H, 5.86; N, 2.91. Found: C, 67.15; H, 5.76; N, 2.88.

16c: tlc: R_f = 0.06 (CH_2Cl_2/EtOAc = 95/5); ir: 3444, 2920, 2850, 1738, 1469, 1296, 1249 cm^{-1}; ^1H nmr ($C_2Cl_4D_2$, 130 °C): δ = 0.91 (s, 3H, CH_3), 1.07 (s, 3H, CH_3), 1.32 (s, 3H, CH_3), 1.77-1.91 (m, 2H, CH_2), 2.16-2.30 (m, 1H, CH_2), 2.52-2.67 (m, 3H, CH_2), 2.81 (br s, 1H, OH), 3.90 (d, J = 11 Hz, 1H, OCH_2), 4.25 (d, J = 11 Hz, 1H, OCH_2), 4.72 (dd, J = 9.0/3.5 Hz, 1H, OCH), 5.50 (t, J = 4.5 Hz, 1H, NCH), 7.17 (d, J = 8.5 Hz, 2H, C_6H_4Cl), 7.23 (d, J = 8.5 Hz, 2H, C_6H_4Cl), 7.31 (d, J= 7.5 Hz, 1H, $H_{isoindol.}$), 7.42 (t, J = 7.5 Hz, 1H, $H_{isoindol.}$), 7.57 (td, J = 7.5/1 Hz, 1H, $H_{isoindol.}$), 7.78 (d, J = 7.5 Hz, 1H, $H_{isoindol.}$); ms (CI, CH_5^+): 482 $[M+H]^+$ (6), 406 (5), 369 (10), 355 (12), 329 (22), 301 (11), 271 (11), 225 (68), 211 (21), 197 (33), 133 (18), 132 (12), 105 (100).

(3*S*)-3-[(2*R*)-2-Hydroxy-2-(4-methylphenyl)ethyl]-2,3-dihydro-1*H*-isoindol-1-one (5a). 689 mg (1.49 mmol) of **15a** were reacted with $LiBH_4$ according to GP5. Purification by CC (CH_2Cl_2/1,4-dioxane = 80/20) yielded 267 mg (66%) of **5a** as a white solid, mp 52 °C; tlc: R_f = 0.18 (CH_2Cl_2/1,4-dioxane = 80/20); ir: 3387, 2922, 1686, 1467, 1079, 820, 747 cm^{-1}; ^1H nmr (CD_2Cl_2): δ = 1.83 (dt, J = 14.5/10.5 Hz, 1H, CH_2), 2.30-2.32 (m, 1H, CH_2), 2.34 (s, 3H, CH_3), 2.69 (s, 1H, OH), 4.76 (dd, J = 10.5/2 Hz, 1H, CH), 5.06 (dd, J = 10.5/3 Hz, 1H, CH), 7.11 (s, 1H, NH), 7.19 (d, J = 8 Hz, 2H, $C_6H_4CH_3$), 7.30 (d, J = 8 Hz, 2H, $C_6H_4CH_3$), 7.44-7.48 (m, 2H, $H_{isoindol.}$), 7.56 (dt, J = 7.5/1 Hz, 1H, $H_{isoindol.}$), 7.77 (d, J = 8 Hz, 1H, $H_{isoindol.}$); ms (CI, CH_5^+): 268 $[M+H]^+$ (40), 250 (12), 225 (39), 211 (15), 197 (25), 132 (41), 105 (100); hrms (EI^+): Calcd. ($C_{17}H_{17}NO_2$): 267.1259, found: 267.1224. *Anal*. Calcd. for $C_{17}H_{17}NO_2$ (267.33): C, 76.38; H, 6.41; N, 5.24. Found: C, 73.99; H, 6.83; N, 5.24.

(3*S*)-3-[(2*R*)-2-Hydroxy-2-(4-nitrophenyl)ethyl]-2,3-dihydro-1*H*-isoindol-1-one (5b). 896 mg (1.82 mmol) of **15b** were reacted with $LiBH_4$ according to GP5. Purification by CC (CH_2Cl_2/THF = 80/20) yielded 488 mg (90%) of **5b** as a white solid; tlc: R_f = 0.23 (CH_2Cl_2/THF = 80/20); ir: 3424, 3321, 2924, 2853, 1674, 1597, 1511, 1472, 1376, 1342, 1262, 1201 cm^{-1}; ^1H nmr (C_2D_6OS): δ = 1.87 (dt, J = 13.5/8 Hz, 1H, CH_2), 2.11 (ddd, J = 13.5/6/5.5 Hz, 1H, CH_2), 4.46 (dd, J = 8/5 Hz, 1H, CH), 5.02 (dd, J = 7.5/6 Hz, 1H, CH), 5.84 (d, J = 4.5 Hz, 1H, OH), 7.48 (td, J = 7/1 Hz, 1H, $H_{isoindol.}$), 7.59 (td, J = 7/1 Hz, 1H, $H_{isoindol.}$), 7.63 (d, J = 7 Hz, 1H, $H_{isoindol.}$), 7.66 (d, J = 7 Hz, 1H, $H_{isoindol.}$), 7.70-7.74 (m, 2H, $C_6H_4NO_2$), 8.21-8.25 (m, 2H, $C_6H_4NO_2$), 8.65 (1, 1H, NH); ms (CI, CH_5^+): 299 $[M+H]^+$ (100), 283 (11), 267 (10), 251 (52), 219 (34), 200 (79), 183 (19), 146 (33); hrms (EI^+): Calcd. ($C_{16}H_{14}N_2O_4$): 298.0954, found: 298.0972.

(3*S*)-3-[(2*R*)-2-Hydroxy-2-(4-chlorphenyl)ethyl]-2,3-dihydro-1*H*-isoindol-1-one (5c). 795 mg (1.65 mmol) of **15c** were reacted according to GP5. Purification by CC (CH_2Cl_2/THF = 80/20) yielded 371 mg (78%) as **5c** white solid; tlc: R_f = 0.23 (CH_2Cl_2/THF = 80/20); ir: 3427, 3316, 2909, 2853, 1675, 1488, 1470, 1410, 1383, 1334, 1294, 1260 cm^{-1}; ^1H nmr (C_2D_6OS, rt): δ = 1.82 (dt, J = 13.5/8 Hz, 1H, CH_2), 2.02-2.09 (m, 1H, CH_2), 4.39 (dd, J = 8/5 Hz, 1H, CH), 4.89 (ddd, J = 7/7/4 Hz, 1H, CH), 5.60 (d, J = 4 Hz, 1H, OH), 7.41 (d, J = 8.5 Hz, 2H, C_6H_4Cl), 7.45-7.40 (m, 1H, $H_{isoindol.}$), 7.47 (d, J = 8.5 Hz, 2H, C_6H_4Cl), 7.56-7.62 (m, 2H, $H_{isoindol.}$), 7.65 (d, J = 7.5 Hz, 1H, $H_{isoindol.}$), 8.63 (s, 1H, NH); ms (CI, CH_5^+): 288 $[M+H]^+$ (71), 200 (16), 160 (8), 146 (10), 132 (100); hrms (EI^+): Calcd. ($C_{16}H_{14}ClNO_2$): 287.0713, found: 287.0750.

{(1*S*)-2-[(1*S*)-3-Oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1-(4-methylphenyl)ethyl} benzoate (19a). 374 mg (1.40 mmol) of **5a** were reacted with benzoic acid according to GP6. CC (*n*-heptane/acetone = 65:35) yielded 249 mg (48%) of **19a** as white solid; mp 56 -59 °C; tlc: R_f = 0.30 (*n*-heptane/acetone = 60:40); $[\alpha]_D^{20}$ = +7.4 (c = 0.175 in CH_3OH); ir: 3265, 2980, 1698, 1468, 1388, 1316, 1270, 1178, 1110 cm^{-1}; ^1H nmr ($CDCl_3$): δ = 1.93 (ddd, J = 14.5/11/4 Hz, 1H, CH_2), 2.36 (s, 3H, $C_6H_4CH_3$), 2.71 (ddd, J = 14.5/10/3 Hz, 1H, CH_2), 4.61 (br d, J = 11 Hz, 1H, NCH), 6.31 (dd, J = 10/4 Hz, 1H, OCH), 6.72 (br s, 1H, NH), 7.21 (d, J = 8 Hz, 2H, $C_6H_4CH_3$), 7.36 (d, J = 8 Hz, 2H, $C_6H_4CH_3$), 7.41 (dd, J = 7.5/1 Hz, 1H, $H_{arom.}$), 7.43-7.50 (m, 3H, $H_{arom.}$), 7.53 (td, J = 7.5/1 Hz, 1H, $H_{arom.}$), 7.60 (tt, J = 7.5/1.5 Hz, 1H, $H_{arom.}$), 7.84 (d, J = 7.5 Hz, 1H, $H_{arom.}$), 8.10-8.14 (m, 2H, $H_{arom.}$) ^{13}C nmr ($CDCl_3$, rt): δ = 21.16 (CH_3), 42.92 (CH_2), 53.36 (NCH), 74.09 (OCH), 122.18 ($C_{arom.}$), 124.03 ($C_{arom.}$), 126.15 (2 C, $C_{arom.}$), 128.36 ($C_{arom.}$), 128.54 (2 C, $C_{arom.}$), 129.58 (2 C, $C_{arom.}$), 129.61 (C_q), 129.84 (2 C, $C_{arom.}$), 131.61 (C_q), 131.88 ($C_{arom.}$), 133.48 ($C_{arom.}$), 136.42 (C_q), 138.45 (C_q), 147.00 (C_q), 166.34 (C=O), 170.33 (C=O). ms (CI, CH_5^+): 372 $[M+H]^+$ (4),

250 (20), 132 (100), 105 (4); hrms (FAB$^+$): Calcd. ($C_{24}H_{22}NO_3$, [M+H]$^+$): 372.1600, found: 372.1605.

{(1*S*)-2-[(1*S*)-3-Oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1-(4-nitrophenyl)ethyl} benzoate (19b). 301 mg (1.01 mmol) of **5b** were reacted with benzoic acid according to GP6. CC (*n*-heptane/EtOAc = 50:50) yielded 317 mg (78%) of **19b** as white solid, mp 84 - 88 °C;tlc: R_f = 0.23 (*n*-heptane/EtOAc = 50:50); $[\alpha]_D^{20}$ = +60.6 (c = 0.165 in CH_3OH); ir: 3209, 3076, 2922, 2855, 1697, 1601, 1522, 1469, 1451, 1420, 1348, 1316 cm^{-1}. ^{1}H nmr ($CDCl_3$): δ = 1.97 (ddd, J = 14/11/3 Hz, 1H, CH_2), 2.68 (ddd, J = 14/11/3 Hz, 1H, CH_2), 4.67 (br d, J = 11 Hz, 1H, NCH), 6.41 (dd, J = 11/3 Hz, 1H, OCH), 6.99 (br s, 1H, NH), 7.38 (d, J = 7.5 Hz, 1H, $H_{arom.}$), 7.45-7.56 (m, 4H, $H_{arom.}$), 7.61-7.67 (m, 3H, $H_{arom.}$), 7.86 (d, J = 7.5 Hz, 1H, $H_{arom.}$), 8.12-8.16 (m, 2H, $C_6H_4NO_2$), 8.23-8.27 (m, 2H, $C_6H_4NO_2$); ^{13}C nmr ($CDCl_3$): δ = 42.91 (CH_2), 53.11 (NCH), 72.76 (OCH), 122.13 ($C_{arom.}$), 124.13 (2 C, $C_{arom.}$), 124.21 ($C_{arom.}$), 126.88 (2 C, $C_{arom.}$), 128.63 ($C_{arom.}$), 128.74 (2 C, $C_{arom.}$), 128.91 (C_q), 129.88 (2 C, $C_{arom.}$), 131.61 (C_q), 132.08 ($C_{arom.}$), 133.96 ($C_{arom.}$), 146.49 (C_q), 146.77 (C_q), 147.76 (C_q), 166.05 (C=O), 170.60 (C=O); ms (CI, CH_5^+): 403 (28), 283 (71), 281 (15), 267 (3), 251 (13), 231 (15), 150 (90), 132 (100), 123 (65); hrms (FAB$^+$): Calcd. ($C_{23}H_{19}N_2O_5$, [M+H]$^+$): 403.1294, found: 403.1244.

{(1*S*)-2-[(1*S*)-3-Oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1-(4-chlorophenyl)ethyl} benzoate (19c). 346 mg (1.2 mmol) of **5c** were reacted with benzoic acid according to GP6. CC (*n*-heptane/acetone = 65:35) yielded 316 mg (67%) of **19c** as white solid, mp 76 - 79 °C; tlc: R_f = 0.33 (n-heptane/acetone = 65:35); $[\alpha]_D^{20}$ = +27.2 (c = 0.25 in CH_3OH); ir: 3204, 3068, 2921, 2854, 1695, 1616, 1599, 1491, 1469, 1450, 1419, 1353, 1315, 1268, 1200 cm^{-1}; ^{1}H nmr ($CDCl_3$): δ = 1.92 (ddd, J = 14.5/11/3.5 Hz, 1H, CH_2), 2.67 (ddd, 14.5/10.5/3 Hz, 1H, CH_2), 4.62 (br d, J = 10 Hz, 1H, NCH), 6.31 (dd, J = 10.5/3.5 Hz, 1H, OCH), 6.88 (br s, 1H, NH), 7.35-7.42 (m, 5H, $H_{arom.}$), 7.44-7.52 (m, 3H, $H_{arom.}$), 7.54 (td, J = 7.5/1 Hz, 1H, $H_{arom.}$), 7.62 (tt, J = 7.5/1.5 Hz, 1H, $H_{arom.}$), 7.85 (d, J = 7.5 Hz, 1H, $H_{arom.}$), 8.10-8.14 (m, 2H, $H_{arom.}$); ^{13}C nmr ($CDCl_3$): δ = 42.96 (CH_2), 53.19 (NCH), 73.26 (OCH), 122.15 ($C_{arom.}$), 124.12 ($C_{arom.}$), 127.52 (2 C, $C_{arom.}$), 128.48 ($C_{arom.}$), 128.64 (2 C, $C_{arom.}$), 129.09 (2 C, $C_{arom.}$), 129.29 (C_q), 129.85 (2 C, $C_{arom.}$), 131.61 (C_q), 131.96 ($C_{arom.}$), 133.69 ($C_{arom.}$), 134.35 (C_q), 138.06 (C_q), 146.78 (C_q), 166.24 (C=O), 170.43 (C=O); ms (CI, CH_5^+): 392 [M+H]$^+$ (3), 270 (8), 146 (2), 133 (17), 132 (100); hrms (FAB$^+$): Calcd. ($C_{23}H_{19}NO_3Cl$, [M+H]$^+$): 392.1065, found: 392.1058. *Anal.* Calcd. for $C_{22}H_{18}NO_3Cl$ (391.86): C, 70.50; H, 4.63; N, 3.57. Found: C, 70.15; H, 4.98; N, 3.37.

(3*S*)-3-[(2*S*)-2-Hydroxy-2-(4-methylphenyl)ethyl]-2,3-dihydro-1*H*-isoindol-1-one (6a). 68 mg (0.18 mmol) of **19a** were dissolved in 1.8 ml of THF and cooled to 0 °C. A solution of 0.9 mmol of Li[$AlH_2(OCH_3)_2$] in THF was added dropwise. The mixture was stirred for 2 hours at 0 °C. Excessive Li[$AlH_2(OCH_3)_2$] was destroyed by addition of KH_2PO_4-solution (10%). The mixture was allowed to warm to room temperature. After gas formation had stopped, Et_2O was added and the organic layer was separated. The aqueous layer was saturated with NaCl and extracted with Et_2O (5x). The combined organic layers were dried with $MgSO_4$ and concentrated *in vacuo*. CC (isohexane/acetone = 60:40) yielded 32 mg (67%) of **6a** as white solid. As despite several attempts **6a** could not be obtained in pure form it was directly used for the subsequent reaction; tlc: R_f = 0.32 (isohexane/acetone = 60:40); ir: 3221, 2950, 2917, 1666, 1616, 1595, 1512, 1469, 1432, 1418,1370, 1327, 1253 cm^{-1}; ^{1}H nmr ($CDCl_3$, rt): δ = 1.86 (ddd, J = 14.5/10.5/4 Hz, 1H, CH_2), 2.35 (s, 3H, CH_3), 2.43 (ddd, J = 14.5/7.5/3 Hz, 1H, CH_2), 4.79 (br dd, J = 10.5/2.5 Hz, 1H, CH), 5.05 (dd, J = 7.5/4 Hz; 1H, CH), 7.09 (br s, 1H, NH), 7.19 (d, J = 8 Hz, 2H, $C_6H_4CH_3$), 7.30 (d, J = 8 Hz, 2H, $C_6H_4CH_3$), 7.35 (d, J = 7.5 Hz, 1H, $H_{isoindol.}$), 7.44 (t, J = 7.5 Hz, 1H, $H_{isoindol.}$), 7.53 (td, J = 7.5/1 Hz, 1H, $H_{isoindol.}$), 7.83 (d, J = 7.5 Hz, 1H, $H_{isoindol.}$); ms (CI, CH_5^+): 268 [M+H]$^+$ (85), 250 (8), 160 (10), 146 (10), 132 (100), 119 (6).

(3*S*)-3-[(2*S*)-2-Hydroxy-2-(4-nitrophenyl)ethyl]-2,3-dihydro-1*H*-isoindol-1-one (6b). 275 mg (0.68 mmol) of **19b** were reacted with $LiBH_4$ according to GP7. CC (isohexane/acetone = 55:45) yielded 183 mg (90%) of **6b** as white solid. As despite several attempts **6b** could not be obtained in pure form it was directly used for the subsequent reaction; tlc: R_f = 0.3 (isohexane/acetone = 60:40); ir: 3219, 2966, 2853, 1665, 1517, 1472, 1420, 1347 cm^{-1}; ^{1}H nmr (C_2D_6OS): δ = 1.55 (ddd, J = 13.5/10/3 Hz, 1H, CH_2), 2.23 (ddd, J = 13.5/10.5/3 Hz, 1H, CH_2), 4.84 (dd, J = 10/3 Hz, 1H, CH), 5.05 (br d, J = 10.5 Hz, 1H, CH), 5.87 (d, J = 4.5 Hz, 1H, OH), 7.43-7.49 (m, 1H, $H_{isoindol.}$), 7.54-7.58 (m, 2H, $H_{isoindol.}$), 7.61-7.67 (m, 1H, $H_{isoindol.}$ and 2H, $C_6H_4NO_2$), 8.19 (d, J = 8.5 Hz, 2H, $C_6H_4NO_2$), 8.97 (s, 1H, NH); ms (CI, CH_5^+): 299 [M+H]$^+$ (100), 269 (5), 251 (13), 200 (11), 146 (20), 132 (24); hrms (EI$^+$): Calcd. ($C_{16}H_{14}N_2O_4$):298.0954, found: 298.0938.

(3*S*)-3-[(2*S*)-2-Hydroxy-2-(4-chlorphenyl)ethyl]-2,3-dihydro-1*H*-isoindol-1-one (6c). 247 mg (0.63 mmol) of **19c** were reacted with $LiBH_4$ according to GP7. CC (isohexane/acetone = 60:40) yielded 151 mg (83%) of **6c** white solid. As despite several attempts **6c** could not be obtained in pure form it was directly used for the subsequent reaction; tlc: R_f = 0.28 (isohexane/acetone = 60:40); ir: 3227, 2942, 2913, 1666, 1490, 1473, 1367, 1323, 1200, 1093 cm^{-1}; ^{1}H nmr (C_2D_6OS, rt): δ = 1.48 (ddd, J = 13.5/10/3 Hz, 1H, CH_2), 2.22 (ddd, J = 13.5/10.5/3 Hz, 1H, CH_2), 4.81 (dd, J = 10/3 Hz, 1H, CH), 4.88-4.93 (m, 1H, CH), 5.61 (d, J = 4 Hz, 1H, OH), 7.37 (s, 4 H, C_6H_4Cl), 7.44-7.48 (m, 1H, $H_{isoindol.}$), 7.55-7.58 (m, 2H, $H_{isoindol.}$), 7.65 (d, J = 8 Hz, 1H, $H_{isoindol.}$), 8.92 (s, 1H, NH); ms (CI, CH_5^+): 288 [M+H]$^+$ (88), 270 (3), 200 (21), 160 (5), 146 (12), 132 (100), 105 (2).

(3*R*,4a*S*)-3-(4-Methylphenyl)-3,4,4a,9-tetrahydrooxazino-[4,3-*a*]isoindole (7a). 113 mg (0.42 mmol) of **5a** were reacted with BMS according to GP8. Purification by CC (*n*-pentane/EtOAc = 70/30) yielded 65 mg (58%) of **7a** as white solid, mp 135 °C; tlc: R_f = 0.15 (*n*-pentane/Et_2O = 70/30); $[\alpha]_D^{20}$ = -53.5 (c = 0.155 in CH_3OH); ir: 451, 2925, 2854, 1461, 1369, 1145, 861, 773, 700 cm^{-1}; ^{1}H nmr ($CDCl_3$): δ = 1.61 (dt, J = 13.5/9.5 Hz, 1H, CH_2), 1.86 (ddd, J = 13.5/4/2 Hz, 1H, CH_2), 2.32 (s, 3H, CH_3), 4.17 (d, J = 12.5 Hz, 1H, NCH_2), 4.49-4.55 (m, 1H, NCH and 1H, OCH), 4.58 (d, J = 12.5 Hz, 1H, NCH_2), 4.86 (d, J = 12.5 Hz, 1H, NCH_2O), 4.94 (d, J = 12.5 Hz, 1H, NCH_2O), 7.13 (d, J = 8.5 Hz, 2H, $H_{arom.}$), 7.18-7.25 (m, 5H, $H_{arom.}$), 7.28-7.32 (m, 1 H, $H_{arom.}$); ms (CI, CH_5^+): 266 [M+H]$^+$ (13), 254 (3), 225 (50), 211 (11), 197 (17), 105 (100). *Anal.* Calcd. for $C_{18}H_{19}NO$ (265.36): C, 81.48; H, 7.22; N, 5.28. Found: C, 81.20; H, 7.35; N, 5.13.

(3*R*,4a*S*)-3-(4-Nitrophenyl)-3,4,4a,9-tetrahydrooxazino-[4,3-*a*]isoindole (7b). 213 mg (0.72 mmol) of **5b** were reacted with BMS according to GP8. Purification by CC (*n*-heptane/Et_2O = 50/50) yielded 65mg (30%) of **7b** as white solid, mp 143-147 °C; tlc: R_f = 0.12 (*n*-heptane/Et_2O = 50/50); $[\alpha]_D^{20}$ = +85.6 (c = 0.160 in CH_3OH); ir: 3029, 2966, 2942, 2912, 2871, 2859, 2801, 1603, 1514, 1475, 1464, 1431, 1383, 1345, 1314 cm^{-1}; ^{1}H nmr

($CDCl_3$): δ = 1.50 (dt, J = 13.5/11.5 Hz, 1H, CH_2), 1.92 (ddd, J = 13.5/4/2 Hz, 1H, CH_2), 4.20 (d, J = 12.5 Hz, 1H, NCH_2), 4.52-4.58 (m, 1H, NCH_2 and 1H, NCH), 4.67 (dd, J = 11.5/2 Hz, 1H, OCH), 4.87 (d, J = 11.5 Hz, 1H, NCH_2O), 4.97 (d, J = 11.5 Hz, 1H, NCH_2O), 7.19-7.26 (m, 3H, $H_{arom.}$), 7.28-7.31 (m, 1H, $H_{arom.}$), 7.49-7.52 (m, 2H, $C_6H_4NO_2$), 8.16-8.20 (m, 2H, $C_6H_4NO_2$); ms (CI, CH_5^+): 297 $[M+H]^+$ (100), 281 (3), 267 (2), 146 (10), 132 (4), 131 (4). *Anal*. Calcd. for $C_{17}H_{16}N_2O_3$ (296.33): C, 68.91; H, 5.44; N, 9.39. Found: C, 69.05; H, 5.39; N, 9.39.

(3*R*,4a*S*)-3-(4-Chlorophenyl)-3,4,4a,9-tetrahydrooxazino-[4,3-*a*]isoindole (7c). 200 mg (0.70 mmol) of **5c** were reacted with BMS according to GP8. Purification by CC (*n*-heptane/Et_2O = 50/50) yielded 105 mg (53%) of **7c** as white solid, mp 154 °C; tlc: R_f = 0.13 (*n*-heptane/Et_2O = 50/50); $[\alpha]_D^{20}$ = +61.3 (c = 0.315 in CH_3OH); ir: 3028, 2936, 1654, 1597, 1491, 1476, 1461, 1427, 1410, 1382, 1352, 1296, 1252, 1208 cm^{-1}; ^1H nmr ($CDCl_3$): δ = 1.54 (dt, J = 13.5/11.5 Hz, 1H, CH_2), 1.86 (ddd, J = 13.5/4/2 Hz, 1H, CH_2), 4.18 (d, J = 12.5 Hz, 1H, NCH_2), 4.50-4.58 (m, 1H, NCH, 1 H, OCH and 1H, NCH_2), 4.85 (d, J = 11.5 Hz, 1H, NCH_2O), 4.94 (d, J = 11.5 Hz, 1H. NCH_2O), 7.17-7.25 (m, 3H, $H_{arom.}$), 7.27-7.32 (m, 5H, H_{arom}); ms (CI, CH_5^+): 286 $[M+H]^+$ (100), 200 (15), 174 (18), 146 (19), 132 (33), 118 (10). *Anal*. Calcd. for $C_{17}H_{16}ClNO$ (285.78): C, 71.45; H, 5.64; N, 4.90. Found: C, 71.40; H, 5.57; N; 4.81.

(3*S*,4a*S*)-3-(4-Methylphenyl)-3,4,4a,9-tetrahydrooxazino-[4,3-*a*]isoindole (8a). 135 mg (0.51 mmol) of **6a** were reacted with BMS according to GP8. CC (*n*-heptane/Et_2O = 55/45) yielded 68 mg (50%) of **8a** as yellow oil; tlc: R_f = 0.15 (*n*-heptane/Et_2O = 55/45); $[\alpha]_D^{20}$ = +61.5 (c = 0.2 in CH_3OH); ir: 3031, 2922, 2865, 1704, 1663, 1515, 1459, 1351, 1299, 1252, 1101, 1052 cm^{-1}; ^1H nmr ($CDCl_3$): δ = 2.13 (ddd, J = 14/6/4.5 Hz, 1H, CH_2), 2.35 (s, 3H, CH_3), 2.42 (ddd, J = 14/7.5/5.5 Hz, 1H, CH_2), 4.24 (d, J = 13 Hz, 1H, NCH_2), 4.39 (d, J = 10.5 Hz, 1H, NCH_2O), 4.49 (dd, J = 13/2 Hz, 1H, NCH_2), 4.70-4.75 (m, 2H, OCH and NCH), 4.84 (d, J = 10.5 Hz, 1H, NCH_2O), 7.18 (d, J = 8 Hz, 2H, $H_{arom.}$), 7.22-7.37 (m, 6H, $H_{arom.}$); ^{13}C nmr ($CDCl_3$): δ = 21.10 (CH_3), 32.59 (CH_2), 54.49 (NCH_2), 59.60 (CH), 71.74 (CH), 76.30 (NCH_2O), 122.10 ($C_{isoindol.}$), 123.18 ($C_{isoindol.}$), 126.48 (2 C, $C_6H_4CH_3$), 127.15 ($C_{isoindol.}$), 127.33 ($C_{-isoindol.}$), 129.20 (2 C, $C_6H_4CH_3$), 137.04 (C_q), 138.21 (C_q), 140.24 (C_q), 143.52 (C_q); ms (CI, CH_5^+): 266 $[M+H]^+$ (100), 239 (2), 211 (5), 197 (7), 174 (13), 162 (7), 146 (31), 132 (70), 118 (31), 105 (21); hrms (EI^+): Calcd. ($C_{18}H_{19}NO$): 265.1467, found: 265.1461.

(3*S*,4a*S*)-3-(4-Nitrophenyl)-3,4,4a,9-tetrahydrooxazino-[4,3-*a*]isoindole (8b). 174 mg (0.58 mmol) of **6b** were reacted with BMS according to GP8. CC (*n*-heptane/ EtOAc = 60:40) yielded 77 mg (45%) of **8b** yellowish solid, mp 122 °C; tlc: R_f = 0.12 (*n*-heptane/EtOAc = 60:40); $[\alpha]_D^{20}$ = +112.1 (c = 0.290 in CH_3OH); ir: 2924, 2859, 2788, 1605, 1519, 1462, 1346, 1159, 1107, 1054 cm^{-1}; ^1H nmr ($CDCl_3$): δ = 2.17 (dt, J = 14.5/4.5 Hz, 1H, CH_2), 2.41 (ddd, J = 14.5/9/6 Hz, 1H, CH_2), 4.32 (d, J = 13.5 Hz, 1H, NCH_2), 4.48 (d, J = 10.5 Hz, 1H, NCH_2O), 4.51 (dd, J = 13.5/2 Hz, 1H, NCH_2), 4.75-4.79 (m, 2H, NCH and OCH), 4.89 (d, J = 10.5 Hz, 1H, NCH_2O), 7.24-7.27 (m, 1H, $H_{arom.}$), 7.28-7.32 (m, 3H, $H_{arom.}$), 7.51-7.55 (m, 2H, $C_6H_4NO_2$), 8.20-8.24 (m, 2H, $C_6H_4NO_2$); ^{13}C nmr ($CDCl_3$): δ = 33.77 (CH_2), 55.11 (NCH_2), 59.96 (CH), 71.06 (CH), 76.93 (NCH_2O), 122.27 ($C_{isoindol.}$), 123.21 ($C_{isoindol.}$), 123.78 (2 C, $C_6H_4NO_2$), 127.03 (2 C, $C_6H_4NO_2$), 127.44 ($C_{isoindol.}$), 127.73 ($C_{isoindol.}$), 140.10 (C_q), 142.61 (C_q), 147.22 (C_q), 149.51 (C_q); ms (CI, CH_5^+): 297 $[M+H]^+$ (100), 281 (5), 267 (1), 146 (14), 132 (11), 131 (7). hrms (EI^+): Calcd. ($C_{17}H_{16}N_2O_3$): 296.1161, found: 296.1158.

(3*S*,4a*S*)-3-(4-Chlorphenyl)-3,4,4a,9-tetrahydrooxazino-[4,3-*a*]isoindole (8c). 155 mg (0.54 mmol) of **6c** were reacted with BMS according to GP8. CC (*n*-heptane/EtOAc = 60:40) yielded 76 mg (50%) of **8c** as yellowish solid, mp 87 °C; tlc: R_f = 0.13 (*n*-heptane/EtOAc = 60:40); $[\alpha]_D^{20}$ = +106.9 (c = 0.275 in CH_3OH); ir: 3053, 2926, 2892, 1654, 1491, 1478, 1458, 1399, 1345, 1334, 1304, 1246, 1229, 1211 cm^{-1}; ^1H nmr ($CDCl_3$): δ = 2.13 (ddd, J = 14.5/5.5/4 Hz, 1H, CH_2), 2.38 (ddd, J = 14.5/8/6 Hz, 1H, CH_2), 4.27 (d, J = 13.5 Hz, 1H, NCH_2), 4.42 (d, J = 10.5 Hz, 1H, NCH_2O), 4.49 (dd, J = 13.5/2 Hz, 1H, NCH_2), 4.71 (dd, J ~8/4 Hz, 1H, CH), 4.73 (br td, J ~5/2 Hz, 1H, CH), 4.84 (d, J = 10.5 Hz, 1H, NCH_2O), 7.22-7.37 (m, 8H, $H_{arom.}$); ^{13}C nmr ($CDCl_3$): δ = 33.08 (CH_2), 54.75 (NCH_2), 59.69 (CH), 71.19 (CH), 76.51 (NCH_2O), 122.13 ($C_{isoindol.}$), 123.16 ($C_{isoindol.}$), 127.22 ($C_{isoindol.}$), 127.46 ($C_{isoindol.}$), 127.82 (2 C, C_6H_4Cl), 128.64 (2 C, C_6H_4Cl), 133.10 (C_q), 140.08 (C_q), 140.17 (C_q), 143.15 (C_q); ms (CI, CH_5^+): 286 $[M+H]^+$ (100), 268 (1), 250 (3), 174 (12), 155 (8), 146 (15), 132 (49), 118 (10); hrms (EI^+): Calcd. ($C_{17}H_{16}NOCl$): 285.0920, Found: 285.0914.

(1*R*)-2-[(1*S*)-2-Methyl-2,3-dihydro-1*H*-isoindol-1-yl]-1-(4-methylphenyl)ethanol hydrochloride (9a). 74 mg (0.28 mmol) of **7a** were reacted with $Na[CNBH_3]$ according to GP9. After centrifugation 28 mg (46%) of **9a** were obtained as white solid, mp 187 °C (decomposition); $[\alpha]_D^{20}$ = +48.2 (c = 0.145 in CH_3OH); ir: 3330, 2923, 2587, 2539, 1513, 1466, 1410, 1203, 1087 cm^{-1}. ^1H nmr (CD_3OD): δ = 2.14-2.23 (m, 2H, CH_2), 2.31 (s, 3H, CH_3), 3.07 (s, 3H, NCH_3), 4.47 (d, J = 15 Hz, 1H, NCH_2), 4.97-5.08 (m, 1H, OCH; 1H, NCH and 1H, NCH_2), 7.16 (d, J = 8 Hz, 2H, $C_6H_4CH_3$), 7.31 (d, J = 8 Hz, 2H, $C_6H_4CH_3$), 7.41-7.48 (m, 4H, $H_{isoindol.}$); ^{13}C nmr ($CDCl_3$): δ = 21.09 (CH_3), 42.03 (CH_2), 43.87 (NCH_3), 60.33 (NCH_2), 73.68 (CH), 75.56 (CH), 123.07 ($C_{isoindol.}$) , 123.20 ($C_{isoindol.}$), 125.93 (2 C, $C_6H_4CH_3$), 129.32 (2 C, $C_6H_4CH_3$), 129.67 (2 C, $C_{isoindol.}$), 131.80 (C_q), 137.15 (C_q), 137.57 (C_q), 140.08 (C_q); ms (CI, CH_5^+): 268 $[M-Cl]^+$ (60), 146 (3), 132 (100); hrms (FAB^+): Calcd. ($C_{18}H_{22}NO$): 268.1701, found: 268.1746. *Anal*. Calcd. for $C_{18}H_{22}ClNO$ (303.83): C, 71.16; H, 7.30; N, 4.61. Found: C, 70.53; H, 7.08; N, 4.50.

(1*R*)-2-[(1*S*)-2-Methyl-2,3-dihydro-1*H*-isoindol-1-yl]-1-(4-nitrophenyl)ethanol hydrochloride (9b). 37 mg (0.13 mmol) of **7b** were reacted with $Na[CNBH_3]$ according to GP9. After centrifugation 29 mg (70%) of **9b** were obtained as yellowish solid, mp 95 °C (decomposition); $[\alpha]_D^{20}$ = +45.80 (c = 0.120 in CH_3OH); ir: 3284, 2942, 2670, 2593, 2528, 1600, 1518, 1463, 1420, 1348 cm^{-1}; ^1H nmr (C_2D_6OS, 130 °C): δ = 2.26-2.37 (m, 1H, CH_2), 2.41-2.54 (m, 1H, CH_2), 2.98 (s, 3H, NCH_3), 4.45 (d, J = 14.5 Hz, 1H, NCH_2), 4.77-4.89 (m, 1H, NCH_2), 4.90-4.97 (m, 1H, CH), 5.08-5.17 (m, 1H, CH), 7.38-7.43 (m, 3H, $H_{isoindol..}$), 7.50-7.56 (m, 1H, $H_{isoindol.}$), 7.73 (d, J = 6.5 Hz, 2H, $C_6H_4NO_2$), 8.19 (d, J = 7.5 Hz, 2H, $C_6H_4NO_2$); ^{13}C nmr ($CDCl_3$): δ = 41.55 (CH_2), 44.18 (NCH_3), 60.40 (NCH_2), 72.93 (CH), 75.55 (CH), 123.07 ($C_{isoindol.}$), 123.38 ($C_{isoindol.}$), 123.85 (2 C, $C_6H_4NO_2$), 126.96 (2 C, $C_6H_4NO_2$), 129.82 ($C_{isoindol.}$), 130.00 ($C_{isoindol.}$), 131.65 (C_q), 136.52 (C_q), 147.47 (C_q), 150.43 (C_q); ^{13}C nmr (free base, $CDCl_3$): δ = 40.65 (CH_2), 44.14 (NCH_3), 59.42 (NCH_2), 72.93 (CH), 73.52 (CH), 122.70 ($C_{isoindol.}$), 122.99 ($C_{isoindol.}$), 123.33 (2 C, $C_6H_4NO_2$), 126.27 (2 C, $C_6H_4NO_2$), 127.27 ($C_{isoindol.}$), 127.55 ($C_{isoindol.}$), 138.35 (C_q), 141.57 (C_q), 146.76 (C_q), 152.85 (C_q); ms (CI, CH_5^+): 299 $[M-Cl]^+$ (41), 283 (3), 269 (1), 251 (8), 150 (13), 146 (9), 136 (7), 132 (100), 120 (38); hrms (FAB^+): Calcd. ($C_{17}H_{19}N_2O_3$): 299.1396, found: 298.1389.

(1*R*)-2-[(1*S*)-2-Methyl-2,3-dihydro-1*H*-isoindol-1-yl]-1-(4-chlorophenyl)ethanol hydrochloride (9c). 65 mg (0.23 mmol) of **7c** were reacted with $Na[CNBH_3]$ according to GP9. After centrifugation 40 mg (54%) of **9c** were obtained as white solid, mp 162-167 °C (decomposition); $[\alpha]_D^{20}$ = -41.6 (c = 0.185 in CH_3OH); ir: 3304, 2925, 2604, 2580, 2538, 1490, 1466, 1408, 1364, 1202, 1089 cm^{-1}; ^1H nmr (CD_3OD): δ = 2.12-2.23 (m, 2H, CH_2), 3.09 (s, 3H, NCH_3), 4.46 (d, J = 15 Hz, 1H, NCH_2), 5.00-5.13 (m, 1H, OCH, 1H, NCH and 1H, NCH_2), 7.34 (d, J = 8.5 Hz, 2H, $H_{arom.}$), 7.40-7.48 (m, 6H, $H_{arom.}$); ^{13}C nmr ($CDCl_3$): δ = 41.77 (CH_2), 43.91 (NCH_3), 60.25 (NCH_2), 72.72 (CH), 75.28 (CH), 123.16 ($C_{isoindol.}$), 123.31 ($C_{isoindol.}$), 127.47 (2 C, C_6H_4Cl), 128.69 (2 C, C_6H_4Cl), 129.65 ($C_{isoindol.}$), 129.75 ($C_{isoindol.}$), 131.69 (C_q), 133.46 (C_q), 136.85 (C_q), 141.80 (C_q); ms (CI, CH_5^+): 288 $[M+H]^+$ (40), 176 (2), 146 (3), 132 (100), 117 (2). hrms (EI^+): Calcd. ($C_{17}H_{19}NOCl$, free base): 288.1155, found: 288.1115.

(1*S*)-2-[(1*S*)-2-Methyl-2,3-dihydro-1*H*-isoindol-1-yl]-1-(4-methylphenyl)ethanol (10a). 60 mg (0.23 mmol) of **8a** were reacted with $Na[CNBH_3]$ according to GP9. This yielded 36 mg (52%) of **10a** as white solid, mp 128-131 °C; $[\alpha]_D^{20}$ = +43.85 (c = 0.135 in CH_3OH); ir: 3108, 3021, 2971, 2941, 2911, 1657, 1513, 1477, 1464, 1354, 1301, 1354, 1285, 1256 cm^{-1}; ^1H nmr ($CDCl_3$): δ = 2.15 (dt, J = 15/2 Hz, 1H, CH_2), 2.24 (ddd, J = 15/10.5/4 Hz, 1H, CH_2), 2.33 (s, 3H, CH_3), 2.65 (s, 3H, NCH_3), 3.69 (dd, J = 13/3 Hz, 1H, NCH_2), 4.10 (br s, 1H, NCH), 4.33 (dd, J = 13/1.5 Hz, 1H, NCH_2), 4.70 (dd, J = 10.5/2 Hz, 1H, OCH), 7.14 (d, J = 7.5 Hz, 2H, $C_6H_4CH_3$), 7.17 (d, J = 7.5 Hz, 2H, $C_6H_4CH_3$), 7.23-7.34 (m, 4H, $H_{arom.}$); ^{13}C nmr ($CDCl_3$): δ = 21.38 (CH_3), 37.94 (CH_2), 40.74 (NCH_3), 60.49 (NCH_2), 70.54 (CH), 71.36 (CH), 122.35 ($C_{isoindol.}$), 122.83 ($C_{isoindol.}$), 125.85 (2 C, $C_6H_4CH_3$), 127.50 ($C_{isoindol.}$), 127.77 ($C_{isoindol.}$), 129.18 (2 C, $C_6H_4CH_3$), 136.74 (C_q), 139.97 (C_q), 141.11 (C_q), 142.40 (C_q); ms (CI, CH_5^+): 268 $[M+H]^+$ (50), 176 (4), 146 (9), 132 (100), 121 (6), 105 (1); hrms (EI^+): Calcd. ($C_{18}H_{21}NO$): 267.1623, found 267.1624.

(1*S*)-2-[(1*S*)-2-Methyl-2,3-dihydro-1*H*-isoindol-1-yl]-1-(4-nitrophenyl)ethanol (10b). 55 mg (0.19 mmol) of **8b** were reacted with $Na[CNBH_3]$ according to GP9. This yielded 36 mg (63%) of **10b** as white solid, mp 163 °C; $[\alpha]_D^{20}$ = +91.6 (c = 0.215 in CH_3OH); ir: 3443, 2923, 2859, 2796, 1600, 1516, 1461, 1346, 1304, 1260 cm^{-1}; ^1H nmr ($CDCl_3$): δ = 2.15-2.22 (m, 2H, CH_2), 2.68 (s, 3H, NCH_3), 3.74 (dd, J = 13.5/2.5 Hz, 1H, NCH_2), 4.17 (br s, 1H, OCH), 4.43 (d, J = 13.5 Hz, 1H, NCH_2), 4.83 (t, J = 6.5 Hz, 1H, NCH), 7.21 (d, J = 7 Hz, 1H, $H_{arom.}$), 7.27-7.37 (m, 3H, $H_{arom.}$), 7.54 (d, J = 8.5 Hz, 2H, $C_6H_4NO_2$), 8.19 (d, J = 8.5 Hz, 2H, $C_6H_4NO_2$); ^{13}C nmr ($CDCl_3$): δ = 37.47 (CH_2), 40.38 (NCH_3), 60.12 (NCH_2), 70.17 (CH), 70.68 (CH), 121.88 ($C_{isoindol.}$), 122.76 ($C_{isoindol.}$), 123.58 (2 C, $C_6H_4NO_2$), 126.32 (2 C, $C_6H_4NO_2$), 127.46 ($C_{isoindol.}$), 127.83 ($C_{isoindol.}$), 139.59 (C_q), 140.13 (C_q), 146.95 (C_q), 152.62 (C_q); ms (CI, CH_5^+): 299 $[M+H]^+$ (29), 288 (4), 280 (3), 268 (6), 251 (7), 150 (10), 146 (8), 132 (100), 120 (32); hrms (EI^+): Calcd. ($C_{17}H_{18}N_2O_3$): 298.1317, found: 298.1317.

(1*S*)-2-[(1*S*)-2-Methyl-2,3-dihydro-1*H*-isoindol-1-yl]-1-(4-chlorophenyl)ethanol (10c). 78 mg (0.27 mmol) of **8c** were reacted with $Na[CNBH_3]$ according to GP9. This yielded 45 mg (57%) of **10c** as white solid, mp 123 °C; $[\alpha]_D^{20}$ = +55.3 (c = 0.17 in CH_3OH); ir: 3108, 3026, 2924, 2944, 2912, 1487, 1462, 1402, 1351, 1294, 1261 cm^{-1}; ^1H nmr ($CDCl_3$): δ = 2.13 (dt, J = 15/2.5 Hz, 1H, CH_2), 2.20 (ddd, J = 15/10/3.5 Hz, 1H, CH_2), 2.66 (s, 3H, NCH_3), 3.71 (dd, J = 13/1.5 Hz, 1H, NCH_2), 4.13 (br s, 1H, CH), 4.41 (d, J = 13 Hz, 1H, NCH_2), 4.70 (dd, J = 10/2.5 Hz, 1H, CH), 7.17 (d, J = 7 Hz, 1H, $H_{arom.}$), 7.25-7.35 (m, 7H, $H_{arom.}$); ^{13}C nmr ($CDCl_3$): δ = 37.62 (CH_2), 40.43 (NCH_3), 60.14 (NCH_2), 70.17 (CH), 70.65 (CH), 121.97 ($C_{isoindol.}$), 122.63 ($C_{isoindol.}$), 127.00 (2 C, C_6H_4Cl), 127.32 ($C_{isoindol.}$), 127.63 ($C_{isoindol.}$), 128.33 (2 C, C_6H_4Cl), 132.46 (C_q), 139.56 (C_q), 140.47 (C_q), 143.56 (C_q); ms (EI, 70 eV): 288 $[M+H]^+$ (49), 270 (1), 176 (2), 160 (1), 146 (2), 132 (100), 117 (2). hrms (EI^+): Calcd. ($C_{17}H_{18}NOCl$): 287.1077, found: 287.1078.

(3*R*,4a*S*)-3-(4-Methylphenyl)-3,4,4a,9-tetrahydrooxazino-[4,3-*a*]isoindol-1-one (22). 50 mg (0.19 mmol) of **5a** were dissolved in 7 ml THF. The solution was cooled in an ice bath and treated with 0.5 ml BMS (2 *M* in THF). The mixture was allowed to warm to room temperature before it was refluxed for 6 hours. Then 1 ml of CH_3OH was added (ice bath). When the gas formation had ceased, the solvent was removed *in vacuo*. To remove decomposition products of BMS the residue was repeatedly dissolved in 5 ml of CH_3OH and the solvent was removed *in vacuo*. Next, the residue was dissolved in 3.6 ml of THF and 5 equivalents of carbonyldiimidazole (CDI) were added. The resulting mixture was stirred for 16 hours. After addition of 2 ml of phosphate buffer (pH7) the mixture was extracted with Et_2O (4x3 ml). The combined extracts were dried over $MgSO_4$ and then concentrated *in vacuo*. Purification by CC (Et_2O) yielded 27 mg (51%) of **22** white solid, mp 158-168 °C; tlc: R_f = 0.4 (Et_2O); $[\alpha]_D^{20}$ = +13.14 (c = 0.175 in CH_3OH); ir: 2922, 1700, 1465, 1412, 1339, 1306, 1284, 1108, 1080, 1050 cm^{-1}; ^1H nmr ($CDCl_3$,): δ = 1.93 (dt, J = 13.5/11.5 Hz, 1H, CH_2), 2.36 (s, 3H, CH_3), 2.72 (ddd, J = 13.5/3.5/2.5 Hz, 1H, CH_2), 4.70 (dd, J = 15/1.5 Hz, 1H, NCH_2), 5.10 (br d, J = 11.5 Hz, 1H, NCH), 5.16 (dd, J = 15/2 Hz, 1H, NCH_2), 5.48 (dd, J = 11.5/2.5 Hz, 1H, OCH), 7.17-7.22 (m, 3H, $H_{arom.}$), 7.28-7.36 (m, 5H, $H_{arom.}$); ^{13}C nmr ($CDCl_3$): δ = 21.19 (CH_3), 35.60 (CH_2), 52.98 (NCH_2), 60.63 (CH), 79.15 (CH), 121.64 ($C_{isoindol.}$), 122.92 ($C_{isoindol.}$), 125.89 (2 C, $C_6H_4CH_3$), 127.79 ($C_{isoindol.}$), 128.44 ($C_{isoindol.}$), 129.31 (2 C, $C_6H_4CH_3$), 135.96 (C_q), 136.73 (C_q), 138.42 (C_q), 139.26 (C_q), 152.66 (C=O); ms (CI, CH_5^+): 280 $[M+H]^+$ (6), 162 (100), 118 (16); hrms (FAB^+): Calcd. ($C_{18}H_{18}NO_2$, $[M+H]^+$): 280.1338, found: 280.1329.

X-ray Diffraction of 4a.

Data collection: MACH3 Diffractometer, crystal mounted in a glass capillary, cell constants from 25 centered reflections. MoK_α-radiation, λ = 0.71073 Å, graphite monochromator, ω-scan, maximum measuring time 60 s, intensity of three standard reflections checked every 7200 s. Structure solution by SHELXS-86 [9] and refinement by SHELXL-97 [10], non-hydrogen atoms refined anisotropically, hydrogens with $U_i = 1.2\ U_{eq}$ of the adjacent non-hydrogen atom. Full matrix refinement against F^2. Weight SHELXL-97. Maximum and minimum of the final Fourier synthesis 0.128 and –0.145 $eÅ^{-3}$. The drawing was made by ZORTEP [11]. The complete data are available from Cambridge Crystallographic Data Center (deposit@ccdc.cam.ac.uk). The deposition number is CCDC-277321.

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