INVESTIGATIONS ON THE CHEMISTRY OF BERBANES 14.[1] A NOVEL STEREOSELECTIVE APPROACH TO BIOLOGICALLY ACTIVE *ALLO*-BERBANE DERIVATIVES

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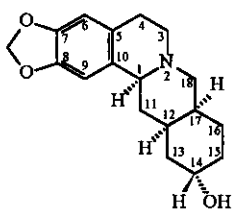
Abstract - Stereoselective total synthesis of α_2 adrenoceptor agents (**1**) and (**2**) with *allo*-berbane skeleton has been performed *via* Knoevenagel-type condensation of ketones (**3**).

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.[2] Pharmacological studies on berbane derivatives and their intermediates revealed that this family of alkaloid-like compounds possesses interesting biological activities.[3-5] First of all two *allo*-berbane derivatives, the 14α-hydroxy-*allo*-berbane (**1**)[4] and the methyl $\Delta^{13,14}$-*allo*-berbane-13-carboxylate (**2**)[5] have been emerged as extremely selective α_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.



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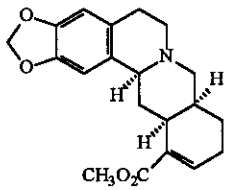

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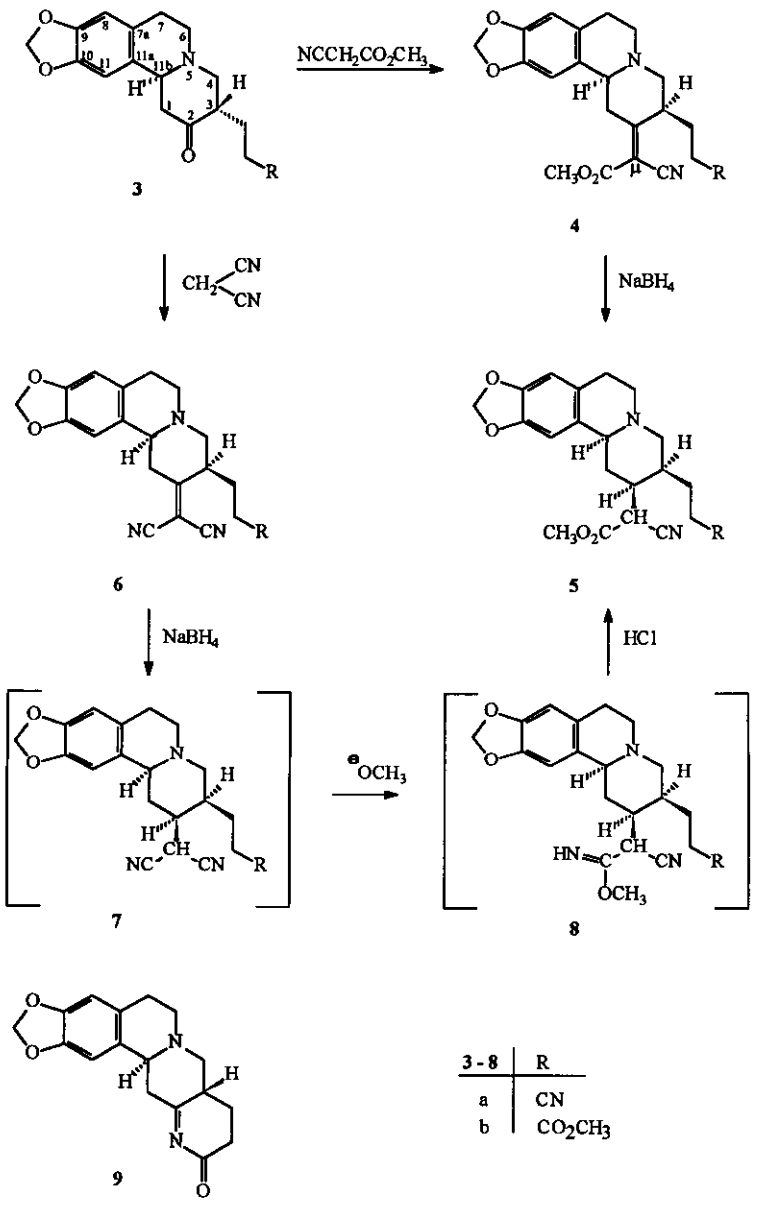
The C(3) epimerization in the course of some condensation reactions of 3-substituted quinolizidin-2-ones is well established. It was **Brossi** and coworkers[6] who observed this phenomenon while performing Knoevenagel condensation of 9,10-dimethoxy-3α-ethylbenzo[*a*]quinolizidin-2-one (type **3**) with ethyl cyanoacetate. The complete epimerization occurring during the reaction was later utilized in the total synthesis of (-)-corynantheidine[7] and of 9,10-dimethoxydespyrrolocorynantheidine,[8] 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_4OAc/AcOH catalyst resulted in epimerization at C(3) and adduct (**4a**)[9] was obtained in 80–85% yield. Sodium borohydride reduction of the exocyclic double bond[7,8] has been performed also with high diastereoselectivity, thus *allo* cyanoacetate (**5a**)[10] 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**)[11] 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 addi-tion. 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 inter-rupting the whole process and working up appropriately, and were characterized by spectroscopical means (^1H– and ^{13}C-nmr, ir, ms).

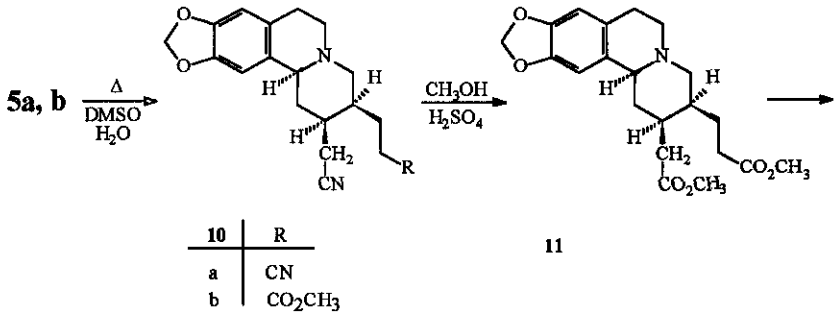
Cyanoacetate condensation of keto ester (**3b**) resulted in a very small amount of adduct (**4b**). The main product of the reaction, the 13-azaberbanone derivative (**9**)[12] can be obtained, of course, if methyl cyanoacetate is

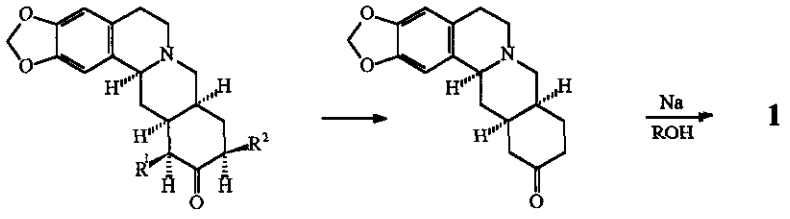
omitted from the reaction mixture. With malononitrile in CH_2Cl_2 at room temperature in the presence of NH_4OAc catalyst the condensation proceeds similarly to that of **3a**, and adduct (**6b**)[13] is obtained in almost quantitative yield. Transformation of **6b** into *allo* cyano ester derivative (**5b**)[10] *via* **7b** and **8b** is analogous to the



3-cyanoethyl series (**6a** → **5a**).

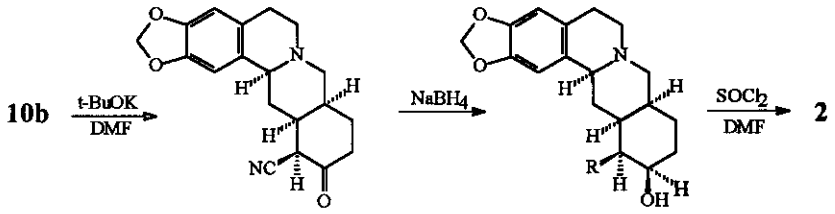
Having these two *allo* precursors in hand the next problem to be solved was to modify the C(2) substituent suitable for the total synthesis of *allo*-berbanol (**1**). This goal has been attained in a one-step demethoxycarbonylation process of **5** by refluxing it in DMF or more preferably in DMSO in the presence of equivalent amount of water for 2–3 hours. Both *allo* acetonitriles (**10a** and **10b**),[14] obtained in 75–80% yield could be then converted into diester (**11**)[15] by methanolysis (H_2SO_4/CH_3OH). From this point our earlier pathway[2] *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[2] resulted in 65–70% stereoselectivity and consequently lower yield (38–40%).





As it has been demonstrated earlier,[5,16] *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**).[17] Direct acidic methanolysis of the cyano group could not be accomplished either in cyano ketone (**15**) or in cyano alcohol (**16**),[18] obtained by $NaBH_4$ reduction of the former. The CN → CO_2CH_3 transformation was, however, performed in two steps: peroxide catalyzed basic hydrolysis of **16** led to amid (**17**),[19] the acidic methanolysis (HCl/CH_3OH) of which gave hydroxy ester (**18**)[20] 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**)[21] in racemic form.



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8. M. Bárczai-Beke, G. Dörnyei, J. Tamás, and Cs. Szántay, *Chem. Ber.*, 1972, **105**, 3244.

9. All new compounds were characterized by ir, ^1H-, ^{13}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 ≈ 4 : 1 on the basis of ^{1}H-nmr measurement of the crude product). This mixture, obtain ed 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_2O); ir(KBr):ν 1620 (C=C), 1715 (conj. C=O), 2220 (conj. CN), 2240 (CN), 2780–2840 cm^{-1} (Bohlmann bands); ^{1}H-nmr($CDCl_3$): δ 4.04 (1H, dd, *J*=12 and 2.5 Hz, C11b–H), 3.91 (3H, s, CO_2CH_3), 4.56 (1H, dd, *J*=14.5 and 2.5 Hz, C1–H_{eq}), 5.95 (2H, s, OCH_2O), 6.59 (1H, s, C8–H), 6.71 ppm (1H, s, C11–H). For Z geometric isomer of **4a** ^{1}H-nmr peaks at δ 3.48 (1H, dd, *J*=14.5 and 2.5 Hz, C1–H_{eq}) and 3.88 ppm (3H, s, CO_2CH_3) are characteristic.

10. **5a** mp: 147 °C (Et_2O); ir(KBr): ν 1725 (C=O), 2235 (CN), 2780–2850 cm^{-1} (Bohlmann bands); ^{1}H–nmr ($CDCl_3$): δ 3.15 (1H, m, C11b–H), 3.44 (1H, d, *J*=10 Hz, μCH), 3.90 (3H, s, CO_2CH_3), 5.90 (2H, s, OCH_2O), 6.55 (1H, s, C8–H), 6.70 (1H, s, C11–H); ms m/z(%): 381(M^+,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): ν 1725 and 1740 (C=O), 2235 cm^{-1} (CN); ^{1}H-nmr($CDCl_3$): δ 3.52 (1H, dd, *J*=10 and 3.5 Hz, C11b–H), 3.67 (3H, s, $CH_2CO_2CH_3$), 3.89 (3H, s, $\mu CHCO_2CH_3$), 5.90 (2H, s, OCH_2O), 6.54 (1H, s, C8–H), 6.72 ppm (C11–H); ^{13}C-nmr($CDCl_3$): δ 29.7 (C7), 41.3 (μC), 51.6 ($CH_2CO_2CH_3$), 53.6 ($\mu CHCO_2CH_3$), 62.7 (C11b), 115.2 (CN), 165.9 (μCH-CO_2CH_3), 173.6 ppm ($CH_2CO_2CH_3$). (Because of an additional chiral center in the side-chain attached to C2, majority of the signals both in ^{1}H and ^{13}C-nmr spectra of **5a** and **5b** are duplicated.); ms m/z(%): 414 (M^+,28), 413(26), 383(16), 355(7), 316(100), 288(14), 216(15), 175(23).
11. **6a** mp: 178 °C (MeOH); ir(KBr): ν 1620 (C=C), 2220 (conj. CN), 2240 cm^{-1} (CN); ^{1}H-nmr($CDCl_3$): δ 3.27 (1H, dd, *J*=11.2 and 3 Hz, C11b–H), 3.41 (1H, dd, *J*=14 and 3 Hz, C1–H_{eq}), 5.94 (2H, s, OCH_2O), 6.58 (1H, s, C8–H), 6.63 ppm (1H, s, C11–H); ^{13}C-nmr($CDCl_3$): δ 15 3 (CH_2CN), 28.4 (CH_2CH_2CN), 29.6 (C7), 37.8 (C1), 42.5 (C3), 51.3 (C6), 58.7 (C4), 63.0 (C11b), 85.6 (μC), 101.1 (OCH_2O), 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).
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13. **6b** mp: 140-141 °C (MeOH), ir(KBr): ν 1735 (C=O), 2215 cm^{-1} (conj. CN); ^{1}H-nmr($CDCl_3$): δ 3.21 (1H, dd, *J*=11.5 and 3 Hz, C11b–H), 3.34 (1H, dd, *J*=14 and 3 Hz, C1–H_{eq}), 3.69 (3H, s, CO_2CH_3), 5.92 (2H, s, OCH_2O), 6.56 (1H, s, C8–H), 6.64 ppm (1H, s, C11–H); ^{13}C-nmr($CDCl_3$): δ 28.2 ($CH_2CH_2CO_2CH_3$), 29.6 (C7), 31.5 (C1), 37.6 ($CH_2CO_2CH_3$), 42.8 (C3), 51.3 (C6), 52.0 (OCH_3), 59.5 (C4), 63.1 (C11b), 84.6 (μC), 101.1 (OCH_2O), 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^+,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_2O); ir(KBr): ν 2235 cm^{-1} (CN); ^{1}H-nmr($CDCl_3$): δ 3.11 (1H, dd, *J*=11.3 and 7 Hz, C11b–H), 5.91 (2H, s, OCH_2O), 6.53 (1H, s, C8–H), 6.66 ppm (1H, s, C11–H); ^{13}C-nmr($CDCl_3$): δ 15.3 (CH_2CH_2CN), 20.9 (CH_2CN), 21.4 (CH_2CH_2CN), 29.8 (C7), 33.3 (C1), 36.0 (C3), 37.3 (C2), 52.5 (C6), 57.8 (C4), 62.8 (C11b), 100.8 (CH_2O), 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_2O); ir(KBr): ν 1735 (C=O), 2240 cm^{-1} (CN); ^{1}H-nmr($CDCl_3$): δ 3.07 (1H, dd, *J*=11 and 3.5 Hz, C11b–H), 3.68 (3H, s, OCH_3), 5.91 (2H, s, OCH_2O), 6.54 (1H, s, C8–H), 6.69 ppm (1H, s, C11–H); ^{13}C-nmr($CDCl_3$): δ 19.0 (CH_2CN), 20.5 ($CH_2CH_2CO_2CH_3$), 28.8 (C7), 31.0 (C1), 35.3 (C3), 32.2 ($CH_2CO_2CH_3$), 36.7 (C2), 50.6 (C6), 51.5 (OCH_3), 57.4 (C4), 61.9 (C11b), 99.7 (OCH_2O), 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^+,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.

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17. **15** yield. 84%, mp 128-223 °C (the compound is really a keto-enol tautomeric mixture); ir(KBr): ν 1720 (C=O), 2240 (CN) for structure **15**, 1660 (C=C), 2210 (conj. CN) and 3400 (OH) for the enol form; 2780–2850 cm^{-1} (Bohlmann bands); ^{1}H-nmr($CDCl_3$): δ 3.88 (1H, d, *J*=5.5 Hz, CHCN), 5.88 and 5.90 (2H, s, OCH_2O), 6.52 (1H, s, C8–H), 6 59 and 6.73 ppm (1H, s, C11–H); ^{13}C-nmr($CDCl_3$): δ 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_2O), 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 13β–CN . 13α–CN ≈ 5 . 1); ms m/z(%): 324(M^+,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) ν 2240 (CN), 2775–2840 (Bohlmann bands), 3400 cm^{-1} (OH); ^{1}H-nmr($CDCl_3$): δ 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_2O), 6.51 (1H, s, C6–H), 6.78 ppm (1H, s, C9–H); ^{13}C-nmr($CDCl_3$): δ 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_2O), 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^+,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_2O-hexane); ir(KBr): ν 1660 (C=O), 2780–2840 (Bohlmann bands), 3400 cm^{-1} (broad, OH and NH_2); ^{1}H-nmr($CDCl_3$): δ 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_2), 5.88 (2H, s, OCH_2O), 6.53 (1H, s, C6–H), 6.67 ppm (1H, s, C9–H); ^{13}C-nmr($CDCl_3$): δ 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_2O), 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^+,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_2O-hexane); ir(KBr). ν 1715 (broad, C=O assoc.), 2770–2840 (Bohlmann bands), 3450 cm^{-1} (broad, OH assoc.); ^{1}H-nmr($CDCl_3$) δ 2.85 (1H, dd, *J*=10 and 3 Hz, C1-H), 3.53 (1H, br s, OH), 3.80 (3H, s OCH_3), 4.24 (1H, q, *J*=3 Hz, C14-H), 5.92 (2H, AB system, *J*=1.5 Hz, OCH_2O), 6 46 (1H, s, C6–H), 6.57 ppm (1H, s, C9–H); ^{13}C-nmr($CDCl_3$): δ 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_3), 52.5 (C3), 62.3 (C18), 63.9 (C1), 65.5 (C14), 100.6 (OCH_2O), 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^+,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). ν 1640 (C=C), 1720 (conj. C=O), 2770–2850 cm^{-1} (Bohlmann bands); ^{1}H-nmr($CDCl_3$): δ 3.07 (1H, dd, *J*=10 and 3 Hz, C1–H), 3.78 (3H, s, OCH_3), 5.88 (2H, AB system, *J*=1.5 Hz, OCH_2O), 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}C-nmr($CDCl_3$): δ 22.2 (C15), 29.7 (C4), 33.5 and 34.9 (C12 and C17), 34.3 (C11), 51.6 (OCH_3), 52.9 (C3), 62.0 (C18), 63.4 (C1), 100.6 (OCH_2O), 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 (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).

Received, 14th February, 1994