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Unprecedented Sigmatropic Rearrangements Leading to 2,3-Dihydro-1*H*-2-benzazepine-3-carboxylic Acid

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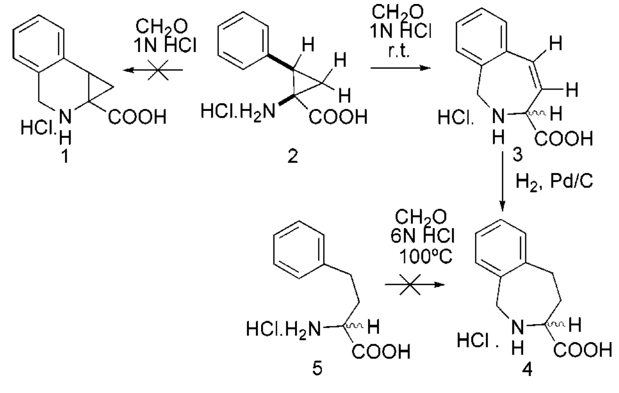
Introduction

Conformationally constrained peptide analogues are attracting considerable attention.[1−5] The cyclization of phenylalanine to 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (Tic) is a particularly successful example of this concept.[1,6−8] We were interested in combining the conformational constraints of Tic with those of a 2,3-methanoamino acid,[9−11] which would yield the novel amino acid 3,4-methano-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid **1**, with reduced structural promiscuity.

Results and Discussion

The synthesis of α-amino acid **1** was planned by a Pictet−Spengler cyclization of *cis*-2,3-methanophenylalanine hydrochloride **2** (Scheme 1). However, under the conditions previously described for the cyclization of L-Phe to L-Tic[8,12] (6 N HCl, 100 °C), extensive decomposition of **2** occurred. By using milder reaction conditions (rt, 1 N HCl) an almost quantitative conversion of the starting material **2** was observed. However, the ^{1}H NMR data of the reaction product were not consistent with the formation of **1** but rather indicated the formation of 2,3-dihydro-1*H*-2-benzazepine-3-carboxylic acid **3**. This structure was further confirmed by hydrogenation to the more stable tetrahydro-analogue **4**, the preparation of which has been reported previously in the patent literature[13] by a multistep procedure. Interestingly, Pictet−Spengler cyclization of homophenylalanine **5** to 2,3,4,5-tetrahydro-1*H*-2-benzazepine-3-carboxylic acid **4**, using the conditions reported for L-Phe[8,12] was unsuccessful; the starting material **5** being recovered unchanged from the reaction.

Scheme 1



The mild reaction conditions under which the methanoamino acid **2** is transformed into the ring expanded **3** raises the issue concerning the mechanism involved in this new rearrangement. The reaction was followed by measuring 1D ^{1}H NMR spectra at regular time intervals. By monitoring the intensity of the cyclopropane signals at δ 1.65, 1.77, and 2.99 ppm, the disappearance of the starting material **2** could be followed, whereas the formation of the benzazepine derivative **3** is observed following the appearance of the signals for the α-H (H_3) at 4.60 ppm and the ethylenic protons at 5.85 (H_4) and 6.67 (H_5) ppm, respectively, each with the expected scalar coupling patterns (Figure 1a−c). When the reaction was run in D_2O as a solvent, an exchange process of the α-H became apparent (Figure 1c−e), leading to the gradual disappearance of its signal. Accordingly, the H_4 double doublet (Figure 1b) is gradually replaced by a doublet (Figure 1e) as the fully protonated isotopomer of **3** is replaced by the deuterated one. The facile monitoring of the reaction allowed a more detailed mechanistic investigation by using suitably deuterated reagents.

First, the possibility of a Pictet−Spengler cyclization of α-amino acid **2** to methano-Tic **1**, followed by an acid-catalyzed cyclopropane ring opening to **3**, was excluded, because the NMR spectrum of **1** (prepared through an independent pathway[14]) remained unchanged after 24 h in 1 N DCl, both in the absence and presence of paraformaldehyde. Therefore, a cyclization through a [3,3] sigmatropic rearrangement is proposed (Scheme 2), in analogy to the *cis*-divinylcyclopropane rearrangement to 1,4-cycloheptadienes[14−16] and to the aza-Claisen [3,3]-

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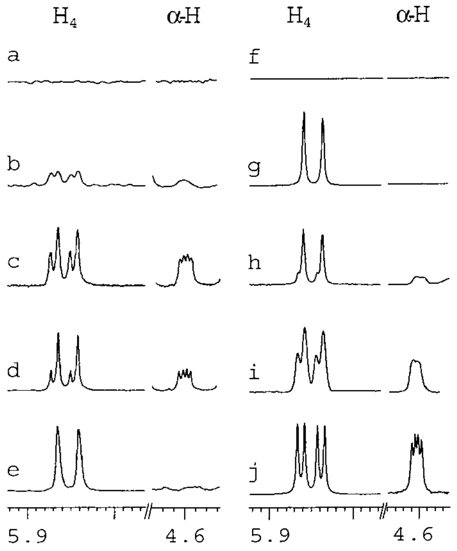
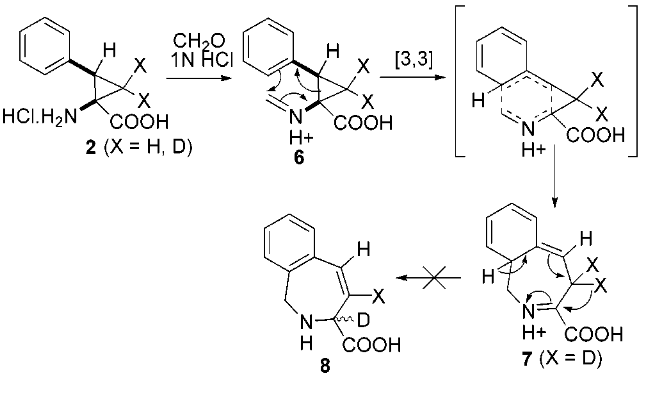


Figure 1. Monitoring by ^{1}H NMR of the transformation of **2** (X = H) into **3** (a–e; left half) and **9** into **13** (f–j; right half) as a function of time. See text for details.

Scheme 2

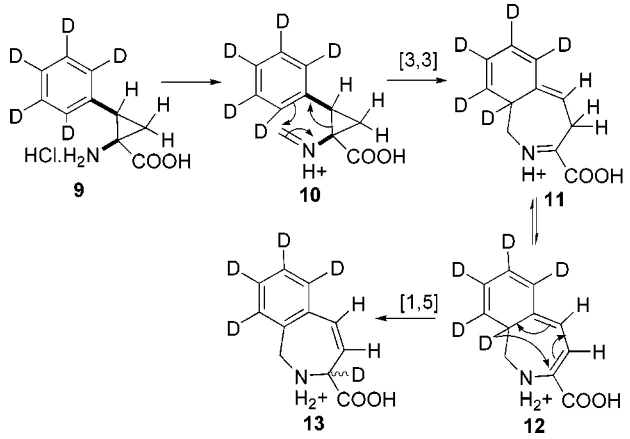


rearrangements of *N*-acyl vinylaziridines to the corresponding tetrahydroazepin-2-ones.[17]

In the case of compound **2**, this novel sigmatropic rearrangement would involve the benzene ring and the iminium ion in **6** to form intermediate **7**, followed by an aromatization with concomitant double bond shift and hydrogen transfer to the iminium ion to yield **3** (Scheme 2).

For the latter step, several pathways were evaluated by using deuterium-labeled precursors. Thus, a first pathway involving a 1,2-hydride shift from **7** to **8** would result in the incorporation of a deuterium at the α-position (C_3), when starting from the dideutero-methanoprecursor **2** (X = D). The latter was prepared following the same method as for the proton-analogue **2** (X = H),[18] using deuteriodiazomethane. However, following the reaction of dideutero **2** (X = D) by NMR spectroscopy in DCl and D_2O clearly indicated the immediate appearance of an α-H during the rearrangement, simultaneous with the ethylenic H_5 proton, thus excluding this pathway.

Scheme 3



The possibility that the excess formaldehyde would be the source of this α-H was excluded by performing the reaction with deuterated paraformaldehyde in DCl and D_2O. NMR monitoring again showed the immediate appearance of an α-H, which slowly exchanged for a deuterium atom. Therefore, the pentadeutero-phenyl precursor **9** (Scheme 3) was prepared starting from pentadeuteriobenzaldehyde and allowed to react with paraformaldehyde in HCl and H_2O, thus leaving the aromatic ring as the only source of deuterium.

The NMR spectra clearly showed the appearance of the ethylenic protons, but the absence of an α-H (Figure 1f and g), indicating the initial incorporation of a deuterium at the α-position. This is confirmed by the delayed appearance of the α-H resonance and its scalar coupling to the ethylenic protons, as a result of the exchange process (Figure 1h–j). Therefore, the transformation of the iminium intermediate **11** to the final compound **13** can be explained by assuming an imine-enamine equilibrium to **12**, followed by a [1,5] hydrogen shift, as already proposed in the formation of benzocycloheptene- and 1*H*-2-benzazepine derivatives.[19–21]

Conclusion

In conclusion, we were able to demonstrate that the conversion of the iminium ion of *cis*-3-methanophenylalanine to the benzapine **3** involves a novel [3,3] sigmatropic rearrangement, followed by a [1,5] hydrogen shift. The scope of this novel rearrangement and the application of the resulting amino acids in biologically active peptides are being investigated.

Experimental Section

General Methods. RP-HPLC was performed using a C-18 column (i.d. = 0.46 cm, L = 25 cm, PS = 5 μ). A linear gradient from A to B in 30 min with mobile phase A (water/acetonitrile (8/2) + 0.1% TFA) and mobile phase B (acetonitrile + 0.1% TFA) was used (flow rate 1.0 mL min^{-1}, $\lambda = 215$ nm). TLC was performed using silicagel 60 F_{254}, eluting with EtOAc/*n*BuOH/AcOH/H_2O 1/1/1/1. CH_3OH was distilled from Mg onto activated molecular sieves (3 Å, 10% w/v). Commercial 10% Pd/C was used. Monitoring of the reaction progress with ^{1}H NMR was performed at 500 MHz. Each sample was prepared by dissolving 5.0 mg of

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3 and its deuterated analogues together with 5.0 mg of paraformaldehyde in 0.5 mL of 1 N DCl/D_2O or HCl/H_2O, followed by vigorous shaking before insertion into the magnet. NMR characterizations were performed at 250 MHz.

2,3-Dihydro-1*H*-2-benzazepine-3-carboxylic Acid 3. A total of 1.50 g (7.02 mmol) of *cis*-2,3-methanophenylalanine hydrochloride **2** was dissolved in 45 mL of a 1 M HCl solution. After the addition of 1.50 g (50 mmol) of paraformaldehyde, the solution was stirred at room temperature for 10 h. The solution was lyophilized to avoid decomposition during evaporation, and the remaining solid was dissolved in dry MeOH and filtered. The solvent was removed in vacuo (quantitative yield). Mp: slow decomposition above 200 °C without melting. ^1H NMR (250 MHz, CD_3OD): δ 4.28 (d, $^2J(H_1,H_{1'}) = 14.4$ Hz, 1H, H_1), 4.48 (d, $^2J(H_1,H_{1'}) = 14.4$ Hz, 1H, $H_{1'}$), 4.92 (m, 1H, H_3), 6.20 (dd, $^3J(H_3,H_4) = 4.3$ Hz, $^3J(H_4,H_5) = 12.3$ Hz, 1H, H_4), 6.94 (dd, $^4J(H_3,H_5) = 2.3$ Hz, $^3J(H_4,H_5) = 12.3$ Hz, 1H, H_5), 7.30−7.50 (m, 4H, $H_{aromatic}$). ^1H NMR (500 MHz, 1 N DCl/D_2O under reaction conditions): δ 3.96 (d, $^2J(H_1,H_{1'}) = 14.2$ Hz, 1H, H_1), 4.12 (d, $^2J(H_1,H_{1'}) = 14.2$ Hz, 1H, $H_{1'}$), 4.60 (m, 1H, H_3), 5.85 (dd, $^3J(H_3,H_4) = 4.3$ Hz, $^3J(H_4,H_5) = 12.0$ Hz, 1H, H_4), 6.67 (dd, $^4J(H_3,H_5) = 3.3$ Hz, $^3J(H_4,H_5) = 12.0$ Hz, 1H, H_5), 7.00−7.15 (m, 4H, $H_{aromatic}$). Accurate MS (ES) $[M + H]^+$ found 190.0837, calcd 190.0868. RP-HPLC: $t_{ret} = 11.85$ min. TLC: $R_f = 0.43$.

2,3,4,5-Tetrahydro-1*H*-2-benzazepine-3-carboxylic Acid 4. A total of 51 mg (0.23 mmol) of **3** was dissolved in 10 mL of dry MeOH, after which 10 mg (20 wt %) of 10% Pd/C was added. After a hydrogenation at 4 bar H_2 for 4 h at room temperature, the catalyst was removed, and the solvent was evaporated in vacuo (yield 50 mg, 97%). Mp: slow decomposition above 240 °C without melting. ^1H NMR (250 MHz, CD_3OD): δ 1.95 (m, 1H, H_4), 2.65 (m, 1H, $H_{4'}$), 3.05−3.30 (m, 2H, H_5, $H_{5'}$), 4.32−4.51 (m, 3H, H_1, $H_{1'}$, $H_{3,}$), 7.20−7.40 (m, 4H, $H_{aromatic}$). Accurate MS (ES) $[M + H]^+$ found 192.1057, calcd 192.1025. RP-HPLC: $t_{ret} = 10.19$ min. TLC: $R_f = 0.43$.

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