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Diastereoselective Synthesis of Highly Constrained Spiro- β -Lactams by the Staudinger Reaction Using an Unsymmetrical Bicyclic Ketene

Andrea Trabocchi,^[a] Claudia Lalli,^[a] Francesco Guarna,^[a] and Antonio Guarna*^[a]

Keywords: Peptidomimetics / Spiro compounds / Lactams / Cycloaddition / Scaffolds

A rigid bicyclic ketene was used to generate highly constrained polycyclic spiro- β -lactams through the Staudinger reaction. Depending on the imine component, high diastereoselectivity was observed in the process, leading to mainly the *cis* diastereoisomer in the case of aromatic imines. This results from an *anti* addition of the imine to the ketene,

followed by a conrotatory ring closure in which the heteroatom at the 6-position of the scaffold rotates outward because of torquoelectronic effects.

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Introduction

Peptidomimetics are important compounds in the fields of molecular diversity and drug discovery. For use in drug discovery, these nonpeptide molecules must mimic the crucial structural properties of bioactive peptides and maintain some or all of their characteristic bioactivities.^[1] Control of the topological arrangement of the residues that constitute the pharmacophore in peptidomimetics is accomplished by the use of molecular scaffolds.^[2] Organic chemists use modern synthetic techniques to make structurally diverse scaffolds for use as peptidomimetic templates, including cyclic, polycyclic and spiro compounds varying in ring size and in their level of functionalization. In particular, lactam or bicyclic lactam formation is commonly used for constraining the torsion angles for the synthesis of peptidomimetics,^[3] and β -lactams have been extensively used as synthetic intermediates in organic synthesis (the β -lactam synthon method),^[4] thus providing a very useful route to a number of α - and β -amino acid derivatives and peptides. The application of spiro- β -lactams in peptidomimetic chemistry is well-documented, and relevant examples include the development of constrained β -turn mimetics.^[5] Also, spiro- β -lactams have received attention in medicinal chemistry owing to their antiviral and antibacterial properties,^[6] as well as recognized activity as cholesterol absorption inhibitors.^[7]

Among the strategies developed for the construction of β -lactams,^[8] the reaction of acyl chlorides with imines (known as the Staudinger reaction^[9]) constitutes one of the most popular procedures. Also, several syntheses of spiro-

β -lactams have been described in the literature,^[10] and in recent years many researchers have accomplished the synthesis of spiro- β -lactams through cycloaddition reactions employing different ketenes and imines.^[11]

In recent years, our interest in the development of heterocycles and constrained amino acids for peptidomimetic chemistry has focused on the synthesis of bicyclic 3-aza-6,8-dioxabicyclo[3.2.1]octane scaffolds as γ/δ -amino acids. These BTAA (bicycles from tartaric and amino acid derivatives), obtained from the condensation of tartaric acid or sugar derivatives and amino carbonyl derivatives, proved to be valuable dipeptide isosteres when inserted into peptide chains.^[12] Accordingly, we reported the synthesis of α -,^[13] β -,^[14] and γ/δ -amino acids,^[12,14,15] as well as tricyclic scaffolds containing the 4-hydroxyproline nucleus^[16] and [4.2.1]- and [5.2.1]-sized heterocyclic analogues.^[17] We were interested in further exploring the skeletal diversity of such constrained scaffolds by generating polycyclic spiro compounds through the Staudinger reaction with different types of imines. Our aim was to generate compounds possessing diverse scaffolds to which different functional groups could be fixed in a stereodefined 3D topological arrangement.

Results and Discussion

Derivatives **2** and **3**, obtained from bicyclic Bn-BTG(O)-OMe (**1**) (BTG: Bicycles from Tartaric acid and Glycin derivatives), were used to assess the yield and selectivity resulting from the reaction of the corresponding BTAA-derived ketene with selected imines (Table 1). Ketenes are commonly generated from acyl chlorides, and the use of Mukaiyama's salt for in situ generation of the reactive species, even in solid-phase chemistry, has also been reported.^[18,19] Both methodologies were thus explored to

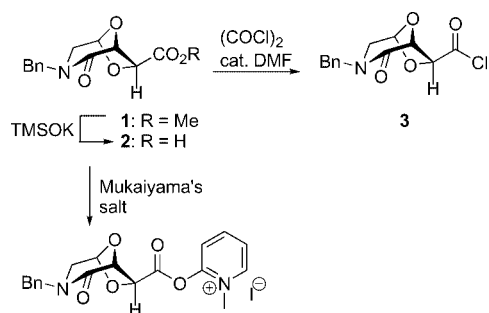
[a] Dipartimento di Chimica Organica "Ugo Schiff", Laboratorio di Progettazione, Sintesi e Studio di Eterocicli Bioattivi (Hetero-BioLab), Università degli Studi di Firenze
Via della Lastruccia 13, 50019 Sesto Fiorentino, Italy
Fax: +39-055-4573569
E-mail: antonio.guarna@unifi.it

Table 1. Selected examples of spiro- β -lactams **4** with general formulas as in Scheme 2.^[a]

Entry	Imine	R'	R	Product	Yield [%]	cis/trans
1	I	Ph	CH(CH ₂ Ph)COOMe	6	33	1.4:1
2	II	Ph	CH ₂ Ph	7	66	1:1.2
3	III	Ph	<i>p</i> -CH ₃ Ph	8	14	15:1
4	IV	Ph	<i>p</i> -NO ₂ Ph	9	—	—
5	V	Ph	<i>p</i> -OMePh	10	39	10:1
6	VI	<i>p</i> -NO ₂ Ph	<i>p</i> -CH ₃ Ph	11	24	20:1
7	VII	<i>p</i> -OMePh	<i>p</i> -CH ₃ Ph	12	59	>50:1
8	VIII	<i>p</i> -BrPh	<i>p</i> -CH ₃ Ph	13	33	7:1

[a] Reactions were all conducted in toluene at 110 °C by using method 1.

verify the reactivity of the unsymmetrical bicyclic ketene at the 7-position of the scaffold with respect to the imine at different temperatures and with different solvent systems (Scheme 1).



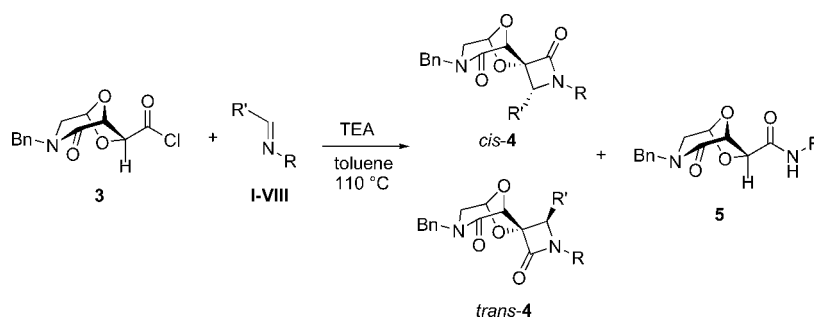
Scheme 1.

Hydrolysis of **1** with potassium trimethylsilanolate (TMSOK) in anhydrous THF furnished corresponding carboxylic acid **2** in quantitative yield (Scheme 1). Activation of the carboxylic function of the BTG scaffold by means of Mukaiyama's salt, followed by reaction of either imine **I** or **VII** (see Table 1) in anhydrous CH₂Cl₂, resulted in the formation of corresponding amides **5**. This was a consequence of the hydrolysis of the iminium salt that resulted from the condensation of the activated acid with the corresponding imine (Scheme 2). Replacement of CH₂Cl₂ with toluene as the solvent and a change in the order of addition of the reagents to the reaction mixture resulted in the same amide byproducts. The effect of temperature was also investigated, but no improvement in the reactivity was obtained in refluxing chloroform or toluene solutions of the reactive Mukaiyama's adduct with imine **I** (Table 1). Thus, the use of Mukaiyama's salt with bicyclic carboxylic acid **2** could

not lead to the preferential formation of the corresponding spiro- β -lactam after conrotatory ring closure, because hydrolysis of the intermediate *N*-acyl iminium species was favoured under all the conditions tested, leading to amide byproducts **5**.

Therefore, more reactive acyl chloride derivative **3** was used to attain title spiro- β -lactams **4**. The addition of preformed acyl chloride **3** to a refluxing CH₂Cl₂ solution of the imine and triethylamine (TEA) resulted in poor conversion to spiro- β -lactam **4** after a reaction time of 18 h. However, spiro- β -lactam **4** was obtained after a reaction time of 24 h by adding a solution of acyl chloride **3** in toluene to a refluxing toluene solution of the imine and TEA (method 1). Also, when the reaction was conducted at lower temperatures, the reverse approach was used, which consisted of the preformation of the ketene by allowing the acyl chloride to react with TEA, followed by the addition of the imine species (method 2). The reaction was explored with imines derived from α -amino esters, benzylamine and aromatic amines and gave different results in terms of yield and diastereoselectivity, as shown in Table 1.

The nucleophilicity of the amine derivatives comprising the imine proved to influence the yield, as the conversion proceeded in the order benzyl > amino ester \approx aryl. In particular, substitution on the aniline ring influenced the reactivity, as *p*-NO₂-aryl-*N*-substituted imine **IV** (Table 1, Entry 4) failed to react with the bicyclic ketene, probably as a result of the unfavourable electronic effects in the Staudinger reaction, whereas *p*-OMe-aryl-*N*-substitution (Table 1, Entry 5) gave the highest yield of the benzaldehyde-derived aryl imines (Table 1, Entries 3–5). Also, the nature of the aromatic aldehyde-derived moiety agreed with the hypothesis that an electron-rich imine could improve the yield of the corresponding spiro- β -lactam, as *p*-NO₂-



Scheme 2.

aryl-*C*-substitution gave **11** in 24% yield, whereas *p*-OMe-aryl-*C*-substitution yielded corresponding spiro compound **12** in 54% yield (Table 1, Entries 6 and 7, respectively). In the latter case (Table 1, Entry 7), the order of addition of the reagents proved to influence the ratio of **4/5** as a consequence of the hydrolysis of the intermediate iminium species. Specifically, method 1 proved to give the spiro- β -lactam even at 60 °C, whereas method 2, consisting of the preformation of the ketene followed by imine addition, resulted in a 1:1 mixture of spiro- β -lactam **4**/amide byproduct **5**. In terms of stereoselectivity, imine **I** (derived from benzaldehyde and phenylalanine methyl ester; Table 1, Entry 1) gave a mixture of two compounds as a result of poor diastereoselectivity, as did imine **II** (derived from benzylamine; Table 1, Entry 2). However, aromatic imines **III–VIII** gave in all cases a major stereoisomer.

Spiro- β -lactam formation by using benzylamine-derived imine **II** (Table 1, Entry 2) was further investigated as a function of the reaction temperature. In this case, method 2, involving preformation of the ketene, was found to be crucial for achieving corresponding spiro compound **7**. Interestingly, we observed an effect of the temperature on the diastereomeric ratio, as shown in Table 2. Specifically, when moving from 110 to 0 °C we observed a slight increase in the stereoselectivity and a shift towards the preferential formation of one of the two diastereoisomers (Figure 1). The structure of the two stereoisomers was assigned by NOESY experiments of the mixture resulting from the reaction at 20 °C (Table 2, Entry 2). In the major stereoisomer, a strong NOE signal was observed between 1-H of the bicyclic compound and 4'-H of the azetidine ring, which suggests that spiro- β -lactam **7** with the general structure of *cis*-**4** as in Scheme 2 was obtained as the major compound at temperatures below 60 °C.

Table 2. Effect of the temperature on the diastereomeric ratio of spiro- β -lactam **7** as in Table 1, Entry 2.^[a]

Entry	Temperature [°C]	Yield [%]	<i>cis/trans</i>
1	0	22	2.7:1
2	20	14	2.2:1
3	60	24	1:1
4	80	19	1.1:1
5	110	66	1:1.2

[a] Reactions were all conducted by using method 2.

X-ray and NMR spectroscopic analysis of compound **12** revealed information about the structure of the major diastereoisomer. NOESY experiments agreed with the X-ray crystal structure of **12** as shown in Figure 2,^[20] as demonstrated by a NOE crosspeak between 4'-H of the azetidine ring and 1-H of the bicyclic scaffold, and also by a weak NOE crosspeak between the CH₂ protons at N-3 and the 4'-*p*-OMePh hydrogen atoms (Figure 3).

The mechanism of the reaction is widely thought to involve nucleophilic attack of the imine on the ketene species to give a zwitterionic intermediate, which undergoes a subsequent conrotatory ring closure to generate the spiro- β -lactam species. In agreement with similar substrates reported in the literature,^[11f] diastereoisomer *cis*-**12**

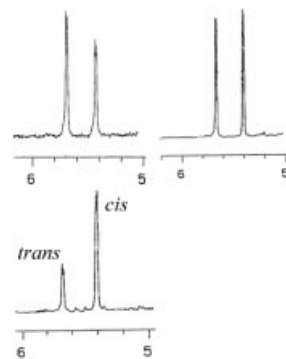


Figure 1. ¹H NMR signal of 5-H of compound **7** resulting from the reaction of **3** with imine **II**. The reactions were carried out at 110 °C (top left), 80 °C (top right) and 20 °C (bottom left).

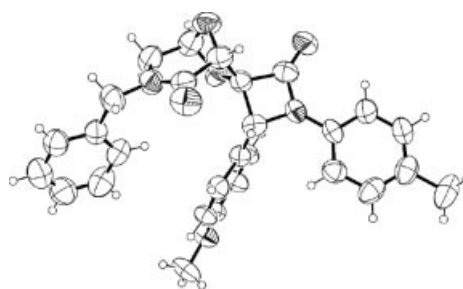


Figure 2. X-ray structure of compound **12**.

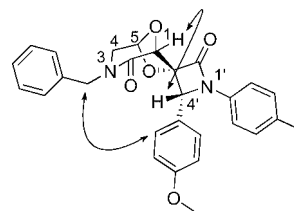


Figure 3. Selected NOE contacts for compound **12**.

(Scheme 2) would thus have resulted from initial attack of the imine species on the bicyclic ketene in the *anti* orientation with respect to the O-6 oxygen atom of the scaffold, followed by a preferential outward conrotatory ring closure of the O-6 substituent favoured by a torquoelectronic effect (Figure 4).

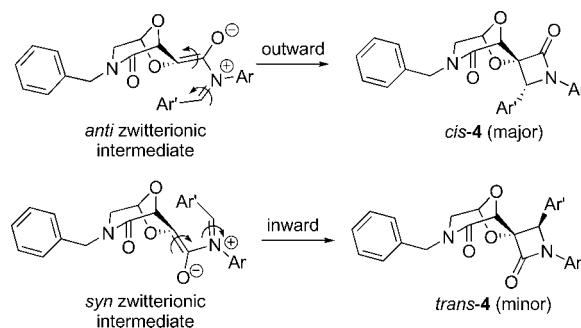


Figure 4. Proposed mechanism for the stepwise Staudinger reaction.

This effect has been demonstrated to be very pronounced for ketenes bearing a heteroatom adjacent to the carbon–carbon double bond,^[11f] thus agreeing with the high stereoselectivity observed in our compounds derived from aromatic imines. The minor stereoisomer could result from *syn* attack of the imine species to give the *trans* compound as shown in Figure 4. This hypothesis is supported by the absence of NOESY peaks either between 4'-H of the azetidine ring and 1-H of the bicyclic scaffold, thus excluding the other possible *cis* stereoisomer, or between the CH₂ protons at N-3 and the 4'-aryl hydrogen atoms, thus excluding the other possible *trans* structure. The loss of stereoselectivity in the case of benzyl- and phenylalanine-derived imines may take account of the higher conformational freedom due to the lack of conjugation within the imine with respect to the aromatic ones.

Conclusions

The synthesis of highly constrained spiro- β -lactams from a bicyclic ketene was achieved by the Staudinger reaction. The outcome of the reaction indicated that the aromatic imines are best choice for the generation of a new molecular architecture bearing aromatic functional groups, as in this case the reaction proceeded with high stereoselectivity to produce the corresponding *cis* spiro- β -lactams as the major compounds. Both aliphatic- and amino acid derived imines provided mixtures of *cis*- and *trans* spiro- β -lactams in variable amounts. Given the potential structural diversity of the ketene bicyclic scaffold,^[12a] this method is of interest for the generation of densely functionalized molecular scaffolds having restricted conformational freedom and a stereo-defined 3D topological array of the substituents. Optimized reaction conditions may be applied for the subsequent generation of polycyclic spiro- β -lactams as peptidomimetics for biomedical research.

Experimental Section

General Remarks: Melting points are uncorrected. Chromatographic separations were performed on silica gel by using flash-column techniques. *R_f* values refer to TLC carried out on 25 mm silica gel plates (Merck F₂₅₄) with the same eluent indicated as for column chromatography. EI mass spectra were carried out at 70 eV ionizing voltage.

General Procedure for the Synthesis of Spiro Compounds 6–13 (Method 1): A solution of the proper imine (1.1 equiv.) and dry TEA (1.5 equiv.) in dry toluene (0.2 M) was heated to reflux under a nitrogen atmosphere; a mixture of Bn-BTG(O)-Cl (**3**; 250 mg, 0.89 mmol, 1 equiv.) in dry toluene (0.4 M) was then added. The mixture was stirred at 110 °C under a nitrogen atmosphere for 16 h, and it was then washed with saturated aqueous NaHCO₃ and brine. The organic layer was dried with Na₂SO₄, filtered and concentrated in vacuo to give a dark oil. The pure products were afforded after purification by flash chromatography (petroleum ether/EtOAc, 1:1).

General Procedure for the Synthesis of Spiro Compound 7 (Method 2): A solution of Bn-BTG(O)-Cl (**3**; 250 mg, 0.89 mmol,

1 equiv.) and dry TEA (1.5 equiv.) in dry toluene (0.4 M) was stirred at the desired temperature under a nitrogen atmosphere for 10 min, and a solution of imine **II** (1.1 equiv.) in dry toluene (0.2 M) was then added. The mixture was stirred at the desired temperature under a nitrogen atmosphere for 15 h, and it was then washed with saturated aqueous NaHCO₃ and brine. The organic layer was dried with Na₂SO₄, filtered and concentrated in vacuo to give a dark oil, which was purified by flash chromatography (petroleum ether/EtOAc, 1:1).

(1R,5S,7R)-3-Benzyl-2-oxo-6,8-dioxo-3-azabicyclo[3.2.1]octane-7-carbonyl Chloride (3**):** Bn-BTG(O)-OMe (**1**) was dissolved in anhydrous THF to give a 0.1 M solution, and TMSOK (1.5 equiv.) was added in one portion. After stirring 1.5 h at room temperature, the mixture was diluted with EtOAc, washed with 5% KHSO₄ and brine and dried with Na₂SO₄. Evaporation of the organic phase gave pure acid **2** in 95% yield. ¹H NMR (200 MHz, CDCl₃): δ = 7.36–7.18 (m, 5 H, Ph), 5.92 (d, ³*J*_{H,H} = 2.2 Hz, 1 H, 5-H), 5.12 (s, 1 H, 1-H), 4.96 (s, 1 H, 7-H), 4.56 (s, 2 H, CH₂-Ph), 3.39 (dd, ²*J*_{H,H} = 12.4 Hz, ³*J*_{H,H} = 2.4 Hz, 1 H, 4-H), 3.14 (d, ²*J*_{H,H} = 12.0 Hz, 1 H, 4-H) ppm. To a solution of acid **2** (1 equiv.) in dry CH₂Cl₂ (0.7 M) was slowly added a solution of oxalyl chloride (5 M, 3 equiv.) in dry CH₂Cl₂, and a drop of dry DMF was then added. The mixture was stirred at room temp. under a nitrogen atmosphere for 15 h, and the solvent was then concentrated in vacuo to give the corresponding acyl chloride, which was immediately used in the Staudinger reaction.

Spiro Compound 6: White solid, 150 mg, 33% yield. ¹H NMR (400 MHz, CDCl₃) 3:2 mixture of diastereomers A and B: δ = 7.40–7.19 (m, 15 H, Ph, A+B), 5.59 (d, ³*J*_{H,H} = 2.4 Hz, 1 H, 5-H, A), 5.32 (d, ³*J*_{H,H} = 2.4 Hz, 1 H, 5-H, B), 4.94 (s, 1 H, 1-H, A), 4.89 (d, ²*J*_{H,H} = 15.1 Hz, CH₂, A), 4.88 (s, 2 H, 4'-H, A+B), 4.82 (s, 1 H, 1-H, B), 4.74 (d, ²*J*_{H,H} = 15.3 Hz, 1 H, CH₂, B), 4.52 (m, 1 H, α -H, B), 4.50 (d, ²*J*_{H,H} = 15.3 Hz, 1 H, CH₂, B), 4.05 (m, 1 H, α -H, A), 3.91 (d, ²*J*_{H,H} = 14.7 Hz, 1 H, CH₂, A), 3.79 (s, 3 H, OMe, B), 3.71 (s, 3 H, OMe, A), 3.56 (dd, ²*J*_{H,H} = 14.0, ³*J*_{H,H} = 11.9 Hz, 1 H, β -H, A), 3.30 (dd, ²*J*_{H,H} = 14.0 Hz, ³*J*_{H,H} = 4.6 Hz, 1 H, β -H A), 3.18 (m, 2 H, 4-H, B), 3.15 (m, 1 H, β -H, B), 3.13 (dd, ²*J*_{H,H} = 12.4 Hz, ³*J*_{H,H} = 3.0 Hz, 1 H, 4-H, B), 3.05 (dd, ²*J*_{H,H} = 12.7 Hz, ³*J*_{H,H} = 2.4 Hz, 1 H, 4-H, A), 3.00 (dd, ²*J*_{H,H} = 14.4 Hz, ³*J*_{H,H} = 9.6 Hz, 1 H, β -H, B), 2.45 (d, ²*J*_{H,H} = 14.0 Hz, 1 H, 4-H, A) ppm. ¹³C NMR (50 MHz, CDCl₃) mixture of diastereomers A and B: δ = 169.2 (s, A), 168.2 (s, B), 164.5 (s, A), 163.3 (s, B), 136.8 (s, A), 136.6 (s, B), 135.3 (s, A), 134.7 (s, B), 134.0 (s, A), 132.7 (s, B), 129.3 (d), 129.2 (d), 128.9 (d), 128.8 (d), 128.7 (d), 128.5 (d), 128.3 (d), 128.2 (d), 127.9 (d), 127.7 (d), 127.6 (d), 127.2 (d), 127.1 (d), 100.5 (d, B), 100.1 (d, A), 92.5 (s, A), 91.9 (s, B), 79.6 (d, A), 76.8 (d, B), 70.9 (d, A), 62.9 (d, B) 58.9 (d), 57.9 (d), 57.1 (d), 52.9 (q), 50.7 (d, A), 50.6 (d, B), 48.6 (d, A), 48.4 (d, B), 36.2 (t, B), 35.6 (d, A) ppm. MS: *m/z* (%) = 512 (3) [M]⁺, 307 (48), 268 (11), 160 (76), 148 (21), 117 (13), 91 (100). IR (CDCl₃): $\tilde{\nu}$ = 3072, 2931, 1792, 1743, 1664, 1493, 1458 cm⁻¹.

Spiro Compound 7: White solid, 258 mg, 66% yield. ¹H NMR (400 MHz, CDCl₃) mixture of diastereomers A and B: δ = 7.48–7.07 (m, 15 H, Ph, A+B), 5.68 (d, ³*J*_{H,H} = 2.6 Hz, 1 H, 5-H, B), 5.42 (d, ³*J*_{H,H} = 2.3 Hz, 1 H, 5-H, A), 4.98 (s, 1 H, 4'-H, B), 4.97 (d, ²*J*_{H,H} = 14.2 Hz, 1 H, CH₂, A), 4.96 (s, 1 H, 4'-H, A), 4.84 (d, ²*J*_{H,H} = 15.2 Hz, 1 H, CH₂, A), 4.83 (d, ²*J*_{H,H} = 14.7 Hz, 1 H, CH₂, B), 4.82 (s, 1 H, 1-H, B), 4.78 (d, ²*J*_{H,H} = 14.8 Hz, 1 H, CH₂, B), 4.55 (s, 1 H, 1-H, A), 4.45 (d, ²*J*_{H,H} = 14.8 Hz, 1 H, CH₂, A), 3.99 (d, ²*J*_{H,H} = 14.8 Hz, 1 H, CH₂, B), 3.97 (d, ²*J*_{H,H} = 14.7 Hz, 1 H, CH₂, B), 3.94 (d, ²*J*_{H,H} = 14.7 Hz, 1 H, CH₂, A), 3.22 (dd, ²*J*_{H,H} = 12.5 Hz, ³*J*_{H,H} = 2.4 Hz, 1 H, 4-H, A), 3.18 (dd, ²*J*_{H,H} = 12.5 Hz,

$^3J_{\text{H,H}} = 2.7$ Hz, 1 H, 4-H, B), 3.10 (dd, $^2J_{\text{H,H}} = 12.5$ Hz, $^3J_{\text{H,H}} = 2.3$ Hz, 1 H, 4-H, A), 2.54 (d, $^2J_{\text{H,H}} = 12.3$ Hz, 1 H, 4-H, B) ppm. ^{13}C NMR (50 MHz, CDCl_3) mixture of diastereomers A and B: $\delta = 166.8$ (s, B), 164.6 (s, B), 164.5 (s, A), 163.6 (s, A), 135.3 (s, A), 134.7 (s, B), 134.4 (s, B), 134.3 (s, A), 133.8 (s, B), 132.8 (s, A), 128.9 (d), 128.8 (d), 128.7 (d), 128.6 (d), 128.5 (d), 128.4 (d), 128.3 (d), 128.2 (d), 128.0 (d), 127.8 (d), 127.7 (d), 127.6 (d), 100.6 (d, B), 100.1 (d, A), 93.2 (s, B), 92.6 (s, A), 79.5 (d, A), 76.7 (d, B), 68.1 (d, B), 62.3 (d, A), 50.8 (t, A), 50.5 (t, B), 48.6 (t, A), 48.4 (t, B), 44.6 (t, 2 C) ppm. MS: m/z (%) = 440 (7) $[\text{M}]^+$, 307 (63), 292 (17), 216 (15), 160 (75), 148 (27), 132 (22), 91 (100), 65 (25). IR (CDCl_3): $\tilde{\nu} = 3055, 2923, 1767, 1676, 1496, 1455\text{ cm}^{-1}$.

Spiro Compound 8: Yellow solid, 55 mg, 14% yield. M.p. 86–89 °C. $[\alpha]_{\text{D}}^{25} = -84.44$ ($c = 0.7$, CH_2Cl_2). ^1H NMR (400 MHz, CDCl_3): $\delta = 7.33\text{--}7.03$ (m, 14 H, Ph), 5.70 (d, $^3J_{\text{H,H}} = 2.6$ Hz, 1 H, 5-H), 5.40 (s, 1 H, PhCHN), 5.09 (s, 1 H, 1-H), 5.04 (d, $^2J_{\text{H,H}} = 14.6$ Hz, 1 H, CH_2Ph), 4.03 (d, $^2J_{\text{H,H}} = 14.3$ Hz, 1 H, CH_2Ph), 3.41 (dd, $^2J_{\text{H,H}} = 12.4$ Hz, $^3J_{\text{H,H}} = 2.6$ Hz, 1 H, 4-H), 2.64 (d, $^2J_{\text{H,H}} = 12.4$ Hz, 1 H, 4-H), 2.23 (s, 3 H, CH_3) ppm. ^{13}C NMR (CDCl_3): $\delta = 164.6$ (s, C=O), 163.7 (s, C=O), 134.6 (s, Ph), 134.5 (s, Ph), 133.9 (s, Ph), 132.9 (s, Ph), 129.5 (d, 2 C, Ph), 128.9 (d, 2 C, Ph), 128.8 (d, Ph), 128.6 (d, 2 C, Ph), 128.5 (d, 2 C, Ph), 128.1 (d, Ph), 127.2 (d, 2 C, Ph), 117.7 (d, Ph), 100.1 (d, C-5), 92.2 (s, C-7), 76.9 (d, PhCHN), 62.5 (d, C-1), 50.9 (t, C-4), 48.9 (t, CH_2Ph), 21.1 (q, CH_3) ppm. MS: m/z (%) = 440 (8) $[\text{M}]^+$, 307 (19), 195 (41), 160 (51), 91 (100), 65 (18). IR (CDCl_3): $\tilde{\nu} = 3067, 2928, 1760, 1673\text{ cm}^{-1}$. $\text{C}_{27}\text{H}_{24}\text{N}_2\text{O}_4$ (440.5): calcd. C 73.62, H 5.49, N 6.36; found C 73.59, H 5.48, N 6.34.

Spiro Compound 10: Yellow solid, 158 mg, 39% yield. M.p. 94–97 °C. $[\alpha]_{\text{D}}^{25} = -124.98$ ($c = 0.8$, CH_2Cl_2). ^1H NMR (400 MHz, CDCl_3): $\delta = 7.35\text{--}7.23$ (m, 12 H, Ph), 6.85–6.81 (m, 2 H, Ph), 5.75 (d, $^3J_{\text{H,H}} = 2.6$ Hz, 1 H, 5-H), 5.41 (s, 1 H, PhCHN), 5.12 (s, 1 H, 1-H), 5.08 (d, $^2J_{\text{H,H}} = 14.6$ Hz, 1 H, CH_2Ph), 4.05 (d, $^2J_{\text{H,H}} = 14.7$ Hz, 1 H, CH_2Ph), 3.78 (s, 3 H, OCH_3), 3.30 (dd, $^2J_{\text{H,H}} = 12.1$, $^3J_{\text{H,H}} = 2.6$ Hz, 1 H, 4-H), 2.67 (d, $^3J_{\text{H,H}} = 12.1$ Hz, 1 H, 4-H) ppm. ^{13}C NMR (50 MHz, CDCl_3): $\delta = 164.7$ (s, C=O), 163.4 (s, C=O), 156.5 (s, Ph), 134.6 (s, Ph), 132.9 (s, Ph), 129.9 (s, Ph), 128.9 (d, Ph), 128.6 (d, Ph), 128.5 (d, Ph), 128.0 (d, Ph), 127.2 (d, Ph), 119.0 (d, Ph), 114.3 (d, Ph), 100.1 (d, C-5), 92.3 (s, C-7), 76.9 (d, PhCHN), 62.6 (d, C-1), 55.5 (q, OCH_3), 50.9 (t, C-4), 48.9 (t, CH_2Ph) ppm. MS: m/z (%) = 456 (25) $[\text{M}]^+$, 307 (23), 211 (66), 196 (33), 160 (75), 148 (18), 91 (100), 77 (17), 65 (13). IR (CDCl_3): $\tilde{\nu} = 3081, 2921, 1758, 1672, 1513\text{ cm}^{-1}$. $\text{C}_{27}\text{H}_{24}\text{N}_2\text{O}_5$ (456.5): calcd. C 71.04, H 5.30, N 6.14; found C 71.06, H 5.32, N 6.13.

Spiro Compound 11: Yellow solid, 104 mg, 24% yield. M.p. 97–100 °C. $[\alpha]_{\text{D}}^{25} = -121.72$ ($c = 0.95$, CH_2Cl_2). ^1H NMR (200 MHz, CDCl_3): $\delta = 8.08$ (d, $^3J_{\text{H,H}} = 8.4$ Hz, 2 H, Ar), 7.42–7.05 (m, 11 H, Ph), 5.74 (d, $^3J_{\text{H,H}} = 2.20$ Hz, 1 H, 5-H), 5.46 (s, 1 H, PhCHN), 5.11 (s, 1 H, 1-H), 4.81 (d, $^2J_{\text{H,H}} = 14.3$ Hz, 1 H, CH_2Ph), 4.25 (d, $^2J_{\text{H,H}} = 14.3$ Hz, 1 H, CH_2Ph), 3.35 (dd, $^2J_{\text{H,H}} = 12.1$, $^3J_{\text{H,H}} = 2.6$ Hz, 1 H, 4-H), 2.74 (d, $^2J_{\text{H,H}} = 12.4$ Hz, 1 H, 4-H), 2.28 (s, 3 H, CH_3) ppm. ^{13}C NMR (50 MHz, CDCl_3): $\delta = 164.5$ (s, C=O), 163.8 (s, C=O), 148.0 (s, Ph), 140.5 (s, Ph), 135.0 (s, Ph), 134.5 (s, Ph), 133.5 (s, Ph), 129.8 (d, Ph), 129.0 (d, Ph), 128.9 (d, Ph), 128.4 (d, Ph), 128.0 (d, Ph), 123.9 (d, Ph), 117.5 (d, Ph), 100.4 (d, C-5), 92.4 (s, C-7), 76.9 (d, PhCHN), 61.5 (d, C-1), 51.0 (t, C-4), 49.2 (t, CH_2Ph), 21.1 (q, CH_3) ppm. MS: m/z (%) = 485 (5) $[\text{M}]^+$, 352 (13), 261 (23), 240 (30), 148 (32), 91 (100), 65 (15). IR (CDCl_3): $\tilde{\nu} = 3053, 2947, 1765, 1673, 1525\text{ cm}^{-1}$. $\text{C}_{27}\text{H}_{23}\text{N}_3\text{O}_6$ (485.5): calcd. C 66.80, H 4.78, N 8.66; found C 66.83, H 4.80, N 8.69.

Spiro Compound 12: Yellow solid, 247 mg, 59% yield. M.p. 99–101 °C. $[\alpha]_{\text{D}}^{25} = -103.63$ ($c = 0.95$, CH_2Cl_2). ^1H NMR (400 MHz,

CDCl_3): $\delta = 7.34\text{--}7.02$ (m, 11 H, Ph), 6.85–6.80 (m, 2 H, Ph), 5.72 (d, $^3J_{\text{H,H}} = 2.6$ Hz, 1 H, 5-H), 5.34 (s, 1 H, PhCHN), 5.07 (s, 1 H, 1-H), 4.98 (d, $^2J_{\text{H,H}} = 14.6$ Hz, 1 H, CH_2Ph), 4.05 (d, $^2J_{\text{H,H}} = 14.6$ Hz, 1 H, CH_2Ph), 3.79 (s, 3 H, OCH_3), 3.26 (dd, $^2J_{\text{H,H}} = 12.4$ Hz, $^3J_{\text{H,H}} = 2.6$ Hz, 1 H, 4-H), 2.68 (d, $^2J_{\text{H,H}} = 12.4$ Hz, 1 H, 4-H), 2.26 (s, 3 H, CH_3) ppm. ^{13}C NMR (50 MHz, CDCl_3): $\delta = 164.6$ (s, C=O), 163.9 (s, C=O), 159.8 (s, Ph), 134.8 (s, Ph), 134.3 (s, Ph), 134.1 (s, Ph), 129.6 (d, Ph), 128.9 (d, Ph), 128.6 (d, Ph), 128.0 (d, Ph), 124.7 (s, Ph), 117.7 (d, Ph), 114.1 (d, Ph), 100.2 (d, C-5), 92.2 (s, C-7), 76.9 (d, PhCHN), 62.2 (d, C-1), 55.3 (q, OCH_3), 50.9 (t, C-4), 48.9 (t, CH_2Ph), 21.2 (q, CH_3) ppm. MS: m/z (%) = 470 (7) $[\text{M}]^+$, 337 (74), 225 (54), 190 (73), 161 (22), 91 (100), 65 (24). IR (CDCl_3): $\tilde{\nu} = 3063, 2926, 1759, 1671, 1515\text{ cm}^{-1}$. $\text{C}_{28}\text{H}_{26}\text{N}_2\text{O}_5$ (470.5): calcd. C 71.47, H 5.57, N 5.95; found C 71.47, H 5.55, N 5.96.

Spiro Compound 13: Yellow solid, 152 mg, 33% yield. M.p. 96–99 °C. $[\alpha]_{\text{D}}^{25} = -123.02$ ($c = 0.95$, CH_2Cl_2). ^1H NMR (200 MHz, CDCl_3): $\delta = 7.42\text{--}7.16$ (m, 9 H, Ph), 7.05–6.99 (m, 4 H, Ph), 5.68 (d, $^3J_{\text{H,H}} = 2.6$ Hz, 1 H, 5-H), 5.37 (s, 1 H, PhCHN), 5.09 (s, 1 H, 1-H), 4.87 (d, $^2J_{\text{H,H}} = 14.6$ Hz, 1 H, CH_2Ph), 4.14 (d, $^2J_{\text{H,H}} = 13.2$ Hz, 1 H, CH_2Ph), 3.26 (dd, $^2J_{\text{H,H}} = 12.4$ Hz, $^3J_{\text{H,H}} = 2.6$ Hz, 1 H, 4-H), 2.69 (d, $^2J_{\text{H,H}} = 12.1$ Hz, 1 H, 4-H), 2.25 (s, 3 H, CH_3) ppm. ^{13}C NMR (50 MHz, CDCl_3): $\delta = 164.5$ (s, C=O), 163.5 (s, C=O), 134.7 (s, Ph), 134.6 (s, Ph), 133.8 (s, Ph), 132.1 (s, Ph), 131.8 (d, Ph), 129.7 (d, Ph), 129.0 (d, Ph), 128.9 (d, Ph), 128.7 (d, Ph), 128.1 (d, Ph), 122.8 (s, Ph), 117.6 (d, Ph), 100.3 (d, C-5), 92.2 (s, C-7), 76.9 (d, PhCHN), 61.9 (d, C-1), 50.9 (t, C-4), 48.9 (t, CH_2Ph), 21.2 (q, CH_3) ppm. MS: m/z (%) = 520 (5) $[\text{M} + 1]^+$, 518 (5) $[\text{M} - 1]^+$, 387 (13), 385 (13), 275 (22), 273 (22), 240 (15), 238 (15). IR (CDCl_3): $\tilde{\nu} = 3054, 2991, 1762, 1672, 1515, 1488\text{ cm}^{-1}$. $\text{C}_{27}\text{H}_{23}\text{BrN}_2\text{O}_4$ (519.4): calcd. C 62.44, H 4.46, N 5.39; found C 62.41, H 4.44, N 5.39.

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