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REGIOSELECTIVE SYNTHESIS OF (±)-GABACULINE

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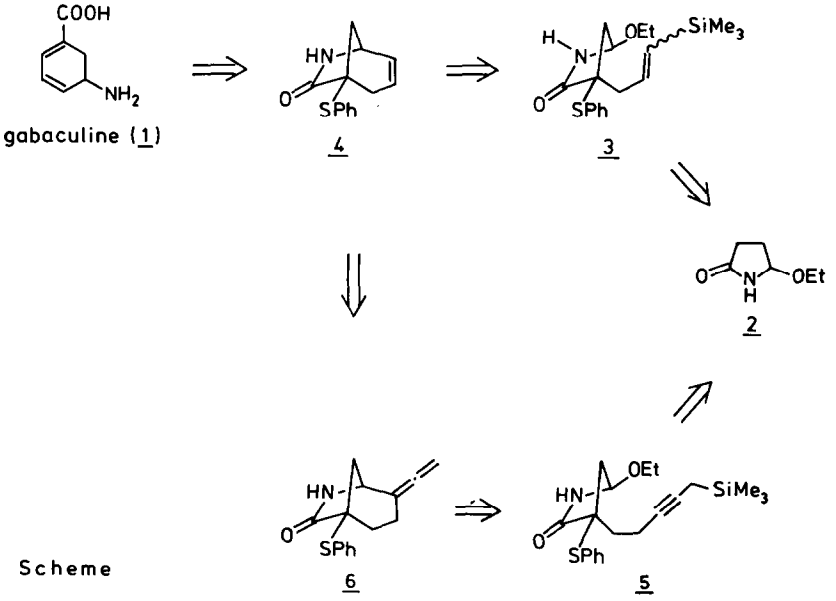
Abstract: (±)-Gabaculine has been synthesized via an intramolecular reaction of an N-acyliminium intermediate with a propargyl silane, followed by allene ozonolysis and a Shapiro reaction.

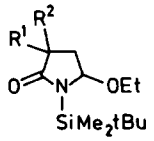
Gabaculine (1) is a natural analogue of GABA (γ-aminobutyric acid), isolated from Streptomyces toyocaensis by Mishima et al[1]. As a potent, irreversible inhibitor of the enzyme γ-aminobutyrate aminotransferase (GABA-T), 1 has aroused considerable interest from pharmacologists[2] and synthetic chemists[1,3]. Four syntheses of 1 have appeared, which all of them utilize an unsaturated cyclohexanecarboxylic acid as starting material, which is then functionalized with a nitrogen substituent[1,3]. We herewith report a conceptually different approach, which is characterized by the presence of nitrogen already in the starting material, and cyclohexane ring formation via an N-acyliminium ion cyclization.

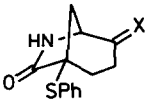


Scheme

Our retrosynthetic analysis (Scheme) is based on the use of 5-ethoxy-2-pyrrolidone (2) as dipolar bifunctional reagent[4]. The most direct route to 1 would then involve cyclization of vinyl silane 3 to the bicyclic system 4, followed by amide hydrolysis and sulfoxide elimination.

Silylation of 2[5] was readily accomplished via reaction with 1.5 eq of $tBuMe_2SiCl$ (CH_2Cl_2, r.t., 17 h) in the presence of 2.5 eq of Et_3N and a catalytic amount of 4-dimethylaminopyridine (DMAP) to give 7[6] in 97% yield[7]. Introduction of the phenylthio group using the procedure of Zoretic[8] (LDA (2 eq), HMPT (1 eq), PhSSPh (1 eq), THF, -78°C, 3-5 h, 81% yield) was followed by alkylation with (Z)-3-bromo-1-(trimethylsilyl)propene[9] (LDA, THF, -78°C, 89% yield) to furnish 9[6]. All attempts to effect ring closure of 9 met with failure. Treatment of 9 with a variety of Lewis and Brönsted acids resulted in elimination of ethanol and/or protodesilylation. No trace of the desired azabicyclo[3.2.1]octenone 4 could be detected[12,13].





7 $R^1 = R^2 = H$

8 $R^1 = PhS$, $R^2 = H$

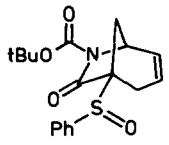
9 $R^1 = PhS$, $R^2 = CH_2C(H)=C(H)-SiMe_3$

10 $R = PhS$, $R = CH_2CH_2C\equiv CCH_2SiMe_3$

11 X = O

12 $X = N(H)-N(H)-SO_2-C_6H_4-Me$

We then decided to explore a less direct route (Scheme), which is based on the cyclization of a propargyl silane of type 5. Alkylation of 8 with 5-iodo-1-trimethylsilyl-2-pentyne[4,14] (LDA, THF, -78°C → -20°C, 85% yield) afforded 10[6]. Dissolution of 10 in formic acid caused ring closure within a few minutes[4]. Continued stirring for 17 h at ambient temperature resulted in complete removal of the silyl group from nitrogen to give allene 6[6] (m.p. 158-159°C) in 87% yield. Ozonolysis at -78°C in CH_2Cl_2, followed by reduction with Me_2S produced ketone 11[6] (m.p. 127-129.5°C) in 86% yield. The Shapiro reaction[15] was deemed suitable to arrive at the desired ring system 4. To this end ketone 11 was first converted into its p-tosylhydrazone 12 ($pTsN(H)NH_2$, EtOH, 83% yield). Upon treatment with n-butyllithium (4 eq, THF/TMEDA 1:1) 12 was deprotonated into its red trianion, which underwent the desired elimination process during slow warm-up to room temperature (17 h) to give 4[6] in 78% yield. Thus, the sequence 2 → 4 via the propargyl silane cyclization 5 → 6 constitutes a convenient entry into the 7-azabicyclo[3.2.1]oct-2-ene ring system[16].



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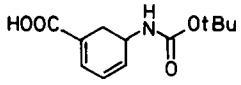

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To complete the gabaculine synthesis lactam 4 was hydrolyzed by using Grieco's method[17]. Attachment of the t-butoxycarbonyl group to nitrogen ($(tBuO_2C)_2O$, Et_3N, DMAP, 82% yield) followed by oxidation of sulfur (mCPBA, CH_2Cl_2, -78°C, 79% yield) gave sulfoxide 13[6]. Compound 13 was easily hydrolyzed with concomitant sulfoxide elimination (LiOH, H_2O, THF, 50°C) to furnish N-t-butoxycarbonylgabaculine 14 (m.p. 147-149°C; lit.[1] 148-150°C) in 53% yield after purification with flash chromatography. Since 14 has been transformed into the natural product by Mishima[1] and Fráter[3c], our work constitutes a formal synthesis of racemic gabaculine (1). Convincing evidence for the structure of 14 was obtained as follows: The ^1H NMR spectrum of 14 in DCl/D_2O as solvent (which causes loss of the t-butoxycarbonyl protecting group) was virtually identical to the ^1H NMR spectrum, recorded in DCl/D_2O as solvent, of a sample of gabaculine, obtained from Sankyo, Japan.

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6. This compound showed spectra[18] (IR, ^{1}H NMR, ^{13}C NMR) in accord with its structure, and satisfactory elemental analyses and/or high resolution mass spectral data.

7. Trimethylsilyl protected lactams were less satisfactory, since these lost the silylgroup during flash chromatography.

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9. This compound was prepared in two steps from 3-(trimethylsilyl)-2-propyn-1-ol[10]: a) partial hydrogenation using P_2Ni[11] as catalyst (86%); b) PBr_3, pyridine, Et_2O, reflux (38%).

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11. a) C.A. Brown, V.K. Ahuja, J.Chem.Soc.Chem.Commun., 553 (1973); b) ibid., J.Org.Chem., 38, 2226 (1973).

12. This failure can be ascribed to a combination of unfavourable geometrical factors and limited nucleophilic reactivity of vinyl silanes, compared to allyl and propargyl silanes. Intramolecular reactions between N-acyliminium ions and vinyl silanes in a less constrained system have been reported: L.E. Overman, T.C. Malone, G.P. Meier, J.Am.Chem.Soc., 105, 6993 (1983).

13. The corresponding (E)-vinyl silane was equally unwilling to cyclize; details will be given in a full paper. The intramolecular reactivity of (E)- versus (Z)-vinyl silanes toward iminium ions has been investigated: L.E. Overman, R.M. Burk, Tetrahedron Lett., 25, 5739 (1984).

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16. For other syntheses of 7-azabicyclo[3.2.1]oct-2-enes see: G.R. Krow, D.A. Shaw, C.S. Jovais, H.G. Ramjit, Synth.Commun., 13, 575 (1983), and references therein.

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18. Some selected spectral data are:

6: IR($CHCl_3$): 3420, 3210, 1965, 1710 cm^{-1}; ^{1}H NMR (100 MHz, $CDCl_3$): δ 7.22-7.72 (m, 5H), 6.82 (m, 1H), 4.73 (m, 2H), 4.05 (br.d, J=6 Hz, 1H), 2.24-2.72 (m, 3H), 1.58-2.18 (m, 3H); ^{13}C NMR (63 MHz, $CDCl_3$): δ 201.9 (s), 176.9 (s), 136.3 (s), 130.1 (d), 128.8 (d), 128.7 (d), 97.8 (s), 76.4 (t), 55.8 (s), 54.3 (d), 44.2 (t), 32.2 (t), 24.3 (t).
4: IR ($CHCl_3$): 3420, 3210, 1705 cm^{-1}; ^{1}H NMR (100 MHz, $CDCl_3$): δ 7.11-7.85 (m, 6H), 6.20 (m, 1H), 5.67 (m, 1H), 3.73 (br t, J=4.5 Hz, 1H), 2.29-2.57 (m, 3H), 1.94 (d, J=10 Hz, 1H).
14: IR($CHCl_3$): 3440, 3000 (v br), 1690, 1640 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.15 (m, 1H), 6.18 (m, 2H), 4.66 (d, J=10 Hz, 1H), 4.45 (m, 1H), 2.68 (m, 2H), 1.42 (s, 9H).

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