

INVESTIGATIONS ON THE CHEMISTRY OF BERBANES 14.<sup>1</sup>  
A NOVEL STEREOSELECTIVE APPROACH TO BIOLOGICALLY  
ACTIVE *ALLO*-BERBANE DERIVATIVES

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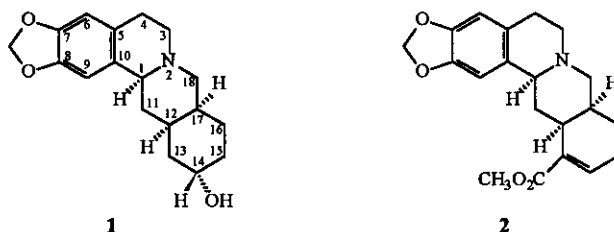
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**Abstract** - Stereoselective total synthesis of  $\alpha_2$  adrenoceptor agents (1) and (2) with *allo*-berbane skeleton has been performed *via* Knoevenagel-type condensation of ketones (3).

*Dedicated to Professor Arnold Brossi on the occasion of his 70th birthday.*

The stereoselective synthesis of *allo*-berbane skeleton as well as of numerous derivatives containing this moiety was published a few years ago.<sup>2</sup> Pharmacological studies on berbane derivatives and their intermediates revealed that this family of alkaloid-like compounds possesses interesting biological activities.<sup>3-5</sup> First of all two *allo*-berbane derivatives, the 14 $\alpha$ -hydroxy-*allo*-berbane (1)<sup>4</sup> and the methyl  $\Delta^{13,14}$ -*allo*-berbane-13-carboxylate (2)<sup>5</sup> have been emerged as extremely selective  $\alpha_2$  adrenoceptor blocking agents. This positive pharmacological behaviour of 1 and 2 turned our attention again to *allo*-berbanes and urged us to find a more efficient and more stereoselective approach to their total synthesis.



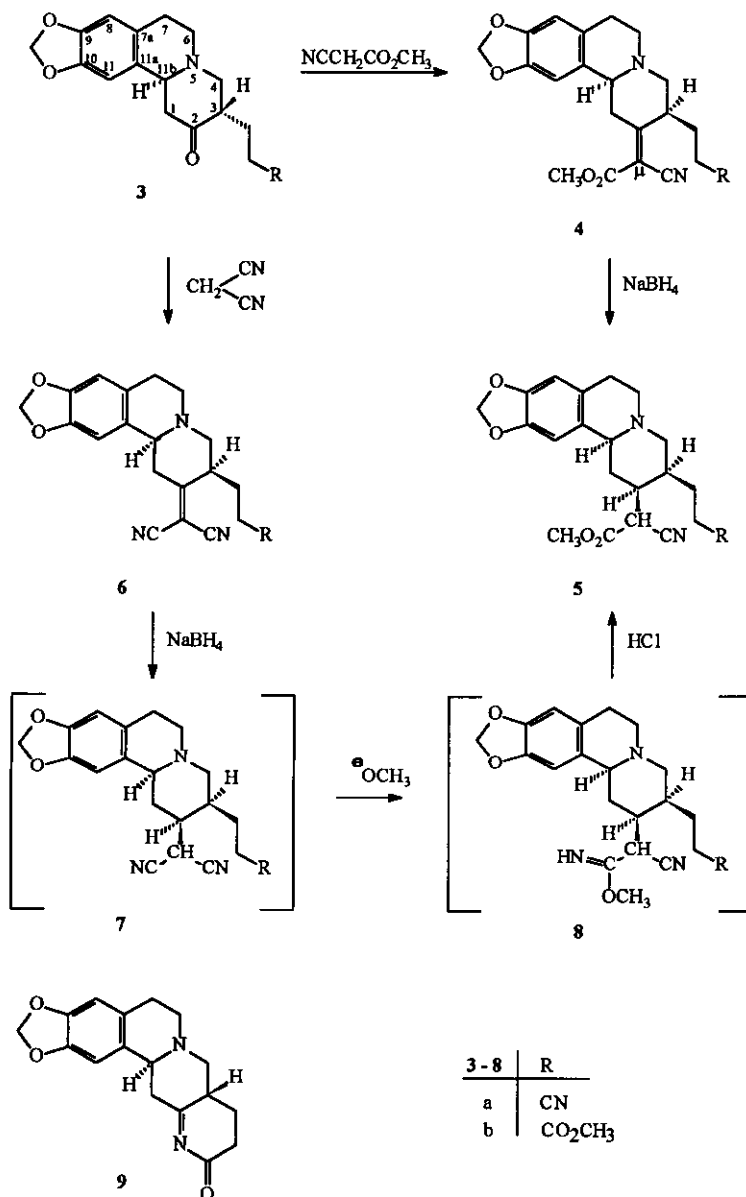
The C(3) epimerization in the course of some condensation reactions of 3-substituted quinolizidin-2-ones is well established. It was **Brossi** and coworkers<sup>6</sup> who observed this phenomenon while performing Knoevenagel condensation of 9,10-dimethoxy-3 $\alpha$ -ethylbenzo[*a*]quinolizidin-2-one (type **3**) with ethyl cyanoacetate. The complete epimerization occurring during the reaction was later utilized in the total synthesis of (-)-corynantheidine<sup>7</sup> and of 9,10-dimethoxydespyrrolocorynantheidine,<sup>8</sup> which was thus accomplished with almost complete stereoselectivity.

In this paper we wish to present the utilization of the Knoevenagel condensation of ketones (**3**) in the stereoselective formation of the *allo*-berbane skeleton through key intermediate (**11**), thus facilitating a highly stereoselective approach to *allo*-berbane derivatives (**1**) and (**2**).

Condensation of cyano ketone (**3a**) with methyl cyanoacetate in boiling benzene in the presence of NH<sub>4</sub>OAc/AcOH catalyst resulted in epimerization at C(3) and adduct (**4a**)<sup>9</sup> was obtained in 80–85% yield. Sodium borohydride reduction of the exocyclic double bond<sup>7,8</sup> has been performed also with high diastereoselectivity, thus *allo* cyanoacetate (**5a**)<sup>10</sup> could be obtained in 65–70% combined yield. Even higher yield was obtained if ketone (**3a**) was reacted with malononitrile; a complete C(3) epimerization and almost quantitative yield of trinitrile (**6a**)<sup>11</sup> was achieved. Sodium borohydride reduction supplied us with *allo* trinitrile (**7a**) as the only stereo-isomer, which upon standing in solution was transformed to imino ether (**8a**) by base catalyzed methanol addition. Imino ether (**8a**), stable in basic and neutral media, is immediately hydrolyzed to *allo* cyanoacetate (**5a**) when treated with HCl. The three-step sequence from **6a** to **5a** could be realized in one pot with 80–85% yield. Of course, both *allo* trinitrile (**7a**) and imino ether (**8a**) could be isolated from the reaction mixture by interrupting the whole process and working up appropriately, and were characterized by spectroscopical means (<sup>1</sup>H- and <sup>13</sup>C-nmr, ir, ms).

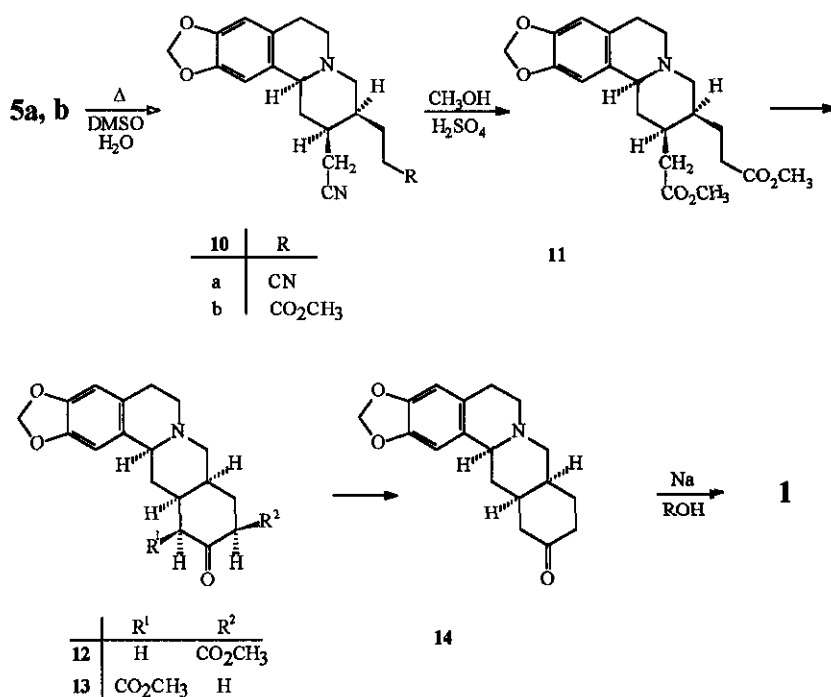
Cyanoacetate condensation of keto ester (**3b**) resulted in a very small amount of adduct (**4b**). The main product of the reaction, the 13-azaberbanone derivative (**9**)<sup>12</sup> can be obtained, of course, if methyl cyanoacetate is

omitted from the reaction mixture. With malononitrile in  $\text{CH}_2\text{Cl}_2$  at room temperature in the presence of  $\text{NH}_4\text{OAc}$  catalyst the condensation proceeds similarly to that of **3a**, and adduct (**6b**)<sup>13</sup> is obtained in almost quantitative yield. Transformation of **6b** into *allo* cyano ester derivative (**5b**)<sup>10</sup> via **7b** and **8b** is analogous to the



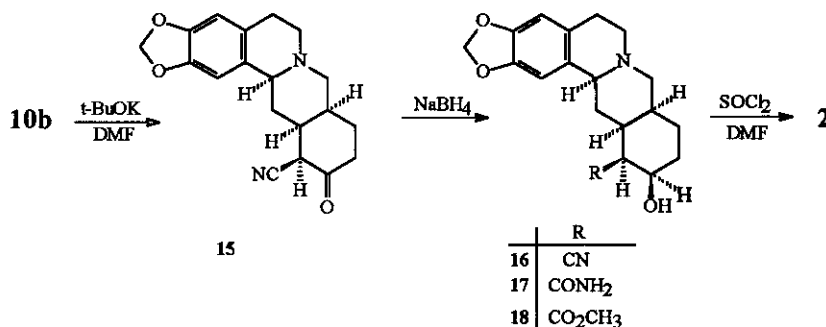
3-cyanoethyl series (6a → 5a).

Having these two *allo* precursors in hand the next problem to be solved was to modify the C(2) substituent suitable for the total synthesis of *allo*-berbanol (1). This goal has been attained in a one-step demethoxycarbonylation process of 5 by refluxing it in DMF or more preferably in DMSO in the presence of equivalent amount of water for 2–3 hours. Both *allo* acetonitriles (10a and 10b),<sup>14</sup> obtained in 75–80% yield could be then converted into diester (11)<sup>15</sup> by methanolysis (H<sub>2</sub>SO<sub>4</sub>/CH<sub>3</sub>OH). From this point our earlier pathway<sup>2</sup> via Dieckmann products (12) and (13) as well as ketone (14) can be applied. Thus in this way *allo* diester (11) can be prepared from ketones (3a) and (3b) in high diastereoselectivity and in 60–65% combined yield, while our original phosphonoacetate method<sup>2</sup> resulted in 65–70% stereoselectivity and consequently lower yield (38–40%).



As it has been demonstrated earlier,<sup>5,16</sup> *allo*-berbene-13-carboxylate (2) can be produced from 13, which could only be isolated by preparative tlc from the mixture of regioisomers (12) and (13), containing the required 13 in slightly smaller amount (12:13 ~ 3:2). The above outlined method provides higher yield and stereoselectivity

than the previously elaborated one. Cyano ester (**10b**), obtained from keto ester (**3b**) via **6b**→[**7b**]→[**8b**]→**5b**→**10b**, underwent regioselective Dieckmann condensation and gave a structurally and stereochemically uniform *allo*-berbanone derivative (**15**).<sup>17</sup> Direct acidic methanolysis of the cyano group could not be accomplished either in cyano ketone (**15**) or in cyano alcohol (**16**),<sup>18</sup> obtained by NaBH<sub>4</sub> reduction of the former. The CN → CO<sub>2</sub>CH<sub>3</sub> transformation was, however, performed in two steps: peroxide catalyzed basic hydrolysis of **16** led to amid (**17**),<sup>19</sup> the acidic methanolysis (HCl/CH<sub>3</sub>OH) of which gave hydroxy ester (**18**)<sup>20</sup> in 48% combined yield from **10b**. Elimination of elements of water from **18** was carried out with thionyl chloride in DMF at room temperature to produce the target molecule (**2**)<sup>21</sup> in racemic form.



## REFERENCES AND NOTES

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- All new compounds were characterized by ir, <sup>1</sup>H-, <sup>13</sup>C-nmr as well as by ms spectroscopy. Selected physi-

cal and spectroscopical data are given below.

Really a mixture of E and Z isomers is formed in the Knoevenagel condensation of **3a** with methyl cyanoacetate (E : Z  $\approx$  4 : 1 on the basis of  $^1\text{H}$ -nmr measurement of the crude product). This mixture, obtained in 80–85% yield, can be used for the synthesis without separation. Repeated recrystallization resulted in a pure sample of the major isomer **4a**; mp: 159 °C (MeOH–Et<sub>2</sub>O); ir(KBr):  $\nu$  1620 (C=C), 1715 (conj. C=O), 2220 (conj. CN), 2240 (CN), 2780–2840 cm<sup>-1</sup> (Bohlmann bands);  $^1\text{H}$ -nmr(CDCl<sub>3</sub>):  $\delta$  4.04 (1H, dd,  $J=12$  and 2.5 Hz, C11b–H), 3.91 (3H, s, CO<sub>2</sub>CH<sub>3</sub>), 4.56 (1H, dd,  $J=14.5$  and 2.5 Hz, C1–H<sub>eq</sub>), 5.95 (2H, s, OCH<sub>2</sub>O), 6.59 (1H, s, C8–H), 6.71 ppm (1H, s, C11–H). For Z geometric isomer of **4a**  $^1\text{H}$ -nmr peaks at  $\delta$  3.48 (1H, dd,  $J=14.5$  and 2.5 Hz, C1–H<sub>eq</sub>) and 3.88 ppm (3H, s, CO<sub>2</sub>CH<sub>3</sub>) are characteristic.

10. **5a** mp: 147 °C (Et<sub>2</sub>O); ir(KBr):  $\nu$  1725 (C=O), 2235 (CN), 2780–2850 cm<sup>-1</sup> (Bohlmann bands);  $^1\text{H}$ -nmr (CDCl<sub>3</sub>):  $\delta$  3.15 (1H, m, C11b–H), 3.44 (1H, d,  $J=10$  Hz,  $\mu\text{CH}$ ), 3.90 (3H, s, CO<sub>2</sub>CH<sub>3</sub>), 5.90 (2H, s, OCH<sub>2</sub>O), 6.55 (1H, s, C8–H), 6.70 (1H, s, C11–H); ms m/z(%): 381(M<sup>+</sup>,70), 380(67), 283(100), 256(28), 217(70), 190(73), 176(41).
- 5b** total yield from **6b**: 85%; mp: 146–147 °C (MeOH); ir(KBr):  $\nu$  1725 and 1740 (C=O), 2235 cm<sup>-1</sup> (CN);  $^1\text{H}$ -nmr(CDCl<sub>3</sub>):  $\delta$  3.52 (1H, dd,  $J=10$  and 3.5 Hz, C11b–H), 3.67 (3H, s, CH<sub>2</sub>CO<sub>2</sub>CH<sub>3</sub>), 3.89 (3H, s,  $\mu\text{CHCO}_2\text{CH}_3$ ), 5.90 (2H, s, OCH<sub>2</sub>O), 6.54 (1H, s, C8–H), 6.72 ppm (C11–H);  $^{13}\text{C}$ -nmr(CDCl<sub>3</sub>):  $\delta$  29.7 (C7), 41.3 ( $\mu\text{C}$ ), 51.6 (CH<sub>2</sub>CO<sub>2</sub>CH<sub>3</sub>), 53.6 ( $\mu\text{CHCO}_2\text{CH}_3$ ), 62.7 (C11b), 115.2 (CN), 165.9 ( $\mu\text{CHCO}_2\text{CH}_3$ ), 173.6 ppm (CH<sub>2</sub>CO<sub>2</sub>CH<sub>3</sub>). (Because of an additional chiral center in the side-chain attached to C2, majority of the signals both in  $^1\text{H}$  and  $^{13}\text{C}$ -nmr spectra of **5a** and **5b** are duplicated.); ms m/z(%): 414 (M<sup>+</sup>,28), 413(26), 383(16), 355(7), 316(100), 288(14), 216(15), 175(23).
11. **6a** mp: 178 °C (MeOH); ir(KBr):  $\nu$  1620 (C=C), 2220 (conj. CN), 2240 cm<sup>-1</sup> (CN);  $^1\text{H}$ -nmr(CDCl<sub>3</sub>):  $\delta$  3.27 (1H, dd,  $J=11.2$  and 3 Hz, C11b–H), 3.41 (1H, dd,  $J=14$  and 3 Hz, C1–H<sub>eq</sub>), 5.94 (2H, s, OCH<sub>2</sub>O), 6.58 (1H, s, C8–H), 6.63 ppm (1H, s, C11–H);  $^{13}\text{C}$ -nmr(CDCl<sub>3</sub>):  $\delta$  15.3 (CH<sub>2</sub>CN), 28.4 (CH<sub>2</sub>CH<sub>2</sub>CN), 29.6 (C7), 37.8 (C1), 42.5 (C3), 51.3 (C6), 58.7 (C4), 63.0 (C11b), 85.6 ( $\mu\text{C}$ ), 101.1 (OCH<sub>2</sub>O), 104.6 (C11), 108.7 (C8), 110.9 and 111.0 (conj. CN), 118.3 (CN), 110.9 and 111.0 (C7a and C11a), 146.5 and 146.7 (C9 and C10), 181.1 ppm (C2).
12. L. Szabó, L. Dobay, L. Radics, and Cs. Szántay, *Nouveau Journal de Chimie*, 1980, 4, 199.
13. **6b** mp: 140–141 °C (MeOH); ir(KBr):  $\nu$  1735 (C=O), 2215 cm<sup>-1</sup> (conj. CN);  $^1\text{H}$ -nmr(CDCl<sub>3</sub>):  $\delta$  3.21 (1H, dd,  $J=11.5$  and 3 Hz, C11b–H), 3.34 (1H, dd,  $J=14$  and 3 Hz, C1–H<sub>eq</sub>), 3.69 (3H, s, CO<sub>2</sub>CH<sub>3</sub>), 5.92 (2H, s, OCH<sub>2</sub>O), 6.56 (1H, s, C8–H), 6.64 ppm (1H, s, C11–H);  $^{13}\text{C}$ -nmr(CDCl<sub>3</sub>):  $\delta$  28.2 (CH<sub>2</sub>CH<sub>2</sub>CO<sub>2</sub>CH<sub>3</sub>), 29.6 (C7), 31.5 (C1), 37.6 (CH<sub>2</sub>CO<sub>2</sub>CH<sub>3</sub>), 42.8 (C3), 51.3 (C6), 52.0 (OCH<sub>3</sub>), 59.5 (C4), 63.1 (C11b), 84.6 ( $\mu\text{C}$ ), 101.1 (OCH<sub>2</sub>O), 104.7 (C11), 108.7 (C8), 111.2 and 111.3 (CN), 128.0 and 128.1 (C7a and C11a), 146.4 and 146.6 (C9 and C10), 172.7 (C=O), 183.2 ppm (C2); ms m/z(%): 379(M<sup>+</sup>,98), 378(76), 348(26), 304(6), 293(26), 292(17), 290(10), 214(19), 189(33), 187(36), 175(100), 174(45).
14. **10a** mp: 138 °C (MeOH–Et<sub>2</sub>O); ir(KBr):  $\nu$  2235 cm<sup>-1</sup> (CN);  $^1\text{H}$ -nmr(CDCl<sub>3</sub>):  $\delta$  3.11 (1H, dd,  $J=11.3$  and 7 Hz, C11b–H), 5.91 (2H, s, OCH<sub>2</sub>O), 6.53 (1H, s, C8–H), 6.66 ppm (1H, s, C11–H);  $^{13}\text{C}$ -nmr(CDCl<sub>3</sub>):  $\delta$  15.3 (CH<sub>2</sub>CH<sub>2</sub>CN), 20.9 (CH<sub>2</sub>CN), 21.4 (CH<sub>2</sub>CH<sub>2</sub>CN), 29.8 (C7), 33.3 (C1), 36.0 (C3), 37.3 (C2), 52.5 (C6), 57.8 (C4), 62.8 (C11b), 100.8 (CH<sub>2</sub>O), 104.7 (C11), 108.5 (C8), 118.2 and 119.5 (CN), 127.9 (C11a), 130.1 (C7a), 146.0 and 146.1 ppm (C9 and C10).

- 10b** mp of HCl salt: 215–216 °C (MeOH–Et<sub>2</sub>O); ir(KBr):  $\nu$  1735 (C=O), 2240 cm<sup>-1</sup> (CN); <sup>1</sup>H-nmr(CDCl<sub>3</sub>):  $\delta$  3.07 (1H, dd,  $J=11$  and 3.5 Hz, C11b–H), 3.68 (3H, s, OCH<sub>3</sub>), 5.91 (2H, s, OCH<sub>2</sub>O), 6.54 (1H, s, C8–H), 6.69 ppm (1H, s, C11–H); <sup>13</sup>C-nmr(CDCl<sub>3</sub>):  $\delta$  19.0 (CH<sub>2</sub>CN), 20.5 (CH<sub>2</sub>CH<sub>2</sub>CO<sub>2</sub>CH<sub>3</sub>), 28.8 (C7), 31.0 (C1), 35.3 (C3), 32.2 (CH<sub>2</sub>CO<sub>2</sub>CH<sub>3</sub>), 36.7 (C2), 50.6 (C6), 51.5 (OCH<sub>3</sub>), 57.4 (C4), 61.9 (C11b), 99.7 (OCH<sub>2</sub>O), 100.3 (C11), 100.7 (C8), 117.7 (CN), 126.9 (C11a), 129.4 (C7a), 144.9 and 145.0 (C9 and C10), 172.9 ppm (C=O); ms m/z(%): 356(M<sup>+</sup>,85), 355(100), 316(75), 288(62), 269(11), 216(52), 175(83).
- 15 Compound (**11**), prepared in this way, proved to be identical (mp, tlc, ir, nmr, ms) with authentic sample.
16. I. Tóth, L. Szabó, G. Bozsár, Cs. Szántay, L. Szekeres, and J.Gy. Papp, *J. Med. Chem.*, 1984, 27, 1411.
17. **15** yield: 84%, mp: 128–223 °C (the compound is really a keto-enol tautomeric mixture); ir(KBr):  $\nu$  1720 (C=O), 2240 (CN) for structure **15**, 1660 (C=C), 2210 (conj. CN) and 3400 (OH) for the enol form; 2780–2850 cm<sup>-1</sup> (Bohlmann bands); <sup>1</sup>H-nmr(CDCl<sub>3</sub>):  $\delta$  3.88 (1H, d,  $J=5.5$  Hz, CHCN), 5.88 and 5.90 (2H, s, OCH<sub>2</sub>O), 6.52 (1H, s, C8–H), 6.59 and 6.73 ppm (1H, s, C11–H); <sup>13</sup>C-nmr(CDCl<sub>3</sub>):  $\delta$  26.4 (C16), 29.7 (C7), 29.8 (C11), 34.8 (C17), 39.7 (C15), 42.1 (C12), 48.0 (C13), 52.3 (C3), 59.9 (C18), 62.9 (C1), 100.8 (OCH<sub>2</sub>O), 104.9 (C9), 108.4 (C6), 115.4 (CN), 127.8 (C5), 129.8 (C10), 146.0 and 146.1 (C7 and C8), 199.7 ppm (C14); (because of C13-epimerization *via* enol form in solution the majority of the nmr peaks are duplicated; in equilibrium 13 $\beta$ -CN : 13 $\alpha$ -CN  $\approx$  5 : 1); ms m/z(%): 324(M<sup>+</sup>,72), 323(100), 295(7), 284(4), 242(20), 228(16), 216(15), 189(74), 175(63).
18. **16** yield: 75–80%, mp: 227–229 °C (MeOH); ir(KBr):  $\nu$  2240 (CN), 2775–2840 (Bohlmann bands), 3400 cm<sup>-1</sup> (OH); <sup>1</sup>H-nmr(CDCl<sub>3</sub>):  $\delta$  2.91 (1H, dd,  $J=9.5$  and 3 Hz, C1–H), 4.20 (1H, q,  $J=3$  Hz, C14–H), 5.89 (2H, AB system,  $J=1.5$  Hz, OCH<sub>2</sub>O), 6.51 (1H, s, C6–H), 6.78 ppm (1H, s, C9–H); <sup>13</sup>C-nmr(CDCl<sub>3</sub>):  $\delta$  18.4 (C16), 28.7 (C4), 30.1 and 30.9 (C11 and C15), 35.1 (C13), 35.5 (C17), 37.7 (C12), 51.5 (C3), 60.9 (C18), 62.9 (C1), 64.9 (C14), 99.7 (OCH<sub>2</sub>O), 104.3 (C9), 107.3 (C6), 119.1 (CN), 126.7 (C5), 129.9 (C10), 144.8 and 145.0 ppm (C7 and C8); ms m/z(%): 326(M<sup>+</sup>,62), 325(100), 309(8), 297(5), 282(6), 267(4), 256 (5), 242(7), 228(9), 215 (14), 189(42), 175(41).
19. **17** yield: 80%; mp: 221–223 °C (Et<sub>2</sub>O–hexane); ir(KBr):  $\nu$  1660 (C=O), 2780–2840 (Bohlmann bands), 3400 cm<sup>-1</sup> (broad, OH and NH<sub>2</sub>); <sup>1</sup>H-nmr(CDCl<sub>3</sub>):  $\delta$  2.83 (1H, dd,  $J=10$  and 3 Hz, C1–H), 3.80 (1H, s, OH), 4.22 (1H, q,  $J=3$  Hz, C14–H), 5.73 and 6.71 (2x1H, s, NH<sub>2</sub>), 5.88 (2H, s, OCH<sub>2</sub>O), 6.53 (1H, s, C6–H), 6.67 ppm (1H, s, C9–H); <sup>13</sup>C-nmr(CDCl<sub>3</sub>):  $\delta$  20.4 (C16), 29.7 (C4), 30.9 (C11), 32.5 (C15), 37.1 (C17), 38.2 (C12), 50.3 (C13), 52.7 (C3), 62.4 (C18), 64.1 (C1), 66.1 (C14), 100.6 (OCH<sub>2</sub>O), 105.2 (C9), 108.3 (C6), 127.8 (C5), 131.3 (C10), 145.6 and 145.8 (C7 and C8), 177.5 ppm (C=O); ms m/z(%): 344 (M<sup>+</sup>,100), 343(78), 300(41), 282 (10), 270(6), 259(13), 242(27), 228(30), 216(20), 202(28), 189(70), 175(55).
20. **18** yield: 75–80%; mp: 159–160 °C (Et<sub>2</sub>O–hexane); ir(KBr):  $\nu$  1715 (broad, C=O assoc.), 2770–2840 (Bohlmann bands), 3450 cm<sup>-1</sup> (broad, OH assoc.); <sup>1</sup>H-nmr(CDCl<sub>3</sub>):  $\delta$  2.85 (1H, dd,  $J=10$  and 3 Hz, C1–H), 3.53 (1H, br s, OH), 3.80 (3H, s OCH<sub>3</sub>), 4.24 (1H, q,  $J=3$  Hz, C14–H), 5.92 (2H, AB system,  $J=1.5$  Hz, OCH<sub>2</sub>O), 6.46 (1H, s, C6–H), 6.57 ppm (1H, s, C9–H); <sup>13</sup>C-nmr(CDCl<sub>3</sub>):  $\delta$  26.4 (C16), 29.8 (C4), 31.2 and 31.6 (C11 and C15), 37.0 and 37.4 (C12 and C17), 49.6 (C13), 51.9 (OCH<sub>3</sub>), 52.5 (C3), 62.3 (C18), 63.9 (C1), 65.5 (C14), 100.6 (OCH<sub>2</sub>O), 105.0 (C9), 108.3 (C6), 128.1 (C5), 131.3 (C10), 145.5 and 145.6 (C7 and C8), 175.8 ppm (C=O); ms m/z(%): 359(M<sup>+</sup>,81), 358(100), 344(24), 328(12), 300(11), 274(7),

258(6), 242(5), 228(13), 216(10), 202(9), 189(36), 175(34).

21. **2** yield: 80%; mp: 124-125 °C (MeOH); ir(KBr).  $\nu$  1640 (C=C), 1720 (conj. C=O), 2770-2850  $\text{cm}^{-1}$  (Bohlmann bands);  $^1\text{H-nmr}(\text{CDCl}_3)$ :  $\delta$  3.07 (1H, dd,  $J=10$  and 3 Hz, C1-H), 3.78 (3H, s,  $\text{OCH}_3$ ), 5.88 (2H, AB system,  $J=1.5$  Hz,  $\text{OCH}_2\text{O}$ ), 6.52 (1H, s, C6-H), 6.72 (1H, s, C9-H), 7.00 ppm (1H, dd,  $J=3$  and 4.5 Hz, C14-H);  $^{13}\text{C-nmr}(\text{CDCl}_3)$ :  $\delta$  22.2 (C15), 29.7 (C4), 33.5 and 34.9 (C12 and C17), 34.3 (C11), 51.6 ( $\text{OCH}_3$ ), 52.9 (C3), 62.0 (C18), 63.4 (C1), 100.6 ( $\text{OCH}_2\text{O}$ ), 105.2 (C9), 108.4 (C6), 127.9 (C5), 130.3 (C10), 133.7 (C13), 140.4 (C14), 145.7 and 145.8 (C7 and C8), 167.5 ppm (C=O); ms  $m/z(\%)$ : 341 ( $\text{M}^+$ , 67), 340(100), 326(87), 310(7), 300(2), 282(11), 268(1), 252(2), 240(3), 214(20), 202(7), 189(85), 175 (23).

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