

Full Paper

Diastereoselective Spiroannulation of Phenolic Substrates: Advances Towards the Asymmetric Formation of the Manumycin m-C₇N Core Skeleton

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Received: 7 September 2007; in revised form: 24 September 2007 / Accepted: 24 September 2007 / Published: 25 September 2007

Abstract: The asymmetric syntheses of two new spirolactones prepared in optically pure form from *L*-3-nitrotyrosine are described. The key step, an oxidative spiroannulation, was carried out on the optically active phenols **11a** and **11b** and afforded the new spirolactones **5a** and **5b** in 85% and 83% yields, respectively, as mixtures (3:1 dr) of diastereomers. The major diastereomers from these mixtures could be isolated in optically pure form by trituration using acetone-hexanes as the solvent. Thus, the optically active spirolactones (+)-**5a** (+ 92.8°, *c*=0.125 acetone) and (+)-**5b** (+112.0°, *c*= 0.125 acetone) were obtained after four synthetic steps from *L*-3-nitrotyrosine in 41% and 43% yield, respectively.

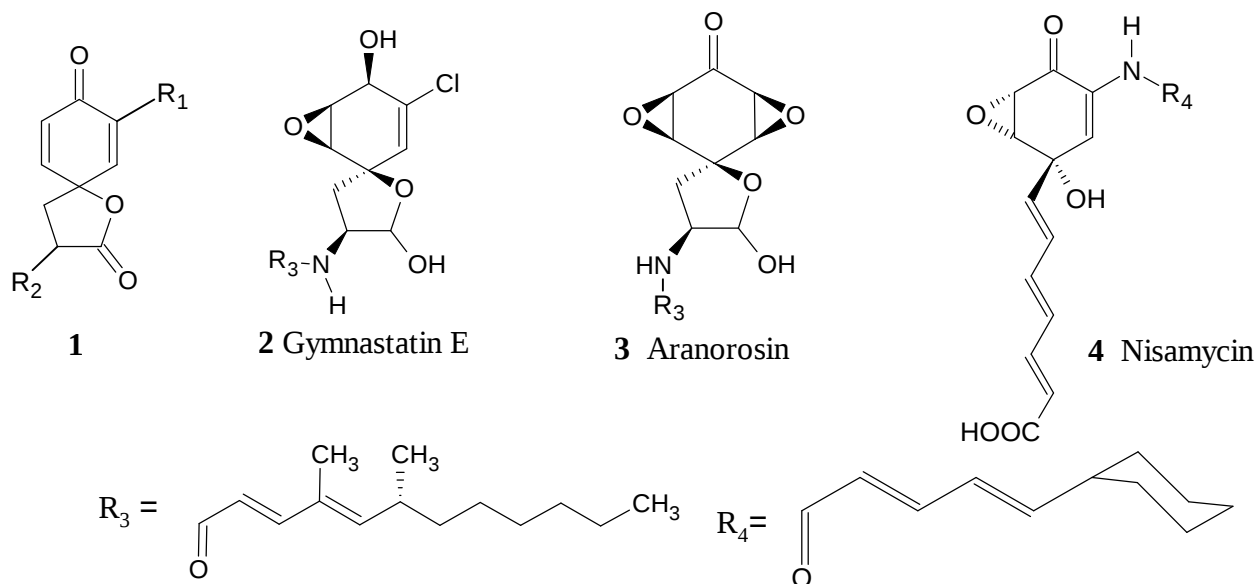
Keywords: Spiroannulation, oxidation, phenol, diastereoselective, asymmetric, Manumycins, Aranorosins, Gymnastatins.

Introduction

Our previous investigations of the diastereoselective spiroannulation of simple phenols have shown that it is possible to obtain facial selectivity in these reactions [1–4]. While only modest diastereoselectivities (~4:1 ratio) have been obtained to date, these results suggested that this method could be used in the design of diastereoselective syntheses of natural products. More accurately, we

felt that spirocompounds of general structure **1** (Figure 1) could be used in the synthesis of the core carbon skeleton of natural products (or analogs) from three families: Gymnastatins (**2**), Aranorosins (**3**) and Manumycins (**4**). A representative example for each family is shown in Figure 1 (structures **2**–**4**).

Figure 1.



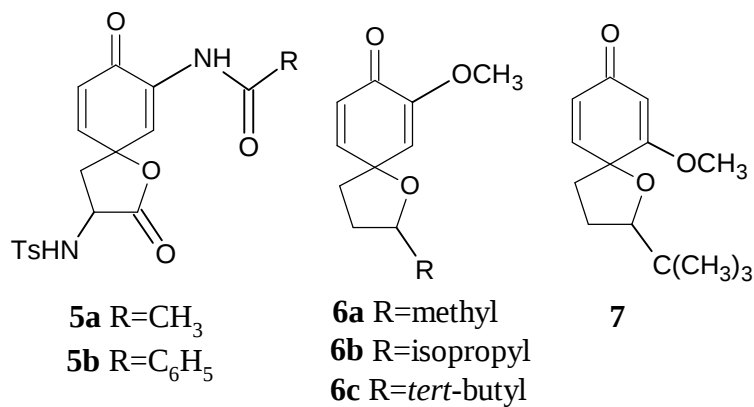
Assuming that the spirocompound **1** bears the proper functional groups at positions R_1 and R_2 , it appears to be a good starting point for the syntheses of these natural products. While there are already numerous syntheses of members of the Manumycins [5–13], Aranorosins [14–16] and Gymnastatins [17], this new approach could be advantageous since it may allow for the synthesis of more than one of these structures from the same starting material. We have investigated the asymmetric synthesis of spirolactones **5** (Figure 2) bearing substituents that would mimic the general functionality found in most members of the Manumycin family (cf. structure **4**). We now wish to report our preliminary results toward the asymmetric synthesis of compound **5**, which we hope will become a precursor for the synthesis of analogs of the Manumycin family of compounds.

Results and Discussion

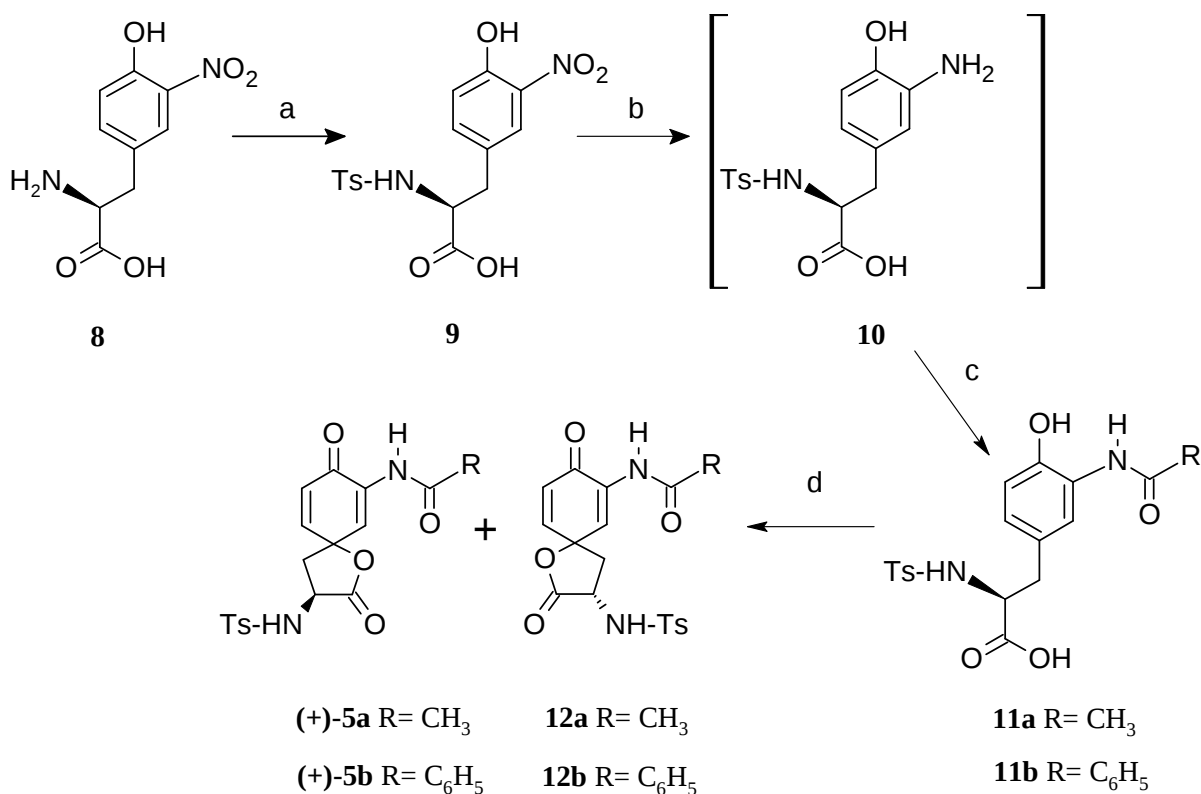
The diastereoselective formation of spirolactones **5a** and **5b** is described in Scheme 1. Commercially available *L*-3-nitrotyrosine **8** was chosen as the starting material for two reasons: (1) it provides the means to generate the amide function found in the Manumycins via its nitro function (see Figure 1), and (2), it bears an optically pure chiral center on the side chain *para* to the hydroxyl, as shown in phenols **11a/11b**. Our previous studies of the diastereoselective spiroannulation of simple phenols have shown that for side chains similar to the one found in **11**, it was possible to induce face selectivity and obtain a 4:1 diastereomeric ratio of spiroethers **6a–c** and **7**, which are analogous in structure to **5/12**, as shown in Figure 2 [1,2,4]. We hoped that in the formation of spirolactones **5/12**, a

similar or greater ratio of diastereomers could be generated since the chiral center in the side chain of **11** is located at a position similar to that of the chiral center used in our previous studies.

Figure 2.



Scheme 1.



(a) 1) TsCl, THF, 1M NaOH 2) 1M KOH, EtOH, 80–85 °C; (b) H₂, 10% Pd/C, THF; (c) CH₃COCl or PhCOCl, THF, rt; (d) PIFA, acetone, 0 °C

Treatment of **8** with *p*-toluenesulfonyl chloride in tetrahydrofuran afforded a mixture of products consisting of the mono-*N*-protected phenol **9** and a product that we identified by $^1\text{H-NMR}$ as a diprotected product, *ie.* both the amino and hydroxyl functions in **8** had reacted with the sulfonyl chloride. Hydrolysis of the resulting mixture with 1M KOH at 80°C afforded only **9** in 86% yield as a yellow solid after recrystallization from benzene. Since the sulfonate ester is easier to hydrolyze than the sulfonamide function, we were able to avoid the extra steps that protection/deprotection of the phenolic hydroxyl would have necessitated. Hydrogenation of the nitro function in **9** afforded the aniline derivative **10** as a white solid. The crude yield for **10** appeared to be quantitative (based on mass recovery), however, every attempt to purify this compound by column chromatography or recrystallization failed. In these cases, we obtained low yields (40–60%), but more importantly, these purification attempts at **10** generated a product that was less pure (based on $^1\text{H-NMR}$) than the crude reaction product itself. Consequently, compound **10** was used without purification in the subsequent reaction and the identity of this compound was based primarily on its $^1\text{H-NMR}$ spectrum.

Treatment of **10** with either acetyl chloride or benzoyl chloride afforded **11a** and **11b** in 84% and 87% yields, respectively, after purification by column chromatography. The spiroannulation of **11a** and **11b** was carried out with phenyliodine(III) bistrifluoroacetate (PIFA) in acetone at 0°C. In the reaction of **11a**, a mixture of diastereomers **5a/12a** was obtained in a 3:1 diastereomeric ratio. The ratio of major/minor diastereomers formed in the spiroannulation was determined by integration for the signals of H-9 (two doublets centered at 6.37 ppm) in the $^1\text{H-NMR}$ spectrum of the crude diastereomeric mixture. In the reaction of **11b**, the two doublets for compounds **5b/12b** (centered at 6.40 ppm) were overlapping slightly, making the determination of the diastereomeric ratio less accurate. However, it was obvious from the $^1\text{H-NMR}$ of the crude reaction mixture that one stereoisomer was produced in a larger amount than the other one. We estimated that for **5b/12b** this ratio was between 3:1 and 4:1. Attempts to separate the major and minor stereoisomers from these mixtures met with limited success. Our first attempt was carried out by column chromatography of the **5a/12a** mixture using 50% ethyl acetate-hexanes as eluant. We were able to separate the major diastereomer **5a** from the mixture under these conditions but this fraction represented only 38% of the total isolated mass (or 32% yield from **11a**). We were not successful in isolating the minor diastereomer from this mixture. We later found that both **5a** and **5b** could be isolated via trituration using an acetone/hexanes mixture. In both cases, we were able to isolate the major diastereomers (+)-**5a** and (+)-**5b** from the crude reaction mixtures. The isolated mass obtained for each compound represents a 57% yield from the corresponding optically active phenols **11a/11b**, or a 41% total yield for (+)-**5a** and 43% for (+)-**5b**. Finally, while we were able to isolate the major diastereomer in these reactions, we have not yet identified the configuration of the newly formed chiral spirocenter in **5a** or **5b**. As a result, in Scheme 1 we have not drawn the stereo bonds of the spirocenters in the structures of **5a/b** or **12a/b**. However, both major diastereomers gave a positive optical rotation and are labeled accordingly in Scheme 1.

Conclusions

We have successfully prepared optically active spirocompounds (+)-**5a** and (+)-**5b**. While the diastereomeric ratio observed in the reaction leading to these compounds is modest at best, it suggests that the method could be useful in the asymmetric synthesis of natural products since we were able to

obtain the major diastereomers in optically pure forms. We have now begun an investigation of the use of these compounds in the synthesis of the core skeleton of the Manumycins. Furthermore, we are attempting to identify the configuration of the new chiral spirocenters in (+)-**5a** and (+)-**5b** as well as ways to enhance the diastereomeric ratios observed in these reactions.

Acknowledgements

We acknowledge the financial contribution of the University of Northern British Columbia in support of this work.

Experimental

General

Melting points were determined on a hot stage instrument and are uncorrected. Infrared spectra were recorded on a Perkin Elmer System 2000 FTIR either as KBr pellets or neat. ^1H - and ^{13}C -NMR spectra were recorded on a Bruker AMX300 spectrometer operating at 300 MHz (^1H) and 75.4 MHz (^{13}C). Chemical shifts are expressed in ppm using TMS (^1H) or the residual solvent signal (^{13}C) as internal standards. Coupling constants (J) are expressed in Hz. Mass spectra were recorded on a Hewlett Packard 5898B spectrometer. Optical rotations were recorded on a Rudolph Research Autopol III Automatic Polarimeter.

(2S)-3-(4-Hydroxy-3-nitrophenyl)-2-[(4-methylphenyl)sulfonyl]amino} propanoic acid [(-)-**9**]

A solution of *p*-toluenesulfonyl chloride (7.012 g, 36.9 mmol, 8.1 eq.) in tetrahydrofuran (150 mL) was added in three portions (5-10 minutes apart) to a solution of 3-nitro-*L*-tyrosine (1.029 g, 4.55 mmol) in 1M NaOH (100 mL). The resulting orange solution was stirred vigorously at room temperature. After 25-30 minutes the solution became yellow, indicating an acidic environment (pH ~ 3), therefore more 1M NaOH (25 mL) was added. The resulting orange solution was stirred overnight (14-16 hours). The reaction mixture was acidified with 10% HCl (pH 2) and extracted with dichloromethane (3 x 50 mL). The organic fractions were combined, dried (MgSO_4) and the solvent evaporated to afford a yellow solid. The crude yellow product was dissolved in ethanol (100 mL) and 1M KOH (50 mL) was added. The solution was stirred at 80-85°C overnight (12-14 hours). The resulting reaction mixture was cooled and acidified with 10% HCl (pH 2), concentrated and extracted with dichloromethane (2 x 150 mL). The organic fractions were combined, dried (MgSO_4), and the solvent was evaporated leaving a yellow solid. Recrystallization from benzene afforded a yellow solid (1.485 g, 86 %); mp: 137-138°C; $[\alpha]_{\text{D}}^{25}$: -10.4° (c: 0.125, acetone); IR (KBr, cm^{-1}): 3291 (OH), 1734 (CO); ^1H -NMR (CDCl_3) δ : 2.40 (s, 3H, H-7'), 2.91 (m, 1H, H-3a), 3.15 (m, 1H, H-3b), 3.74 (broad s, 1H, OH), 4.16 (m, 1H, H-2), 5.42 (d, 1H, $J=8.5$, N-H), 7.01 (d, 1H, $J=8.6$, H-8), 7.20 (d, 2H, $J=8.3$, H-2', H-6'), 7.38 (dd, 1H, $J=2.2, 8.6$, H-9), 7.56 (d, 2H, $J=8.3$, H-3', H-5'), 7.74 (d, 1H, $J=2.2$, H-5), 10.46 (broad s, 1H, CO_2H); ^{13}C -NMR (CDCl_3) δ : 21.7, 37.7, 56.6, 120.4, 125.6, 127.2, 127.7, 129.9, 133.3, 136.4, 139.2, 144.4, 154.5, 174.7; MS m/z (rel. %): 380 (32, M^+), 293 (22), 258 (25), 228 (43), 209 (31), 178 (26), 155 (98), 135 (92), 117 (32), 106 (52), 91 (100), 77 (42), 65 (83), 51 (49).

(2S)-3-(3-Amino-4-hydroxyphenyl)-2-[[4-methylphenyl)sulfonyl]amino} propanoic acid [(+)-**10**]

To a solution of (-)-**9** (925 mg, 2.43 mmol) in tetrahydrofuran (100 mL) was added 10% Pd/C (250 mg). The resulting mixture was placed in a hydrogenator, flushed (five times) with H₂ and left to agitate under pressure (32 psi) for 16 hrs. The reaction mixture was vented, filtered through Celite® and solvent evaporated to afford a whitish solid. Initial attempts to purify by recrystallization or column chromatography failed and characterization of this product was carried out using the crude product; mp: 112–113°C; [α]_D: +10.2° (c: 0.125, CH₃CN); ¹H-NMR (D₂O + Na₂CO₃) δ : 2.35 (s, 3H, H-7'), 2.45 (m, 1H, H-3a), 2.78 (m, 1H, H-3b), 3.59 (m, 1H, H-2), 6.33 (m, 3H, H-5, H-8, H-9), 7.22 (d, 2H, *J*=8.6, H-3', H-5'), 7.39 (d, 2H, *J*=8.3, H-2', H-6'); MS *m/z* (rel. %): 350 (5, M⁺), 179 (4), 155 (5), 122 (100), 91 (16), 77 (8), 65 (11).

(2S)-3-[3(Acetylamino)-4-hydroxyphenyl]-2-[[4-methylphenyl)sulfonyl]amino} propanoic acid [(-)-**11a**]

To a solution of (+)-**10** (188 mg, 0.54 mmol) in tetrahydrofuran (10 mL) was added acetyl chloride (79 mg, 1.02 mmol, 1.9 eq.) and the solution was stirred at room temperature overnight (19 hours). The reaction mixture was diluted with CH₂Cl₂ (50 mL), washed with brine (15 mL), dried (MgSO₄) and evaporated. Chromatography on silica gel using 20% methanol-chloroform as eluant afforded a beige solid (176 mg, 84%); mp: 153–154°C; [α]_D: -7.3° (c: 0.137, acetone); IR (KBr, cm⁻¹): 3416 (NH), 3257 (NH), 1777 (CO), 1721 (CO); ¹H-NMR (acetone-d₆) δ : 2.20 (s, 3H, H-2''), 2.38 (s, 3H, H-7'), 2.83 (m, 1H, H-3a), 2.93 (m, 1H, H-3b), 4.04 (m, 1H, H-2), 6.64 (d, 1H, NH), 6.70 (d, 1H, *J*=8.2, H-8), 6.83 (dd, 1H, *J*=2.1, 8.2, H-9), 7.15 (broad s, 1H, H-5), 7.25 (d, 2H, *J*=7.9, H-2', H-6'), 7.55 (d, 2H, *J*=8.3, H-3', H-5'), 9.25 (broad s, 1H, CO₂H); ¹³C-NMR (acetone-d₆) δ : 21.5, 23.5, 37.7, 58.3, 119.0, 123.0, 127.3, 127.7, 127.9, 128.7, 130.3, 139.1, 143.8, 148.3, 172.6; MS *m/z* (rel. %): 392 (1.2, M⁺), 203 (17), 155 (11), 147 (74), 146 (100), 122 (18), 105 (17), 91 (60), 77 (35), 65 (22), 51 (17).

(2S)-3-[3(Benzoylamino)-4-hydroxyphenyl]-2-[[4-methylphenyl)sulfonyl]amino}propanoic acid [(-)-**11b**]

To a solution of (+)-**10** (568 mg, 1.62 mmol) in tetrahydrofuran (40 mL) was added benzoyl chloride (258 mg, 1.84 mmol, 1.2 eq.) and the solution was stirred at room temperature overnight (20 hours). The reaction mixture was diluted with CH₂Cl₂ (50 mL), washed with brine (15 mL), dried (MgSO₄) and evaporated. Chromatography on silica gel using 20% methanol-chloroform as eluant afforded a grey solid (640 mg, 87%); mp: 183–186°C; [α]_D: -18.3° (c: 0.09, CH₃CN); IR (KBr, cm⁻¹): 3417 (NH), 3279 (NH), 1719 (CO), 1652 (CO); ¹H-NMR (acetone-d₆) δ : 2.31 (s, 3H, CH₃), 2.83 (dd, 1H, *J*=5.3, 8.3, H-3a), 3.01 (dd, 1H, *J*=5.3, 13.8, H-3b), 4.07 (m, 1H, H-2), 6.80 (m, 3H, Ar-H), 7.21 (d, 2H, *J*=7.9, H-2', H-6'), 7.54 (m, 4H, Ar-H), 8.04 (d, 2H, *J*=7.9, H-3', H-5'), 9.18 (broad s, 1H, exchangeable with D₂O, NH), 9.45 (broad s, 1H, exchangeable with D₂O, OH); ¹³C-NMR (acetone-d₆) δ : 21.7, 39.0, 58.6, 118.6, 124.4, 127.5, 127.8, 128.1, 128.7, 129.1, 129.8, 130.4, 133.2, 134.0, 135.1, 139.3, 143.9, 148.6, 167.4, 172.9; MS *m/z* (rel. %): M⁺ not observed, 266 (2.3), 209 (22), 208 (37), 155 (9), 105 (100), 91 (74), 77 (92), 65 (27), 51 (40).

N-((3*S*)-3-[[*(4*-Methylphenyl)sulfonyl]amino}-1-oxaspiro[4.5]deca-6,9-dien-2,8-dien-7-yl) acetamide [(+)-**5a**]

To a cold (0°C) solution of (-)-**11a** (602 mg, 1.54 mmol) in acetone (100 mL) was added PIFA (727 mg, 1.69 mmol, 1.1 eq.) in one portion. The orange solution was stirred at 0°C for 45 minutes, diluted with EtOAc (200 mL) and washed with cold water (2 x 100 mL). The aqueous portion was extracted with EtOAc (2 x 50 mL), the organic fractions combined, dried (MgSO₄) and evaporated to afford a brown solid (508 mg, 85%). The crude product was purified by trituration (acetone-hexanes) providing the major diastereomer as a beige solid (340 mg, 57%); mp: 173–174°C; [α]_D: +92.8° (c: 0.125, acetone); IR (KBr, cm⁻¹): 3327 (NH), 1778 (CO), 1654 (CO), 1645 (CO); ¹H-NMR (CD₃CN) δ : 2.16 (s, 3H, H-7'), 2.28 (m, 1H, H-4a), 2.45 (s, 3H, H-2''), 2.46 (m, 1H, H-4b), 3.54 (m, 1H, H-3), 6.12 (d, 1H, *J*=8.0, NH), 6.25 (d, 1H, *J*=10.0, H-9), 7.06 (dd, 1H, *J*=3.1, 10.0, H-10), 7.38 (d, 2H, *J*=8.0, H-2', H-6'), 7.52 (d, 1H, *J*=3.1, H-6), 7.78 (d, 2H, *J*=8.3, H-3', H-5'), 8.18 (broad s, 1H, NH); ¹³C-NMR (CD₃CN) δ : 21.6, 24.7, 40.0, 53.0, 78.4, 124.8, 127.5, 128.0, 130.8, 133.5, 138.8, 145.2, 147.4, 170.9, 173.6; MS *m/z* (rel. %): 390 (0.4, M⁺), 203 (5), 155 (11), 147 (52), 146 (78), 139 (9), 122 (9), 105 (8), 91 (100), 77 (20), 65 (57), 51 (6).

N-((3*S*)-3-[[*(4*-Methylphenyl)sulfonyl]amino}-1-oxaspiro[4.5]deca-6,9-dien-2,8-dien-7-yl) benzamide [(+)-**5b**]

To a cold (0°C) solution of (-)-**11b** (710 mg, 1.56 mmol) in acetone (100 mL) was added PIFA (677 mg, 1.57 mmol, 1.0 eq.) in one portion. The orange solution was stirred at 0°C for 45 minutes, diluted with EtOAc (200 mL) and washed with cold water (2 x 100 mL). The aqueous portion was extracted with EtOAc (2 x 50 mL), the organic fractions combined, dried (MgSO₄) and evaporated to afford a brown solid (586 mg, 83%). The crude product was purified by trituration (acetone-hexanes) providing the major diastereomer as an off-white solid (404 mg, 57%); mp: 174–175°C; [α]_D: +112.0° (c: 0.125, acetone); IR (KBr, cm⁻¹): 3397 (NH), 3290 (NH), 1775 (CO), 1665 (CO), 1626 (CO); ¹H-NMR (CDCl₃) δ : 2.43 (s, 3H, H-7'), 2.54 (dd, 1H, *J*=11.7, 13.6, H-4a), 2.76 (dd, 1H, *J*=8.7, 13.6, H-4b), 4.40 (m, 1H, H-3), 5.66 (d, 1H, *J*=5.1, NH), 6.39 (d, 1H, *J*=10.1, H-9), 6.92 (dd, 1H, *J*=3.1, 10.1, H-10), 7.33 (d, 2H, *J*=8.0, H-2', H-6'), 7.54 (m, 3H, H-6, H-3', H-5'), 7.83 (m, 5H, aromatic Hs), 8.79 (broad s, 1H, NH); ¹³C-NMR (CDCl₃) δ : 21.8, 40.8, 52.2, 77.4, 78.4, 124.4, 127.4, 129.2, 129.9, 130.3, 132.5, 132.8, 133.6, 136.5, 144.6, 145.9, 166.3, 172.6, 179.3; MS *m/z* (rel. %): 452 (0.2, M⁺), 208 (12), 155 (5), 139 (10), 123 (9), 122 (9), 105 (33), 92 (38), 91 (100), 77 (37), 65 (42), 51 (10).

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Sample availability: Available from the authors.