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Synthesis of monoterpenic α-amino ketones

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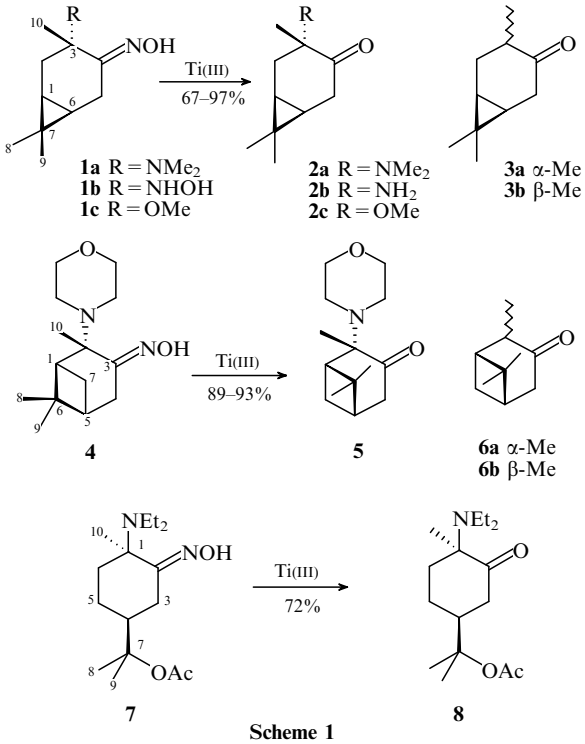
Terpenic α-amino ketones have been prepared in good yield by treatment of the corresponding α-amino oximes with Ti(III) salts; all other known methods of deoximation give unacceptably low yields.

Optically active α-amino alcohols are among the most promising ligands for preparing chiral transition metal ion complexes and for use in enantioselective organic synthesis. It is known in particular that reduction of prochiral ketones by complex hydrides in the presence of chiral α-amino alcohols results in the corresponding secondary alcohols in more than 90% optical purity.[1]

The simplest route to α-amino alcohols, preserving the complex carbon frame of natural origin, seems to be reduction of the appropriate α-amino ketones. In addition, α-amino ketones are of interest in themselves as biologically active compounds possessing antitumor activity[2] and analgesic properties.[3] Natural terpenes, being one of the primary sources of chirality,[4] are very promising in view of their use as starting compounds for the synthesis of diverse chiral bifunctional derivatives. Methods for the transformation of unsaturated terpenic hydrocarbons, which predominate among accessible natural terpenoids, to α-amino ketones have not yet been developed.

Conversion of terpene hydrocarbons to α-amino ketones is possible with the intermediate formation of α-amino oximes, which belong to the most readily available nitrogen-containing terpenic derivatives.[5] The conversion of α-amino oximes to the corresponding α-amino ketones requires removal (hydrolysis)



Scheme 1

of the oxime group. Many methods for the transformation of oximes to ketones are known, including simple hydrolysis as well as oxidizing and reducing methods.[6] We tried most of them but all failed resulting in various products, none containing a substituted amino group (^{1}H and ^{13}C NMR). Reductive hydrolysis of oximes with Ti(III)[7] salts was found to be the only method allowing a transformation of α-amino oximes to α-amino ketones.

The reaction can be conducted with commercially available salts as well as with the Ti(III) salts generated *in situ* by reduction of Ti(IV) under the action of Zn. However, use of the *in situ* generated reagent results in lower yields of α-amino ketones. This may be due to the presence of Zn(II) salts in the reaction mixture. On the one hand, Zn(II) salts are favourably disposed towards formation of a stable complex with α-amino oximes.[8] On the other hand, being Lewis acids, Zn(II) salts can cause Beckman's fragmentation resulting in the corresponding *seco*-ketonitrile,[9] which is always detected among the reaction products (TLC). With a 13% water solution of $TiCl_3$ (Fluka Chemie AG) α-amino oxime is transformed to the corresponding α-amino ketone in good yield (Scheme 1). An aqueous solution of $TiCl_3$ (13%, 3.50 ml, 3.5 mmol) was added during 15 min, dropwise at room temperature and with vigorous stirring, to a suspension of α-amino oxime **1a** [0.30 g, 1.4 mmol, prepared from natural (+)-3-carene[5]] and AcONa (1.45 g) in a mixture of glacial AcOH (0.30 ml) and DMF (5 ml). The mixture was stirred for 2.5 h followed by addition of aqueous ammonia (25%, 7 ml). The reaction mixture was extracted with Et_2O (3×10 ml) and the combined ethereal solutions were extracted with aqueous HCl (20%, 10 ml). The aqueous phase was washed with Et_2O (2×7 ml), neutralized with aqueous NaOH (20%, 13 ml) and extracted with Et_2O (2×10 ml). The aqueous phase was saturated with NaCl and extracted again with Et_2O (10 ml). The combined organic extracts were washed with brine and dried ($MgSO_4$). Removal of solvents followed by chromatography of the crude product on a silica gel column gave pure ketone **2a** (0.18 g, 65%).†

In the same way α-hydroxylamino oxime **1b**[10] was transformed to ketone **2b**; the hydroxylamino group was reduced to an amino group under the reaction conditions.‡

The reaction is not very sensitive to steric hindrance and also takes place smoothly in the case of much more sterically hindered derivatives of the pinane series. Even in the case of derivative **4**, possessing an additional bulky substituent (morpholino-) on the α-carbon of the oxime group, the corresponding ketone **5** was prepared in good yield.§ The method is also suitable for desoximation of terpenic oximes with other electron-donating substituents attached to the α-carbon of the oxime moiety. Thus, treatment of α-methoxy oxime **1c** under the same conditions results in α-methoxy ketone **2c** in excellent yield.¶ Dimethylamino oxime derived from α-terpenylacetate **7*** is also transformed to the corresponding ketone **8** in 72% yield.**

The best deoximation result was achieved by using a 2.5-fold molar excess of titanium salt, a greater excess leading to formation of the products of further reduction. Thus, treatment of α-amino oxime **1a** with a 4.5-fold excess of $TiCl_3$ results in saturated ketone **3** as a mixture of C-3 epimers in 95% yield, ratio 4-isocaranone **3b** : 4-caranone **3a** = 5:1 being about the same as in the case of the equilibrium mixture.[11] Under the same reaction conditions, amino oxime **4** is transformed in 93% yield to a *ca.* 1:3 mixture of isopinocamphone **6a** and pinocamphone **6b**, the ratio of epimeric ketones also resembling that of the equilibrium mixture.[12]

† (1*S*,3*S*,6*R*)-3-*N,N-Dimethylamino*-4-*caranone* **2a**. Yield 65%, [Found (HRMS): 195.16283 (M^+); Calc. for $C_{12}H_{21}NO$: 195.16230]; $[\alpha]_{578}^{17}$ +42.8° (*c* 1.9 in $CHCl_3$); ν_{max} ($CHCl_3$, *c* 1%, *d* = 0.4 mm)/cm^{-1} 1710; δ_H (200 MHz; $CDCl_3$) 0.72 (ddd, 1H, *J* 10.0, 9.5, 6.5 Hz, H1), 0.78 (s, 3H, H8), 0.79 (s, 3H, H9), 0.98 (s, 3H, H10), 1.22 (dd, 1H, *J* 16.5, 6.5 Hz, H2β), 1.25 (ddd, 1H, *J* 10.0, 9.5, $w_{1/2}$ = 3.5 Hz, H6), 2.17 (s, 6H, NMe_2), 2.20 (d, 1H, *J* 17.0 Hz, $w_{1/2}$ = 3.5 Hz, H5β), 2.32 (dd, 1H, *J* 16.5, 9.5 Hz, H2α), 2.75 (dd, 1H, *J* 17.0, 9.5 Hz, H5α); δ_C (50 MHz, $CDCl_3$) 10.21 (C10), 14.71 (C8), 16.60 (C1), 19.40 (C7), 24.99 (C6), 27.80 (C9), 33.57 (C2), 35.37 (C5), 38.54 (NMe_2), 64.28 (C3), 218.05 (C4).

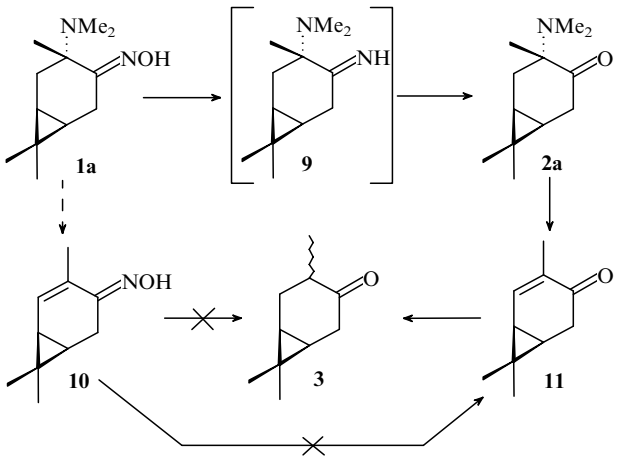
‡ (1*S*,3*S*,6*R*)-3-*Amino*-4-*caranone* **2b**. Yield 87%, [Found (HRMS): 167.13060 (M^+); Calc. for $C_{10}H_{17}NO$: 167.13101]; $[\alpha]_{578}^{22}$ +85.4° (*c* 5.5 in $CHCl_3$); ν_{max} ($CHCl_3$, *c* 1%, *d* = 0.4 mm)/cm^{-1} 1700, 3320, 3390; δ_H (200 MHz, $CDCl_3$) 0.81 (ddd, 1H, *J* 9.5, 9.5, 6.5 Hz, H1), 0.9–1.2 (m, H6), 0.86 (s, 3H, H8), 1.03 (s, 3H, H10), 1.04 (s, 3H, H9), 1.43 (dd, 1H, *J* 15.5, 6.5 Hz, H2β), 1.81 (br.s, 2H, $w_{1/2}$ = 9 Hz, H_{NH_2}), 2.11 (dd, 1H, *J* 15.5, 9.5 Hz, H2α), 2.13 (dd, 1H, *J* 19.0, 4.0, H5β), 2.78 (dd, 1H, *J* 19.0, 9.5 Hz, H5α); δ_C (50 MHz; $CDCl_3$) 14.23 (C10), 16.94 (C1), 19.56 (C7), 21.45 (C6), 23.78 (C8), 27.71 (C9), 33.25 (C5), 34.42 (C2), 54.86 (C3), 215.43 (C4).

§ (±)-(1*S**,2*S**,5*S**)-2-*Morpholino*-3-*pinanone* **5**. Yield 89%, mp 74–76 °C (from CH_3CN) (Found C, 71.9, H, 10.2, N, 5.7; Calc. for $C_{14}H_{23}NO_2$: C, 70.85, H, 9.8, N, 5.9%); ν_{max} ($CHCl_3$, *c* 1%, *d* = 0.4 mm)/cm^{-1} 1710; δ_H (200 MHz; $CDCl_3$) 0.81 (s, 3H, H8), 0.98 (s, 3H, H10), 1.29 (s, 3H, H9), 1.95 (m, 1H, H5), 1.99 (dd, 1H, *J* 6.0, 6.0 Hz, H1), 2.02 (d, 1H, *J* 10.5 Hz, H7α), 2.22 (dddd, 1H, *J* 10.5, 6.5, 6.5, 3.5 Hz, H7β), 2.38 (ddd, 1H, *J* 18.0, 6.0, $w_{1/2}$ = 3 Hz, H4β), 2.3–2.6 (m, 4H, H_{CH_2N}), 2.67 (dd, 1H, *J* 18.0, $w_{1/2}$ = 3.5 Hz, H4α), 3.52 (t, 4H, *J* 4.6 Hz, H_{CH_2O}); δ_C (50 MHz; $CDCl_3$) 12.79 (C10), 22.30 (C8), 27.47 (C7), 27.81 (C9), 38.25 (C5), 38.73 (C6), 43.72 (C4), 45.22 (CH_2N), 49.30 (C1), 66.69 (C2), 67.48 (CH_2O), 208.89 (C3).

¶ (1*S*,3*S*,6*R*)-3-*Methoxy*-4-*caranone* **2c**. Yield 97%, mp 130–132 °C (from CH_3CN) [Found (HRMS): 182.13067 (M^+); Calc. for $C_{11}H_{18}O_2$: 182.13067]; $[\alpha]_{578}^{22}$ +98° (*c* 3.5 in $CHCl_3$); ν_{max} ($CHCl_3$, *c* 1%, *d* = 0.4 mm)/cm^{-1} 1115, 1710; δ_H (200 MHz; $CDCl_3$) 0.76 (s, 3H, H8), 0.78 (ddd, 1H, *J* 9.0, 9.0, 5.0 Hz, H1), 0.98 (s, 3H, H10), 1.07 (s, 3H, H9), 1.21 (ddd, 1H, *J* 9.0, 9.0, 1.5 Hz, H6), 1.45 (dd, 1H, *J* 16.0, 5.0 Hz, H2β), 2.28 (d, 1H, *J* 18.0 Hz, $w_{1/2}$ = 3.5 Hz, H5β), 2.40 (dd, 1H, *J* 16.0, 9.0 Hz, H2α), 2.74 (dd, 1H, *J* 18.0, 9.0 Hz, H5α), 3.14 (s, 3H, H_{OCH_3}); δ_C (50 MHz; $CDCl_3$) 14.58 (C8), 16.73 (C1), 17.23 (C10), 19.14 (C7), 24.25 (C6), 27.78 (C9), 35.17 (C2), 35.17 (C5), 51.47 ($COCH_3$), 77.40 (C3), 214.55 (C4).

* Prepared by a standard technique[5] from α-terpenyl acetate nitrosochloride and $HNEt_2$; mp 93–95 °C (from CH_3CN).

** (±)-(1*R**,4*S**)-7-*Acetoxy*-1-*N,N-diethylamino*-*p*-*menth*-2-*one* **8**. Yield 72%, [Found (HRMS): 283.21470 (M^+); Calc. for $C_{16}H_{29}NO_3$: 283.21473]; ν_{max} (CCl_4, *c* 3%, *d* = 0.1 mm)/cm^{-1} 1250, 1712, 1731; δ_H (200 MHz; $CDCl_3$) 0.7–1.9 (m, 5H, H4, H5α, H5β, H6α, H6β), 0.83 (s, 3H, H10), 0.94 [t, 6H, *J* 7.0 Hz, $N(CH_2CH_3)_2$], 1.33 (s, 3H, H9), 1.34 (s, 3H, H8), 1.84 (s, 3H, CH_3COO), 2.02 (ddd, 1H, *J* 13.0 3.0 2.5 Hz, H3α), 2.14 (dq, 2H, *J* 14.0 7.0 Hz) and 2.51 (dq, 2H, *J* 14.0 7.0 Hz) [$N(CH_2CH_3)_2$], 2.91 (m, 1H, H3β); δ_C (50 MHz; $CDCl_3$) 14.42 (C10), 15.38 (NCH_2CH_3), 20.58 (C5), 21.96 (CH_3CO), 22.67 (C8), 23.11 (C9), 37.59 (C6), 38.45 (C3), 42.64 (NCH_2CH_3), 49.32 (C4), 68.44 (C1), 83.23 (C7), 169.79 (CO), 215.22 (C2).



Scheme 2

The formation of saturated ketone can be explained as shown in Scheme 2. Such a mechanism assumes intermediate formation of unsaturated ketone **11** as a result of amino group elimination from the α-amino ketone molecule. The fact that deoximation proceeds prior to amino group elimination is confirmed by the transformations of the carane-type derivatives. When treated with $TiCl_3$, α,β-unsaturated oxime **10**[13] gives a mixture of products, and this mixture contains neither saturated ketone **3** nor unsaturated derivative **11**. At the same time, unsaturated ketone **11**[14] (prepared by a known technique[15]) reacts with $TiCl_3$ under precisely the same conditions to give saturated ketone **3** (90%).

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