

# Cycloaddition of Benzyne with Alkoxy-Substituted Pyrroline-*N*-oxides: Unexpected Rearrangement to an *N*-Phenylpyrrole

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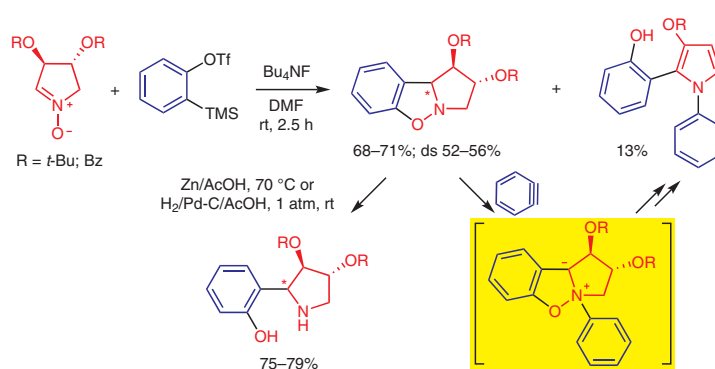
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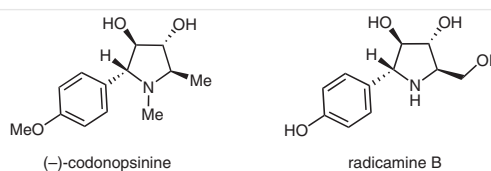
**Abstract** Reaction of enantiopure 3,4-dialkoxy-pyrroline *N*-oxides with benzyne affords the expected tetrahydrobenzo[*d*]pyrrolo[1,2-*b*]isoxazoles along with an unexpected 2,3-disubstitued-*N*-phenyl-pyrrole derived from an unprecedented rearrangement of the adduct of nitrene with two molecules of benzyne. A mechanism for the unusual rearrangement is proposed. The benzo[*d*]isoxazolidine derivatives are conveniently converted into 2-(2-hydroxyphenyl)-3,4-dialkoxy-pyrrolidines by reductive opening of the *N*-O bond.

**Key words** arynes, fused-ring systems, heterocycles, pyrroles, rearrangement, 1,3-dipolar cycloaddition, nitrones

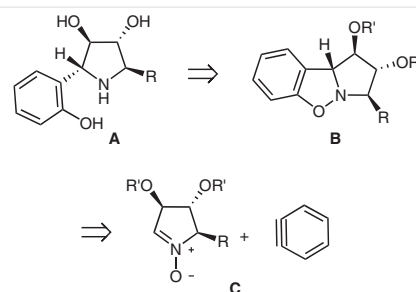
Highly reactive arynes are recognized as an important synthetic tool in organic synthesis. The development of milder methods for the generation of arynes has increased the interest in employing them in the synthesis of complex polycyclic systems and in the total synthesis of natural products.<sup>1</sup> The use of *ortho*-silyl aryl triflates as aryne precursors by Kobayashi has enabled the generation of the reactive intermediate under almost neutral conditions.<sup>2</sup> Cycloaddition reactions of arynes have the advantage of functionalizing instantly an aromatic ring by forming multiple carbon-carbon or carbon-heteroatom bonds in a single step. Among these processes, 1,3-dipolar cycloaddition of hydroxylated pyrroline *N*-oxide nitrones with arynes can be a useful entry to analogues of bioactive natural products such as the codonopsinine and radicamine alkaloids<sup>3</sup> (Figure 1), according to the strategy outlined in Scheme 1.<sup>4</sup>

Hydroxylated pyrroline *N*-oxides are a class of compounds readily achievable from natural sources through straightforward high yielding procedures.<sup>5</sup> In our group,

3,4-dialkoxy pyrroline *N*-oxides have been widely used in the synthesis of bioactive pyrrolidine, pyrrolizidine, and indolizidine heterocycles.<sup>6</sup>



**Figure 1** Structures of natural pyrrolidines codonopsinine and radicamine B



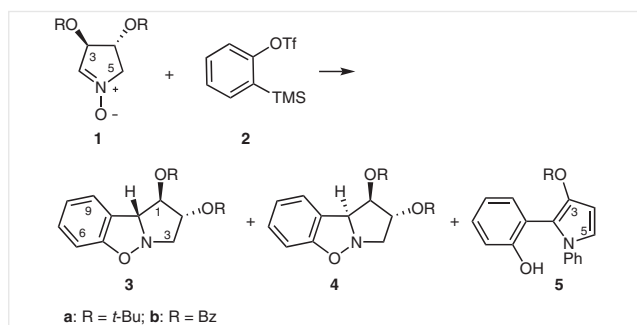
**Scheme 1** Retrosynthetic analysis of 2-aryl-polyhydroxy-pyrrolidines

Although several dipoles have been systematically studied for their reactivity with arynes, leading to interesting heterocycles, only a few nitrones, mostly acyclic and achiral ones, have been investigated as dipole partners for arynes.<sup>7,8</sup> Following the seminal work of Kaliappan's group,<sup>4</sup> we studied the cycloaddition of dialkoxy-pyrroline *N*-oxides with benzyne as another entry to radicamine or codonopsinine analogues. In particular, the lack of substitution on C-5 of the nitrene could allow the introduction of various substituents by following the well-known alkylation of the nitrene following the oxidative opening of the hexahydro-pyrrolo[1,2-*b*]isoxazolidine ring.<sup>5,9</sup>

The 1,3-dipolar cycloaddition of 3,4-bis-*tert*-butoxypyrroline-*N*-oxide (**1a**)<sup>6d</sup> with 2.4 equivalents of 2-(trimethylsilyl)phenyl trifluoromethanesulfonate (**2**) in the presence of CsF as fluoride source in anhydrous tetrahydrofuran (THF) afforded two new diastereomeric cycloadducts **3** and **4** with low diastereoselectivity (58–64% ds) along with an unexpected third product, which was found to be the pyrrole derivative **5a** (see below) (Scheme 2 and Table 1).

In particular, the reaction of **1a** with 2.4 equivalents of **2** in the presence of an excess of CsF in THF was not complete at room temperature after 5 days and afforded **3** and **4** in 57% overall yield along with traces of **5a** (Table 1, entry 1). By heating at 65 °C, adducts **3** and **4** were obtained with a similar overall yield (56%), whereas **5a** was isolated in 18% yield (entry 2). In this case, the conversion was incomplete and unreacted nitrone was recovered after chromatography.

In the presence of 3 equivalents of **2**, nitrone **1a** was completely consumed (TLC analysis) after 20 h at room temperature, affording **3** and **4** in 71% overall yield along with 23% **5a** (Table 1, entry 3). Lower yields of the products were obtained when the same reaction was performed at 60 °C (entry 4). When MeCN was used as solvent, nitrone **1a** was totally consumed after only 2 h at room temperature, but unfortunately analysis of the reaction mixture showed that pyrrole **5a** was the main product (29%) whereas adducts **3** and **4** were only present in trace amounts (entry 5).



**Scheme 2** Cycloaddition reactions of nitrones **1a** and **1b** with benzyne

Finally, the best result was observed by using Bu<sub>4</sub>NF as fluoride source and anhydrous DMF as solvent. In this case, a lower excess of **2** was necessary (1.5 equiv) to consume **1a** at room temperature.<sup>10</sup> The reaction was faster than in THF and after only 2.5 h, **3** and **4** were obtained in an acceptable 68% overall yield (1.3:1 ratio) along with **5a** (13% yield) (Table 1, entry 6).

Major and minor adducts **3a**<sup>11</sup> and **4a**<sup>12</sup> form as the result of *anti*-3-*Ot*Bu and *syn*-3-*Ot*Bu approach, respectively, of benzyne to nitrone **1a**. The relative configuration was assigned on the basis of a less intense NOE difference effect between hydrogens 1-H and 9b-H in **3a** than in **3b** (1% vs. 2%) in accord with the proposed structures.

**Table 1** Optimization of Cycloaddition Reaction of Nitrone **1a** with Benzyne

Entry	<b>2</b> (equiv)	Fluoride source (equiv)	Reaction conditions	Yield (%) <sup>a</sup>		
				<b>3</b>	<b>4</b>	<b>5</b>
1	2.4 <sup>b</sup>	CsF (6)	THF, r.t., 5 d	37 (41)	20 (22)	trace
2	2.4 <sup>b</sup>	CsF (6)	THF, 65 °C, 39 h	33 (39)	23 (27)	18 (22)
3	3	CsF (6)	THF, r.t., 20 h	41	30	23
4	3	CsF (6)	THF, 60 °C, 23 h	35	20	15
5	3	CsF (6)	MeCN, r.t., 2 h	trace	trace	29
6	1.5	Bu <sub>4</sub> NF (1.2)	DMF, r.t., 2.5 h	39	29	13

<sup>a</sup> Isolated yield after chromatography; yields based on conversion given in parentheses.

<sup>b</sup> Nitrone conversion: 91% (entry 1), 83% (entry 2).

Comparing our results with those obtained by Kaliappan,<sup>4</sup> the cycloaddition yields are similar. In contrast, however, the diastereoselectivity observed is poor in our case. This is likely due to the third benzyloxy substituent on the nitrones such as **C** (R' = Bn; R = CH<sub>2</sub>OBn, Scheme 1) used by Kaliappan, which can induce a much higher diastereofacial control in cycloadditions.<sup>5,9b,9c,13</sup>

As noted above, side product **5a** was always found in the reaction mixture with a yield up to 29%, according to the different reaction conditions. Compound **5a** contains a phenol substituted pyrrole ring, a substructure that recalls the occurrence of a cycloaddition process, but the pyrrolidine ring, besides aromatization, has lost a *t*-BuO substituent, and, moreover, has undergone *N*-phenyl substitution. Structure **5a** was readily assigned by NMR spectroscopic analysis.<sup>14</sup> In particular, <sup>1</sup>H NMR deuterium exchange experiments showed that the singlet at 8.18 ppm disappears on addition of D<sub>2</sub>O, consistent with the presence of a phenol moiety. Moreover, the NMR resonances corresponding to 4-H and 5-H [6.14 and 6.84 ppm (d, *J* = 3.2 Hz)] and C-4 and C-5 [105.1 ppm (dd, *J* = 173.3, 7.2 Hz) and 122.4 (dd, *J* = 187.6, 7.0 Hz)] are very similar to the corresponding signals previously measured on analogously substituted pyrroles.<sup>15</sup>

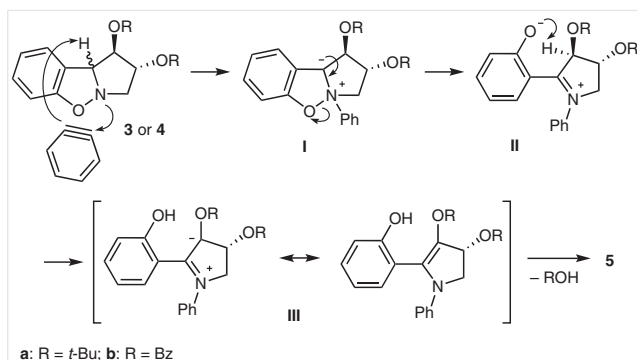
Switching to a differently protected nitrone, bis-benzyloxy nitrone **1b**<sup>6c</sup> was reacted with benzyne under the same conditions (Bu<sub>4</sub>NF/DMF/r.t.).<sup>10</sup> The reaction afforded an inseparable mixture of cycloadducts **3b** and **4b**, and, again, the corresponding pyrrole derivative **5b** in roughly 1.1:1:0.4 ratio, respectively. In this case, as expected, the cycloaddition diastereoselectivity was lower compared with the corresponding cycloaddition of **1a**, because of the minor steric demand of the benzyloxy group. Adducts **3b** and **4b** are characterized by 1-H/9b-H coupling constant values similar to the corresponding *tert*-butoxy derivatives **3a** and **4a** [*J*<sub>1/9b</sub>(Hz): **3a** and **3b** ca. 0; **4a** and **4b** 6.8 and 6.3].

The  $^1\text{H}$  NMR spectrum of pyrrole **5b** shows the same AX system of **5a** due to the resonance of protons 4-H and 5-H [7.02 and 6.43 ppm (d,  $J = 3.2$  Hz)].

It has therefore been demonstrated that formation of the side-product **5** occurs in the presence of both the *tert*-butyl and benzoyl protecting groups. Moreover, control experiments of mixing **4a** with **2** under the usual reaction conditions established that **5** originates from reaction of a molecule of cycloadduct with a second molecule of benzyne.

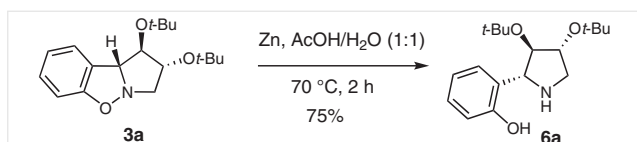
The mechanism shown in Scheme 3 is consistent with the experimental data. The rather nucleophilic cycloadduct adds to the electrophilic benzyne, which, in turn, can extract the benzylic 9b-H proton. Intermediate **I** then undergoes N–O bond cleavage to **II**. Intramolecular deprotonation and aromatization by elimination of a molecule of ROH provides pyrrole **5**.

To our knowledge this is the first example of such a rearrangement of nitrono-aryne cycloadducts. In Kaliappan's work<sup>4</sup> there is no mention of such a rearrangement product. However, the absence of the side product in those reactions can be explained by the lower nucleophilicity of the isoxazolidine nitrogen in **B** ( $R' = \text{Bn}$ ;  $R = \text{CH}_2\text{OBn}$ , Scheme 1), which is shielded by a bulky adjacent benzyloxymethylene group.



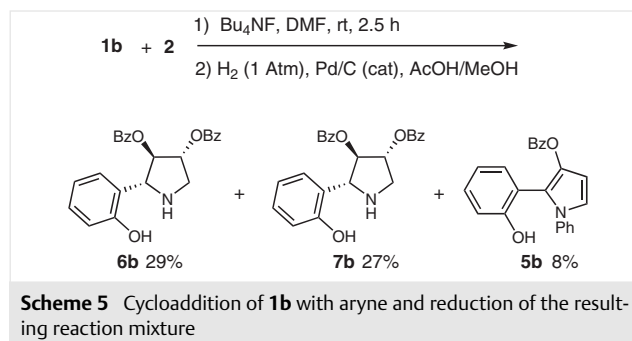
**Scheme 3** Proposed mechanism for conversion of adducts **3** and **4** into pyrrole **5**

Cycloadduct **3a** was smoothly reduced with Zn in acetic acid/water (1:1) at 70 °C for 2 h to obtain *o*-hydroxyaryl pyrrolidine **6a**<sup>16</sup> in 75% yield (Scheme 4).



**Scheme 4** Reduction of **3a**

The inseparable cycloaddition mixture of **3b**, **4b**, and **5b** was more conveniently reduced by hydrogenation on Pd/C to obtain pyrrolidines **6b**<sup>17</sup> and **7b**<sup>18</sup> and pyrrole **5b**<sup>19</sup> in 29, 27, and 8% two-step yield, respectively, after chromatographic separation (Scheme 5).



In summary, 1,3-dipolar cycloaddition of enantiopure cyclic nitrones **1** with benzyne affords benzisoxazole derivatives that can be employed to produce analogues of radicamine and codonopsinine alkaloids; this is work that is in progress in our laboratory. The adducts of both 3,4-di-*tert*-butoxy- and 3,4-bis(benzoyloxy)-pyrroline *N*-oxides **1** with benzyne undergo an unprecedented rearrangement involving a second molecule of benzyne under the reaction conditions. This novel rearrangement influences the overall yield of the cycloaddition process and should be taken into consideration by the scientific community involved in studies of alkoxyppyrraline nitrono reactions with arynes.

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## Supporting Information

Supporting information for this article is available online at <https://doi.org/10.1055/s-0037-1609082>.

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- (10) **General Procedure for the Cycloaddition Reaction:** A mixture of nitrone **1** (300 mg), **2** (1.5 equiv), and Bu<sub>4</sub>NF (1 M in THF, 1.2 equiv) in anhydrous DMF (final nitrone concentration of 0.09–0.1 M) was stirred at room temperature for 2.5 h. The DMF was evaporated under a flow of nitrogen and the crude residue was purified by chromatography on silica gel
- (11) **Compound 3a:** R<sub>f</sub> = 0.33 (EtOAc/petroleum ether, 1:16); [α]<sub>D</sub><sup>24</sup> = –90.6 (c = 0.25, CHCl<sub>3</sub>). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz): δ = 7.25 (dm, J = 7.4 Hz, 1 H, 9-H), 7.17–7.12 (m, 1 H, 7-H), 6.90 (pseudo dt, J = 0.9, 7.4 Hz, 1 H, 8-H), 6.73 (br d, J = 8.0 Hz, 1 H, 6-H), 4.77 (br s, 1 H, 9b-H), 4.13–4.10 (m, 1 H, 1-H), 3.96 (ddd, J = 6.0, 4.9, 3.6 Hz, 1 H, 2-H), 3.58 (dd, J = 11.6, 4.9 Hz, 1 H, 3-Ha), 3.16 (ddm, J = 11.6, 6.0 Hz, 1 H, 3-Hb), 1.29 (s, 9 H, 3 × CH<sub>3</sub>), 1.06 (s, 9 H, 3 × CH<sub>3</sub>). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 50 MHz): δ = 156.3 (s, C-5a), 128.5 (d, C-7), 127.1 (s, C-9a), 123.4 (d, C-9), 120.9 (d, C-8), 107.1 (d, C-6), 82.0 (d, C-1), 76.6 (d, C-2), 75.6 (d, C-9b), 74.5 (s, CMe<sub>3</sub>), 73.6 (s, CMe<sub>3</sub>), 62.1 (t, C-3), 28.7 (q, 3C, 3 × CH<sub>3</sub>), 28.3 (q, 3C, 3 × CH<sub>3</sub>). IR (CDCl<sub>3</sub>): 2977, 2871, 1597, 1480, 1456, 1390, 1365, 1253, 1190, 1099, 1079 cm<sup>-1</sup>. MS (\*ESI): m/z = 306 [M+H]<sup>+</sup>, 250 [M+H-(isobutene)]<sup>+</sup>, 194 [M+H-2(isobutene)]<sup>+</sup>. C<sub>18</sub>H<sub>27</sub>NO<sub>3</sub> (305.41): calcd. C, 70.79; H, 8.91; N, 4.59; found: C, 70.56; H, 8.69; N, 4.98
- (12) **Compound 4a:** R<sub>f</sub> = 0.23 (EtOAc/petroleum ether, 1:16); [α]<sub>D</sub><sup>21</sup> = –12.7 (c = 0.22, CHCl<sub>3</sub>). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz): δ = 7.32 (br d, J = 7.5 Hz, 1 H, 9-H), 7.17 (pseudo tm, J = 8.0 Hz, 1 H, 7-H), 6.91 (pseudo dt, J = 0.8, 7.4 Hz, 1 H, 8-H), 6.76 (br d, J = 8.1 Hz, 1 H, 6-H), 4.87 (d, J = 6.8 Hz, 1 H, 9b-H), 4.24 (pseudo t, J = 7.2 Hz, 1 H, 1-H), 3.82 (pseudo q, J = 7.9 Hz, 1 H, 2-H), 3.49 (dd, J = 14.0, 7.6 Hz, 1 H, 3-Ha), 3.23 (dd, J = 14.0, 8.6 Hz, 1 H, 3-Hb), 1.28 (s, 9 H, 3 × CH<sub>3</sub>), 1.11 (s, 9 H, 3 × CH<sub>3</sub>). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 50 MHz): δ = 157.2 (s, C-5a), 128.4 (d, C-7), 125.9 (d, C-9), 125.2 (s, C-9a), 120.8 (d, C-8), 107.2 (d, C-6), 77.6 (d, C-1), 74.3 (s, CMe<sub>3</sub>), 73.7 (s, CMe<sub>3</sub>), 73.0 (d, C-2), 68.4 (d, C-9b), 62.5 (t, C-3), 28.5 (q, 6C, 6 × CH<sub>3</sub>). IR (CDCl<sub>3</sub>): 2977, 2935, 1593, 1474, 1458, 1390, 1365, 1236, 1192, 1119 cm<sup>-1</sup>. MS (ESI): m/z = 306 [M+H]<sup>+</sup>, 250 [M+H-(isobutene)]<sup>+</sup>, 194 [M+H-2(isobutene)]<sup>+</sup>. C<sub>18</sub>H<sub>27</sub>NO<sub>3</sub> (305.41): calcd. C, 70.79; H, 8.91; N, 4.59; found: C, 70.51; H, 9.12; N, 4.56
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- (14) **Compound 5a:** R<sub>f</sub> = 0.35 (EtOAc/petroleum ether, 1:32), one orange spot with p-anisaldehyde stain. Mp = 110–112 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz): δ = 8.18 (s, 1 H, OH, disappears on addition of D<sub>2</sub>O), 7.30–7.25 (m, 2 H, H<sub>Ar</sub>), 7.24–7.18 (m, 1 H, H<sub>Ar</sub>), 7.11–7.01 (m, 4 H, H<sub>Ar</sub>), 6.84 (d, J = 3.2 Hz, 1 H, 5-H), 6.60–6.51 (m, 2 H, H<sub>Ar</sub>), 6.14 (d, J = 3.2 Hz, 1 H, 4-H), 1.23 (s, 9 H, 3 × CH<sub>3</sub>). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz): δ = 153.7 (s, C<sub>Ar</sub>), 140.7 (s, C<sub>Ar</sub>), 139.5 (s, C<sub>Ar</sub>), 130.8 (d, CH<sub>Ar</sub>), 128.9 (d, 2C, CH<sub>Ar</sub>), 128.0 (d, CH<sub>Ar</sub>), 126.3 (d, CH<sub>Ar</sub>), 125.3 (d, 2C, CH<sub>Ar</sub>), 122.4 (d, C-5), 120.9 (s, C<sub>Ar</sub>), 119.6 (d, CH<sub>Ar</sub>), 119.0 (s, C<sub>Ar</sub>), 118.3 (d, CH<sub>Ar</sub>), 105.1 (d, C-4), 81.6 (s, CMe<sub>3</sub>), 28.0 (q, 3C, 3 × CH<sub>3</sub>). C/H coupled <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz): δ = (selection of signals) = 122.4 (dd, J = 187.6, 7.0 Hz, C-5), 105.1 (dd, J = 173.3, 7.2 Hz, C-4). IR (CDCl<sub>3</sub>): 3255 (broad), 3075, 2981, 2934, 1599, 1556, 1502, 1352, 1235, 1164 cm<sup>-1</sup>. MS (\*ESI): m/z = 330 [M+Na]<sup>+</sup>. MS (-ESI): m/z = 307 [M]<sup>-</sup>. HRMS (\*ESI): m/z [MH]<sup>+</sup> calcd for C<sub>20</sub>H<sub>22</sub>NO<sub>2</sub><sup>+</sup>: 308.16451; found: 308.16444
- (15) (a) McNab, H.; Monahan, L. C. *J. Chem. Soc., Perkin Trans. 2* **1991**, 1999. (b) Zhang, M.; Fang, X.; Neumann, H.; Beller, M. *J. Am. Chem. Soc.* **2013**, *135*, 11384.
- (16) **Compound 6a:** R<sub>f</sub> = 0.31. Mp = 124–125 °C. [α]<sub>D</sub><sup>21</sup> = –43.4 (c = 0.43, CHCl<sub>3</sub>). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz): δ = 7.13 (pseudo dt, J = 1.7, 7.7 Hz, 1 H, H<sub>Ar</sub>), 7.00 (dd, J = 7.5, 1.7 Hz, 1 H, H<sub>Ar</sub>), 6.80 (dd, J = 8.1, 1.1 Hz, 1 H, H<sub>Ar</sub>), 6.74 (pseudo dt, J = 1.1, 7.4 Hz, 1 H, H<sub>Ar</sub>), 4.08 (dd, J = 7.9, 5.3 Hz, 1 H, 3-H), 3.99 (dd, J = 7.4, 5.3 Hz, 1 H, 4-H), 3.94 (d, J = 7.9 Hz, 1 H, 2-H), 3.30 (dd, J = 10.6, 7.4 Hz, 1 H, 5-Ha), 3.01 (dd, J = 10.6, 4.4 Hz, 1 H, 5-Hb), 1.19 (s, 9 H, 3 × CH<sub>3</sub>), 0.93 (s, 9 H, 3 × CH<sub>3</sub>). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz): δ = 158.0 (s, C<sub>Ar</sub>), 129.6 (d, CH<sub>Ar</sub>), 128.7 (d, CH<sub>Ar</sub>), 123.3 (s, C<sub>Ar</sub>), 118.4 (d, CH<sub>Ar</sub>), 116.7 (d, CH<sub>Ar</sub>), 80.7 (d, C-3), 76.3 (d, C-4), 74.6 (s, CMe<sub>3</sub>), 73.8 (s, CMe<sub>3</sub>), 66.6 (d, C-2), 50.9 (t, C-5), 28.7 (q, 3C, 3 × CH<sub>3</sub>), 28.6 (q, 3C, 3 × CH<sub>3</sub>). IR (CDCl<sub>3</sub>): 2977, 2935, 1589, 1489, 1392, 1367, 1257, 1190, 1106, 1068 cm<sup>-1</sup>. MS (\*ESI):

$m/z = 308$   $[M+H]^+$ . MS (-ESI):  $m/z = 306$   $[M-H]^-$ .  $C_{18}H_{29}NO_3$  (307.43): calcd. C, 70.32; H, 9.51; N, 4.56; found: C, 70.53; H, 9.66; N, 4.17

- (17) **Compound 6b**:  $R_f = 0.15$  (EtOAc/petroleum ether, 1:4). Mp = 162–164 °C.  $[\alpha]_D^{27} = -57.4$  ( $c = 1.0$ ,  $CHCl_3$ ).  $^1H$  NMR ( $CDCl_3$ , 400 MHz):  $\delta = 8.08$ – $8.03$  (m, 2 H,  $H_{Bz}$ ), 8.96–7.91 (m, 2 H,  $H_{Bz}$ ), 7.63–7.58 (m, 1 H,  $H_{Bz}$ ), 7.57–7.52 (m, 1 H,  $H_{Bz}$ ), 7.50–7.44 (m, 2 H,  $H_{Bz}$ ), 7.43–7.37 (m, 2 H,  $H_{Bz}$ ), 7.23 (dd,  $J = 7.6$ , 1.6 Hz, 1 H,  $H_{Ar}$ ), 7.18 (pseudo dt,  $J = 1.6$ , 7.7 Hz, 1 H,  $H_{Ar}$ ), 6.88 (dd,  $J = 8.2$ , 1.2 Hz, 1 H,  $H_{Ar}$ ), 6.80 (pseudo dt,  $J = 1.2$ , 7.4 Hz, 1 H,  $H_{Ar}$ ), 5.71 (dd,  $J = 4.3$ , 1.6 Hz, 1 H, 3-H), 5.62 (pseudo dt,  $J = 5.5$ , 1.6 Hz, 1 H, 4-H), 4.68 (d,  $J = 4.3$  Hz, 1 H, 2-H), 3.70 (dd,  $J = 12.1$ , 5.5 Hz, 1 H, 5-Ha), 3.44 (dm,  $J = 12.1$  Hz, 1 H, 5-Hb).  $^{13}C$  NMR ( $CDCl_3$ , 100 MHz):  $\delta = 165.7$  (s, CO), 165.3 (s, CO), 157.8 (s,  $C_{Ar}$ ), 133.5 (d,  $CH_{Bz}$ ), 133.3 (d,  $CH_{Bz}$ ), 129.9 (d, 2C,  $CH_{Bz}$ ), 129.7 (d, 2C,  $CH_{Bz}$ ), 129.3 (s,  $C_{Bz}$ ), 129.2 (s,  $C_{Bz}$ ), 129.1 (d,  $CH_{Ar}$ ), 128.5 (d, 2C,  $CH_{Bz}$ ), 128.4 (d,  $CH_{Ar}$ ), 128.3 (d, 2C,  $CH_{Bz}$ ), 121.1 (s,  $C_{Ar}$ ), 119.2 (d,  $CH_{Ar}$ ), 117.4 (d,  $CH_{Ar}$ ), 83.0 (d, C-3), 77.3 (d, C-4), 67.0 (d, C-2), 51.2 (t, C-5). IR ( $CDCl_3$ ): 3348, 3065, 2959, 2858, 1719, 1602, 1585, 1491, 1451, 1278, 1258, 1110  $cm^{-1}$ . MS (+ESI):  $m/z = 404$   $[M+H]^+$ . MS (-ESI):  $m/z = 402$   $[M-H]^-$ .  $C_{24}H_{21}NO_5$  (403.43): calcd. C, 71.45; H, 5.25; N, 3.47; found: C, 71.08; H, 5.07; N, 3.44
- (18) **Compound 7b**:  $R_f = 0.34$  (EtOAc/petroleum ether, 1:4). Mp = 60–62 °C.  $[\alpha]_D^{26} = -45.3$  ( $c = 0.5$ ,  $CHCl_3$ ).  $^1H$  NMR ( $CDCl_3$ , 400 MHz):  $\delta = 8.11$ – $8.07$  (m, 2 H,  $H_{Bz}$ ), 7.97–7.93 (m, 2 H,  $H_{Bz}$ ), 7.66–7.60 (m, 1 H,  $H_{Bz}$ ), 7.54–7.47 (m, 3 H,  $H_{Bz}$ ), 7.40–7.35 (m, 2 H,  $H_{Bz}$ ), 7.08–7.00 (m, 2 H,  $H_{Ar}$ ), 6.76 (dd,  $J = 8.2$ , 1.2 Hz, 1 H,  $H_{Ar}$ ), 6.72 (pseudo dt,  $J = 1.2$ , 7.4 Hz, 1 H,  $H_{Ar}$ ), 5.77 (dd,  $J = 4.7$ ,

1.1 Hz, 1 H, 3-H), 5.55 (dm,  $J = 5.1$  Hz, 1 H, 4-H), 4.97 (d,  $J = 4.7$  Hz, 1 H, 2-H), 3.85 (dd,  $J = 12.6$ , 5.1 Hz, 1 H, 5-Ha), 3.35 (dd,  $J = 12.6$ , 2.3 Hz, 1 H, 5-Hb).  $^{13}C$  NMR ( $CDCl_3$ , 100 MHz):  $\delta = 165.3$  (s, CO), 165.2 (s, CO), 159.2 (s,  $C_{Ar}$ ), 133.6 (d,  $CH_{Bz}$ ), 133.2 (d,  $CH_{Bz}$ ), 129.9 (d, 2C,  $CH_{Bz}$ ), 129.8 (d, 2C,  $CH_{Bz}$ ), 129.3 (s,  $C_{Bz}$ ), 129.1 (s,  $C_{Bz}$  + d,  $CH_{Ar}$ ), 128.6 (d, 2C,  $CH_{Bz}$ ), 128.5 (d,  $CH_{Ar}$ ), 128.3 (d, 2C,  $CH_{Bz}$ ), 118.8 (d,  $CH_{Ar}$ ), 118.4 (s,  $C_{Ar}$ ), 117.1 (d,  $CH_{Ar}$ ), 78.8 (d, C-3), 77.1 (d, C-4), 65.0 (d, C-2), 50.3 (t, C-5). IR ( $CDCl_3$ ): 3366, 3065, 2958, 2871, 1721, 1601, 1586, 1492, 1452, 1316, 1260, 1109  $cm^{-1}$ . MS (+ESI):  $m/z = 404$   $[M+H]^+$ . MS (-ESI):  $m/z = 402$   $[M-H]^-$ .  $C_{24}H_{21}NO_5$  (403.43): calcd. C, 71.45; H, 5.25; N, 3.47; found: C, 71.44; H, 5.13; N, 3.37

- (19) **Compound 5b**:  $R_f = 0.52$  (EtOAc/petroleum ether, 1:4), one red spot with *p*-anisaldehyde stain. Mp = 135–137 °C (dec).  $^1H$  NMR ( $CDCl_3$ , 400 MHz):  $\delta = 8.15$ – $8.09$  (m, 2 H,  $H_{Bz}$ ), 7.62–7.56 (m, 1 H,  $H_{Bz}$ ), 7.49–7.42 (m, 2 H,  $H_{Bz}$ ), 7.31–7.11 (m, 6 H,  $H_{Ar}$ ), 7.03 (d,  $J = 3.2$  Hz, 1 H, 5-H), 6.93 (dm,  $J = 8.2$  Hz, 1 H,  $H_{Ar}$ ), 6.88 (dd,  $J = 7.6$ , 1.6 Hz, 1 H,  $H_{Ar}$ ), 6.76–6.69 (m, 1 H,  $H_{Ar}$ ), 6.44 (d,  $J = 3.2$  Hz, 1 H, 4-H), 6.06 (br s, 1 H, OH).  $^{13}C$  NMR ( $CDCl_3$ , 100 MHz):  $\delta = 165.8$  (s, CO), 154.8 (s,  $C_{Ar}$ ), 139.6 (s,  $C_{Ar}$ ), 136.8 (s,  $C_{Ar}$ ), 133.6 (d,  $CH_{Bz}$ ), 132.1 (d,  $CH_{Ar}$ ), 130.3 (d, 2C,  $CH_{Bz}$ ), 130.1 (d,  $CH_{Ar}$ ), 129.0 (d, 2C,  $CH_{Ar}$ ), 128.9 (s,  $CH_{Bz}$ ), 128.5 (d, 2C,  $CH_{Bz}$ ), 126.8 (d,  $CH_{Ar}$ ), 124.9 (d, 2C,  $CH_{Ar}$ ), 121.6 (d, C-5), 120.1 (d,  $CH_{Ar}$ ), 117.3 (s,  $C_{Ar}$ ), 116.4 (s,  $C_{Ar}$ ), 116.1 (d,  $CH_{Ar}$ ), 103.3 (d, C-4). IR ( $CDCl_3$ ): 3072, 2927, 1726, 1600, 1502, 1356, 1267, 1228, 1068, 1025  $cm^{-1}$ . MS (+ESI):  $m/z = 356$   $[M+1]^+$ . MS (-ESI):  $m/z = 354$   $[M-1]^-$ . HRMS (+ESI):  $m/z$   $[MH]^+$  calcd for  $C_{23}H_{18}NO_3^+$ : 356.12812; found: 356.12788