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Hydroarylation of bicyclic, unsaturated dicarboximides: access to aryl-substituted, bridged perhydroisoindoles

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Abstract

The C–C coupling of the two bicyclic, unsaturated dicarboximides **6** and **8** with aryl and hetaryl halides gave under reductive Heck conditions the 5-substituted *N*-phenylbicyclo[2.2.1]heptane-2,3-dicarboximides **7** and **9**. Reduction of these imides opens a new access to the bridged perhydroisoindole derivatives **12** and **14** with prospective biological activity.

Keywords: Palladium; Homogenous catalysis; C–C coupling; Reduction; Amine; Aromatics

N-Substituted imides, such as maleimides **1**,[1] isohematinic acids **2**[2] and especially bicyclic derivatives such as tandospirone **3** derivatives[3,4] (Fig. 1) are known for their broad spectrum of pharmacological properties, thus showing antibiotic, fungicidal, analgesic, anxiolytic, and cytostatic effects.

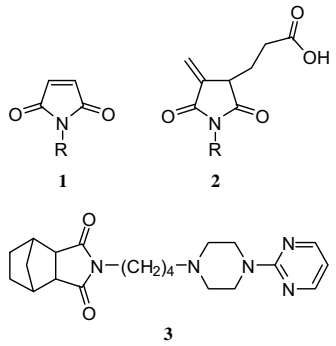

Fig. 1. Maleimides **1**, isohematinic acids **2** and tandospirone **3**.

Derivatives of the *exo*-5,6-dehydronorcantharidin **5** (Fig. 2) are also pharmacologically active.[5] Norcantharidin shows a comparable activity with cantharidin **4** (Fig. 2) which is the major effective ingredient in pharmaceuticals for the treatment of certain malignant tumors in China. Compound **5** has been widely employed in clinical practice, as it is less toxic and much easier to synthesize.[6,7] Furthermore, in connection with an additional imide unit this type of structure has recently become a topic in heterocyclic chemistry because of its anti-tumor, anti-virus, analgesic, sedative, and fungicidal activities.[7]

We therefore became interested in the synthesis of bioactive cantharidin analogues that represent aryl-modified bicyclic imide systems, too. We first synthesized *endo*-*N*-phenylbicyclo[2.2.1]hept-5-ene-2,3-dicarboximide **6** from cyclopentadiene and *N*-phenylmaleimide and *exo*-*N*-phenyl-7-oxa-bicyclo[2.2.1]hept-5-ene-2,3-dicarboximide, **8**

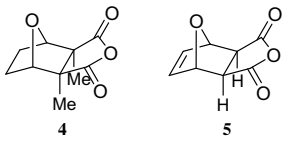

Fig. 2. Cantharidin **4** and *exo*-5,6-dehydronor-cantharidin **5**.

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from furan and *N*-phenylmaleimide as starting compounds according to the literature.[8,9]

Kaufmann and co-workers have a long-standing experience in palladium-catalyzed hydroarylation[10] and domino reactions of heterobicyclic and tricyclic systems[11] toward bioactive compounds such as epibatidine[12] and analogues,[13] diazanorbornanes[14] and *N*-aminoimides.[15] In reductive arylation reactions triphenylarsine has proved to be superior to triphenylphosphine and carbenes as ligands in both selectivity and yield.[12]

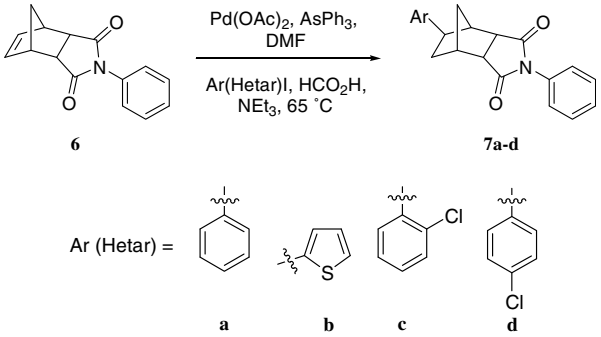
Treatment of **6** with iodobenzene, 2-iodothiophene, *o*-chloroiodobenzene and *p*-chloroiodobenzene under reductive Heck conditions[16] gave the pure products **7a–d** after chromatographic separation on silica gel as single diastereomers in isolated yields of 51–89%[17] (Scheme 1). The stereochemistry was inferred from their NMR spectra including diagnostic spin–spin interactions.

The *exo*-position of the C-5 substituent was confirmed by the fact that H_5 showed no significant interaction with H_1 but did show a cross-peak as a result of W-coupling to $H_{7\text{-}syn}$. The geminal protons on C-6 were identified by vicinal coupling to H_1 and W-coupling to $H_{3\text{-}exo}$, respectively. In addition, Table 1 shows selected ^{1}H NMR data of the hydroarylation products **7a–d**.

The same reductive Heck arylation conditions were successfully applied to the reaction of **8** with iodobenzene, 2-iodothiophene, 4-chloro-1-iodobenzene, 2,4-dichloro-1-iodobenzene, and 2-chloro-5-iodopyridine to give the new *exo*-arylated heterocycles **9a–f** in good yields after chromatographic separation[18] (Scheme 2). Again, a characteristic coupling pattern between the bridgehead and the H_5 and H_6 protons appeared in the ^{1}H NMR spectra. Additionally, H–H COSY spectra showed cross peaks between H_2 and H_3 and between H_5 and H_6, respectively.

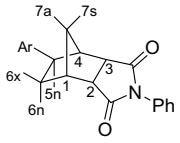
In addition to the ^{13}C NMR and FTIR spectral data which were in agreement with the proposed structures, the mass spectra of all new compounds showed the expected molecular ion peaks.

A number of structurally related bicyclic amines have proved to be useful in the treatment of physiologically or drug induced psychosis or dyskinesia in mammals.[19] Perhydroisoindoles are selective sigma receptor antagonists, and have a low potential for movement disorder side effects

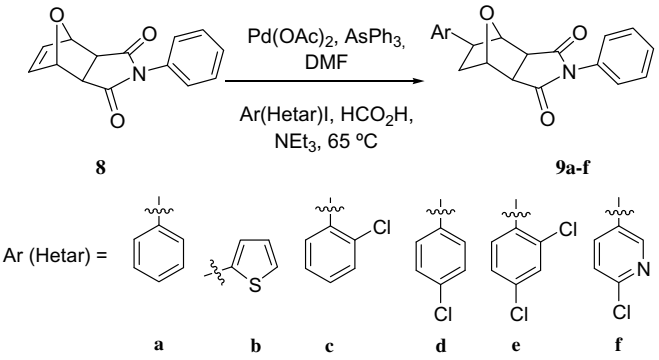


Scheme 1.

Table 1
Selected ^{1}H NMR data for compounds **7a–d**



	7a	7b	7c	7d
H_{7a}	1.64–1.67, d	1.68–1.72, d	1.69–1.80, m	1.64–1.67, d
H_{7s}	1.94–1.98, dt	1.95–2.05, m	1.69–1.80, m	1.88–1.91, dt
H_1	3.00–3.08, m	3.02, br s	3.13–3.15, d	2.95–2.97, br d
H_4	3.00–3.08, m	3.02, br s	3.00–3.03, br d	3.00–3.05, m



Scheme 2.

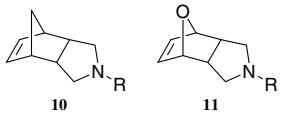
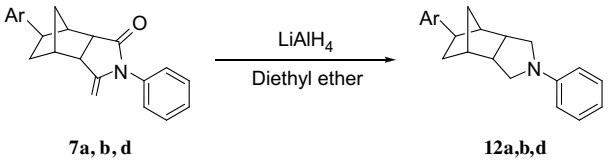


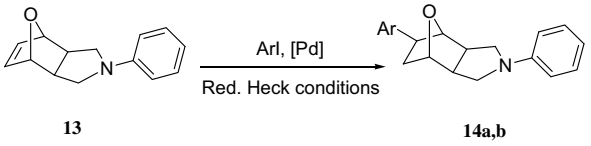
Fig. 3. Alkyl substituted perhydroisoindoles **10** and **11**.

associated with typical antipsychotic agents.[20,21] Some dialkylaminoalkyl perhydroisoindole derivatives, being similar to **10** and **11**, are also displaying hypotensive activities (Fig. 3). The compounds were prepared by reduction of the corresponding imides.[22,23] Thus, it also seemed interesting to obtain perhydroisoindoles from new 5,6-dehydronorcantharidin derivatives.

As a part of our continuing study to obtain new perhydroisoindole derivatives, we reduced compounds **7a**,**b**,**d** using an excess of $LiAlH_4$ in refluxing diethyl ether. After regular workup the crude product was purified by column chromatography to yield **12a**,**b**,**d** in 50–60% (Scheme 3).



Scheme 3.



13 14a,b

Scheme 4.

The structural identification of the new reduced compounds **12a**,**b**,**d** succeeded.[24] In the FTIR spectra the characteristic C=O band (1702–1710 cm^{-1}) of **7a**,**b**,**d** was absent. NMR and MS/EI spectra were also in agreement with the proposed structures.

Additionally, we tried the reduction of **9a**,**b** by $LiAlH_4$ under the same reaction conditions. Yields were very low after workup, though, probably due to opening of the oxygen bridge. Therefore, we first reduced precursor **8** at room temperature (2 h), then worked up at 0 °C by dropwise addition of ethyl acetate, and then water. The crude product was purified by column chromatography (SiO_2, hexane/ethyl acetate 1:2) to yield **13** in 84%. Reductive arylation of **13** with iodobenzene and 2-iodothiophene under Heck conditions gave the pure products **14a**,**b** after chromatographic separation on silica in isolated yields of 50% and 37%, respectively[25] (Scheme 4).

In conclusion, in the presence of triphenylarsine as a ligand, the palladium-catalyzed hydroarylation of the easily accessible tricyclic *N*-phenyl derivatives of the unsaturated imides **6** and **8** has been proven to be a stereoselective, versatile, and high-yield approach for the synthesis of aryl and heteroaryl derivatives. Our results have also demonstrated that the reductive access to aryl-substituted bridged perhydroisoindoles will be useful for the construction of novel heterocycles of potential pharmacological interest.

Acknowledgment

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References and notes

1. Zentz, F.; Valla, A.; Le Guillou, R.; Labia, R.; Mathot, A.; Sirot, D. *Il Farmaco* **2002**, *57*, 421–442.
2. DiPardo, R. M.; Patane, M. A.; Newton, R. C.; Price, R.; Broten, T. P.; Chang, R. S. L.; Ransom, R. W.; Di Salvo, J.; Freidinger, R. M.; Bock, M. G. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1959–1962.
3. Kossakowski, J.; Jarocka, M. *Il Farmaco* **2001**, *56*, 785–789.
4. Stack, G. P.; Abou-Gharbia, M. A.; Podlesny, E. J. U.S. Patent 4,748,240, American Home Products Corporation NY, 1988; *Chem. Abstr.* **1988**, *109*, 211085.
5. Hart, M. E.; Chamberlin, A. R.; Walkom, C.; Sakoff, J. A.; McCluskey, A. *Bioorg. Med. Chem. Lett* **2004**, *14*, 1969–1973.
6. Deng, L.; Yongzhou, H. *J. Heterocycl. Chem.* **2007**, *44*, 597–601.
7. Deng, L.-P.; Liu, F.-M.; Wang, H.-Y. *J. Heterocycl. Chem.* **2005**, *42*, 13–18.
8. William, J. B.; William, B. L. *J. Am. Chem. Soc.* **1957**, *79*, 1444–1447.
9. Anderson, W. K.; Milowsky, A. S. *J. Org. Chem.* **1985**, *50*, 5423–5424.
10. Namyslo, J. C.; Kaufmann, D. E. *Chem. Ber. Recl.* **1997**, *130*, 1327–1331.
11. Yolacan, C.; Bagdatli, E.; Öcal, N.; Kaufmann, D. E. *Molecules* **2006**, *11*, 603–614.
12. Namyslo, J. C.; Kaufmann, D. E. *Synlett* **1999**, 804–806.
13. Otten, A.; Namyslo, J. C.; Stoermer, M.; Kaufmann, D. E. *Eur. J. Org. Chem.* **1998**, *9*, 1997–2001.
14. Storsberg, J.; Nandakumar, M. V.; Sankaranarayanan, S.; Kaufmann, D. E. *Adv. Synth. Catal.* **2001**, *343*, 177–180.
15. Bagdatli, E.; Öcal, N.; Kaufmann, D. E. *Helv. Chim. Acta* **2007**, *90*, 2380–2385.
16. *Reductive Heck reactions, general procedure*: A solution of $Pd(OAc)_2$ (5.6 mg, 0.025 mmol) and $AsPh_3$ (33.7 mg, 0.11 mmol) in anhydrous DMF or DMSO (3 mL) was stirred under nitrogen at 65 °C for 15 min. Then, compound **6** (239 mg, 1 mmol) or **8** (241 mg, 1 mmol), respectively, Et_3N (488 μL, 3.5 mmol), aryl(heteroaryl) iodide (1.5 mmol) and HCOOH (138 mg, 3 mmol) were added. The reaction mixture was stirred for 8–24 h. After cooling to room temperature EtOAc and brine were added, the organic layer was separated, dried ($MgSO_4$), filtered, and the solvent evaporated. The residue was purified by column chromatography (SiO_2).
17. Compound (**7a**): Colorless crystals, mp 125–8 °C (89% from hexane/ethyl acetate (3:2)), ^1H NMR (400 MHz, $CDCl_3$ δ: 1.64–1.67 (d, $J = 13.2$ Hz, 1H, H_{7a}); 1.94–1.98 (dt, $J = 1.5$; 10.4 Hz, 1H, H_{7s}); 2.01–2.04 (m, 2H, H_{6x} and H_{6n}); 3.00–3.08 (m, 3H, H_{5n}, H_1 and H_4); 3.32–3.36 (dd, $J = 5.01$; 9.65 Hz, 1H, H_2); 3.38–3.42 (dd, $J = 5.01$; 9.65 Hz, 1H, H_3); 7.21–7.25 (m, 3H, ar); 7.30–7.35 (m, 4H, ar); 7.42–7.46 (m, 1H, ar); 7.50–7.55 (m, 2H, ar). ^{13}C NMR (100 MHz, $CDCl_3$ δ): 32.4; 39.3; 40.1; 42.0; 46.4; 48.3; 48.8; 117.5; 126.2; 126.6; 127.1; 128.5; 128.8; 129.3; 131.7; 144.2; 177.1; 177.2. GC–MS (EI, 70 eV): 317 (M^+); 175; 129; 119; 104; 77. Compound (**7b**): Colorless crystals, mp 91 °C (51% from hexane/ethyl acetate (3:1)), ^1H NMR (400 MHz, $CDCl_3$ δ): 1.68–1.72 (d, $J = 14.4$ Hz, 1H, H_{7a}); 1.95–2.05 (m, 2H, H_{7s} and H_{6x}); 2.09–2.15 (m, 1H, H_{6n}); 3.02 (2H, br s, 2H, H_1 and H_4); 3.24–3.28 (dd, $J = 5.38$; 8.56 Hz, 1H, H_2); 3.31–3.35 (m, 1H, H_{5n}); 3.37–3.41 (dd, $J = 5.50$; 9.90 Hz, 1H, H_3); 6.84–6.85 (dt, $J = 2.20$; 4.52 Hz, 1H, ar); 6.94–6.96 (dd, $J = 3.55$; 5.13 Hz, 1H, ar); 7.17–7.18 (dd, $J = 1.1$; 5.13 Hz, 1H, ar); 7.29–7.32 (m, 2H, ar); 7.41–7.46 (m, 1H, ar); 7.49–7.54 (m, 2H, ar). ^{13}C NMR (100 MHz, $CDCl_3$ δ): 34.9; 38.1; 39.7; 39.8; 47.7; 48.0; 48.4; 123.5; 123.6; 126.6; 126.8; 128.8; 129.3; 131.7; 149.1; 176.8; 176.9. MS (EI, 70 eV): 324 (M^+); 323; 175; 147; 119; 77. Compound (**7c**): Colorless crystals, mp 174–5 °C (63% from hexane/ethyl acetate (2:1)), ^1H NMR (400 MHz, $CDCl_3$ δ): 1.69–1.80 (m, 2H, H_{7a} and H_{7s}); 2.00–2.04 (dt, $J = 1.46$; 11.98 Hz, 1H, H_{6x}); 2.23–2.29 (ddd, $J = 2.56$; 9.17; 11.61 Hz, 1H, H_{6n}); 3.00–3.03 (br s, 1H, H_4); 3.13–3.15 (br d, $J = 6.23$ Hz, 1H, H_1); 3.32–3.38 (m, 2H, H_2 and H_3); 3.41–3.45 (dd, $J = 5.26$; 9.65 Hz, 1H, H_{5n}); 7.15–7.20 (m, 1H, ar); 7.23–7.30 (m, 1H, ar); 7.33–7.47 (m, 4H, ar); 7.50–7.55 (m, 2H, ar). ^{13}C NMR (100 MHz, $CDCl_3$ δ): 34.3; 39.8; 40.5; 40.6; 44.4; 48.7; 49.2; 126.5; 127.1; 127.3; 127.9; 129.3; 129.8; 130.4; 132.3; 134.9; 142.4; 177.3; 177.5. MS (EI, 70 eV): 352 (M^+), 351; 175; 147; 119; 77. Compound (**7d**): Colorless crystals, mp 167–8 °C (62% from hexane/ethyl acetate (2:1)). ^1H NMR (400 MHz, $CDCl_3$ δ): 1.64–1.67 (d, $J = 14.3$ Hz, 1H, H_{7a}); 1.88–1.91 (dt, $J = 1.46$; 12.10 Hz, 1H, H_{7s}); 1.92–2.05 (m, 2H, H_{6n} and H_{6x}); 2.95–2.97 (br d, $J = 6.4$ Hz, 1H, H_1); 3.00–3.05 (m, 2H, H_2 and H_4); 3.31–3.35 (m, 1H, H_3); 3.38–3.42 (dd, $J = 5.26$; 9.65 Hz, 1H, H_{5n}); 7.14–7.18 (m, 2H, ar); 7.27–7.33 (m, 4H, ar); 7.42–7.46 (m, 1H, ar); 7.49–7.54 (m, 2H, ar). ^{13}C NMR (100 MHz, $CDCl_3$ δ): 32.5; 39.2; 40.1; 41.5; 46.3; 48.1; 48.7; 126.6; 128.4; 128.5; 128.8; 129.3; 131.7; 132.0; 142.6; 177.0; 177.1. MS (EI, 70 eV): 353 (M^+), 351; 175; 147; 119; 77.
18. Compound (**9a**): Colorless crystals, mp 148 °C (70% from hexane/ethyl acetate (3:1)), ^1H NMR (200 MHz, $CDCl_3$ δ): 1.96–1.99 (m, 1H, H_{6n}); 2.01–2.03 (dd, $J = 8.96$; 11.86 Hz, 1H, H_{6x}); 3.05–3.09 (dd, $J = 5.06$; 8.84 Hz, 1H, H_{5n}); 3.14–3.18 (d, $J = 7.20$ Hz, 1H,

H_2); 3.20–3.23 (d, $J = 7.20$, 1H, H_3); 4.91 (s, 1H, H_4); 5.13–5.16 (d, $J = 5.30$ Hz, 1H, H_1); 7.24–7.25 (m, 2H, ar); 7.26–7.47 (m, 8H, ar). ^{13}C NMR (50 MHz, $CDCl_3$ δ): 40.0; 47.4; 49.8; 50.2; 79.6; 85.2; 12.5–127.1; 128.7; 129.2; 131.7; 133.1; 143.9; 176.2; 175.9. GC–MS (EI, 70 eV): 319 (M^+); 290; 174; 128; 117; 91. Compound (**9b**): Colorless crystals, mp 174.6 °C (40% from hexane/ethyl acetate (3:1)), ^{1}H NMR (400 MHz, $CDCl_3$ δ): 2.09–2.16 (m, 1H, H_{6n}); 2.31–2.36 (dd, $J = 8.80$; 12.83 Hz, 1H, H_{6x}); 3.16–3.18 (d, $J = 7.09$ Hz; 1H, H_2); 3.23–3.25 (d, $J = 7.09$ Hz; 1H, H_3); 3.47–3.50 (dd, $J = 4.52$; 8.92 Hz, 1H, H_{5n}); 4.95 (s, 1H, H_1); 5.18–5.19 (d, $J = 5.38$ Hz, 1H, H_4); 6.92–6.98 (m, 1H, thienyl); 6.96–6.98 (dd, $J = 3.55$; 5.14 Hz, 1H, thienyl); 7.20–7.22 (dd, $J = 0.89$; 5.13 Hz, 1H, thienyl); 7.29–7.32 (m, 2H, Ph); 7.42–7.53 (m, 3H, Ph). ^{13}C NMR (100 MHz, $CDCl_3$ δ): 40.9; 43.4; 49.9; 49.9; 79.9; 85.8; 124.4–126.9; 127.2; 129.3; 129.7; 132.1; 147.4; 176.2; 176.4. GC–MS (EI, 70 eV): 325 (M^+); 297; 175; 160; 149; 77. Compound (**9c**): Colorless crystals, mp 189 °C (41% from hexane/ethyl acetate (3:1)). ^{1}H NMR (400 MHz, $CDCl_3$ δ): 1.96–2.02 (m, 1H, H_{6n}); 2.31–2.36 (dd, $J = 9.05$; 12.96 Hz, 1H, H_{6x}); 3.08–3.12 (dd, $J = 4.89$; 9.05 Hz, 1H, H_{5n}); 3.18–3.20 (d, $J = 7.09$ Hz, 1H, H_2); 3.23–3.25 (d, $J = 7.09$ Hz, 1H, H_3); 4.91 (s, 1H, H_4); 5.17–5.18 (d, $J = 5.25$ Hz, 1H, H_1); 7.26–7.23 (m, 2H, ar); 7.29–7.32 (m, 4H, ar); 7.53–7.42 (m, 3H, aromatic). ^{13}C NMR (100 MHz, $CDCl_3$ δ): 40.6; 47.2; 50.1; 50.5; 79.9; 85.5; 126.9–128.9; 129.2; 129.3; 129.7; 132.0; 133.1; 142.9; 176.2; 176.5. GC–MS (EI, 70 eV): 354 ($M+1^+$); 325; 175; 139; 103. Compound (**9d**): Colorless crystals, mp 179 °C (45% from hexane/ethyl acetate (3:1)). ^{1}H NMR (400 MHz, $CDCl_3$ δ): 1.92–1.98 (m, 1H, H_{6n});2.38–2.40 (dd, $J = 9.05$; 12.84 Hz, 1H, H_{6x}); 3.24–3.26 (d, $J = 7.09$ Hz, 1H, H_2); 3.30–3.32 (d, $J = 7.09$ Hz, 1H, H_3); 3.66–3.70 (dd, $J = 0.01$; 8.92 Hz, 1H, H_{5n}); 5.06 (s, 1H, H_4); 5.18–5.19 (d, $J = 5.38$ Hz, 1H, H_1); 7.19–7.23 (m, 1H, ar); 7.27–7.33 (m, 3H, ar); 7.39–7.54 (m, 5H, ar). ^{13}C NMR (100 MHz, $CDCl_3$ δ): 39.6; 43.4; 50.2; 50.5; 80.1; 85.5; 126.3–127.9–128.4; 129.6–129.7; 132.1; 133.6; 141.5; 176.2; 176.5. GC–MS (EI, 70 eV): 353 (M^+); 325; 175; 191; 102. Compound (**9e**): Colorless crystals, mp 170.2 °C (56% from hexane/ethyl acetate (3:1)), ^{1}H NMR (400 MHz, $CDCl_3$ δ): 1.85–1.91 (m, 1H, H_{6n}); 2.36–2.41 (dd, $J = 9.05$; 12.96 Hz, 1H, H_{6x}); 3.21–3.23 (d, $J = 7.09$ Hz, 1H, H_2); 3.27–3.29 (d, $J = 7.09$ Hz, 1H, H_3); 3.59–3.63 (dd, $J = 4.89$; 9.05 Hz, 1H, H_{5n}); 5.00 (s, 1H, H_4); 5.16–5.17 (d, $J = 5.25$ Hz, 1H, H_1); 7.26–7.28 (dd, $J = 2.20$; 8.56 Hz, 1H, ar); 7.30–7.32 (m, 2H, ar); 7.42–7.43 (m, 2H, ar); 7.45–7.46 (m, 1H, ar); 7.49–7.54 (m, 2H, ar). ^{13}C NMR (100 MHz, $CDCl_3$ δ): 39.6; 43.0; 50.1; 50.4; 80.1; 84.4; 126.9–128.2–128.9; 129.3; 129.5; 129.5; 132.1; 133.4; 134.2–140.2; 176.1; 176.1. GC–MS (EI, 70 eV): 388 (M^+); 325; 175; 191; 103. Compound (**9f**): Colorless crystals, mp 152 °C (97% from hexane/ethyl acetate (3:1)), ^{1}H NMR (200 MHz, $CDCl_3$ δ): 1.89–1.96 (m, 1H, H_{6n}); 2.30–2.40 (dd, $J = 10.00$; 13.00 Hz, 1H, H_{6x}); 3.08–3.11 (dd, $J = 5.02$; 9.11 Hz, 1H, H_{5n}); 3.17–3.20 (d, $J = 7.08$, 1H, H_2); 3.22–3.25 (d, $J = 7.09$ Hz, 1H, H_3); 4.87 (s, 1H, H_4); 5.16–5.19 (d, $J = 5.30$ Hz, 1H, H_1); 7.26–7.48 (m, 6H, ar); 7.61–7.66 (dd, $J = 2.52$; 8.34 Hz, 1H, ar); 8.27–8.28 (d, $J = 2.26$ Hz, 1H, ar). ^{13}C NMR (50 MHz, $CDCl_3$ δ): 40.1; 44.1; 49.6; 49.8; 79.5; 84.8; 126.4; 128.9–129.2; 131.3; 131.5; 138.4; 150.2; 175.4; 175.7. GC–MS (EI, 70 eV): 354 (M^+); 325; 139; 119; 117; 91; 68.

19. de Costa, B. R.; He, X. S.; Linders, J. T.; Dominguez, C.; Gu, Z. Q.; Williams, W.; Bowen, W. D. *J. Med. Chem.* **1993**, *36*, 2311–2320.
20. Ciganek, E. U.S. Patent 5,216,018, Du Pont Merck Pharmaceutical Company, 1993; *Chem. Abstr.* **1993**, *119*, 225816.
21. Gilligan, P. J. U.S. Patent 5532243, Du Pont Merck Pharmaceutical Company, 1996; *Chem. Abstr.* **1994**, *120*, 134304.
22. Rice, L. M.; Grogan, C. H.; Reid, E. E. *J. Am. Chem. Soc.* **1953**, *75*, 4911–4915.
23. Otzenberger, R. D.; Lipkowitz, K. B.; Mundy, B. P. *J. Org. Chem.* **1974**, *39*, 319–321.
24. Compound (**12a**): Yellow oil, (60% from hexane/ethyl acetate (2:1)), ^{1}H NMR (400 MHz, $CDCl_3$ δ): 1.57–1.60 (m, 2H, H_{10a} and H_{10b}); 1.83–1.86 (d, $J = 9.90$ Hz, 1H, H_{9x}); 2.09–2.15 (dt, $J = 2.44$; 12.16 Hz, 1H, H_{9n}); 2.44 (br s, 1H, H_1); 2.51–2.52 (br d, $J = 4.52$ Hz, 1H, H_7); 2.72–2.86 (m, 2H, H_2 and H_6); 2.95–3.03 (AB, $J = 8.31$ Hz, 2H, H_5); 3.07–3.11 (dd, $J = 5.13$; 8.80 Hz, 1H, H_{8n}); 3.57–3.60 (d, $J = 11.6$ Hz, 1H, H_3); 3.66–3.69 (d, $J = 10$ Hz, 1H, H_3); 6.76–6.80 (m, 3H, ar); 7.15–7.18 (m, 1H, ar); 7.22–7.24 (m, 2H, ar); 7.28–7.32 (m, 4H, ar). ^{13}C NMR (100 MHz, $CDCl_3$ δ): 32.2; 39.6; 40.3; 42.4; 43.2; 44.5; 47.9; 49.5; 49.6; 113.9; 117.1; 125.7; 127.6; 128.6; 129.5; 147.7; 149.2. MS (EI, 70 eV): 289 (M^+); 144; 106; 77. Compound (**12b**): Yellow oil, (50% from hexane/ethyl acetate (2:1)), ^{1}H NMR (400 MHz, $CDCl_3$ δ): 1.43–1.47 (m, 2H, H_{10a} and H_{10b}); 1.71–1.75 (d, $J = 10.00$ Hz, 1H, H_{9x}); 2.04–2.13 (dt, $J = 2.46$; 12.15 Hz, 1H, H_{9n}); 2.35 (br s, 1H, H_1); 2.43–2.45 (br d, $J = 4.53$ Hz, 1H, H_7); 2.64–2.83 (m, 2H, H_2 and H_6); 3.12–3.17 (AB, $J = 8.48$ Hz, 2H, H_5); 3.37–3.41 (dd, $J = 5.22$; 9.57 1H, H_{8n}); 3.74–3.78 (d, $J = 11.6$ Hz, 1H, H_3); 3.97–4.00 (d, $J = 8.93$ Hz, 1H, H_3); 6.69 (m, 1H, ar); 6.75–6.76 (d, $J = 3.44$ Hz, 1H, ar); 6.83–6.92 (m, 1H, ar); 7.05–7.11 (m, 2H, ar); 7.14–7.28 (m, 3H, ar). ^{13}C NMR (100 MHz, $CDCl_3$ δ): 30.1; 34.2; 36.2; 40.6; 42.1; 42.9; 44.2; 47.2; 48.6; 114.0; 117.6; 122.5; 122.6; 126.5; 127.6; 129.2; 130.4; 148.7; 152.5. MS (EI, 70 eV): 295 (M^+); 211; 179; 165; 149; 110; 83. Compound (**12c**): Yellow oil, (50% from hexane/ethyl acetate (2:1)), ^{1}H NMR (250 MHz, $CDCl_3$ δ): 1.45–1.53 (m, 2H, H_{10a} and H_{10b}), 1.72–1.75 (d, $J = 9.45$ Hz, 1H, H_{9x}), 2.02–2.10 (m, 1H, H_{9n}), 2.30 (br s, 1H, H_1), 2.35–2.42 (m, 1H, H_7), 2.65–2.79 (m, 2H, H_2 and H_6), 2.87–2.91 (AB, $J = 10$ Hz, 2H, H_5), 2.95–3.02 (dd, $J = 5.10$; 8.68 Hz, 1H, H_{8n}), 3.50–3.53 (d, $J = 11.5$ Hz, 1H, H_3), 3.57–3.60 (d, $J = 11.6$ Hz, 1H, H_3), 6.68–6.74 (m, 3H, ar), 7.05–7.10 (d, $J = 12.50$ Hz, 2H, ar), 7.15–7.25 (m, 4H, ar). ^{13}C NMR (62.5 MHz, $CDCl_3$ δ): 30.2; 31.7; 38.8; 39.7; 41.8; 42.6; 43.9; 48.9; 49.1; 113.3; 116.6; 125.2; 127.8; 128.1; 128.2; 128.8; 145.3; 148.4. MS (EI, 70 eV): 323 (M^+); 289; 213; 172; 136; 96; 77.
25. Compound (**14a**). Colorless crystals, mp 142 °C (47% from hexane/ethyl acetate (1:2)), ^{1}H NMR (400 MHz, $CDCl_3$ δ): 1.68–1.73 (m, 1H, H_{9n}); 1.99–2.03 (dd, $J = 9.27$; 12.69 Hz, 1H, H_{9x}); 2.62–2.64 (m, 2H, H_2 and H_3); 2.80–2.83 (m, 1H, H_{8n}); 2.87–2.90 (AB, $J = 4.88$ Hz, 2H, H_5); 3.55–3.64 (td, $J = 10.74$; 18.06 Hz, 2H, H_3); 4.22 (s, 1H, H_1); 4.43–4.45 (d, $J = 4.50$ Hz, 1H, H_7); 6.52–6.55 (dd, $J = 7.82$; 8.78 Hz, 2H, ar); 6.62–6.64 (m, 1H, ar); 7.10–7.11 (m, 2H, ar); 7.12–7.13 (m, 2H, ar); 7.18–7.19 (m, 2H, ar); 7.21–7.22 (m, 1H, ar). ^{13}C NMR (100 MHz, $CDCl_3$ δ): 40.5; 47.5; 48.1; 48.7; 53.1; 54.0; 81.1; 87.2; 113.3–117.2; 126.5; 127.5–128.7; 129.3–129.6; 130.2; 131.7–132.4; 146.3; 148.6. GC–MS (EI, 70 eV): 291 (M^+); 172; 144; 91; 77. Compound (**14b**). Colorless crystals, mp 149 °C (37% from hexane/ethyl acetate (1:2)), ^{1}H NMR (400 MHz, $CDCl_3$ δ): 1.80–1.82 (m, 1H, H_{9n}); 2.02–2.04 (dd, $J = 8.78$; 13.05 Hz, 1H, H_{9x}); 2.59–2.65 (td, $J = 5.85$; 8.30 Hz, 2H, H_2 and H_6); 2.84–2.89 (m, 2H, H_3); 3.18–3.21 (dd, $J = 5.05$; 9.12 Hz, 1H, H_{8n}); 3.59–3.64 (td, $J = 3.06$; 7.20 Hz, 2H, H_5); 4.25 (s, 1H, H_1); 4.46–4.47 (d, $J = 5.37$ Hz, 1H, H_7); 6.51–6.55 (dd, $J = 7.85$; 8.82 Hz, 2H, ar); 6.63–6.64 (m, 2H, ar); 6.67–6.78 (m, 1H, ar); 6.81–6.82 (m, 2H, ar); 7.03–7.05 (m, 1H, ar). ^{13}C NMR (100 MHz, $CDCl_3$ δ): 40.9; 43.0; 47.9; 48.0; 53.8; 54.0; 80.9; 87.5; 113.8; 117.2; 123.4–123.7; 126.7; 128.4–128.0; 129.2–129.0; 148.5; 149.5. GC–MS (EI, 70 eV): 297 (M^+); 184; 144; 83; 77.