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LETTERS

From Phenylaziridine to Phenylkainoids. A formal Synthesis of (±)-Phenylkainic Acid.[1]

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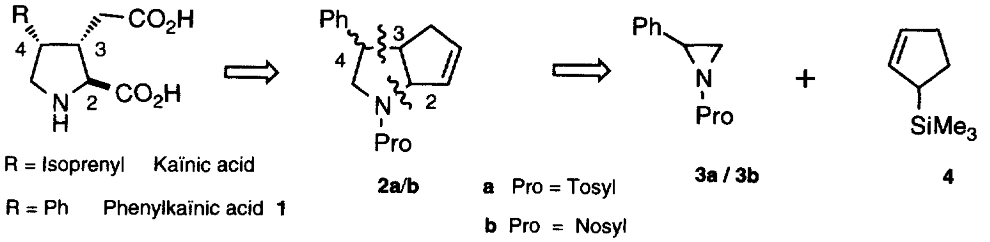
Abstract : The condensation of phenylaziridines (**3a/3b**) with 3-cyclopentenylsilane (**4**) in presence of $BF_3.Et_2O$ yielded amino-cyclopentenyl adducts (**5a-8a**) and (**5b-8b**). Heterocyclisation of the ω-amino-olefins assisted by $Pd(OAc)_2$ afforded the azabicyclo adducts **2a/2'a** and **2b/2'b**. Oxidation of the internal double bond, followed by epimerization at C(2) was realized by KH in presence of 18-crown-6 yielding **11**, the fully protected phenylkainic acid.

Keywords : Aziridine; Allylsilane; Pyrrolidine; Phenylkainoid.

Kainic acid is a conformationally restricted analogue of the endogenous mammalian neurotransmitter glutamic acid and has been used for the identification of a specific binding site among the glutamate receptors.[2] Structure/activity studies performed on kainic acid revealed that the configurations of the three adjacent stereocenters is of crucial importance.[3] Furthermore the replacement of the isopropenyl at C(4) by a phenyl residue, giving phenylkainic acid (**1**), enhanced considerably the biological potency.[4] This observation has stimulated the design of various syntheses of phenylkainoids.[5,6]



Scheme 1.

In this letter, we report our approach to the synthesis of (±)-**1**. The retrosynthetic plan, depicted in Scheme 1, is based on the disconnection of two bonds N(1) and C(2), and C(3) and C(4). The key compounds **2a/b** could be prepared by the reaction of phenylaziridines (**3a/b**) with cyclopentenylallylsilane (**4**), as activated phenylaziridines can be regioselectively opened by mild nucleophiles such as allylsilanes.[7] Some comments have to be made first : (i) in preliminary experiments, the tosyl group was used to activate the aziridinyl nitrogen, but the nosyl group was prefered for its easier manipulation in the deprotection step;[8] (ii) in the present work all the compounds are in racemic form. The starting materials are easily accessible : the aziridines **3a/b** by using an aziridination procedure of styrene,[9] and the allysilane **4** from 3-chlorocyclopentene.[9] The reaction between **3a/b** and **4** was performed in CH_2Cl_2 at 0°C in presence of 0.3 to 1 equivalent of

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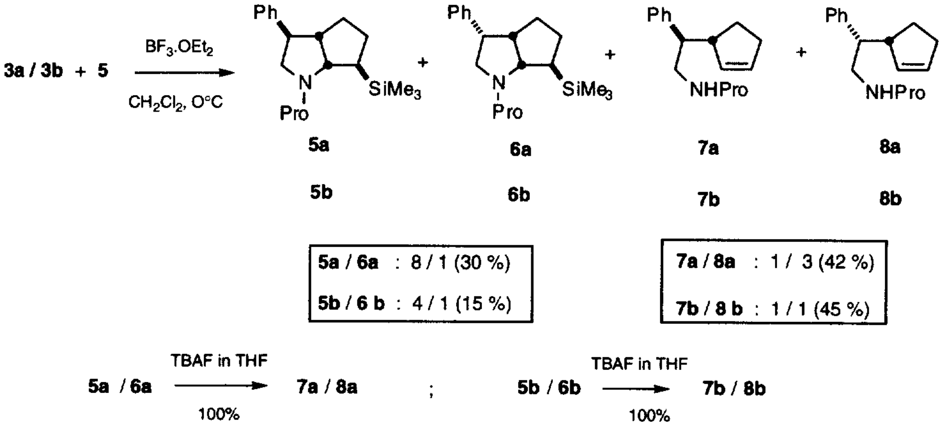
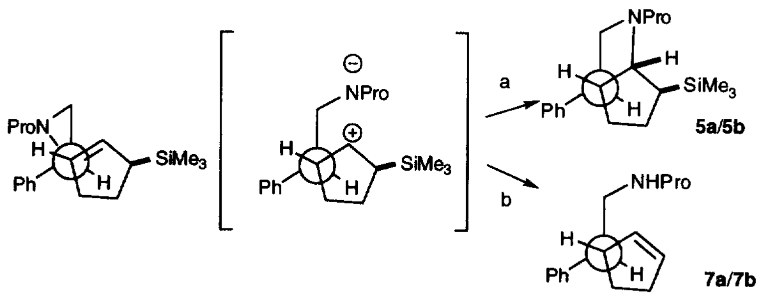
$BF_3.OEt_2$ for 4 h. The products, after purification by column chromatography over silica gel, were carrefully analyzed by NMR spectroscopy. Two separable sets of diastereomers were obtained with the tosyl protection, the first one corresponding to a mixture of the inseparable azabicyclo adducts **5a**/**6a** (8/1 : 30%), and the other one to inseparable amino-olefins **7a**/**8a** (1/3 : 42%); with the nosyl protection, similar results were obtained : **5b**/**6b** (4/1 : 15%) and **7b**/**8b** (1/1 : 45%). Each set of diastereomers was analysed by COSY and NOESY experiments which permitted not only to determine the mixture composition but to attribute the relative configuration of each component (see Scheme 2). For instance **5a**, the major diastereomer in the **5a**/**6a** mixture has been identified as the *exo/exo* adduct, and **6a**, the minor diastereomer as the corresponding *endo/exo* adduct.



Scheme 2.

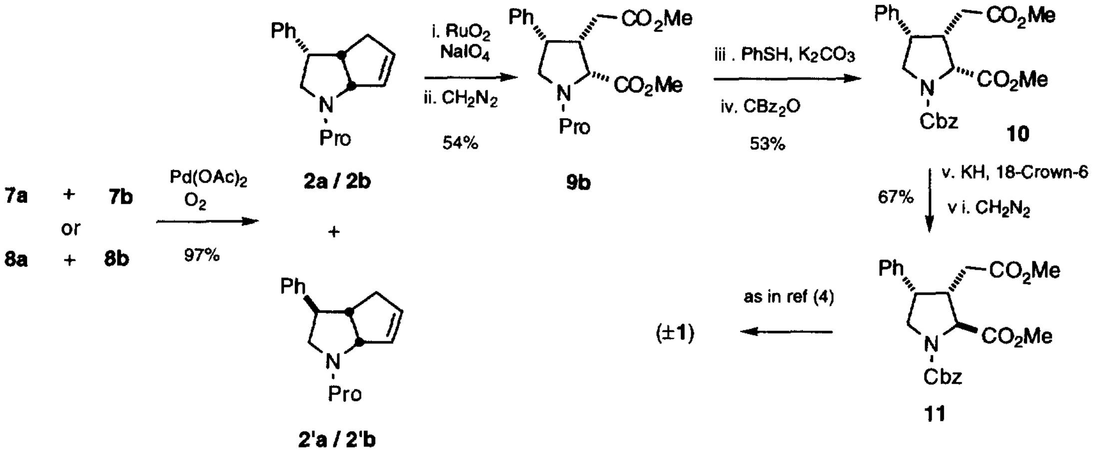
Finally a brief treatment in refluxing TBAF of the azabicycles (**5a**/**6a** or **5b**/**6b**) produced the related desilylated adducts **7a**/**8a** and **7b**/**7b** for which the configuration was assigned by direct correlation (Scheme 2).[11] From the composition of the above mixtures the following points are deduced : (i) after the opening of the aziridine, two chemical pathways have to be considered : (a) the internal quenching of the β-silicon cation by the transient amide produces **5a/6a** or **5b**/**6b** or (b) desilylation producing **7a**/**8a** or **7b**/**8b**, (ii) the diastereomeric enrichment in each set suggests that



Scheme 3.

different stereoelectronic factors operate in the two pathways. This last observation would be useful, if one could find experimental conditions for a better diastereomeric enrichment. Some attempts (change of the nature of the Lewis acid, stoechiometry or temperature) to increase the amount of the major diastereomer in each mixture failed.

The synthesis was pursued in the following way : the four component mixtures (**5a-8a**) and (**5b-8b**) was refluxed in a TBAF solution in THF (1 M) yielding a two component mixtures (**7a-8a**) and (**7b-8b**) which were submitted to an intramolecular heterocyclisation assisted by $Pd(OAc)_2$[12] to yield quantitatively the azabicycles **2a-2'a** and **2b-2'b**. At this stage each diastereomer could be obtained pure after column chromatography. Compound **2b**, with the suitable configuration for the kainoid system, was chosen to perform the final steps of our synthesis. Oxidation of the intramolecular double bound to the diacid was best realized under Sharpless conditions[13] affording diester **9b**, after diazomethane treatment. The nosyl protection was exchanged for the Cbz group to reach **10**.[14]. As none of the reported conditions for the epimerization at C(2) applied to **10** was satisfactory in our hands, we found that the epimerization could be realized with KH (3 eq.) and 18-crown-6 (0.1 eq) in C_6H_6 (0.03 M) at room temperature for 48 h with concomittant saponification. An additionnal treatment with diazomethane furnished **11**. The final transformation to (±)-**1** has already been described by Shirahama.[4]



Scheme 4.

In conclusion, we have presented a new and short approach to (±)-phenylkainic acid, with some merits over the existing syntheses : (i) cheap starting materials : phenylaziridine and 3-cyclopentenysilane, (ii) a short sequence (3 steps) to reach the substituted pyrrolidine ring, and (iii) a new procedure for the epimerization at C(2).

References and Notes.

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11. Some selected physical data :

    5a (major dia) R_f (Hex/ether : 7/3) 0.54; ^{1}H RMN (200 MHz, $CDCl_3$) δ 0.13 (s, 9 H); 1.51-1.58 (m, 2 H); 1.60-1.77 (m, 1 H); 1.90-1.96 (m, 1 H); 2.02-2.21 (m, 1 H); 2.48 (s, 3 H); 2.44-2.60 (m, 1 H); 2.90 (dd, J = 8.7 and 10.4 Hz, 1 H) ; 2.90-3.11 (m, 1 H); 3.83-3.90 (m, 2 H); 7.07 (dd, J = 2 and 8.4 Hz, 2 H); 7.11-7.32 (m, 3 H); 7.36 (d, J = 8.3 Hz); 7.75 (d, J = 8.3 Hz, 2 H). ^{13}C RMN (50 MHz, $CDCl_3$) δ -1.8; 21.5; 25.3; 30.7; 33.8; 49.0; 51.6; 56.5; 67.3; 126.8; 127.9; 127.3; 128.5; 129.5; 132.8; 140.2; 143.3.

    6a (minor dia) R_f (Hex/ether : 7/3) 0.54; ^{1}H RMN (200 MHz, $CDCl_3$) δ 0.12 (s, 9 H); 1.44-1.58 (m, 3 H); 1.60-1.77 (m, 1 H): 1.90-1.96 (m, 1 H); 2.44 (s, 3 H); 2.73-2.99 (m, 2 H); 3.65 (t, J = 11.5 Hz, 1 H); 3.93-3.98 (m, 1 H); 4.18 (dd, J = 1.6 and 7.2 Hz); 7.07-7.38 (m, 7H,); 7.79 (d, J = 8.3 Hz, 2 H). ^{13}C RMN (50 MHz, $CDCl_3$) δ -2.5; 21.4; 27.4; 31.5; 35.8; 45.5; 49.5; 56.65; 69.3; 127.2; 127.3; 128.2; 128.5; 129.5.; 132.8;.140.0; 143.3. Anal. Calcd for $C_{23}H_{31}NO_2SSi$: C, 66.78; H, 7.55; N, 3.39. Found C, 67.13; H, 7.60; N, 3.39.

    7a (minor dia) R_f (Hex/ether : 7/3) ^{1}H RMN (200 MHz, $CDCl_3$) δ 1.21-1.44 (m, 1 H); 1.59-1.77 (m, 1 H); 2.12-2.19 (br t, 2 H); 2.42 (s, 3 H), 2.52 (dt, J = 4.5 and 9.7 Hz, 1 H); 2.82-2.92 (m, 1 H); 3.02-3.15 (m, 1 H); 3.36-3.48 (m, 1 H); 5.38-4.42 (br s, 1 H); 5.74-5.81 (m, 2 H); 7.0 (dd, J= 2 and 6.8 Hz, 2H); 7.19-7.29 (m, 4 H); 7.62 (d, J = 8.3 Hz, 2 H). ^{13}C RMN (50 MHz, $CDCl_3$) δ 21.3; 28.1; 31.2; 46.3; 48.7; 50.4; 126.8; 126.9; 128.1; 128.5; 129.5; 131.7; 132.5;136.5; 140.6; 143.1.

    8a (major dia) R_f (Hex/ether : 7/3) 0.24; ^{1}H RMN (200 MHz, $CDCl_3$) δ 1.42-1.52 (m, 1 H); 2.02-2.21 (m, 3 H);2.41 (s, 3 H); 2.43-2.58 (m, 1 H); 2.84-2.88 (m, 1 H); 2.18-3.15 (m, 1 H); 3.31-3.51 (m, 1 H); 4.52-4.62 (m, 1 H); 5.19-5.64 (m, 2 H); 7.00 (dd, J = 2 and 7.7 Hz, 2 H); 7.14-7.22 (m, 5 H); 7.62 (d, J = 8.1 Hz, 2 H). ^{13}C RMN (50 MHz, $CDCl_3$) δ 21.4; 28.4; 32.1; 46.6; 49.1; 51.2; 126.8; 128.0; 128.5; 129.4; 131.4; 132.2; 136.5; 140.65; 143.1. Anal. Calcd for $C_{20}H_{23}NO_2S$: C, 70.35; H, 6.79; N, 4.10. Found C, 70.58; H, 6.85; N, 4.05

    2a R_f (Hex/ether : 7/3) 0.36; ^{1}H RMN (200 MHz, $CDCl_3$) δ 1.82-1.95 (m, J = 17.9 Hz, 1 H); 2.06-2.20 (m, with J = 1.6 and 17.8 Hz, 1 H); 2.44 (s, 3 H); 3.11-3.25 (m, 2 H); 3.42 (t, J = 10.9 Hz, 1 H); 3.84 (dd, J = 6.7 and 10.9 Hz, 1 H): 4.95 (br d, J = 7.3 Hz, 1H); 5.72-5.84 (m, 2 H,); 7.07 (d, J = 7.8 Hz, 2 H); 7.21-7.38 (m, 5 H); 7.80-(d, J = 8.2 Hz, 2 H). ^{13}C RMN (50 MHz, $CDCl_3$) δ 21.5; 33.6. 44.4; 46.0; 49.7; 70.2; 126.6; 127.2; 127.4; 127.8; 128.4; 129.8; 134.3; 134.6; 136.5; 138.9; 143.3. Anal. Calcd for $C_{20}H_{21}NO_2S$: C, 70.76; H, 6.41; N, 4.15. Found C, 70.88; H, 6.55; N, 4.25
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