Trifluoromethyl syn- or anti-γ-amino alcohols by one-pot solvent-free Mannich-type reactions under temperature control

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**Determination of the absolute configuration of the new chiral centre**

**i. By 2D NOESY $^1$H NMR spectra**

As reported,\(^1\) starting from a reference cross peak whose interproton distance is known, it was possible to calculate the distances between other protons according to equation \(V_X/V_R = (d_R/d_X)^6 \) (\(V_R\) = volume of the reference cross peak; \(d_R\) = corresponding interproton distance; \(V_X\) = volume relative to the unknown distance; \(d_X\) = unknown distance).

Considering that the chiral centre on the amine residue is always in \(R\) configuration, the interproton distance between \(H_b\) and the protons \(H_c\) is considered as a fixed value and employed as a ruler to determine the distance between \(H_a\) and \(H_b\).

![Diagram of the molecule](image)

On the basis of the optimized geometries of diastereomers, 2.68 Å was found as the medium value of the interproton distance (\(d_R\)) between \(H_b\) and the protons \(H_c\) and the corresponding volume \(V_R\) was set at 10 arbitrary units (au). Then, starting from the volumes relative to the cross peaks between \(H_a\) and \(H_b\) (\(V_X\)) determined by NOESY analyses, the interproton distance (\(d_X\)) between \(H_a\) and \(H_b\) were calculated and compared with those determined by optimized geometries.\(^4\)

**ii. By chemical transformation**

Following a synthetic procedure similar to that reported in the literature, after reaction of \textit{anti-9’a} with benzoyl chloride, a hydrogenolysis reaction permitted to remove the benzyl group\(^2\) leading to the known chiral primary amine 10,\(^3\) the \([\alpha]_D\) value of which corresponds with that reported in the literature {found: \([\alpha]_D = -10.8 (c = 1.5, \text{CHCl}_3); \text{literature}^3 [\alpha]_D = -11.5 (c = 1.5, \text{CHCl}_3)\}.

![Chemical reaction](image)


(2R*,3R*)-3-(Benzylationo)-4,4,4-trifluoro-2-isopropylbutan-1-ol (syn-2a)
(2R*,3R*)-4,4,4-Trifluoro-2-isopropyl-3-(4-methoxyphenylamino)butan-1-ol (syn-2b)
Chiral HPLC analysis of syn-2b

Reaction performed with L-proline at 25 °C

Reaction performed with D,L-proline at 25 °C

Reaction performed with L-proline at −20 °C

Chiralcel column; eluent: hexane/2-propanol = 95:5, flow 0.9 mL/min
(2R*)-2-[(1R*)-1-(Benzylamino)-2,2,2-trifluoroethyl]pentan-1-ol (syn-3a)
(2R*)-2-[(1R*)-(2,2,2-Trifluoro)-1-(4-methoxyphenylamino)ethyl]pentan-1-ol (syn-3b)
(2R*,3R*)-3-(Benzylamino)-4,4,4-trifluoro-2-methylbutan-1-ol (syn-4a)
(R,E)-1-(4-Methoxyphenyl)-N-(2,2,2-trifluoroethylidene)ethanamine (6b)
(2S,3S)-4,4,4-Trifluoro-2-isopropyl-3-[(R)-1-phenylethylamino]butan-1-ol (syn-7a)
NOESY spectrum of (S,S,R)-7a

The cross peaks corresponding to the interproton correlations H_b/H_c (distance ruler setted to 10.00 au) and H_a/H_b (1.38 au), corresponding to an interproton distance of 3.74 Å, are evidenced. In Fig. 1 the interproton distance determined on the optimized geometries are reported.

Fig. 1. Optimized geometries of (S,S,R)-7a and of its possible diastereomer (R,R,R)
(2R,3S)-4,4,4-Trifluoro-2-isopropyl-3-[(R)-1-phenylethylamino]butan-1-ol (anti-7′a)
The cross peaks corresponding to the interproton correlations $H_b/H_c$ (distance ruler setted to 10.00 au) and $H_a/H_b$ (2.28 au), corresponding to an interproton distance of 3.44 Å, are evidenced. In Fig. 2 the interproton distance determined on the optimized geometries are reported.

**Fig. 2.** Optimized geometries of $(R,S,R)$-7'a and of its possible diastereomer $(S,R,R)$
(2S,3S)-4,4,4-Trifluoro-2-isopropyl-3-\(\{(R)\}-1-(4\text{-methoxyphenyl})\text{ethylamino}\)butan-1-ol (\text{syn}\text{-}7b)
(2R,3S)-4,4,4-Trifluoro-2-isopropyl-3-[\((R)-1-(4\text{-methoxyphenyl})\text{ethylamino}\)butan-1-ol \((anti-7'b)\)
(2S)-2-[(1S)-2,2,2-Trifluoro-1-{(1R)-1-phenylethyl}amino]ethyl]pentan-1-ol (syn-8a)

\[
(\text{S},\text{S},\text{R})-8a
\]

\[
\begin{align*}
&\text{H} & \text{F}_3\text{C} & \text{OH} \\
&\text{NH} & & & \\
\end{align*}
\]
(2R)-2-[(1S)-2,2,2-Trifluoro-1-{[(1R)-1-phenylethyl]amino}ethyl]pentan-1-ol (anti-8'a)
(2S,3S)-2-Ethyl-4,4,4-trifluoro-3-\{[(1R)-1-phenylethyl]amino\}butan-1-ol (syn-9a)
(2R,3S)-2-Ethyl-4,4,4-trifluoro-3-((1R)-1-phenylethylamino)butan-1-ol (anti-9'a)

\[ \text{F}_3\text{C} \]

\[ \text{OH} \]

\[ \text{(R,S,R)-9'a} \]