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 α2 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 Δ13,14-allo-berbane-13-carboxylate (2)5 have been emerged as extremely selective α2 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\(^6\) 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-dimethoxydespyrilocorynantheidine,\(^8\) 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 \(\text{NH}_4\text{OAc/AcOH}\) 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 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 (\(^1\)H- 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$_2$Cl$_2$ at room temperature in the presence of NH$_4$OAc 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 \(6a \rightarrow 5a\).

Having these two \textit{allo} precursors in hand the next problem to be solved was to modify the C(2) substituent suitable for the total synthesis of \textit{allo-berbanol} (1). This goal has been attained in a one-step demethoxy-carbonylation 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 \textit{allo} acetonitriles (10a and 10b), obtained in 75–80% yield could be then converted into diester (11) by methanolysis \((\text{H}_2\text{SO}_4/\text{CH}_3\text{OH})\). From this point our earlier pathway via Dieckmann products (12) and (13) as well as ketone (14) can be applied. Thus in this way \textit{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 resulted in 65–70% stereoselectivity and consequently lower yield (38–40%).

As it has been demonstrated earlier, \textit{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 \(\sim 3:2\)). 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). Direct acidic methanolysis of the cyano group could not be accomplished either in cyano ketone (15) or in cyano alcohol (16), obtained by NaBH₄ reduction of the former. The CN → CO₂CH₃ transformation was, however, performed in two steps: peroxide catalyzed basic hydrolysis of 16 led to amid (17), the acidic methanolysis (HCl/CH₂OH) of which gave hydroxy ester (18) 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) in racemic form.

![Chemical reaction diagram]

**REFERENCES AND NOTES**

9. All new compounds were characterized by ir, ¹H-, ¹³C-nmr as well as by ms spectroscopy. Selected physi-
14. L.
12. L.
11. 6a mp: 178
454
(1Kdd, J=11.2 and 3 Hz, C1, H), 130.1
(C1), 138 (1H, s, C8-H), 6.71 ppm (1H, s, C11-H). For Z geometric isomer of 4a 1H-nmr peaks at δ 3.48 (1H, dd, J=14.5 and 2.5 Hz, C1-H) and 3.88 ppm (3H, s, CO2CH3) are characteristic.

10. 5a mp: 147 °C (Et2O); ir(KBr): v 1725 (C=O), 2235 (CN), 2780–2850 cm⁻¹ (Bohmann bands); 1H-nmr(CDC13): δ 3.52 (1H, d, J=10 Hz, μCH), 3.90 (3H, s, CO2CH3), 5.90 (2H, s, OCH2O), 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): v 1725 and 1740 (C=O), 2235 cm⁻¹ (CN); 1H-nmr(CDC13): δ 3.52 (1H, d, J=10 and 3.5 Hz, C11b-H), 3.67 (3H, s, CH2CO2CH3), 3.89 (3H, s, μCHCO2CH3), 5.90 (2H, s, OCH2O), 6.54 (1H, s, C8-H), 6.72 ppm (C11-H); 13C-nmr(CDC13): δ 29.7 (C7), 41.3 (μC), 51.6 (CH2CO2CH3), 53.6 (μCHCO2CH3), 62.7 (C11b), 115.2 (CN), 165.9 (μCHCO2CH3), 173.6 ppm (CH2CO2CH3). (Because of an additional chiral center in the side-chain attached to C2, majority of the signals both in 1H and 13C-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): v 1720 (C=O), 2220 (conj. CN), 2240 cm⁻¹ (CN); 1H-nmr(CDC13): δ 3.27 (1H, dd, J=11.2 and 3 Hz, C11b-H), 3.41 (1H, dd, J=14 and 3 Hz, C1-H), 5.94 (2H, s, OCH2O), 6.58 (1H, s, C8-H), 6.63 ppm (1H, s, C11-H); 13C-nmr(CDC13): δ 15 3 (CH2CN), 28.4 (CH2CH2CN), 29.6 (C7), 37.8 (C1), 42.5 (C3), 51.3 (C6), 58.7 (C4), 63.0 (C11b), 85.6 (μC), 101.1 (OCH2O), 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).


13. 6b mp: 140-141 °C (MeOH), ir(KBr): v 1735 (C=O), 2215 cm⁻¹ (conj. CN); 1H-nmr(CDC13): δ 3.21 (1H, dd, J=11.5 and 3 Hz, C11b-H), 3.34 (1H, dd, J=14 and 3 Hz, C1-H), 3.69 (3H, s, CO2CH3), 5.92 (2H, s, OCH2O), 6.56 (1H, s, C8-H), 6.64 ppm (1H, s, C11-H); 13C-nmr(CDC13): δ 28.2 (CH2CH2CO2CH3), 29.6 (C7), 31.5 (C1), 37.6 (CH2CO2CH3), 42.8 (C3), 51.3 (C6), 52.0 (OCH2), 59.5 (C4), 63.1 (C11b), 84.6 (μC), 101.1 (OCH2O), 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-Et2O); ir(KBr): v 2235 cm⁻¹ (CN); 1H-nmr(CDC13): δ 3.11 (1H, dd, J=11.3 and 7 Hz, C11b-H), 5.91 (2H, s, OCH2O), 6.53 (1H, s, C8-H), 6.66 ppm (1H, s, C11-H); 13C-nmr(CDC13): δ 15.3 (CH2CH2CN), 20.9 (CH2CN), 21.4 (CH2CH2CN), 29.8 (C7), 33.3 (C1), 36.0 (C3), 37.3 (C2), 52.5 (C6), 57.8 (C4), 62.8 (C11b), 100.8 (CH2O), 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).
18. mp of HCl salt: 215-216 °C (MeOH–Et₂O); ir(KBr): v 1735 (C=O), 2240 cm⁻¹ (CN); ¹H-nmr(CDCl₃): δ 3.07 (1H, dd, J=11 and 3.5 Hz, C11b–H), 3.68 (3H, s, OCH₃), 5.91 (2H, s, OCH₂O), 6.54 (1H, s, C8–H), 6.69 ppm (1H, s, C11–H); ¹³C-nmr(CDCl₃): δ 19.0 (CH₂CN), 20.5 (CH₂CH₂CO₂CH₂), 28.8 (C7), 31.0 (C1), 35.3 (C3), 32.2 (CH₂CO₂CH₂), 36.7 (C2), 50.6 (C6), 51.5 (OCH₃), 57.4 (C4), 61.9 (C11b), 99.7 (OCH₂O), 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 (I), prepared in this way, proved to be identical (mp, tlc, ir, nmr, ms) with authentic sample.


17. yield: 84%; mp 128-223 °C (the compound is really a keto-enol tautomeric mixture); ir(KBr): v 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 (Bohllman bands); ¹H-nmr(CDCl₃): δ 3.88 (1H, d, J=5.5 Hz, CHCN), 5.88 and 5.90 (2H, s, OCH₂O), 6.52 (1H, s, C8–H), 6.59 and 6.73 ppm (1H, s, C11–H); ¹³C-nmr(CDCl₃): 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 (OCH₂O), 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(23), 216(15), 189(74), 175(63).

18. yield: 75–80%; mp: 227–229 °C (MeOH); ir(KBr): v 2240 (CN), 2775–2840 (Bohllman bands), 3400 cm⁻¹ (OH); ¹H-nmr(CDCl₃): 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, OCH₂O), 6.51 (1H, s, C6–H), 6.78 ppm (1H, s, C9–H); ¹³C-nmr(CDCl₃): 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 (OCH₂O), 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. yield: 80%; mp: 221–223 °C (Et₂O-hexane); ir(KBr): v 1660 (C=O), 2780–2840 (Bohllman bands), 3400 cm⁻¹ (broad, OH and NH₂); ¹H-nmr(CDCl₃): 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, NH₂), 5.88 (2H, s, OCH₂O), 6.53 (1H, s, C6–H), 6.67 ppm (1H, s, C9–H); ¹³C-nmr(CDCl₃): 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 (C14), 66.1 (C14), 100.6 (OCH₂O), 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(7), 228(30), 216(20), 202(28), 189(70), 175(55).

20. yield: 75–80%; mp: 159–160 °C (Et₂O-hexane); ir(KBr): v 1715 (broad, C=O assoc.), 2770–2840 (Bohllman bands), 3450 cm⁻¹ (broad, OH assoc.); ¹H-nmr(CDCl₃): δ 2.85 (1H, dd, J=10 and 3 Hz, C1-H), 3.53 (1H, br s, OH), 3.80 (3H, s OCH₃), 4.24 (1H, q, J=3 Hz, C14–H), 5.92 (2H, AB system, J=1.5 Hz, OCH₂O), 6.46 (1H, s, C6–H), 6.57 ppm (1H, s, C9–H); ¹³C-nmr(CDCl₃): 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 (OCH₂), 52.5 (C3), 62.3 (C18), 63.9 (C1), 65.5 (C14), 100.6 (OCH₂O), 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). v 1640 (C=C), 1720 (conj. C=O), 2770–2850 cm⁻¹ (Bohlmann bands); ¹H-nmr(CDCl₃): δ 3.07 (1H, dd, J=10 and 3 Hz, C1–H), 3.78 (3H, s, OCH₃), 5.88 (2H, AB system, J=1.5 Hz, OCH₂O), 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); ¹³C-nmr(CDCl₃): δ 22.2 (C15), 29.7 (C4), 33.5 and 34.9 (C12 and C17), 34.3 (C11), 51.6 (OCH₃), 52.9 (C3), 62.0 (C18), 63.4 (C1), 100.6 (OCH₂O), 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