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Acid-catalyzed rearrangement of 1-benzyl-2-methyl-3-piperidone to 1-benzyl-2-acetylpyrrolidine

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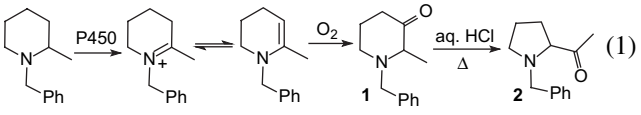
Abstract—We report that 1-benzyl-2-methyl-3-piperidone, conveniently prepared from 3-hydroxy-2-methylpyridine, undergoes rearrangement to 1-benzyl-2-acetylpyrrolidine in aqueous 6 N HCl at reflux. Studies showing that the 2,2-dimethyl analog is inert under the same conditions support a mechanism of reversible tautomeric equilibria via ring-opened intermediates, one of which was independently synthesized and shown to be a kinetically competent intermediate to product.

1. Introduction

Piperidine and pyrrolidine rings are ubiquitous structural features of many alkaloid natural products[1] and drug candidates,[2] and their derivatives are important intermediates in organic synthesis. We have been interested in the chemistry of reactive intermediates generated in the oxidative metabolism of the *N*-alkyl tertiary amine ring systems. In particular, we have been interested in the oxygenation of endocyclic enamines in equilibrium with the initial endocyclic iminium forms that result from cytochrome P450-mediated metabolism (e.g., Eq. 1). During an investigation into the chemistry of *N*-benzyl-3-piperidones,[3,4] resulting from autoxidation of the corresponding *N*-benzyl-Δ^2-tetrahydropyridines, we found that the 2-methyl compound **1** rearranges in hot aqueous HCl to 2-acetylpyrrolidine **2**.



(1)

A number of nonoxidative[5] and oxidative[6] examples of rearrangements of α-amino ketones have been observed, but the exact type of rearrangement we observed has not, to our knowledge, been reported before. A possibly related rearrangement was observed more than 50 years ago by Leonard and co-workers in Clemmensen reduction of cyclic amine 3-ones, exemplified in Eq. 2. The rearrangement proceeded smoothly for 2-unsubstituted, mono 2-alkyl, and 2,2-dialkyl reactants **3a**–**d**.[7] The mechanism of Clemmensen reduction had only been postulated at that time, and Leonard rationalized the rearrangement he observed in terms of carbonyl O-protonation followed by 1,2-shift of nitrogen to the adjacent carbonyl carbon, with concomitant[8] or subsequent[9] delivery of a zinc-derived hydride equivalent to the migration origin (Eq. 3). Such mechanism would not accommodate the *nonreductive* rearrangement we are now reporting.

Although there may be no relationship between the rearrangements observed by Leonard and by us, two conceivable mechanisms that could be considered for both are shown in Eqs. 4 and 5, assuming that under Clemmensen conditions, these 3-piperidones underwent rearrangement *prior to zinc-mediated reduction*. The mechanism in Eq. 4 would explain our observed conversion of **1** to **2**, as well as Leonard's observations for **3a** and **3b**, whereas for the 2,2-dialkyl reactants **3c** and **3d**, reduction would have to occur at the level of intermediate **6**. Another possible mechanism (Eq.5) would involve two consecutive 1,2-alkyl shifts, based on the aza equivalent of the α-ketol rearrangement,[10] namely the interconversion between α-hydroxy imines and α-amino ketones,[11] which has been observed (α-amino aldehyde) to be catalyzed by Lewis acids.[12] Again, the mechanism in Eq. 5 would explain our observed conversion of **1** to **2** and Leonard's observations for **3a** and **3b**, whereas in the 2,2-dialkyl reactants **3c** and **3d** an additional rapid 1,2-alkyl shift would be needed, with reduction occurring only after generation of an intermediate **6**.

Keywords: Rearrangement; Piperidone; Pyrrolidone; Clemmensen reduction.
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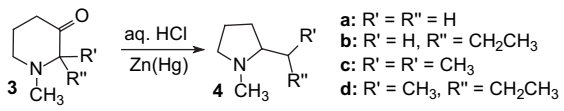

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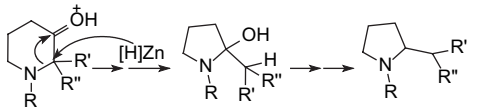

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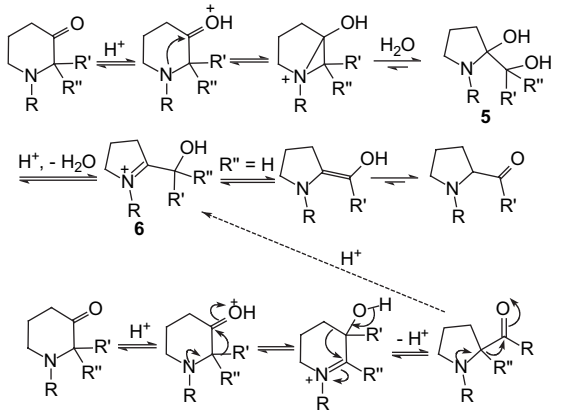


(4)

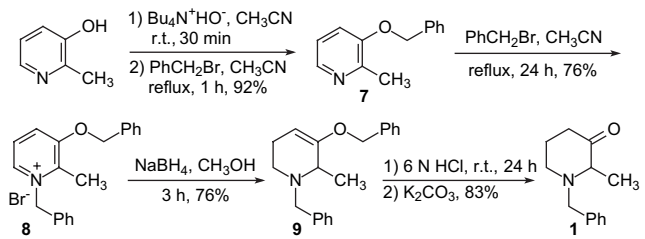
(5)

The purpose of this study was to clarify the mechanism of the nonreductive rearrangement responsible for conversion of **1** to **2**. Based on these results, we further propose a mechanism for the rearrangement observed under Clemmensen conditions that is consistent with recent views on the chemistry of this reduction process.

2. Results and discussions

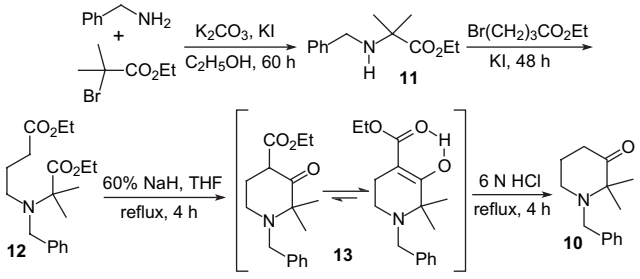
2.1. Preparation of 1-benzyl-3-piperidones 1 and 10

The required 2-methyl-3-piperidone **1** was prepared from commercially available 3-hydroxy-2-methylpyridine in four steps (Scheme 1). The key *N*,*O*-dibenzyl-protected intermediate **8**[13] was most conveniently obtained by the two-step benzylation sequence as shown. Yield of **8** obtained without isolation of **7** was inferior. Reduction ($NaBH_4$) of **8** and *O*-deprotection of the resulting **9**[14] by treatment with 6 N HCl at room temperature gave **1**[15] in 83% yield. This scheme might be adapted to offer a useful synthesis of other 3-piperidone analogs.



Scheme 1.

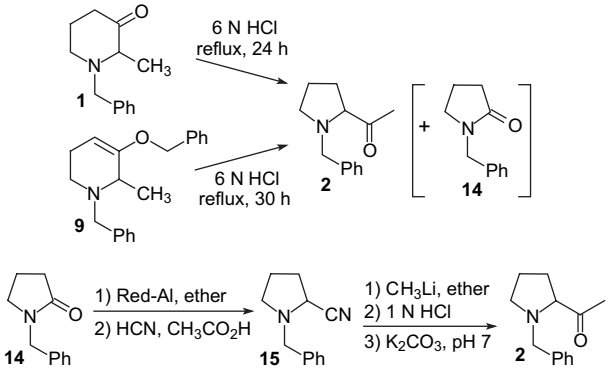
Synthesis of the 2,2-dimethyl-3-piperidone **10** was achieved according to the route shown in Scheme 2.[16] Heating benzylamine with ethyl 2-bromoisobutyrate in ethanol in the presence of a catalytic amount of KI gave **11** in 52% yield. Conversion of secondary amine **11** to tertiary amine **12** with ethyl 4-bromobutyrate under the same conditions was more sluggish, even in refluxing *n*-butanol, but could be achieved by heating in solvent-free conditions. Dieckmann condensation of diester **12** with sodium ethoxide in THF gave keto ester **13** (as the enol) in a low yield, but a more satisfactory result (95% yield) was obtained using 60% sodium hydride. Hydrolytic decarboxylation (6 N HCl) afforded **10** in 89% yield.



Scheme 2.

2.2. Rearrangement of 1-benzyl-2-methyl-3-piperidone (1) to 1-benzyl-2-acetylpyrrolidine (2)

Heating **1** in 6 N aqueous HCl at reflux for 24 h under argon resulted in its rearrangement in 90% yield (remaining is recovered **1**) to 2-acetylpyrrolidine **2** (Scheme 3), accompanied by a trace amount of 1-benzyl-2-pyrrolidine **14**, representing oxidation of rearrangement product **2**.[17] Compound **2** was also obtained directly from **9** by heating the latter in 6 N HCl at reflux for 30 h. The identity of **2** was verified by comparison with an authentic sample prepared from **14** by reduction of the latter with Red-Al followed by treatment with aqueous HCN solution, and reaction of the resulting nitrile **15**[18] with methyllithium in benzene, followed by hydrolytic workup.



Scheme 3.

Various reaction conditions were tested in order to evaluate the ease of rearrangement of **1**. Compound **1** was generated from **9** by exposure to 6 N HCl at *room temperature* for 24 h, and we verified that **1** is stable under these conditions. Heating **1** at reflux in 6 N HCl for periods of time shorter

than 24 h resulted in a lower yield of conversion to **2** (e.g., 55% in 6 h). The importance of acid concentration in this rearrangement was easily recognized by the finding that heating **1** at reflux in 0.5 N HCl for 6 h gave **2** in only 38% yield.

2.3. Attempted rearrangement of 1-benzyl-2,2-dimethyl-3-piperidone (10)

The mechanism considered in Eq. 5 would predict that 2,2-dimethyl substitution would still allow rearrangement to a 2-acylpyrrolidine. According to Eq. 4, whereas 2,2-dimethyl substitution would prevent rearrangement to a 2-acylpyrrolidine, the reaction could still proceed to the stage of intermediates **5/6**. Thus, according to these mechanisms, one might predict that 1-benzyl-2,2-dimethyl-3-piperidone (**10**) would undergo, in refluxing aqueous 6 N HCl, conversion to either 2-acetyl-2-methylpyrrolidine or to a product derived from **5/6**, possibly the ring-opened amino ketone. However, heating **10** in 6 N HCl at reflux for 24 h resulted in total recovery of starting material. The inertness of **10** is inconsistent with Eq. 4 or 5 as the mechanism of the nonreductive rearrangement, and suggests consideration of a mechanism relying on an initial enolization step. At the same time, we found that the unsubstituted parent compound 1-benzyl-3-piperidone also does not undergo the rearrangement.

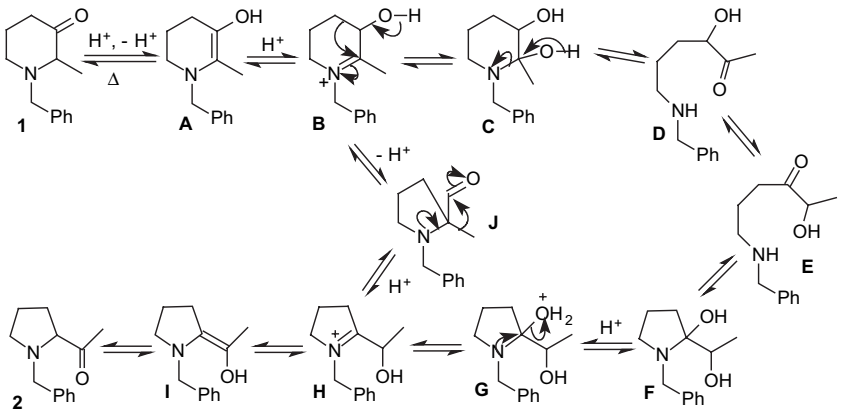
2.4. Mechanism of rearrangement

Two plausible mechanisms that would explain the rearrangement of **1** to **2** but the inertness of **10** are outlined in Scheme 4. In acid, the 3-piperidone would exist in equilibrium with enol–enamine **A** and iminium form **B**. The latter would further be in equilibrium with the hydrate **C** and ring-opened ketone **D**, with the overall conversion of **1** to **D** corresponding to the reverse of the well-known Amadori rearrangement that occurs following condensation of reducing sugars with amines.[19] If ketol **D** could be interchanged in acid with ketol **E**,[20] then the latter would be in equilibrium with **2** through the reverse sequence of analogous intermediates containing a five- rather than a six-membered ring. This would suggest that the conversion of **1** to **2** merely represents an equilibrium process and the thermodynamic predominance of **2**. Precedent for these types of proposed keto–enol tautomerizations has been reported.[21] Why the unsubstituted parent 1-benzyl-3-piperidone would not undergo rearrangement according to this mechanism may reflect the insufficient enol/iminium stability of the intermediates, or the instability of the aldehyde equivalents of **D** and **2**.

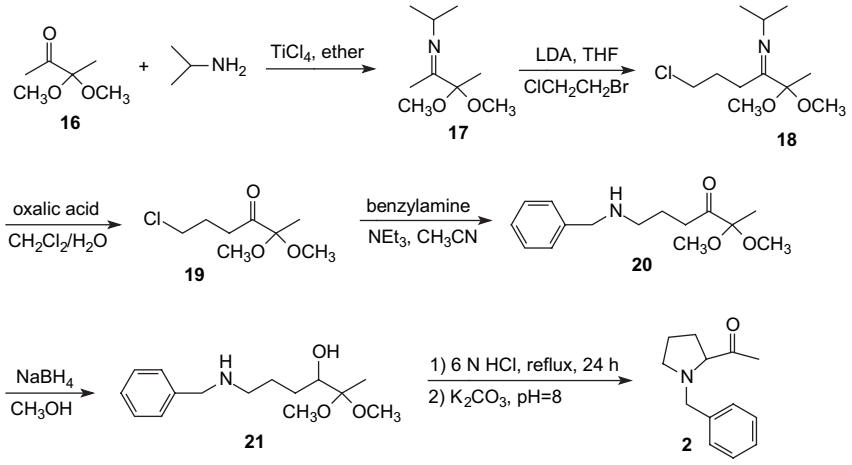
Another possible pathway, based on the aza equivalent of the α-ketol rearrangement,[11,12] is that α-hydroxy iminium intermediate **B** could undergo two subsequent 1,2-alkyl shifts, first a ring contraction to give **J** and then a methyl shift to give **H**. Although this mechanism would involve a lesser number of steps, we believe that the sequence of tautomerizations through **D** and **E** provides a more likely overall low energy pathway.

To determine whether the sequence of tautomerizations through **D** and **E** provides at least a kinetically competent mechanism for the rearrangement of **1** to **2**, it would be important to show that one of the two proposed ring-opened intermediates could convert to **2** at least as rapidly as **1** converts to **2** under the same reaction conditions. We chose to prepare intermediate **D**, which could be obtained by deprotection of the dimethyl ketal **21**, independently synthesized as shown in Scheme 5. On the basis of a previous report,[22] γ-chloroketone **19** was selected as the key synthetic intermediate, and was obtained by alkylation with 1-bromo-2-chloroethane of the lithium derivative formed from deprotonation of the *N*-isopropylimine of butane-2,3-dione monoketal **16**. Without isolation of the intermediate **18** following workup, selective hydrolysis of the imino function in the presence of the ketal function was conveniently achieved using aqueous oxalic acid. Alkylation of benzylamine with **19**, and $NaBH_4$ reduction of the resulting amino ketone **20** without its isolation, afforded **21**. An attempt to prepare **21** by first reducing **19** and then reacting with benzylamine was abandoned due to sluggish and low yield reactions. Heating **21** in 6 N HCl at reflux was indeed found to give **2**, presumably through initial hydrolysis to intermediate **D** and rearrangement of the latter.

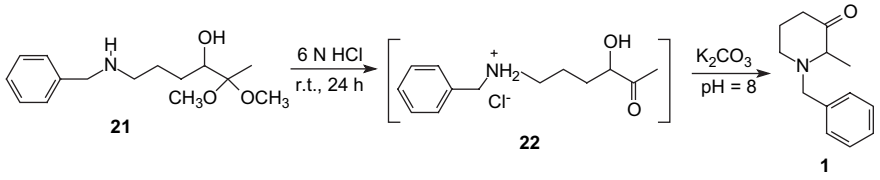
On the other hand, deprotection of **21** by treatment with 6 N HCl for 24 h at *room temperature* followed by neutralization gave **1** (Scheme 6). Assuming Scheme 4 is operative, this result suggests that the interconversion between intermediate **D** (six-membered ring manifold) and intermediate **E** (five-membered ring manifold) is mainly rate-limiting in the rearrangement of **1** that requires higher temperature. At the same time, this result also suggests the possibility that in acid, **21** first undergoes conversion to **1**, which at



Scheme 4.



Scheme 5.



Scheme 6.

elevated temperature then proceeds to **2** along a route that is distinct from that shown in Scheme 4. However, evidence that **D** is a kinetically competent intermediate on the lowest energy pathway from **1** to **2**, was provided by following the time course of conversion of both **1** and **21** to **2** under the conditions of refluxing 6 N HCl. As shown in Figure 1, the fraction of **2** (remainder is **1**), as determined by neutralization and extraction, was significantly greater at early time (1–3 h) when starting with **21** than with **1**. After 24 h, however, the amount of **2** (90%) was the same, and this appears to be close to the equilibrium distribution between **1** and **2** under the conditions of refluxing 6 N HCl.

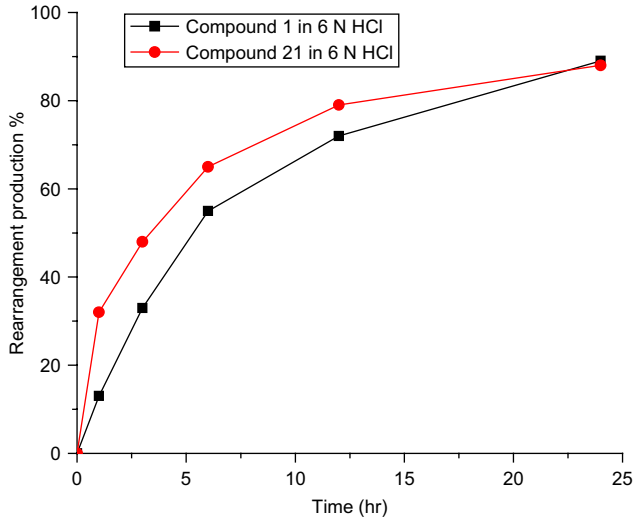


Figure 1. The relative amount of rearrangement product **2** formed from 3-piperidone **1** or compound **21** in 6 N HCl with heating at reflux for different reaction times, followed by neutralization and product analysis by ^{1}H NMR spectroscopy.

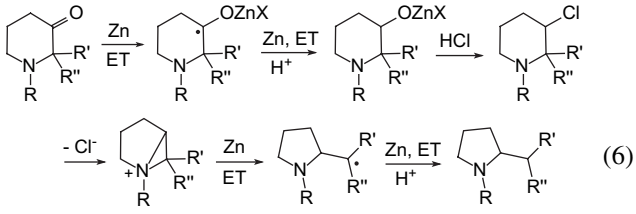
Additional information on the mechanism was provided by following the fate of **21** in 6 N deuterium chloride–deuterium oxide in an NMR tube. At room temperature, deprotection occurred immediately to reveal signals expected for the protonated form of **22**. Signals at δ 2.1 (CH_3) and δ 4.4 (CH) gradually disappeared over the course of 24 h due to deuterium exchange, but otherwise no other changes were observed. Although rapid neutralization and extraction at this point affords **1**, this result suggests that in the strongly acidic medium at room temperature, ring-opened amino ketone **D** does not interconvert with **E** or any of the ring-closed amino ketone forms.

In the same manner, the solution forms of both the six- and five-membered amino ketones were investigated, in these cases most readily by ^{13}C NMR spectroscopy in DCl–D_2O. 1-Benzyl-3-piperidone·HCl is known to exist as its hydrate in aqueous solution,[23] as verified in this study, where the free base form exhibited a carbonyl signal at 207.1 ppm, whereas for the DCl salt in D_2O, this signal was replaced by one at 91.6 ppm assigned to the carbon bearing two OH groups. The ^{13}C NMR spectrum of the 2-methyl analog **1** shows that it also exists mainly as the hydrate in 6 N DCl–D_2O, as apparent from the lack of a carbonyl signal and presence of a geminal dihydroxy ^{13}C signal at 93.8 ppm. The 2,2-dimethyl analog **10** in 6 N DCl–D_2O exists as a mixture of ketone and hydrate forms (^{13}C NMR signals are seen at both 207.6 and 95.3 ppm). On the other hand, 1-benzyl-2-acetylpyrrolidine **2** exists as such in 6 N DCl–D_2O (^{13}C NMR carbonyl signal at 205.0 ppm). The tendency of the 3-piperidones but not **2** to form the hydrate likely reflects

the well-known tendency of six-membered rings to become entirely sp^3 tetrahedral to minimize torsional strain,[24,25] with the lack of hydration of **2** indicating that there is no intrinsic electronic preference for protonated α-amino ketones to exist as their hydrates.

As expected from these results, when the NMR tube containing **21** in 6 N DCl–D_2O was heated at 95 °C, the ^{13}C NMR spectrum after 5 h revealed a mixture of **1** (as its hydrate) and **2**, whereas continued heating resulted in mainly **2**, as is seen when starting with **1**. The main importance of these experiments is the demonstration that equilibration between the ring-opened and ring-closed forms of both the six- and five-membered ring manifolds shown in Scheme 4 occurs only at elevated temperature. Thus, although the **D**⇌**E** interconversion has been ascribed to be the main rate-limiting step in the rearrangement, other steps in the overall mechanism may additionally be partially rate-limiting.

Over the years, although the mechanism of Clemmensen reduction has still not been totally elucidated, the most recent studies on this subject suggest a stepwise electron/proton transfer mechanism via radical and probably alkyl chloride intermediates,[26] with the additional possible intermediacy of an organozinc species. It is known that the corresponding carbinols are not intermediates, though dimeric pinacol side-products are sometimes observed, suggestive of coupling of a α-oxycarbon radical intermediate. A possible mechanism that follows this line of reasoning and that would explain the ring-contractions for **3a**–**d** and the racemization of **3d** observed by Leonard and co-workers[9] is given in Eq. 6. Since the first of the four electron reduction steps would, according to this mechanism, occur prior to any rearrangement step, this would then clearly be a distinct process from the *nonreductive* rearrangement we proposed in Scheme 4.



(6)

3. Conclusions

In summary, we have developed an efficient route to 1-alkyl-2-methyl-3-piperidones and demonstrated that the 1-benzyl compound undergoes rearrangement to 1-benzyl-2-acetylpyrrolidine in refluxing 6 N HCl. The reaction reaches an equilibrium state at ~90% conversion, with the driving force apparently being the thermodynamic preference of a five-membered ring over a sp^2 carbon-containing six-membered ring because of torsional strain in the latter.[24,25] A mechanism has been proposed for the rearrangement involving a series of acid-catalyzed tautomerization and hydration/dehydration steps that is distinct from a seemingly similar rearrangement known to accompany Clemmensen reduction of the same starting materials.

4. Experimental

4.1. General

All melting points are uncorrected. ^1H NMR spectra were obtained with Varian Gemini 200 MHz (^{13}C NMR at 50 MHz) or 300 MHz (^{13}C NMR at 75 MHz) instruments. In all cases, tetramethylsilane (TMS) or the solvent peak served as internal standard for reporting chemical shifts, which are expressed as parts per million downfield from TMS (δ scale). In the ^{13}C NMR line listings, attached proton test designations are given as (+) or (−) following the chemical shifts. High-resolution mass spectra (HRMS) using electron impact (EI) or fast atom bombardment (FAB), were obtained at 20–40 eV on a Kratos MS-25A instrument. TLC was performed on glass plates precoated with silica gel $60GF_{254}$. Compounds on the developed plate were visualized by short-wavelength UV light (λ=254 nm) or by spraying with either ninhydrin or 2,4-dinitrophenylhydrazine solutions. All evaporations were conducted at reduced pressure using a rotary evaporator. All new compounds were determined to be >95% pure by ^1H NMR spectroscopy.

4.2. 3-Benzyloxy-2-methylpyridine (7)

A mixture of 2-methyl-3-pyridinol (2.0 g, 0.018 mol) and tetra-*n*-butylammonium hydroxide (40% solution in water, 11.68 g, 0.018 mol) in 50 mL of CH_3CN was stirred at room temperature for 30 min and then evaporated to dryness, and the resulting ammonium salt was dried in vacuo. Benzyl bromide (2.14 mL, 0.018 mol) was added to a solution of the ammonium salt in 100 mL of CH_3CN, and the mixture was heated at reflux for 1 h. The reaction mixture was cooled and filtered, and the filtrate was evaporated to afford a yellowish oil. The crude product was purified by silica gel flash chromatography using EtOAc–CH_2Cl_2 (1:4) to give **7** as a pale yellowish oil (3.36 g, 92%): ^1H NMR ($CDCl_3$) δ 2.54 (s, 3H), 5.06 (s, 2H), 7.08 (m, 2H), 7.32–7.43 (5H), 8.09 (d, 1H, *J*=4.6 Hz); ^{13}C NMR ($CDCl_3$) δ 19.6 (−), 64.9 (+), 117.8 (−), 121.7 (−), 127.2 (−), 128.1 (−), 128.7 (−), 136.6 (+), 140.7 (−), 149.3 (+), 153.0 (+); EI HRMS *m/z* calcd for $C_{13}H_{13}NO$ $(M+H)^+$ 199.0998, found 199.0997.

4.3. 1-Benzyl-3-benzyloxy-2-methylpyridinium bromide (8)

Benzyl bromide (2.4 mL, 0.02 mol) was added to a solution of **7** (3.36 g, 0.017 mol) in 100 mL of CH_3CN. The reaction mixture was heated at reflux for 24 h under argon. The solvent was then evaporated, and the residue was washed with diethyl ether (3×10 mL) and then dried in vacuo to give pyridinium salt **8** (4.8 g, 76%): mp 186–188 °C; ^1H NMR ($CDCl_3$) δ 2.72 (s, 3H), 5.28 (s, 2H), 6.20 (s, 2H), 7.24–7.35 (10H), 7.88 (dd, 1H, *J*=6.2 and 8.6 Hz), 8.22 (d, 1H, *J*=8.6 Hz), 9.16 (d, 1H, *J*=6.2 Hz); ^{13}C NMR ($CDCl_3$, two carbons overlapped) δ 14.3 (−), 62.4 (+), 72.6 (+), 126.2 (−), 127.1 (−), 127.9 (−, 2C), 128.9 (−, 2C), 129.3 (−), 129.5 (−), 132.2 (+), 134.1 (+), 138.1 (−), 147.2 (−), 156.0 (+); FAB HRMS *m/z* calcd for $C_{20}H_{20}NO$ (M^+) 290.1546, found 290.1548.

4.4. 1-Benzyl-3-benzyloxy-2-methyl-1,2,5,6-tetrahydropyridine (9)

To a solution of **8** (3.0 g, 8.11 mmol) in 50 mL of methanol at 0 °C was added $NaBH_4$ (0.613 g, 16.2 mmol) over 15 min. The reaction mixture was stirred at room temperature for 3 h and then methanol was evaporated. To the solid residue were added 50 mL of ether and 25 mL of saturated aqueous K_2CO_3 solution. The reaction mixture was stirred vigorously at room temperature for 1 h and separated, and the aqueous layer was extracted with diethyl ether (3×20 mL). The combined ether extract was dried (Na_2SO_4) and evaporated to furnish **9** as a brownish oil (1.8 g, 76%) that was of satisfactory purity (NMR) to be used directly in the next step: ^{1}H NMR ($CDCl_3$) δ 1.36 (d, 3H, J=6.6 Hz), 2.03–2.09 (m, 1H), 2.25–2.35 (m, 1H), 2.19 (m, 1H), 3.24 (q, 1H, J=6.6 Hz), 3.67 (d, 1H, J=13.5 Hz), 3.87 (d, 1H, J=13.5 Hz), 4.73–4.83 (m, 3H), 7.14–7.46 (10H); ^{13}C NMR ($CDCl_3$) δ 16.2 (−), 22.4 (+), 44.2 (+), 55.4 (−), 58.0 (+), 68.6 (+), 92.3 (−), 126.9 (−), 127.4 (−), 127.7 (−), 128.2 (−), 128.5 (−), 128.9 (−), 137.7 (+), 139.5 (+), 156.5 (+); EI HRMS m/z calcd for $C_{20}H_{30}NO$ $(M+H)^+$ 293.1781, found 293.1781.

4.5. 1-Benzyl-2-methyl-3-piperidone (1)

A solution of **9** (1.0 g, 3.7 mmol) in 25 mL of 6 N HCl was stirred at room temperature for 24 h. The reaction mixture was extracted with ether. The aqueous phase was separated and neutralized with K_2CO_3 to pH 8. The solution was then extracted with diethyl ether (3×20 mL). The combined ether layer was dried (Na_2SO_4) and evaporated to give **1** as an oil (0.58 g, 83%): ^{1}H NMR ($CDCl_3$) δ 1.29 (d, 3H, J=6.8 Hz), 1.87–1.96 (2H), 2.30–2.38 (m, 1H), 2.40–2.57 (2H), 2.88–2.96 (m, 1H), 3.18 (q, 1H, J=6.8 Hz), 3.47 (d, 1H, J=13.5 Hz), 3.87 (d, 1H, J=13.5 Hz), 7.23–7.39 (5H); ^{13}C NMR ($CDCl_3$) δ 12.2 (−), 24.2 (+), 37.8 (+), 47.6 (+), 57.8 (+), 66.2 (−), 127.2 (−), 128.3 (−), 128.8 (−), 138.6 (+), 210.2 (+); EI HRMS m/z calcd for $C_{13}H_{17}NO$ $(M+H)^+$ 203.1311, found 203.1310.

4.6. 1-Benzyl-2-acetylpyrrolidine (2)

A solution of **1** (0.5 g, 2.5 mmol) in 25 mL of 6 N HCl was heated at reflux for 24 h under argon. The reaction mixture was extracted with diethyl ether. The aqueous phase was separated, neutralized with K_2CO_3 to pH 8, and extracted with diethyl ether (3×15 mL). The combined ether layer was dried (Na_2SO_4) and evaporated, and the residue was fractionated by flash silica gel chromatography with CH_2Cl_2–EtOAc (4:1) as eluent to yield **2** as an oil (0.39 g, 78%): ^{1}H NMR ($CDCl_3$) δ 1.76–1.88 (3H), 2.03–2.11 (m, 1H), 2.14 (s, 3H), 2.29 (dd, 1H, J=8.3 and 12.0 Hz), 3.04–3.13 (2H), 3.44 (d, 1H, J=13.1 Hz), 3.81 (d, 1H, J=13.1 Hz), 7.23–7.32 (5H); ^{13}C NMR ($CDCl_3$) δ 23.6 (+), 25.3 (−), 28.8 (+), 53.9 (+), 59.4 (+), 73.6 (−), 127.2 (−), 128.4 (−), 129.0 (−), 138.6 (+), 212.1 (+); EI HRMS m/z calcd for $C_{13}H_{17}NO$ $(M)^+$ 203.1311, found 203.1309. A trace of the known 1-benzyl-2-pyrrolidone (**14**) was also obtained in this experiment: ^{1}H NMR ($CDCl_3$) δ 1.96 (m, 2H), 2.42 (t, 2H), 3.24 (t, 2H), 4.43 (s, 2H), 7.27 (5H); ^{13}C NMR ($CDCl_3$) δ 17.8 (+), 31.0 (+), 46.6 (+), 46.7 (+), 127.6 (−), 128.2 (−), 128.7 (−), 136.6 (+), 175.0 (+).

4.7. 1-Benzyl-2-cyanopyrrolidine (15)[18]

To a solution of 1-benzyl-2-pyrrolidone **14** (ICN Pharmaceuticals, 15.0 g, 0.0856 mL) in 300 mL of dry ether was added 15 mL of Red-Al (3.4 M solution in toluene, 0.051 mol) at 0 °C. The reaction mixture was stirred at 0 °C under argon for 3 h. A cold solution of NaCN (12.0 g) in 8 mL of H_2O was slowly added to the reaction mixture, and the pH of the reaction mixture was adjusted to 5 with glacial acetic acid. The solution was stirred for 1 h at room temperature and then extracted with diethyl ether (3×50 mL). The combined ether extract was dried (Na_2SO_4) and evaporated to yield an oily crude product that was purified by silica gel flash chromatography using CH_2Cl_2–EtOAc (4:1) to give **15** as an oil (10.5 g, 66%): ^{1}H NMR ($CDCl_3$) δ 1.88–2.20 (4H), 2.59 (dd, 1H, J=8.2 and 10.0 Hz), 2.95 (m, 2H), 3.70 (d, 1H, J=13.1 Hz), 3.93 (d, 1H, J=13.1 Hz), 7.35 (5H); ^{13}C NMR ($CDCl_3$) δ 22.0 (+), 29.6 (+), 51.3 (+), 53.3 (−), 56.6 (+), 118.0 (+), 127.6 (−), 128.56 (−), 128.57 (−), 128.60 (−), 128.9 (−), 137.7 (+); EI HRMS m/z calcd for $C_{12}H_{14}N_2$ (M^+) 186.1158, found 186.1157.

4.8. 1-Benzyl-2-acetylpyrrolidine (2, alternate method)

To a solution of 1-benzyl-2-cyanopyrrolidine **15** (0.62 g, 3.33 mmol) in 30 mL of dry benzene at 0 °C was added 2.84 mL of methyllithium (1.4 M solution in ether, 3.98 mmol) under argon. The reaction mixture was allowed to warm to room temperature and was then heated at reflux for 2 h. The reaction solution was hydrolyzed with 1 N HCl, and then extracted with diethyl ether. The aqueous phase was separated and neutralized with aqueous K_2CO_3 solution to pH 7. The solution was then extracted with CH_2Cl_2. The combined organic extract was dried (Na_2SO_4) and evaporated, and the crude oily product was purified by silica gel column chromatography using CH_2Cl_2–EtOAc (4:1) to give **2** as an oil (0.473 g, 70%). The NMR data were identical with the data obtained for the rearrangement product.

4.9. Ethyl 2-benzylamino-2-methylpropionate (11)[27]

A solution of benzylamine (10.7 g, 0.1 mol), ethyl 2-bromoisobutyrate (12.5 mL, 0.085 mol), potassium carbonate (13.8 g, 0.1 mol), and potassium iodide (166 mg, 1 mmol) in 120 mL of ethanol was stirred at reflux for 60 h. After filtration of ethanol to remove suspended salts, the filtrate was evaporated under reduced pressure, and the residue was subjected to silica gel column chromatography using hexane–ethyl acetate (6:1) as eluent to give the known amino ester **11** (9.5 g, 43%) as an oil: ^{1}H NMR ($CDCl_3$) δ 1.31 (t, 3H), 1.38 (s, 6H), 3.63 (s, 2H), 4.18 (q, 2H), 7.33 (5H).

4.10. Ethyl 4-[*N*-benzyl-*N*-(1-ethoxycarbonyl-1-methylethyl)]aminobutyrate (12)

A mixture of compound **11** (4.4 g, 20 mmol), ethyl 4-bromobutyrate (3.3 mL, 22 mmol), and potassium iodide (166 mg, 1 mmol) was stirred at 120–130 °C for 48 h. The mixture was then subjected to silica gel column chromatography using hexane–ethyl acetate (8:1) as eluent to give the product **12** (3.41 g, 51%): ^{1}H NMR ($CDCl_3$) δ 1.20 (t, 3H,

J=7.0 Hz), 1.29 (t, 3H, J=7.0 Hz), 1.35 (s, 6H), 1.53 (m, 2H), 2.17 (t, 2H, J=7.2 Hz), 2.62 (t, 2H, J=7.5 Hz), 3.82 (s, 2H), 4.03 (q, 2H, J=7.0 Hz), 4.14 (q, 2H, J=7.0 Hz), 7.35 (5H); ^{13}C NMR ($CDCl_3$) δ 14.3, 14.4, 25.2, 25.4, 31.8, 51.5, 55.8, 60.2, 60.5, 63.8, 126.4, 127.7, 128.1, 142.8, 173.7, 176.2; FAB HRMS m/z calcd for $C_{19}H_{30}NO_4$ $(M+H)^+$ 336.2175, found 336.2182.

4.11. 1-Benzyl-2,2-dimethyl-4-carbethoxy-3-piperidone (13)

Sodium hydride (240 mg, 6.6 mmol, 60%) was suspended in a solution of **12** (2.0 g, 6.0 mmol) in 50 mL of dry THF. The mixture was heated at reflux for 4 h. After evaporation of the solvent, the viscous product was treated with H_2O and the resulting mixture was acidified to pH 5, maintaining the temperature under 10 °C with an ice bath. The aqueous solution was neutralized with solid K_2CO_3 and extracted with Et_2O. Evaporation of the dried (Na_2SO_4) organic extract yielded **13** (1.27 g, 74%) as an oil that NMR showed to exist as the enol tautomer: ^{1}H NMR ($CDCl_3$) δ 1.30 (t, 3H, J=7.0 Hz), 1.41 (s, 6H), 2.18 (t, 2H, J=5.8 Hz), 2.52 (t, 2H, J=5.8 Hz), 3.62 (s, 2H), 4.21 (q, 2H, J=7.0 Hz), 7.35 (5H); ^{13}C NMR ($CDCl_3$) δ 14.4 (−), 21.4 (−), 23.2 (+), 42.6 (+), 53.2 (+), 58.4 (+), 60.4 (+), 95.6 (+), 126.8 (−), 128.3 (−), 140.7 (+), 172.9 (+), 175.5 (+). FAB HRMS m/z calcd for $C_{17}H_{24}NO_3$ $(MH)^+$ 290.1756, found 290.1756.

4.12. 1-Benzyl-2,2-dimethyl-3-piperidone (10)

A solution of **13** (0.58 g, 2.0 mmol) in 10 mL of 6 N HCl was heated at reflux for 3 h. The reaction mixture was cooled to room temperature, neutralized with solid K_2CO_3 to pH 8.0, and extracted with ether. The organic layer was washed, filtered, and evaporated to give pure piperidone **10** (0.39 g, 90%) as an oil: ^{1}H NMR ($CDCl_3$) δ 1.31 (s, 6H), 1.82 (m, 2H), 2.50 (t, 2H, J=7.1 Hz), 2.65 (t, 2H, J=6.1 Hz), 3.63 (s, 2H), 7.31 (5H); ^{13}C NMR ($CDCl_3$) δ 20.0 (−), 23.9 (+), 36.2 (+), 44.9 (+), 53.7 (+), 66.6 (+), 126.9 (−), 128.2 (−), 128.3 (−), 140.5 (+), 212.2 (+); FAB HRMS m/z calcd for $C_{14}H_{20}NO$ $(M+H)^+$ 218.1545, found 218.1545.

4.13. *N*-(3,3-Dimethoxy-2-butylidene)isopropylamine (17)[22]

The preparation of **17** was carried out exactly according to the literature report.[22] The final residual oil was distilled in vacuum to afford the product **17** (15.3 g, 89%) as a colorless liquid: bp 70–76 °C/25 mmHg (lit.[22] 60–63 °C/11 mmHg); ^{1}H NMR ($CDCl_3$) δ 1.09 (d, 3H, J=6.1 Hz), 1.12 (d, 3H, J=6.2 Hz), 1.33 (s, 3H), 1.81 (s, 3H), 3.17 (s, 3H), 3.19 (s, 3H), 3.65 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 13.0 (+), 20.9 (+), 23.1 (+), 49.2 (+), 50.9 (+), 102.3 (−), 165.4 (−).

4.14. 6-Chloro-2,2-dimethoxy-3-hexanone (19)

A solution of lithium diisopropylamide (6 mL of 2.0 M, 0.012 mol) in 30 mL of dry tetrahydrofuran at 0 °C was treated dropwise with 1.73 g (0.01 mol) of *N*-(3,3-dimethoxy-2-butylidene)isopropylamine, dissolved in 3 mL of dry tetrahydrofuran. The mixture was stirred for 2 h at 0 °C after which 1.72 g (0.012 mol) of 1-bromo-2-chloroethane was added dropwise. The solution was stirred for 20 h at ambient temperature. The reaction mixture was poured into 100 mL of 0.05 N sodium hydroxide and extracted three times with ether. The combined organic extracts were dried with K_2CO_3, filtered, and evaporated to afford *N*-(6-chloro-2,2-dimethoxy-3-hexylidene)isopropylamine (**18**, 2.1 g, 89%) as an oil. The compound was used without further purification in the next step.

To a solution of imine **18** (2.1 g, 9 mmol) in 120 mL of CH_2Cl_2 was added oxalic acid dihydrate (1.7 g, 13 mmol) in 100 mL of water. The mixture was heated at reflux with vigorous stirring for 1 h and extracted three times with CH_2Cl_2. The combined organic layer was dried (Na_2SO_4) and filtered, and the resulting oil obtained upon evaporation of solvent was subjected to silica gel flash chromatography using hexane–ethyl acetate (15:1) as eluent to give the keto acetal **19** (0.81 g, 42% overall for two steps) as an oil: ^{1}H NMR ($CDCl_3$) δ 1.37 (s, 3H), 2.05 (quintuplet, 2H), 2.80 (t, 2H, J=7.0 Hz), 3.24 (s, 6H), 3.59 (t, 2H, J=6.4 Hz); ^{13}C NMR ($CDCl_3$) δ 19.9 (−), 26.0 (+), 35.0 (+), 44.4 (+), 49.7 (−), 102.6 (+), 206.1 (+); FAB HRMS calcd for $C_7H_{12}^{35}ClO_2$ (M^+-OCH_3) m/z 163.0526, found 163.0518.

4.15. 6-Benzylamino-2,2-dimethoxy-3-hexanol (21)

A solution of 6-chloro-2,2-dimethoxy-3-hexanone **19** (0.35 g, 1.8 mmol), potassium iodide (300 mg, 1.8 mmol), benzylamine (0.29 g, 2.7 mmol), and triethylamine (0.4 mL, 2.9 mmol) in 50 mL of acetonitrile was heated at reflux for 20 h under argon. The reaction mixture was filtered and evaporated to dryness. The residue was extracted with CH_2Cl_2, and the organic extract was washed with water, dried (Na_2SO_4), and concentrated. The residue was purified by chromatography using CH_2Cl_2–methanol (30:1) as eluent to give 6-benzylamino-2,2-dimethoxy-3-hexanone (**20**, 185 mg, 38%) as an oil, which has a low stability and was used quickly for the next step: ^{1}H NMR ($CDCl_3$) δ 1.34 (s, 3H), 1.78 (quintuplet, 2H), 2.61 (m, 4H), 3.19 (s, 6H), 3.77 (s, 2H), 7.29 (5H); ^{13}C NMR ($CDCl_3$) δ 19.9, 23.2, 35.6, 48.4, 49.6, 53.5, 102.7, 127.1, 128.3, 128.4, 139.5, 209.1.

To a solution of **20** (270 mg, 1 mmol) in 10 mL of methanol, sodium borohydride (57 mg, 1.5 mmol) was added portionwise at 0 °C. The reaction mixture was stirred at room temperature for 3 h. After removal of methanol, the viscous product was treated with H_2O and then extracted with ether. The organic layer was dried (Na_2SO_4) and evaporated to dryness. The residue was purified by chromatography with CH_2Cl_2–methanol (15:1) as eluent to afford the product **21** (201 mg, 76%) as an oil: ^{1}H NMR ($CDCl_3$) δ 1.29 (s, 3H), 1.25 (m, 2H), 1.78 (m, 2H), 2.61 (m, 1H), 2.86 (m, 1H), 3.18 (s, 3H), 3.23 (s, 3H), 3.61 (d, 1H, J=9.8 Hz), 3.87 (s, 1H), 7.34 (5H); ^{13}C NMR ($CDCl_3$) δ 16.3 (−), 26.7 (+), 30.3 (+), 48.2 (−), 48.5 (−), 48.6 (+), 53.0 (+), 72.3 (−), 102.7 (+), 127.8 (−), 128.7 (−), 128.9 (−), 137.0 (+); FAB HRMS m/z calcd for $C_{15}H_{26}NO_3$ $(M+H)^+$ 268.1912, found 268.1915.

4.16. The reactions of compound 21 in 6 N HCl

A solution of compound **21** (50 mg, 0.19 mmol) in 5 mL of 6 N HCl solution was heated at reflux for 24 h under argon.

The reaction mixture was extracted with ether. The aqueous phase was separated and neutralized with K_2CO_3 to pH 8. The solution was then extracted with ether, which was dried (Na_2SO_4) and evaporated to give **2** (33 mg, 87%) as an oil. A solution of compound **21** (50 mg, 0.18 mmol) in 5 mL of 6 N HCl solution was stirred at room temperature for 24 h under argon. The reaction mixture was neutralized with K_2CO_3 to pH 8. The solution was extracted with ether. The combined ether layer was dried (Na_2SO_4) and evaporated to give **1** (30 mg, 79%) as an oil.

4.17. Time profile for conversion of compounds 1 or 21 to compound 2 in 6 N HCl solution

A solution of compound **1** or **21** in 25 mL of 6 N HCl solution was heated at reflux under argon. Aliquots were taken at 1, 3, 6, 12, and 24 h. The aliquots were neutralized with K_2CO_3 to pH 8 and extracted with ether. The ether layers were dried (Na_2SO_4) and evaporated to give mixtures of **1** and **2** (oils) that were analyzed by ^{1}H NMR spectroscopy. The fraction of rearrangement was calculated from the integral ratio of the ketone methyl group in **2** (δ 2.1 ppm) and the piperidine ring 2-methyl group in **1** (δ 1.3 ppm).

4.18. NMR spectral data of compounds in DCl–D_2O

4.18.1. 1-Benzyl-3-piperidone (free base). ^{1}H NMR ($CDCl_3$) δ 1.94 (m, 2H), 2.36 (t, 2H), 2.65 (t, 2H), 3.01 (s, 2H), 3.58 (s, 2H), 7.29 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 24.04 (+), 38.81 (+), 51.60 (+), 62.60 (+), 64.63 (+), 127.41 (−), 128.42 (−), 129.08 (−), 137.26 (+), 207.12 (+).

4.18.1.1. 1-Benzyl-3-piperidone·HCl. ^{13}C NMR (6 N DCl–D_2O) δ 20.5 (+), 34.2 (+), 53.1 (+), 58.9 (+), 61.1 (+), 91.6 (+), 128.8 (+), 130.1 (−), 131.1 (−), 132.1 (−).

4.18.2. 1-Benzyl-2-methyl-3-piperidone·HCl. ^{13}C NMR (6 N DCl–D_2O, mixture of cis and trans isomers) δ 7.1 (−), 10.1 (−), 19.6 (+), 23.5 (+), 29.2 (+), 35.2 (+), 47.3 (+), 51.5 (+), 61.3 (−), 65.7 (−), 92.6 (+), 93.7 (+), 128.6 (+), 129.2 (+), 129.7 (−), 130.0 (−), 130.5 (−), 130.7 (−), 132.3 (−).

4.18.3. 1-Benzyl-2,2-dimethyl-3-piperidone·HCl. ^{13}C NMR (6 N DCl–D_2O) δ 16.07 (−), 19.18 (−), 19.52 (−), 20.13 (+), 20.59 (−), 20.85 (+), 31.33 (+), 35.31 (+), 46.93 (+), 47.67 (+), 55.89 (+), 55.93 (+), 71.15 (+), 73.01 (+), 95.29 (+), 130.08 (+), 130.21 (−), 130.29 (+), 130.48 (−), 131.15 (−), 131.33 (−), 132.21 (−), 132.81 (−), 207.57 (+).

4.18.4. 1-Benzyl-2-acetylpyrrolidine·HCl. ^{1}H NMR (6 N DCl–D_2O) δ 1.94 (m, 2H), 2.16 (s, 3H), 2.22 (m, 1H), 2.67 (m, 1H), 3.38 (m, 1H), 3.68 (m, 1H), 4.37 (d, 2H), 4.75 (t, 1H), 7.49 (m, 5H); ^{13}C NMR (6 N DCl–D_2O) δ 23.34 (+), 27.20 (−), 28.30 (+), 56.12 (+), 59.37 (+), 72.96 (−), 129.96 (−), 130.22 (+), 130.87 (−), 131.34 (−), 205.03 (+).

4.18.5. 6-Benzylamino-2,2-dimethoxy-3-hexanol·HCl. ^{1}H NMR (6 N DCl–D_2O) δ 1.8 (m, 4H), 2.15 (s, 3H, exchangeable), 3.10 (m, 2H), 4.21 (s, 2H), 4.40 (m, 1H, exchangeable), 7.45 (m, 5H); ^{13}C NMR (6 N DCl–D_2O) δ 22.05 (+), 26.15 (−), 29.57 (+), 47.21 (+), 51.55 (+), 76.44 (−), 129.64 (−), 130.10 (−), 130.35 (−), 130.84 (+), 215.16 (+).

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