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A Chemical Method for the Preparation of Novel 1,5-Benzodiazepines Acting as CCK-B Antagonists in High Enantiomeric Purity.

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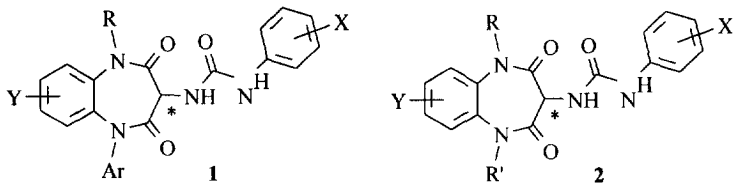
Abstract: A series of new N-(1,5-benzodiazepin-3-yl)-N'-arylureas, **2**, bearing an alkyl substituent at the N5 position of the benzodiazepine nucleus has been studied as potential CCK-B antagonists. The homochiral compounds were obtained by resolving their precursors (amines **4**) with a new resolution method based on the reaction between the amines and the chiral auxiliary **5**, the subsequent separation of the diastereomers (**6** and **7**) and the eventual removal of the auxiliary moiety by hydrogenation. The resolved amines and the corresponding final ureas showed good enantiomeric excesses.

INTRODUCTION

Following the discovery of the involvement of cholecystokinin (CCK) in CNS disorders,[1] an extensive programme aimed at the identification of a number of CCK-B antagonists was undertaken in our laboratories. The synthetic efforts in this area led to the preparation and evaluation of many N-(1,5-benzodiazepin-3-yl)-N'-arylureas[2,3] with the general formula **1** shown in **Fig. 1**:

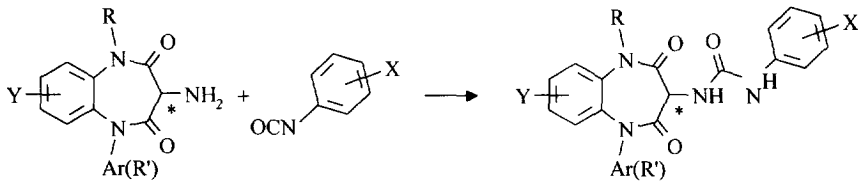


R'=alkyl, substituted alkyl

Fig. 1

Subsequently, in an attempt to synthesize compounds endowed with improved physico-chemical properties (such as solubility), our efforts were directed towards the synthesis of modified N-(1,5-benzodiazepin-3-yl)-N'-arylureas,[4,5] bearing an alkyl substituent at the 5 position of the benzodiazepine nucleus in place of the arylic one (structures of type **2**, **Fig. 1**).

The consideration that the two enantiomers, caused by the stereogenic center at C3, could exhibit different pharmacological activities prompted us to search for a general and versatile method by which we could obtain the pure optical isomers. The aforementioned compounds were obtained through different synthetic methods[2-5] involving the synthesis of key amino intermediates of type **3** (or **4**) which were eventually transformed into the target ureidic compounds **1** (or **2**), as depicted in **Scheme 1**:



Scheme 1

Initially, most of the racemates were resolved by preparative chiral HPLC carried out on the final ureas **1** or **2**. However such a method is feasible only on a small scale, while the most interesting compounds were required in larger quantities for *in vivo* experiments. Based on the consideration that the reaction depicted in **Scheme 1**, is unlikely to cause racemization at C3, we directed our efforts towards the establishment of a method for the resolution of the free amine precursors of the ureas (*i.e.* compounds **3** or **4**). Compounds of type **3** were generally resolved by formation of diastereomeric salts with homochiral camphorsulfonic acid, and subsequent preferential crystallization of the diastereomers.[2,3b-d] Unfortunately this methodology gave relatively poor results when applied to amines of type **4**.

The general principle of resolving racemic amines by formation of covalent diastereomeric derivatives by means of homochiral amine-reactive resolving agents prompted us to explore a wide range of such reagents such as: (i) chiral chloroformates or carbonates,[6] (ii) chiral ketones, (iii) carbohydrate derivatives,[7] or (iv) amino acids.[8] Only the latter gave acceptable results when applied to our substrates.[2d,5d,9] However, this method involves a large number of chemical steps which affects the final chemical yields and therefore a more general and effective procedure was sought. For this purpose, we needed to set up a method characterized by a high flexibility and a low number of chemical steps.

We previously reported that the use of the 4-toluenesulfonyl derivative of (*S*)-(+)-methyl mandelate, **5**, (**Fig. 2**) as homochiral amine-reactive auxiliary, is suitable for separating amines of type **3**.[2d,5d,10]

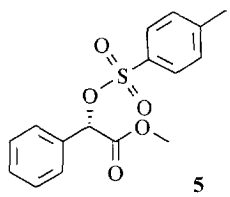
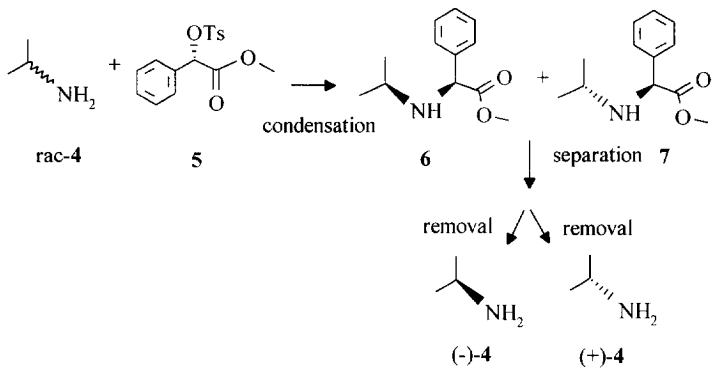


Fig. 2

In this paper we wish to describe our studies towards the definition of such a method and the results obtained when it was applied on compounds representative of type **4**.

CHEMISTRY

The reaction between the racemic amines **4** and tosylate **5** leads to two diastereomers (formally two phenylglycine derivatives, **6** and **7**) which can be separated by flash chromatography. Removal of the chiral auxiliary affords the corresponding homochiral amines (**Scheme 2**).

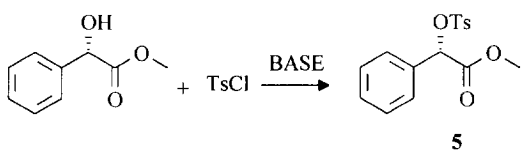


Scheme 2

In setting up this resolution method, particular attention had to be paid to 1) the synthesis of the chiral auxiliary, 2) finding suitable condensation conditions with the racemic amines and 3) finding suitable conditions for the removal of the chiral auxiliary.

Synthesis of the chiral auxiliary

The chiral auxiliary **5**, can be easily prepared by reacting the (*S*)-(+)-methyl mandelate, which is commercially available in a 99.6% e.e., and tosyl chloride in the presence of a base (**Scheme 3**):



Scheme 3

Although this reaction does not involve the stereocenter, the relatively high acidity of the proton at C2 may cause a diminished optical purity of the chiral auxiliary.[11] To the best of our knowledge, the only preparation of homochiral compound **5** reported to date involves silver oxide as the base.[12] In our hands this method (see entry 1 of **Table 1**) resulted in a poor yielding and very sluggish reaction. In order to find a more convenient method, several conditions for the synthesis of compound **5** were examined. The results are reported in **Table 1**:

Table 1. Conditions for the Synthesis of **5**

#	Conditions	Yield	e.e. of **5**(*)
1	Ag_2O, butyl ether, 100 °C, 16 hrs.	20%	99.2%
2	TEA, CH_2Cl_2 , 0 °C 40' then r.t. 20'	96%	82.8%
3	Py, CH_2Cl_2 , 0 °C 15' then r.t. 4 hrs.	38%	99.6%
4	Py (neat), 0 °C, 10' then r.t. 30'	46%	98.4%
5	DIPEA, CH_2Cl_2 , 0 °C 10' then r.t. 48 hrs.	29%	96.0%
6	DIPEA, CH_2Cl_2 , 40 °C 4 hrs.	17%	95.4%
7	Py, DMAP (0.3 eq.), r.t., 2 hrs.	27%	99.2%
8	TEA, CH_2Cl_2 , 0 °C, 1 hrs.	28%	98.6%
9	TEA, CH_2Cl_2 , 0 °C, 5 hrs.	74%	98.0%

(*) e.e. of the starting material: 99.6%

A first synthesis using triethylamine (TEA) at room temperature (entry 2) gave the tosylate in excellent chemical yield but with an appreciable decrease in the enantiomeric excess (82.8%). Many other bases and conditions (entries 3-8) gave unsatisfactory results in terms either of chemical or optical yields. The best results were those obtained using TEA as the base at 0 °C for 5 hours (entry 9) where good chemical yield was accompanied by an excellent optical purity.

Condensation

The stereochemistry at C2 can, in principle, be affected also during the condensation reaction (see **Scheme 2**). In order to obtain the best efficiency of the resolution, the stereocenter of the chiral auxiliary should not undergo racemization either 1) *before* (i.e. as not yet reacted tosylate) or 2) *during* (i.e. the reaction mechanism must be unambiguously S_N2) or 3) *after* (i.e. as phenylglycine derivative) the condensation with the amine.

Since a base is needed to quench the 4-toluenesulfonic acid formed in this reaction, the tosylate **5** can, theoretically, undergo racemization before reacting with the amine due to the presence of this base in the reaction medium. This would obviously result in a decreased efficiency of the method. To test the stereochemical stability of the chiral auxiliary under condensation conditions, we carried out a set of model reactions where the tosylate **5** was submitted to conditions suitable for an N-alkylation type reaction. After each experiment the degree of racemization of the tosylate was determined by HPLC analysis. The results are summarized in **Table 2** reported below.

As can be seen from the table, pyridine seemed to be a good base (entry 1) when the reaction time was limited to 8 hours. However, when the reaction was allowed to proceed for longer time, a lower optical purity of **5** was found (entry 2). With 2,6-lutidine, even after 19 hours, no significant racemization was observed (entry 3) as well as with diisopropylethyl amine (DIPEA) even on prolonged heating (entry 4). A certain degree of racemization was obtained by using N-methylmorpholine (entry 5) while potassium carbonate in a biphasic system did not cause substantial racemization of the tosylate either in tetrahydrofuran (entry 6) or in

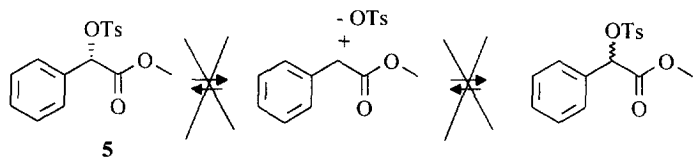
acetone (entry 7). The use of dimethylformamide (as a more polar solvent it could increase the rate of the nucleophilic displacement) caused decomposition of the tosylate (entry 8).

Table 2. Racemization Trials - Model Reactions

#	Base	Solvent	Conditions	Final e.e. of **5**(*)
1	Py	THF	70 °C, 8 hrs.	80.8%
2	Py	THF	70 °C, 19 hrs then r.t., 72 hrs.	66%
3	2,6-Lutidine	THF	70 °C, 19 hrs.	84%
4	DIPEA	THF	70 °C, 19 hrs.	80%
5	N-Me-Morpholine	THF	70 °C, 8 hrs.	56%
6	K_2CO_3	THF	70 °C, 8 hrs.	82%
7	K_2CO_3	Acetone	60 °C, 4 hrs.	82.6%
8	K_2CO_3	DMF	80 °C, 8 hrs.	dec.

(*) The initial e.e. of **5** was in each case 82.8 %

As for the mechanism of the nucleophilic displacement, a racemization trial carried out by heating the tosylate **5** in THF without any base, showed that no substantial racemization occurred in these conditions (initial e.e. of **5**=82.8% final, e.e.=80.8%). This demonstrates that the tosylate **5** is not prone to racemize by means of an elimination of the tosyl group and a reattack on the other side (**Scheme 4**).



Scheme 4

The presence of the carboxyl group vicinal to the stereogenic centre renders very unfavoured a unimolecular (S_N1) mechanism for the nucleophilic displacement for such a substrate.

Finally, as the calculated pKa (CAMEO) of the stereocenter of the phenylglycine moiety is three orders of magnitude higher than that of the tosylate **5** (22 *vs.* 19), we can be sufficiently confident that racemization of the auxiliary-stereogenic center does not occur after the condensation is accomplished, provided this is carried out in suitable conditions for the tosylate **5**.

Removal of the chiral auxiliary

The use of **5** as the chiral auxiliary also has the advantage of its easy removal from the diastereomeric products under hydrogenolytic conditions[13] which are unlikely to cause racemization of 3-amino-1,5-benzodiazepines.

The racemic amines

The precursors of the ureas of class **2** on which we focused our attention are amines **4a-c** (**Fig. 3**):

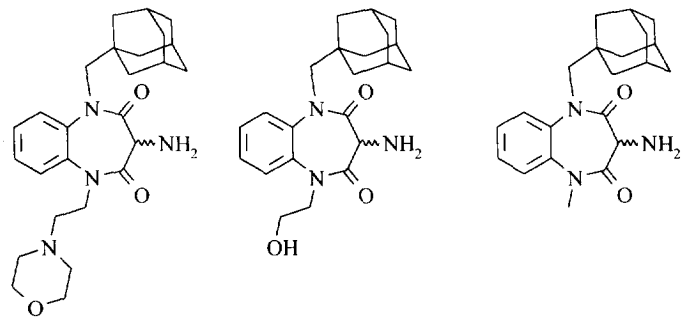


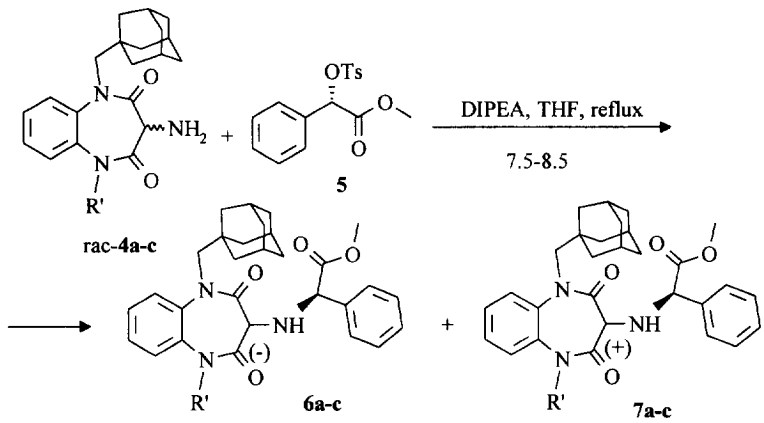
Fig. 3

While the amine **4c** carries a *non*-functionalized alkyl at N5, in the other examples the N5-alkyl chain bears either basic (**4a**) or hydroxyl (**4b**) groups. The syntheses of these compounds has been described elsewhere.[4a-b,5b-f] The 1-adamantanemethyl group had been previously shown to be important for biological potency and selectivity in the N5-aryl series (class **1**).[4,5]

DISCUSSION AND RESULTS

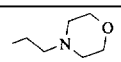
In order to define the best conditions for the nucleophilic substitution, some of these reactions were carried out in the conditions which appeared to be promising from the racemization trials (see **Table 2**). In order to get satisfactory conversions into phenylglycine derivatives, it was often necessary to increase the reaction times with respect to those used in the racemization trials. But, as previously shown (entry 2 of **Table 2**), the longer the reaction time, the greater the racemization of **5**, thus decreasing the effectiveness of the procedure. Therefore the enantiomeric excesses of the diastereomers obtained by using bases such as pyridine or potassium carbonate in refluxing THF or acetone for 14-19 hours, were considerably lower than predicted on the basis of the model reactions. On the other hand, the use of DIPEA represented the best compromise considering both the chemical yield and the degree of racemization of **5**.

The results of the application of these "best conditions" (DIPEA, refluxing THF, 8 hours) to the reactions between amines **4a-c** and the tosylate **5**, are summarized in **Table 3** (see **Scheme 5**).



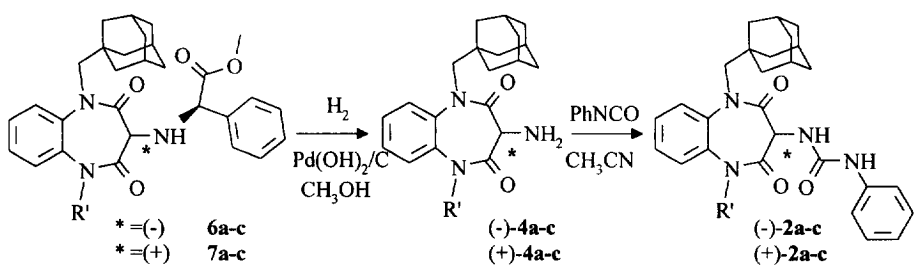
Scheme 5

Table 3. Data Related to **Scheme 5**

	R'	Yield	e.e. of starting **5**(*)	e.e. of recov. **5**(*)	d.e. of **6** after separation (*)	d.e. of **7** after separation (*)
a		66%	98%	91.2%	100%	90.6%
b		58%	98.6%	93.6%	100%	100%
c	CH_3	85%	99.6%	91.8%	100%(#)	97.8%

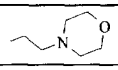
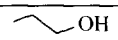
(*) by HPLC analysis if not differently specified, (#) by NMR analysis

Once separated, the diastereomers were hydrogenated to easily afford the homochiral amines, (+)-**4a-c** and (-)-**4a-c**. These were then reacted with phenylisocyanate to achieve the desired final ureas (+)-**2a-c** and (-)-**2a-c** (**Scheme 6** and **Table 4**):



Scheme 6

Table 4. Data Related to **Scheme 6**

	R'	e.e. of (-)-**2**(*)	e.e. of (+)-**2**(*)
a		94.0%	86.0%
b		93.2%	94.8%
c	CH_3	92%	96.6%

(*) by HPLC analysis

The results obtained give rise to two principal considerations: I) looking at compounds **4a** the question of a possible racemization of tosylate **5** could arise if the basicity of the morpholine group was too high. The question is relevant since a considerable degree of racemization of tosylate **5** was found in the racemization trial with the N-methylmorpholine as the base (entry 5 of **Table 2**). However, in this case, there is an appreciable difference between the results obtained in the model reaction and in the actual substitution. The experimental data (see **Tables 3** and **4**) for compounds (-)-**2a** and (+)-**2a** gave enantiomeric excesses which are consistent with a relatively low racemization degree of the chiral auxiliary during the substitution. II) Assuming that the enantiomeric excesses of two related diastereomers are the same (this is true if the tosylate **5** reacts with the two enantiomers of the amines with similar rates), the higher is the diastereomeric excess the higher should be the enantiomeric excess of the urea derived from that diastereomer. Thus the apparent incongruity between data of **Table 3** and data of **Table 4** (entry **c** and, in a minor extent, entry **b**) has to be ascribed to the experimental errors connected with the determination of the relative percentages of the isomers.

CONCLUSIONS

In conclusion, a chemical method was established to prepare *N*-(1,5-benzodiazepin-3-yl)-*N'*-arylureas, **2**, in an enantiomerically pure or enriched form to be tested as potential CCK-B antagonists. The method is based upon the reaction of the racemic amines, **4**, precursors of the desired compounds (**2**), with the tosylate **5**, as chiral auxiliary. The subsequent separation of the two diastereomers formed and hydrogenation of the separated compounds gave the free homochiral amines. The latter were then allowed to react with the appropriate arylisocyanates to afford the desired homochiral ureas, **2**.

The method was successfully applied to various kinds of substrates, thus showing its wide applicability. The number of chemical steps required to prepare chiral ureas from the racemic amines is considerably reduced by adopting this method with respect to those previously studied, and the overall chemical yields were enhanced. The separation of the diastereomers was carried out by using chromatographic methods, but in view of larger preparations a preferential crystallization method appears to be preferable and feasible. The

enantiomeric excesses of the final ureas were in all cases high enough to allow for the *in vitro* evaluation of the most interesting compounds. The biological results will be published in due course.

Furthermore, as compound **5** and its enantiomer are available at the same cost, it is possible to apply the same method changing the absolute configuration of the chiral auxiliary, if this may represent an advantage in the purification of the preferred diastereomer.

ACKNOWLEDGEMENTS

The authors wish to acknowledge Dr. P. Cassara', Dr. G. Kennedy, Dr. B. Oliosi and Dr. F. van Amsterdam as well as all the personnel of the Spectroscopy Laboratory, of the Chemical Analysis Laboratory and of the Mass Spectrometry Laboratory.

EXPERIMENTAL SECTION

General

Melting points are uncorrected and were determined on a Buchi melting point apparatus. Infrared spectra were recorded in Nujol on a IFS48 Bruker, ^{1}H-NMR spectra were recorded in $CDCl_3$ on a Varian VXR300S 300 MHz or a Varian Unity 400 MHz spectrometers. Chemical shifts are reported on the δ scale using residual $CHCl_3$ as internal reference (δ=7.26 ppm). ^{13}C-NMR spectra were recorded in Acetone-d_6 on a Varian VXR300S 75.4 MHz spectrometer. Chemical shifts are reported on the δ scale using residual acetone signals (δ=29.80 ppm) as internal. Low resolution mass spectra (LRMS) were performed on a triple quadrupole instrument (Micromass VG Quattro), while high resolution mass spectra (HRMS) were obtained on a trisector instrument (Micromass VG Autospec). Both LRMS and HRMS were obtained using positive FAB ionization, therefore the values refer to the protonated molecules. Optical rotations were measured at 20 °C in $CHCl_3$ on a Jasco DIP-360 polarimeter. Flash column chromatography was carried out on Merck Art. 9385, Silica gel 60 (230-400 mesh ASTM). Thin layer chromatography (TLC) was carried out on Merck Art. 715, Silica gel 60 F_{254} plates. Solvents were dried by standard methods. All experiments were performed under anhydrous conditions in a nitrogen atmosphere unless otherwise specified. All the compounds obtained resulted to be pure by ^{1}H-NMR and HPLC analysis.

(S)-(+)-2-(4-toluenesulfonyloxy)-phenylacetic acid methyl ester, **5**

(*S*)-(+)-Methyl mandelate (2.0 g, 12 mmol) and triethylamine (1.67 ml, 12 mmol) were dissolved in dry dichloromethane (50 ml). The mixture was cooled to 0 °C then a solution of 4-toluenesulfonyl chloride

(9.151 g, 48 mmol) in dry dichloromethane (100 ml) was slowly added dropwise under stirring mantaining the temperature between -5 and 5 °C. The solution was kept at this temperature for 7.5 hrs. After this time, the mixture was washed with 10% aqueous hydrochloric acid (100 ml) and brine (100 ml), dried and concentrated *in vacuo*. The crude material was purified by flash chromatography (eluting with cyclohexane/ethyl acetate 5:1 then 2:1) to give the title compound, **5**, as a white wax (2.302 g, 7.18 mmol, yield=60%). TLC: (cyclohexane/ethyl acetate 2:1) R_f=0.54, $[\alpha]_D$ =+61.7 (c=1.085), HPLC: (+)/(-)=99/1 e.e.=98%, M.p.: 57-58 °C, ^{1}H-NMR: 7.75 (d, 2H), 7.27-7.35 (m, 7H), 5.78 (s, 1H), 3.67 (s, 3H), 2.42 (s, 3H), IR: 1753, 1600 cm^{-1}. LRMS: 321 (MH+), 261. Anal. Calcd. for $C_{16}H_{16}O_5S$: C 59.98 H 5.04, Found: C 59.81 H 5.01

PREPARATION OF FINAL COMPOUNDS (-)-2a AND (+)-2a

[1-(Adamantane-1-methyl)-2,4-dioxo-5-[2-(4-morpholino)ethyl]-2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-3-yl]aminophenylacetic acid methyl ester, **6a** *and* **7a**

Diisopropylethylamine (0.348 ml, 2.0 mmol) was added to a solution of compound rac-**4a** (0.905 g, 2.0 mmol) and compound **5** (1.28 g, 4.0 mmol) in dry THF (30 ml). The mixture was refluxed for 8 hrs., then it was diluted with dichloromethane (100 ml) and washed with a saturated NH_4Cl solution (100ml) and brine (100 ml). The organic phase was dried and concentrated under reduced pressure. The obtained crude material (2.746 g) was purified by flash chromatography (eluting with ethyl acetate/cyclohexane 3:1 then 4:1 then 9:1 then ethyl acetate/methanol 4:1). The title compound, **6a**, (0.255 g, 0.42 mmol) was obtained as a white solid. The remaining material was further purified by flash chromatography (eluting with ethyl acetate/cyclohexane 4:1) to give the title compound, **7a**, as white foam (0.081 g, 0.13 mmol) and 0.270 g of the diastereomeric mixture (thus the overall alkylation yield was 66%).

Compound **6a**: TLC: (ethyl acetate/methanol 24:1) R_f=0.65, HPLC: d.e.=100%, $[\alpha]_D$=-93.5 (c=0.700), M.p.: 133-136 °C, ^{1}H-NMR: 7.64 (m, 1H), 7.33-7.18 (m, 8H), 4.57 (s, 1H), 4.39 (d, 1H), 4.10 (m, 1H), 3.88 (d, 1H), 3.73 (m, 4H), 3.76-3.66 (m, 1H), 3.62 (s, 3H), 3.40 (bd, 1H), 3.17 (d, 1H), 2.91-2.84 (m, 1H), 2.74-2.68 (m, 1H), 2.61-2.49 (m, 4H), 1.81 (bm, 3H), 1.57 (bd, 3H), 1.44 (bd, 3H), 1.24-1.16 (m, 6H); IR: 1742, 1700, 1666 cm^{-1}. LRMS: 601 (MH+, base peak). HRMS Calcd. for $C_{35}H_{45}N_4O_5$ 601.338996 Found 601.337880

Compound **7a**: TLC: (ethyl acetate/methanol 24:1) R_f=0.61, HPLC: d.e.=90.6%, $[\alpha]_D$=-20.5 (c=0.896), M.p.: 160-165 °C. ^{1}H-NMR: 7.70 (m, 1H), 7.40-7.20 (m, 8H), 4.62 (s, 1H), 4.39 (d, 1H), 4.13 (m, 1H), 3.98 (m, 1H), 3.80-3.60 (m, 5H), 3.61 (s, 3H), 3.20 (m, 1H), 3.16 (d, 1H), 2.94 (m, 1H), 2.75 (m, 1H), 2.59 (m, 4H), 1.81 (m, 3H), 1.52-1.15 (m, 12H). IR: 3300-3400, 1734, 1688, 1663, 1600 cm^{-1}. LRMS: 601 (MH+, base peak), 541, HRMS Calcd. for $C_{35}H_{45}N_4O_5$ 601.338996 Found 601.334970

1-(Adamantane-1-methyl)-3-amino-2,4-dioxo-5-[2-(4-morpholino)ethyl]-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine, (-)-**4a**

20 % Palladium (II) hydroxide on charcoal (0.218 g, 0.31 mmol) was added to a solution of compound **6a** (0.187 g, 0.31 mmol) in methanol (10 ml). The mixture was hydrogenated at atmospheric pressure for 5 hrs. Then the mixture was filtered on a celite pad and evaporated under reduced pressure. The crude material was purified by flash chromatography (eluting with ethyl acetate/cyclohexane 1:1 then ethyl acetate/methanol 3:2) to give the title compound, (-)-**4a**, as a white solid (0.140 g, 0.31 mmol). TLC: (ethyl acetate/cyclohexane 1:1) R_f=0.44, $[\alpha]_D$=-36.3 (c=0.7350), M.p.: 180-185 °C, Yield=100%. ^{1}H-NMR: 7.75 (m, 1H), 7.40-7.28 (m, 3H), 4.42 (d, 1H), 4.13 (m, 1H), 4.05 (bs, 1H), 3.82 (t, 1H), 3.76 (t, 4H), 3.22 (d, 1H), 2.93 (m, 1H), 2.74 (m, 1H), 2.70-2.54 (m, 5H), 1.84 (bm, 3H), 1.70-1.20 (m, 12H). IR: 3371, 3179, 1693, 1666, 1597 cm^{-1}. LRMS: 453 (MH+), HRMS Calcd. for $C_{26}H_{37}N_4O_3$ 453.286566 Found 453.286500

1-(Adamantane-1-methyl)-3-amino-2,4-dioxo-5-[2-(4-morpholino)ethyl]-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine, (+)-**4a**

20 % Palladium (II) hydroxide on charcoal (0.082 g, 0.12 mmol) was added to a solution of compound **7a** (0.070 g, 0.12 mmol) in methanol (10 ml). The mixture was hydrogenated at atmospheric pressure for 4.5 hrs. Then the mixture was filtered on a celite pad and evaporated under reduced pressure. The crude material was purified by flash chromatography (eluting with ethyl acetate/cyclohexane 1:1 then ethyl acetate/methanol 3:2) to give the title compound, (+)-**4a**, as a white foam (0.037 g, 0.082 mmol). TLC: (ethyl acetate/cyclohexane 1:1) R_f=0.43. This was used for the preparation of the urea (+)-**2a** with no further characterization.

N-[1-(Adamantane-1-methyl)-2,4-dioxo-5-[2-(4-morpholino)ethyl]-2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-3-yl]-N'-phenylurea, (-)-**2a**

Phenyl isocyanate (0.049 ml, 0.46 mmol) was added to a solution of intermediate (-)-**4a** (0.102 g, 0.23 mmol) in dry acetonitrile (5 ml). The mixture was allowed to stand at 23 °C for 5 min. The crude material obtained after concentration *in vacuo* was purified by trituration with ethyl ether/hexane 1:1 and acetonitrile. The title compound, (-)-**2a**, was obtained as a white solid (0.094 g, 0.16 mmol). TLC: (ethyl acetate/cyclohexane 1:1) R_f=0.18, HPLC: e.e.=94%, $[\alpha]_D$=-40.1 (c=0.7500) , M.p.: 157-159 °C, Yield=71%, ^{1}H-NMR: 7.80 (m, 1H), 7.44-7.24 (m, 7H), 7.05 (m, 1H), 6.75 (bs, 1H), 6.21 (bd, 1H), 5.12 (d, 1H), 4.39 (d, 1H), 4.14 (m, 1H), 3.78-3.75 (m, 5H), 3.22 (d, 1H), 2.93 (m, 1H), 2.75 (m, 1H), 2.57 (m, 4H), 1.83 (m, 3H), 1.64-1.18 (m, 12H). ^{13}C-NMR: 166.93, 166.21, 154.96, 141.31, 137.32, 136.97, 129.45, 127.88, 127.02, 125.39, 125.17, 122.45, 118.85, 67.48, 58.56, 57.72, 56.20, 54.92, 48.56, 41.23, 37.46, 37.09, 29.05. IR: 3400, 1699, 1668, 1641 cm^{-1}. LRMS: 572 (MH+), 479 (base peak) HRMS: Calcd. for $C_{33}H_{42}N_5O_4$ 572.323680 Found 572.322370

N-[1-(Adamantane-1-methyl)-2,4-dioxo-5-[2-(4-morpholino)ethyl]-2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-3-yl]-N'-phenylurea, (+)-**2a**

Phenyl isocyanate (0.014 ml, 0.13 mmol) was added to a solution of intermediate (+)-**4a** (0.030 g, 0.066 mmol) in dry acetonitrile (5 ml). The mixture was allowed to stand at 23 °C for 15 min. A white solid precipitated during this time. After filtration the title compound, (+)-**2a**, was obtained as a white solid (0.018 g, 0.03 mmol). Yield=48%. TLC: (ethyl acetate/cyclohexane 1:1) R_f=0.18, HPLC: e.e.=86%, $[\alpha]_D$=40.4 (c=0.6000), M.p.: 156-160 °C, ^{1}H-NMR: 7.80 (m, 1H), 7.44-7.24 (m, 7H), 7.05 (m, 1H), 6.75 (bs, 1H), 6.21 (bd, 1H), 5.12 (d, 1H), 4.39 (d, 1H), 4.14 (m, 1H), 3.78-3.75 (m, 5H), 3.22 (d, 1H), 2.93 (m, 1H), 2.75 (m, 1H), 2.57 (m, 4H), 1.83 (m, 3H), 1.64-1.18 (m, 12H). ^{13}C-NMR: 166.93, 166.21, 154.96, 141.31, 137.32, 136.97, 129.45, 127.88, 127.02, 125.39, 125.17, 122.45, 118.85, 67.48, 58.56, 57.72, 56.20, 54.92, 48.56, 41.23, 37.46, 37.09, 29.05. IR: 3400, 1699, 1668, 1641 cm^{-1} LRMS: 572 (MH+, base peak), HRMS Calcd. for $C_{33}H_{42}N_5O_4$ 572.323680 Found 572.324110

PREPARATION OF FINAL COMPOUNDS (-)-2b AND (+)-2b

[1-(Adamantane-1-methyl)-2,4-dioxo-5-(2-hydroxyethyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-3-yl]aminophenylacetic acid methyl ester, **6b** *and* **7b**

Diisopropylethylamine (0.366 ml, 2.1 mmol) was added to a suspension of compound rac-**4b** (0.805 g, 2.1 mmol) and compound **5** (1.34 g, 4.2 mmol) in dry THF (50 ml). The mixture was refluxed for 8.5 hrs. then it was concentrated under reduced pressure and diluted with dichloromethane (60 ml), washed with a saturated aqueous ammonium chloride solution (50 ml), brine (50 ml) and dried. After concentration *in vacuo* the crude material was purified by flash chromatography (eluting with ethyl acetate/cyclohexane 1:1 then 3:1) to separate the unreacted tosylate **5**. The resulting diastereomeric mixture (0.645 g, 1.2 mmol, overall alkylation yield=58%) was purified again by flash chromatography (eluting with ethyl acetate/cyclohexane 1:1) to give the title compound, **6b**, as a white solid foam (0.213 g, 0.40 mmol) and an enriched mixture of the second diastereomer which was further purified (eluting with ethyl acetate/cyclohexane 1:1 then 2:1) to give the title compound, **7b**, as a white foam (0.097 g, 0.18 mmol)

Compound **6b**: TLC: (ethyl acetate/cyclohexane 3:2) R_f=0.40, HPLC: d.e.=100%, $[\alpha]_D$=-125 (c=0.7060), M.p.: 100-107 °C. ^{1}H-NMR: 7.56 (m, 1H), 7.34-7.20 (m, 8H), 4.58 (d, 1H), 4.42 (d, 1H), 4.22-4.17 (m, 2H), 3.95 (m, 2H), 3.71 (m, 1H), 3.65 (s, 3H), 3.43 (bdd, 1H), 3.16 (d, 1H), 2.79 (t, 1H), 1.81 (m, 3H), 1.62-1.14 (m, 12H). IR: 3437-3377, 1720, 1693 cm^{-1}, LRMS: 532 (MH+, base peak), HRMS Calcd. for $C_{31}H_{38}N_3O_5$ 532.281147 Found 532.282110

Compound **7b**: TLC: (ethyl acetate/cyclohexane 3:2) R_f=0.36, HPLC: d.e.=100%, $[\alpha]_D$=0 (c=0.6350), M.p.: 130-133 °C. ^{1}H-NMR: 7.61 (m, 1H), 7.40-7.20 (m, 8H), 4.61 (s, 1H), 4.41 (d, 1H), 4.30-4.20 (m, 2H), 4.06 (s, 1H), 3.98 (m, 1H), 3.71 (m, 1H), 3.61 (s, 3H), 3.16 (d, 1H), 3.00-2.90 (bm, 1H), 1.81 (bs, 3H), 1.70-1.50 (m, 6H), 1.20 (m, 6H); IR: 1740, 1695 cm^{-1}; LRMS: 532 (MH+, base peak), 472. HRMS Calcd. for $C_{31}H_{38}N_3O_5$ 532.281147 Found 532.279170

1-(Adamantane-1-methyl)-3-amino-2,4-dioxo-5-(2-hydroxyethyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine, (-)-**4b**

20 % Palladium (II) hydroxide on charcoal (0.260 g, 0.37 mmol) was added to a solution of compound **6b** (0.195 g, 0.37 mmol) in methanol (15 ml). The mixture was hydrogenated at atmospheric pressure during 2 hrs. Then the mixture was filtered on a celite pad and evaporated under reduced pressure. The crude material was purified by flash chromatography (eluting with ethyl acetate/methanol 3:1) to give the title compound, (-)-**4b**, as a white foam (0.125 g, 0.33 mmol). TLC: (ethyl acetate/methanol 4:1) R_f=0.38, $[\alpha]_D$=-44.6 (c=0.7445), M.p. 152-157 °C, Yield=88% ^{1}H-NMR: 7.64 (m, 1H), 7.40-7.28 (m, 3H), 4.43 (d, 1H), 4.30-4.20 (m, 3H), 4.00 (m, 1H), 3.79 (m, 1H), 3.22 (d, 1H), 1.84 (bs, 3H) 1.60-1.40 (m, 6H), 1.24 (m, 6H); IR: 3356-3194, 1693, 1653 cm^{-1}; LRMS: 384 (MH+, base peak), HRMS Calcd. for $C_{22}H_{30}N_3O_3$ 384.228717 Found 384.228550

1-(Adamantane-1-methyl)-3-amino-2,4-dioxo-5-(2-hydroxyethyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine, (+)-**4b**

20 % Palladium (II) hydroxide on charcoal (0.106 g, 0.15 mmol) was added to a solution of compound **7b** (0.080 g, 0.15 mmol) in methanol (15 ml). The mixture was hydrogenated at atmospheric pressure during 2 hrs. Then the mixture was filtered on a celite pad and evaporated under reduced pressure. The crude material was purified by flash chromatography (eluting with ethyl acetate/methanol 3:1) to give the title compound, (+)-**4b**, as a white foam (0.053 g, 0.14 mmol).TLC: (ethyl acetate/methanol 4:1) R_f=0.39, $[\alpha]_D$=51.3 (c=0.5170) M.p. 142-148 °C, Yield=92% ^{1}H-NMR: 7.64 (m, 1H), 7.40-7.28 (m, 3H), 4.43 (d, 1H), 4.30-4.20 (m, 3H), 4.00 (m, 1H), 3.79 (m, 1H), 3.22 (d, 1H), 1.84 (bs, 3H) 1.60-1.40 (m, 6H), 1.24 (m, 6H); IR: 3356-3194, 1693, 1653 cm^{-1}; LRMS: 384 (MH+, base peak), HRMS Calcd. for $C_{22}H_{30}N_3O_3$ 384.228717 Found 384.9030

N-[1-(Adamantane-1-methyl)-2,4-dioxo-5-(2-hydroxyethyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-3-yl]-N'-phenylurea, (-)-**2b**

Phenyl isocyanate (0.051 ml, 0.47 mmol) was added to a solution of intermediate (-)-**4b** (0.120 g, 0.31 mmol) in dry dichloromethane (5 ml). The mixture was allowed to stand at 23 °C for 5 min, then it was evaporated under reduced pressure. The crude material obtained was purified by flash chromatography (eluting with ethyl acetate/cyclohexane 1:2 then 2:1) to give the title compound, (-)-**2b**, as a white solid (0.133g,

0.26mmol). TLC (ethyl acetate/cyclohexane 2:1) R_f=0.58, HPLC: e.e.=93.2%, $[\alpha]_D$=-50.2 (c=0.7350), M.p.: 165-170 °C, Yield=85%, ^{1}H-NMR: 7.78 (dd, 1H), 7.38 (dd, 1H), 7.33 (m, 2H), 7.25 (m, 2H), 7.21 (t, 2H), 6.99 (t, 1H), 6.52 (d, 1H), 5.13 (d, 1H), 4.40 (d, 1H), 4.30-4.18 (m, 2H), 3.91 (m, 1H), 3.81 (m,1H), 3.62 (t, 1H), 3.23 (d, 1H), 1.83 (s, 3H), 1.53 (m, 6H), 1.24 (m, 6H). ^{13}C-NMR: 166.98, 166.33, 154.95, 141.30, 137.44, 137.38, 129.44, 127.95, 127.88, 126.01, 125.05, 122.46, 118.88, 60.26, 58.63, 56.19, 53.99, 41.20, 37.46, 37.14, 29.10. IR: 3314-3144, 1693, 1663, 1639 cm^{-1}; LRMS: 503 (MH+, base peak), 384; HRMS Calcd. for $C_{29}H_{35}N_4O_4$ 503.265831 Found 503.266520

N-[1-(Adamantane-1-methyl)-2,4-dioxo-5-(2-hydroxyethyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-3-yl]-N'-phenylurea, (+)-**2b**

Phenyl isocyanate (0.028 ml, 0.26 mmol) was added to a solution of intermediate (+)-**4b** (0.049 g, 0.13 mmol) in dry dichloromethane (5 ml). The mixture was allowed to stand at 23 °C for 5 min, then it was evaporated under reduced pressure. The crude material obtained was purified by flash chromatography (eluting with ethyl acetate/cyclohexane 1:2 then 2:1) to give the title compound, (+)-**2b**, as a white solid (0.030 g, 0.06 mmol). TLC: (ethyl acetate/cyclohexane 2:1) R_f=0.55, HPLC: e.e.=94.8%, $[\alpha]_D$=+52.1 (c=0.5285) M.p.: 173-175 °C, Yield=46%. ^{1}H-NMR: 7.78 (dd, 1H), 7.38 (dd, 1H), 7.33 (m, 2H), 7.25 (m, 2H), 7.21 (t, 2H), 6.99 (t, 1H), 6.52 (d, 1H), 5.13 (d, 1H), 4.40 (d, 1H), 4.30-4.18 (m, 2H), 3.91 (m, 1H), 3.81 (m,1H), 3.62 (t, 1H), 3.23 (d, 1H), 1.83 (s, 3H), 1.53 (m, 6H), 1.24 (m, 6H). ^{13}C-NMR: 166.98, 166.33, 154.95, 141.30, 137.44, 137.38, 129.44, 127.95, 127.88, 126.01, 125.05, 122.46, 118.88, 60.26, 58.63, 56.19, 53.99, 41.20, 37.46, 37.14, 29.10. IR: 3360, 1695, 1684 cm^{-1}; LRMS: 503 (MH+, base peak), 384; HRMS Calcd. for $C_{29}H_{35}N_4O_4$ 503.265831 Found 503.265831.

PREPARATION OF FINAL COMPOUNDS (-)-2c AND (+)-2c

[1-(Adamantane-1-methyl)-2,4-dioxo-5-methyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-3-yl]aminophenylacetic acid methyl ester, **6c** *and* **7c**

Diisopropylethylamine (0.315 ml, 1.8 mmol) was added to a solution of compound rac-**4c** (0.640 g, 1.8 mmol) and compound **5** (1.441 g, 4.5 mmol) in dry THF (20 ml). The mixture was refluxed for 7.5 hrs. then it was concentrated under reduced pressure and diluted with dichloromethane (60 ml), washed with a saturated aqueous ammonium chloride solution (35 ml), brine (35 ml) and dried. After concentration *in vacuo* the crude material was purified by flash chromatography (eluting with ethyl acetate/cyclohexane 1:3 then 1:2 and 2:3) to eliminate the unreacted tosylate **1**. After this column the title compound, **6c**, (0.160 g, 0.32 mmol, as a yellow oil) and an enriched diastereomeric mixture (0.611 g, 1.22 mmol, overall alkylation yield=85%) were obtained. After a further purification process by flash chromatography a further amount of **6c** (0.105 g, 0.21

mmol, white foam) was obtained. A third column (eluting with ethyl acetate/cyclohexane 2:3) and a recrystallization from methanol gave the title compound, **7c**, (0.110 g, 0.22 mmol) as a white foam.

Compound **6c**: TLC: (ethyl acetate/cyclohexane 2:3) R_f=0.36, d.e.(by NMR)=100%, $[\alpha]_D$=-127.5 (c=0.6450), M.p.: 105-110 °C, ^{1}H-NMR: 7.40-7.20 (m, 9H), 4.60 (s, 1H), 4.41 (d, 1H), 3.96 (d, 1H), 3.63 (s, 3H), 3.46 (s, 3H), 3.34 (bd, 1H), 3.13 (d, 1H), 1.80 (bm, 3H), 1.70-1.10 (m, 12H), IR: 1742, 1666, 1599 cm^{-1}, LRMS: 502 (MH+, base peak), 442 HRMS Calcd. for $C_{30}H_{36}N_3O_4$ 502.270582 Found 502.271460

Compound **7c**: TLC: (ethyl acetate/cyclohexane 2:3) R_f=0.29, HPLC: d.e.=97.8%, $[\alpha]_D$=0 (c=0.6700), M.p.: 209-210 °C, ^{1}H-NMR: 7.40-7.20 (m, 9H), 4.61 (s, 1H), 4.40 (d, 1H), 4.02 (d, 1H), 3.61 (s, 3H), 3.46 (s, 3H), 3.36 (bd, 1H), 3.12 (d, 1H), 1.80 (bm, 3H), 1.68-1.10 (m, 12H), IR: 1742, 1697, 1666, 1601 cm^{-1}, LRMS: 502 (MH+, base peak), 442 HRMS Calcd. for $C_{30}H_{36}N_3O_4$ 502.270582 Found 502.271320

1-(Adamantane-1-methyl)-3-amino-2,4-dioxo-5-methyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine, (-)-**4c**

20 % Palladium (II) hydroxide on charcoal (0.130 g, 0.185 mmol) was added to a solution of compound **6c** (0.093 g, 0.185 mmol) in methanol (10 ml). The mixture was hydrogenated at atmospheric pressure during 2 hrs. Then the mixture was filtered on a celite pad and evaporated under reduced pressure. The crude material was purified by flash chromatography (eluting with dichloromethane/methanol 19:1) to give the title compound, (-)-**4c**, as a colorless oil (0.058 g, 0.016 mmol). TLC: (dichloromethane/methanol 9:1) R_f=0.70, Yield=89%. This was used for the synthesis of the urea (-)-**2c** with no further characterization.

1-(Adamantane-1-methyl)-3-amino-2,4-dioxo-5-methyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine, (+)-**4c**

20 % Palladium (II) hydroxide on charcoal (0.140 g, 0.20 mmol) was added to a solution of compound **7c** (0.100 g, 0.20 mmol) in methanol (30 ml). The mixture was hydrogenated at atmospheric pressure during 1hr. Then the mixture was filtered on a celite pad and evaporated under reduced pressure. The crude material was purified by flash chromatography (eluting with dichloromethane/methanol 19:1) to give the title compound, (+)-**4c**, as a white foam (0.061g, 0.17mmol). TLC:. (dichloromethane/methanol 9:1) R_f=0.70, $[\alpha]_D$=+65 (c=0.8370), M.p. 126-130 °C, Yield=86%, ^{1}H-NMR: 7.40-7.25 (m, 4H), 4.43 (d, 1H), 4.09 (bs, 1H), 3.50 (s, 3H), 3.19 (d, 1H), 1.82 (bs, 3H), 1.75-1.40 (m, 6H), 1.22 (m, 6H), IR: 3440-3370, 1695, 1668 cm^{-1}, LRMS: 354 (MH+, base peak), HRMS Calcd. for $C_{21}H_{28}N_3O_2$ 354.218152 Found 354.220130

N-[1-(Adamantane-1-methyl)-2,4-dioxo-5-methyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-3-yl]-N'-phenylurea, (-)-**2c**

Phenyl isocyanate (0.032 ml, 0.30mmol) was added to a solution of intermediate (-)-**4c** (0.050 g, 0.14 mmol) in dry acetonitrile (1 ml). The mixture was allowed to stand at 23 °C for 5 min, then it was evaporated

under reduced pressure. The crude material obtained was purified by flash chromatography (eluting with ethyl acetate/cyclohexane 1:2) to give the title compound, (-)-**2c**, as a white solid (0.49 g, 0.10 mmol). TLC: (ethyl acetate/cyclohexane 2:3) R_f=0.39, HPLC: e.e.=92%, $[\alpha]_D$=-75.2 (c=0.6530), M.p.: 173-178 °C, Yield=74%, ^{1}H-NMR: 7.44-7.24 (m, 8H), 7.05 (t, 1H), 6.98 (bs, 1H), 6.17 (d, 1H), 5.14 (d, 1H), 4.40 (d, 1H), 3.50 (s, 3H), 3.18 (d, 1H), 1.82 (m, 3H), 1.60-1.14 (m, 12H). ^{13}C-NMR: 166.79, 166.39, 154.99, 141.31, 137.54, 137.29, 129.43, 128.07, 127.77, 125.30, 124.40, 122.43, 118.83, 58.65, 55.94, 41.27, 37.48, 37.20, 35.43, 29.06. IR: 3300-3200, 1703, 1659, 1599 cm^{-1}, LRMS: 473 (MH+, base peak), HRMS Calcd. for $C_{28}H_{33}N_4O_3$ 473.255266 Found 473.257380

N-[1-(Adamantane-1-methyl)-2,4-dioxo-5-methyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-3-yl]-N'-phenylurea, (+)-**2c**

Phenyl isocyanate (0.034 ml, 0.031 mmol) was added to a solution of intermediate (+)-**4c** (0.055 g, 0.156 mmol) in dry acetonitrile (5 ml). The mixture was allowed to stand at 23 °C for 5 min, then it was evaporated under reduced pressure. The crude material obtained was purified by flash chromatography (eluting with ethyl acetate/cyclohexane 1:2) to give the title compound, (+)-**2c**, as a white solid (0.55 g, 0.12 mmol). TLC: (ethyl acetate/cyclohexane 2:3) R_f=0.40, HPLC: e.e.=96.6%, $[a]_D$=+76.4 (c=0.6630) M.p.: 180-182 °C, Yield=75%; ^{1}H-NMR: 7.44-7.24 (m, 8H), 7.05 (t, 1H), 6.98 (bs, 1H), 6.17 (d, 1H), 5.14 (d, 1H), 4.40 (d, 1H), 3.50 (s, 3H), 3.18 (d, 1H), 1.82 (m, 3H), 1.60-1.14 (m, 12H). ^{13}C-NMR: 166.79, 166.39, 154.99, 141.31, 137.54, 137.29, 129.43, 128.07, 127.77, 125.30, 124.40, 122.43, 118.83, 58.65, 55.94, 41.27, 37.48, 37.20, 35.43, 29.06. IR: 3315, 1701, 1668, 1637 cm^{-1}, LRMS: 473 (MH+, base peak), 354 HRMS Calcd. for $C_{28}H_{33}N_4O_3$ 473.255266 Found 473.256230.

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