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Unexpected retro-Michael reaction of (−)-(1′*S*,4a*S*,8a*R*)- and (+)-(1′*S*,4a*R*,8a*S*)-4a-ethyl-1-(1-phenylethyl)octahydroquinolin-7-ones

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Abstract—An unexpected retro-Michael reaction of (−)-(1′*S*,4a*S*,8a*R*)-and (+)-(1′*S*,4a*R*,8a*S*)-4a-ethyl-1-(1′-phenylethyl)octahydroquinolin-7-ones **1** and **2** is described. In addition, a diastereospecific intramolecular Michael reaction of **3**·HCl and **4**·HCl is reported. © 2002 Elsevier Science Ltd. All rights reserved.

1. Introduction

Meyers et al.[1] have reported that when (4*R*)-4-ethyl-4-(2-carbamoylethyl)-2-cyclohexen-1-one **I** is heated in benzene containing a catalytic amount of *p*-toluenesulfonic acid (TsOH) **II** was produced as a 3:1 mixture of *cis–trans* isomers. They subsequently found that adding ethylene glycol to **II** and heating at reflux with the acid catalyst converted the 3:1 mixture to the single dioxolane **III** and proposed that such a conversion was undoubtedly the result of acid-catalyzed equilibration via a retro-Michael reaction. They also reported that heating **I** in benzene/*p*-toluenesulfonic acid and adding ethylene glycol after several hours gave the ketal lactam **III** as a single isomer in good yield (Scheme 1).

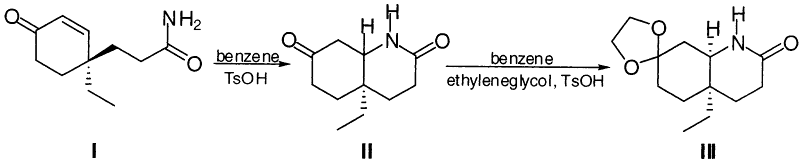
In a previous publication[2] we described the synthesis of **1** and **2** and additionally the preparation of (+)-(4a*S*,8a*R*)-4a-ethyl-octahydroquinolin-7-one by catalytic hydrogenation of **1** in MeOH, HCl, Pd/C at pH ca. 5–6.

Herein, we report an unexpected retro-Michael reaction of **1** and **2** in diethyl ether/hydrochloric acid.[3] Under these conditions, the compounds were transformed into (−)-(4*S*,1″*S*)- and (+)-(4*R*,1″*S*)-4-ethyl-4-[3′-(1″-phenylethylamine)-propyl]-2-cyclohexen-1-one hydrochlorides **3**·HCl and **4**·HCl, respectively (Scheme 2).

2. Results and discussion

Ethereal[4] solutions of **1** or **2** were saturated with gaseous hydrochloric acid and stirred for 15 min at room temperature to give the retro-Michael products **3**·HCl and **4**·HCl, respectively, in quantitative yield. Assignments of the ^{1}H NMR of **3**·HCl[5] and **4**·HCl[6] were confirmed via ^{13}C–^{1}H NMR correlation techniques.

Thereafter, these compounds were crystallized and analyzed by X-ray diffraction. The absolute configuration for C(4) of **3**·HCl[7] and **4**·HCl[8] was assigned as 4*S* and



Scheme 1.

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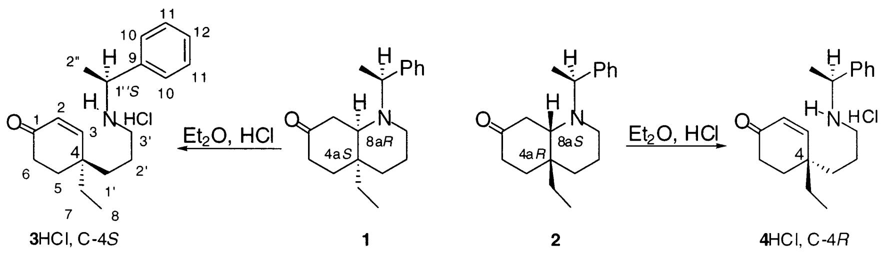


Scheme 2.

4*R*, respectively, on the basis of the configuration at the auxiliary center (1″*S*) and was confirmed by the refinement of a Flack parameter.[7,8] Source of chirality: (–)-(*S*)-1-phenylethylamine (Fig. 1).

In order to investigate the diastereoselectivity of the intramolecular Michael reaction of **3**·HCl and **4**·HCl, these compounds were treated with a sodium bicarbonate aqueous solution (pH ca. 8) for 30 min at room temperature and the reaction mixture extracted with dichloromethane (4×20 mL) dried over Na_2SO_4 and the solvent removed in vacuo to give **1** and **2** in quantitative yield, respectively. All spectral properties of these compounds were in complete agreement with those reported in our previous paper.[2]

The diastereospecific intramolecular Michael reaction observed in this process can be explained by the presence of a rigid transition state, where the amino group in each case is located exclusively over the favorable diastereotopic face of the α,β-unsaturated cyclohexen-2-one system with maximum orbital overlap to give the enantiopure compounds **1** and **2**[1,9] (Scheme 3).

3. Conclusion

To our knowledge, this is the first report that describes the conditions to transform **1** and **2** into **3**·HCl and **4**·HCl, respectively, via a retro-Michael reaction and a diastereospecific intramolecular Michael-reaction of **3**·HCl and **4**·HCl, which led to the corresponding enantiopure compounds **1** and **2**, respectively, under mild basic conditions, via a rigid transition state.

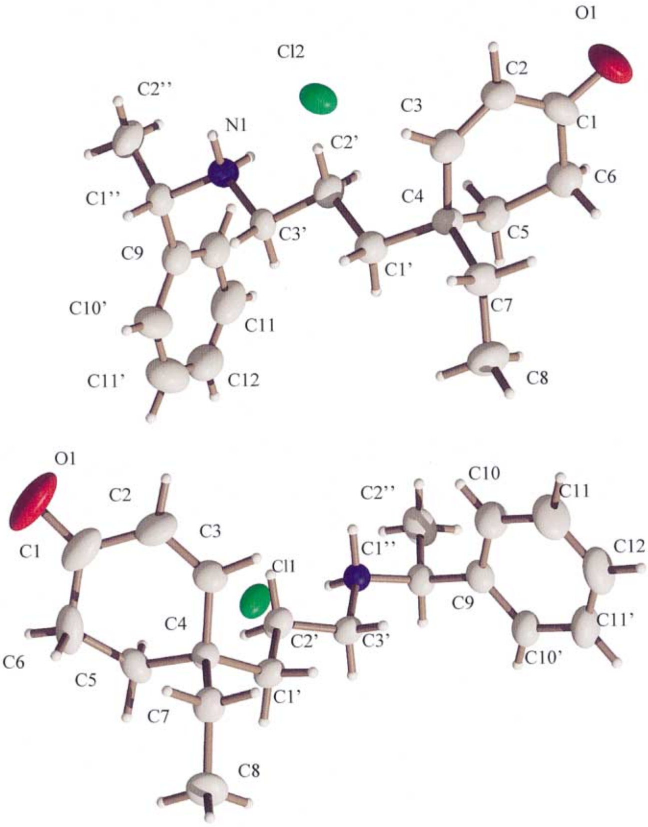
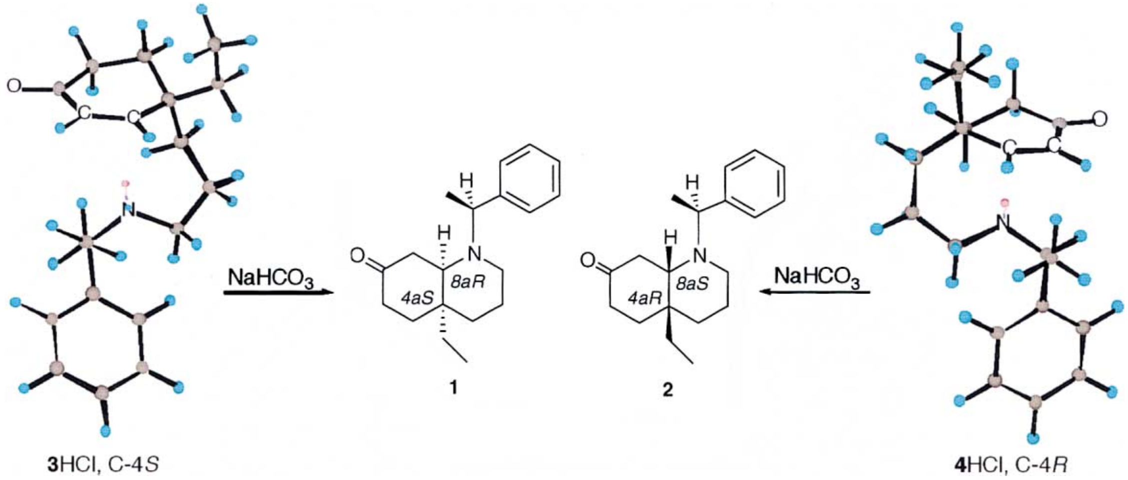


Figure 1. ORTEP view of the crystal structure of compounds **3**·HCl and **4**·HCl. For **3**·HCl, disordered toluene molecule is omitted for clarity and only one of the two molecules of the asymmetric unit is shown.



Scheme 3.

Acknowledgements

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2. Vázquez, E.; Galindo, A.; Gnecco, D.; Bernès, S. *Tetrahedron: Asymmetry* **2001**, *12*, 2099–2102 and references cited therein.
3. Compounds **1** and **2** were converted to the corresponding hydrochlorides at pH ca. 5–6.
4. The same behavior in methanolic and ethanolic solutions of **1** or **2** saturated with gaseous hydrochloric acid was observed.
5. Compound **3**·HCl. $R_f=0.45$ (SiO$_2$/CH$_2$Cl$_2$:MeOH = 90:10); $[\alpha]_D$−50.5 (*c* 1.0, CH$_2$Cl$_2$). Mp 174–175°C; IR (film): 3434, 2942, 2752, 1678, 1460, 703 cm^{-1}. ^{1}H NMR (CDCl$_3$, δ ppm, *J* Hz): 0.84 (t, 3H-8, 7.33); 1.20–1.60 (m, 2H-1′, 2H-2′); 1.70–1.85 (m, 2H-5, 2H-7); 1.89 (d, 3H-2″, 5.83); 2.25–2.50 (m, 2H-6); 2.55–2.75 (broad signal, 2H-3′); 4.10–4.30 (broad signal, 1H-1″); 5.86 (d, 1H-2, 10.26); 6.63 (d, 1H-3, 10.26); 7.30–7.70 (m, 5H, ϕ-H); 9.95–10.20 (two broad signals, NH). ^{13}C NMR: δ (ppm, CDCl$_3$): 8.47 (C-8); 20.73 (C-7); 20.80 (C-2″); 30.22 (C-1′); 30.31 (C-5); 33.83 (C-6); 34.69 (C-2′); 38.20 (C-4); 46.10 (C-3′); 59.00 (C-1″); 127.83 (2C-10); 128.70 (C-2); 129.52 (2C-11); 129.60 (C-12); 135.85 (C-9); 157.50(C-3); 199.20 (C-1).
6. Compound **4**·HCl. $R_f=0.45$ (SiO$_2$/CH$_2$Cl$_2$:MeOH = 90:10); $[\alpha]_D$+16.0 (*c* 1.0, CH$_2$Cl$_2$). Mp 166–168°C. IR (film) 3427, 2965, 2753, 1681, 1460, 703 cm^{-1}. ^{1}H NMR (CDCl$_3$, δ ppm, *J* Hz): 0.85 (t, 3H-8, 7.33); 1.20–1.60 (m, 2H-1′, 2H-2′); 1.70–1.80 (m, 2H-5, 2H-7); 1.88 (d, 3H-2″, 6.23); 2.30–2.45 (m, 2H-6); 2.60–2.80 (broad signal, 2H-3′); 4.10–4.30 (broad signal, 1H-1″); 5.86 (d, H-2, 10.26); 6.64 (d, H-3, 10.26); 7.20–7.80 (m, 5H, ϕ-H); 9.95–10.20 (two broad signals, NH). ^{13}C NMR: δ (ppm, CDCl$_3$): 8.47 (C-8); 20.75 (C-7); 20.83 (C-2″); 30.20 (C-1′); 30.30 (C-5); 33.85 (C-6); 34.60 (C-2′); 38.16 (C-4); 46.24 (C-3′); 59.15 (C-1″); 127.90 (2C-10); 128.60 (C-2); 129.45 (2C-11); 129.55 (C-12); 135.92 (C-9); 157.68 (C-3); 199.35 (C-1).
7. X-Ray analysis for **3**·HCl[10] (crystallized from toluene/acetonitrile). Empirical formula: C$_{19}$H$_{28}$ClNO (C$_6$H$_5$CH$_3$)$_{0.5}$ pale yellow, irregular, crystal size: 0.28×0.18×0.06 mm^3, crystal system: triclinic, space group: $P1$, unit cell dimensions: $a=7.280(2)$, $b=11.9321(14)$, $c=13.2735(15)$ Å, $\alpha=77.780(6)$, $\beta=88.113(15)$, $\gamma=88.525(12)$°, volume 1126.1(4) Å^3, $Z=2$, density (calcd) = 1.085 g cm^{-3}, absorption coefficient = 0.179 mm^{-1}, $F(000)$: 398; diffractometer used Bruker P4, radiation: Mo-K$_\alpha$ ($\lambda=0.71073$ Å), 2θ range: 3.14–50.00°, scan speed, 3.50–45° mn^{-1} in ω, independent reflections: 4491, R_1 [2893 $I>2\sigma(I)$] = 6.82%, wR_2 = 19.75% for all data. Flack parameter = −0.03 (12). The crystallographic data have been deposited in CDCC, UK (No. 175496).
8. X-Ray analysis for **4**·HCl.[10] (Crystallized from dichloromethane/diethyl ether). Empirical formula: C$_{19}$H$_{28}$ClNO, colorless needles, crystal size: 0.70×0.20×0.14 mm^3, crystal system: monoclinic, space group: $P2_1$, unit cell dimensions: $a=11.3016(12)$, $b=7.4150(8)$, $c=11.5933(11)$ Å, $\beta=99.948(4)$, volume 956.82(17) Å^3, $Z=2$, density (calcd) = 1.117 g cm^{-3}, absorption coefficient = 0.202 mm^{-1}, $F(000)$: 348; diffractometer used Bruker P4, radiation: Mo-K$_\alpha$ ($\lambda=0.71073$ Å), 2θ range: 3.66–54.98°, scan speed, 2.50–25° mn^{-1} in ω, independent reflections: 2703, R_1 [1960 $I>2\sigma(I)$] = 4.52%, wR_2 = 14.12% for all data. Flack parameter = +0.02 (10). The crystallographic data have been deposited in CDCC, UK (No. 175497).
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