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

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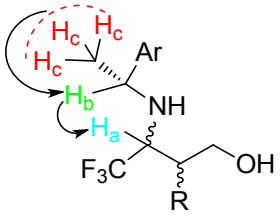
Determination of the absolute configuration of the new chiral centre

i. By 2D NOESY ^{1}H NMR spectra

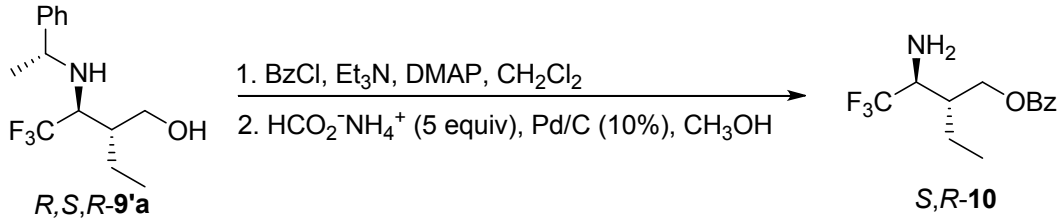
As reported,[1] starting from a reference cross peak whose interproton distance is known, it was possible to calculate the distances between other protons according to equation $V_X/V_R = (d_R/d_X)^6$ (V_R = volume of the reference cross peak; d_R = corresponding interproton distance; V_X = volume relative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



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

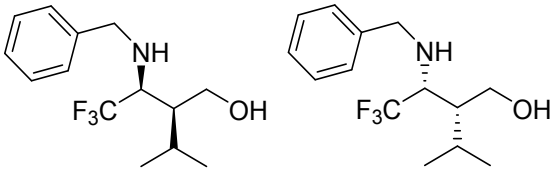
Following a synthetic procedure similar to that reported in the literature, after reaction of *anti*-**9'a** with benzoyl chloride, a hydrogenolysis reaction permitted to remove the benzyl group[2] leading to the known chiral primary amine **10**,[3] the $[\alpha]_D$ value of which corresponds with that reported in the literature {found: $[\alpha]_D = -10.8$ (c = 1.5, $CHCl_3$); literature[3] $[\alpha]_D = -11.5$ (c = 1.5, $CHCl_3$)}.



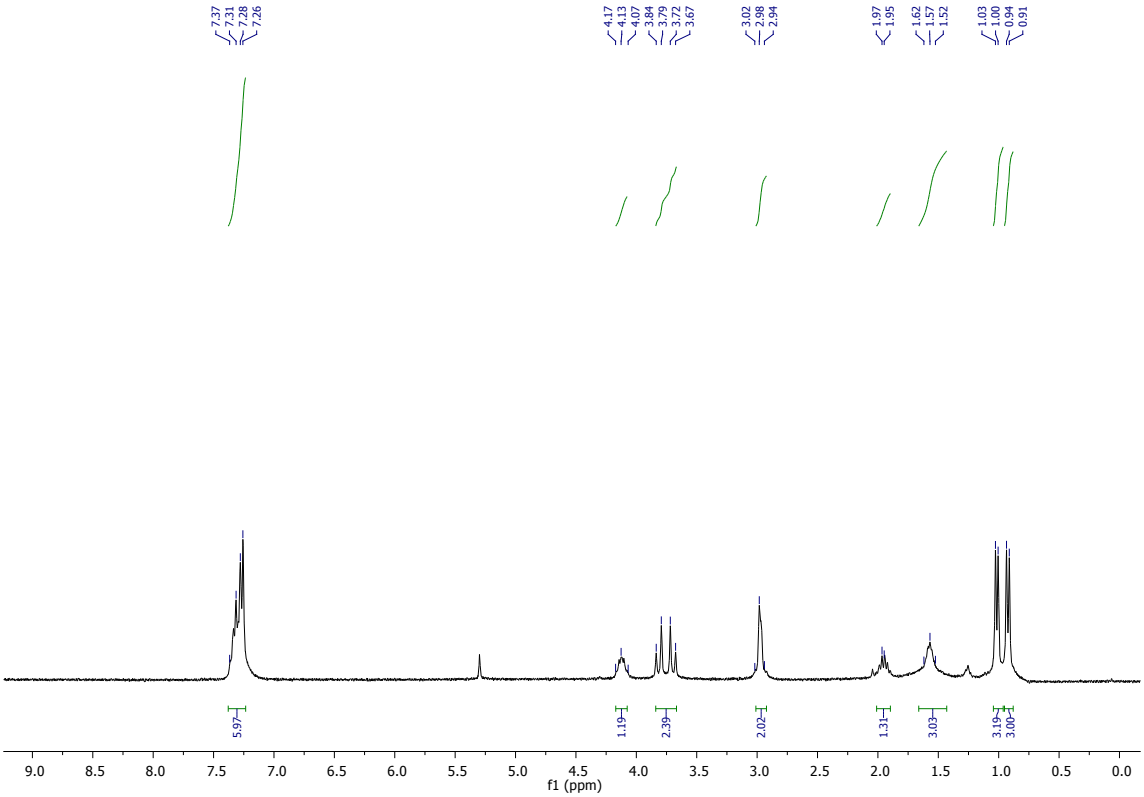
R,S,R-**9'a** → *S,R*-**10**

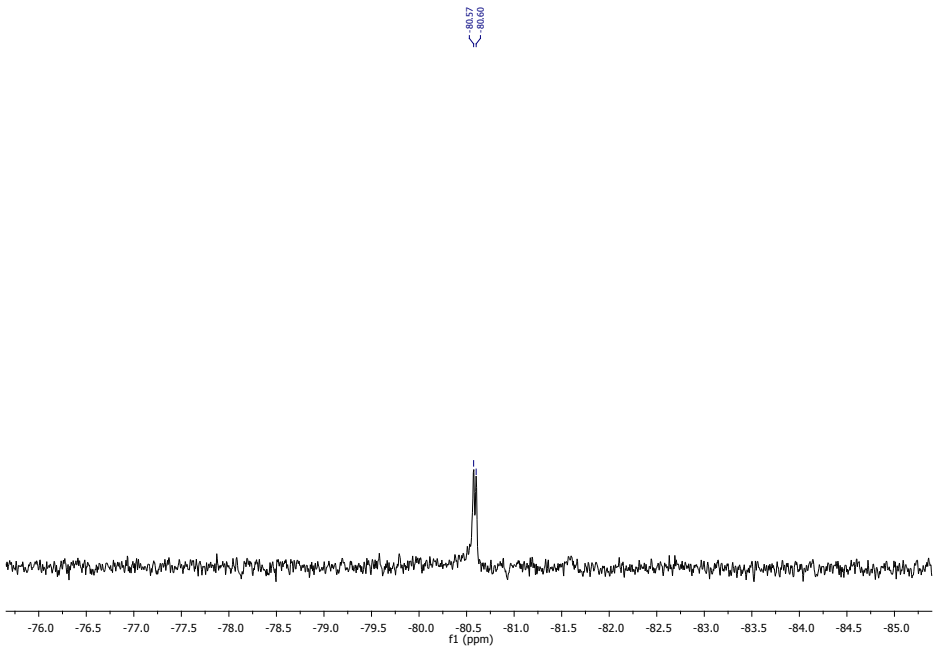
1. J. Jeener, B. H. Meier, P. Bachmann and R. R. Ernst, *J. Chem. Phys.*, 1979, **71**, 4546.
2. S. Fioravanti, A. Pelagalli, L. Pellacani, F. Sciubba and M. C. Vergari, *Amino Acids,* 2014, **46**, 1961.
3. S. Fustero, F.; Mojarrad, M. D. P. Carrion, J. F. Sanz-Cervera and J. L. Acena, *Eur. J. Org. Chem.*, **2009**, 5208.

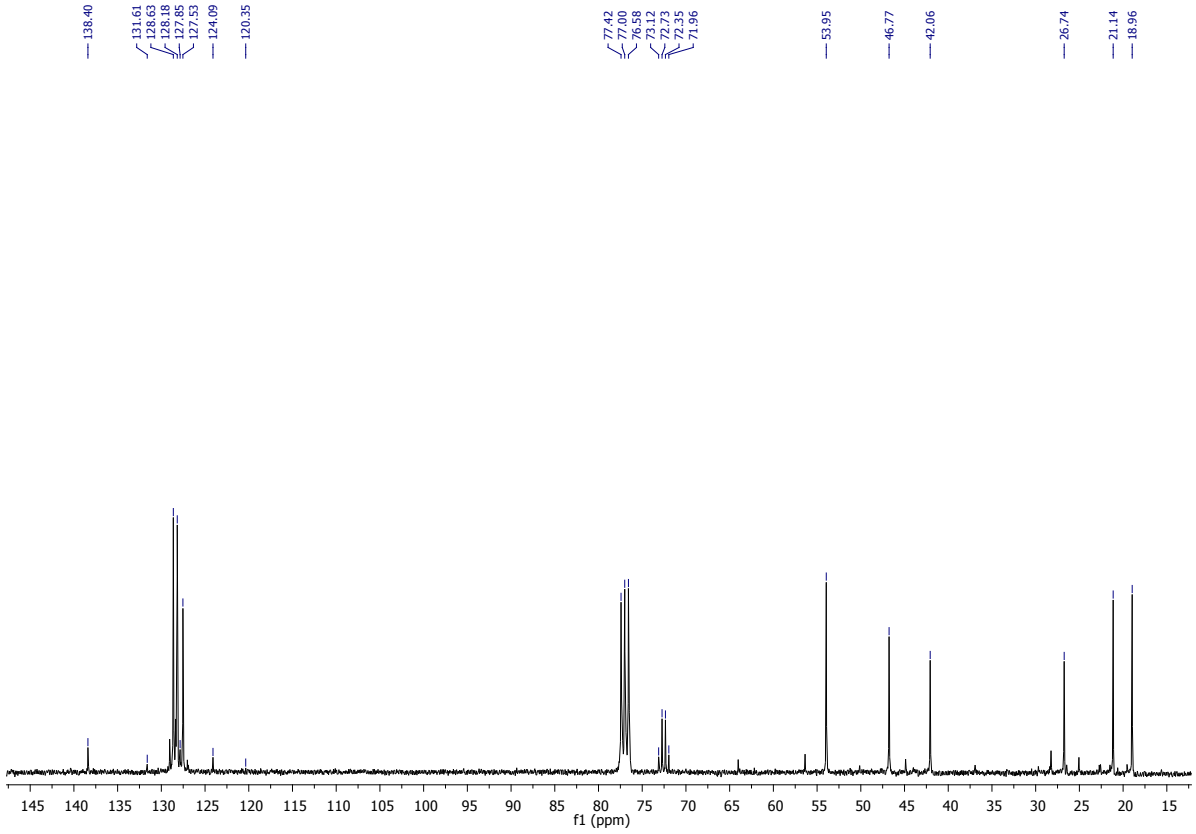
(2*R**,3*R**)-3-(Benzylamino)-4,4,4-trifluoro-2-isopropylbutan-1-ol (*syn*-2a)



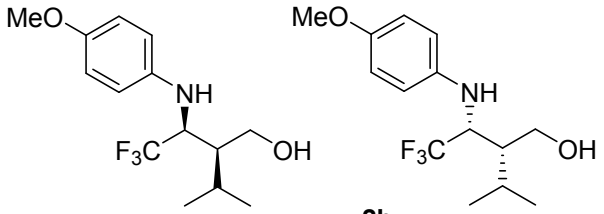
syn-**2a**



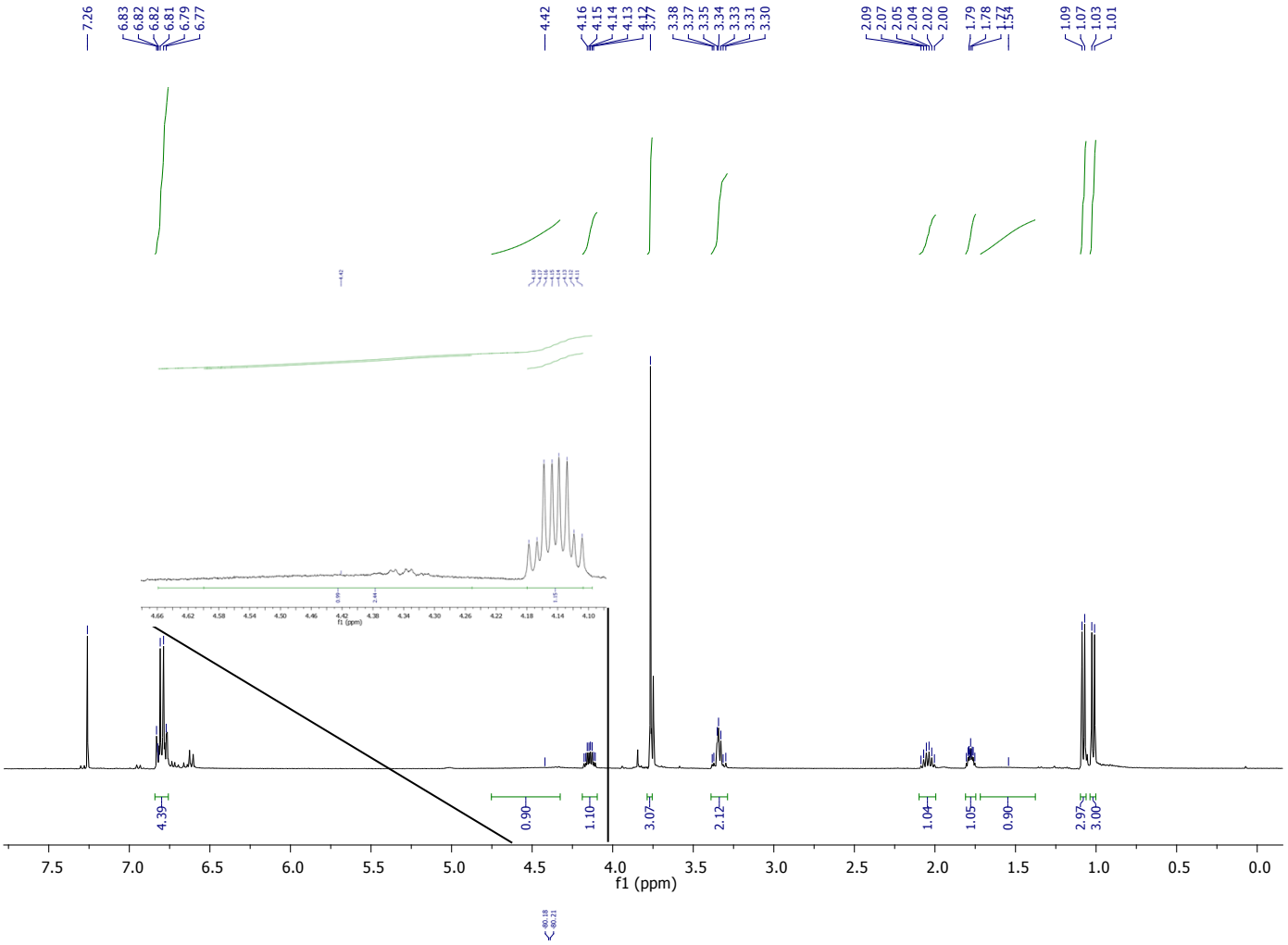


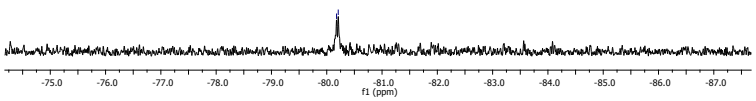


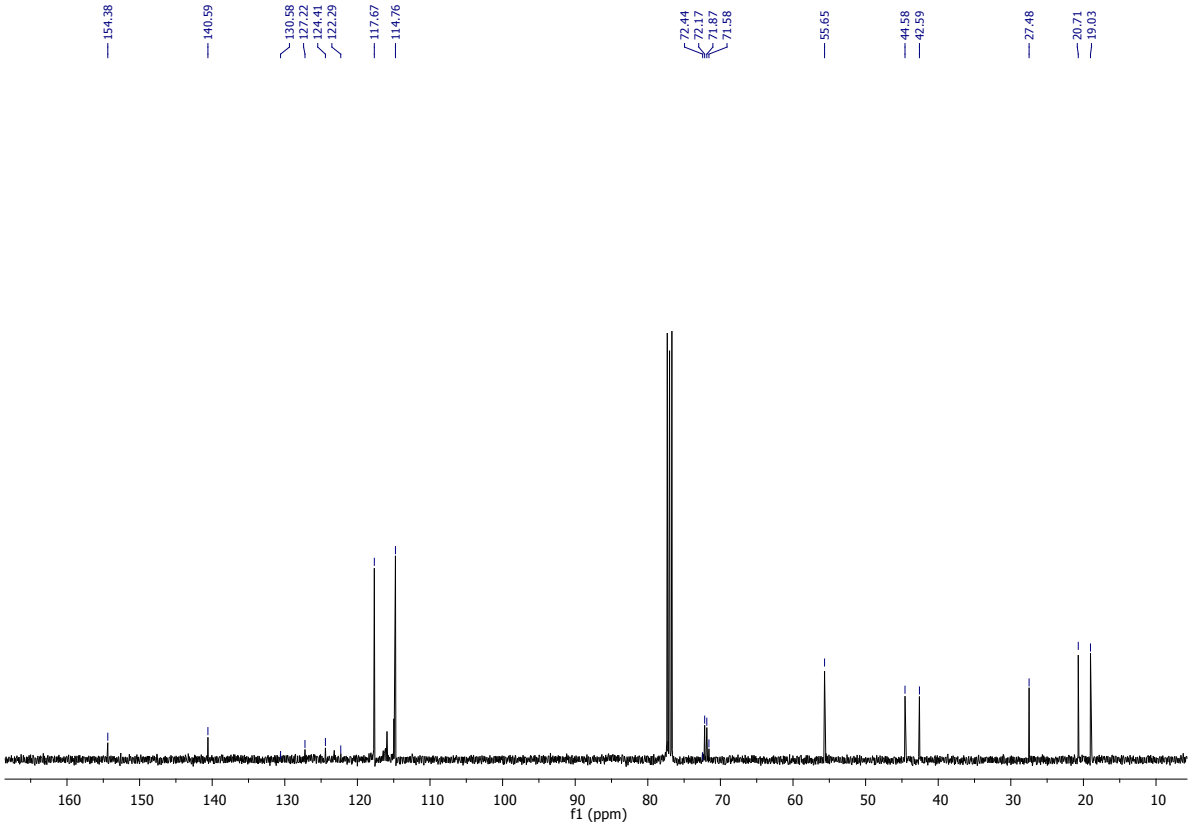
(2*R,3*R**)-4,4,4-Trifluoro-2-isopropyl-3-(4-methoxyphenylamino)butan-1-ol (*syn*-2b)**



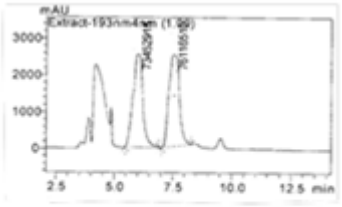
syn-**2b**



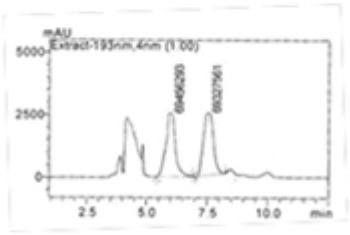




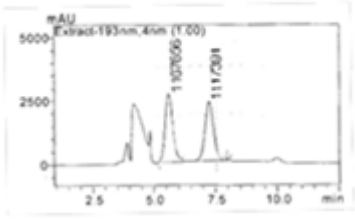
Chiral HPLC analysis of *syn*-2b



Reaction performed with L-proline at 25 °C



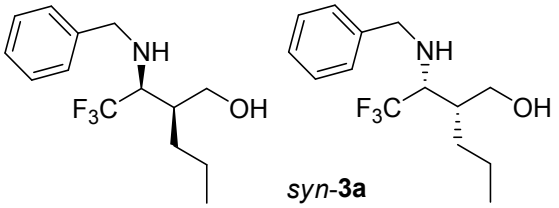
Reaction performed with D,L-proline at 25 °C



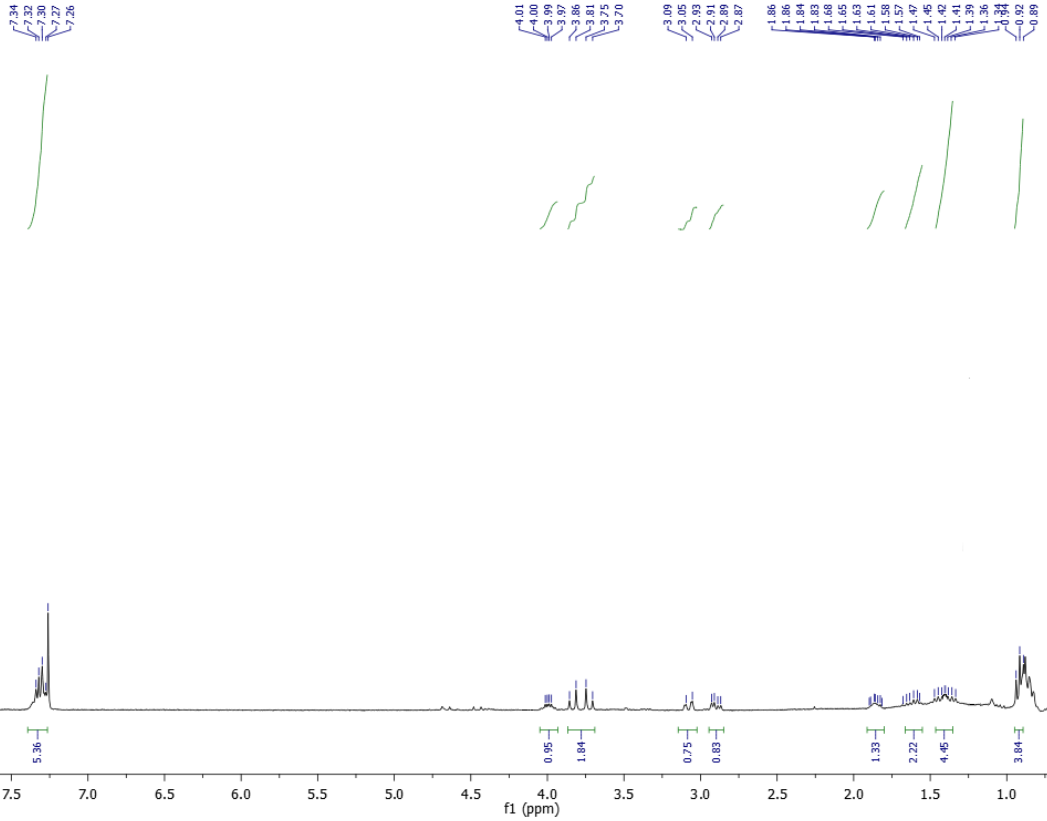
Reaction performed with L-proline at –20 °C

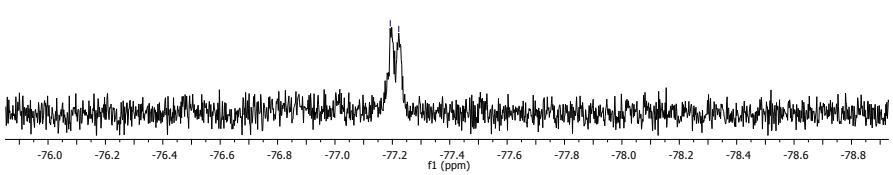
Chiralcel column; eluent: hexane/2-propanol = 95:5, flow 0.9 mL/min

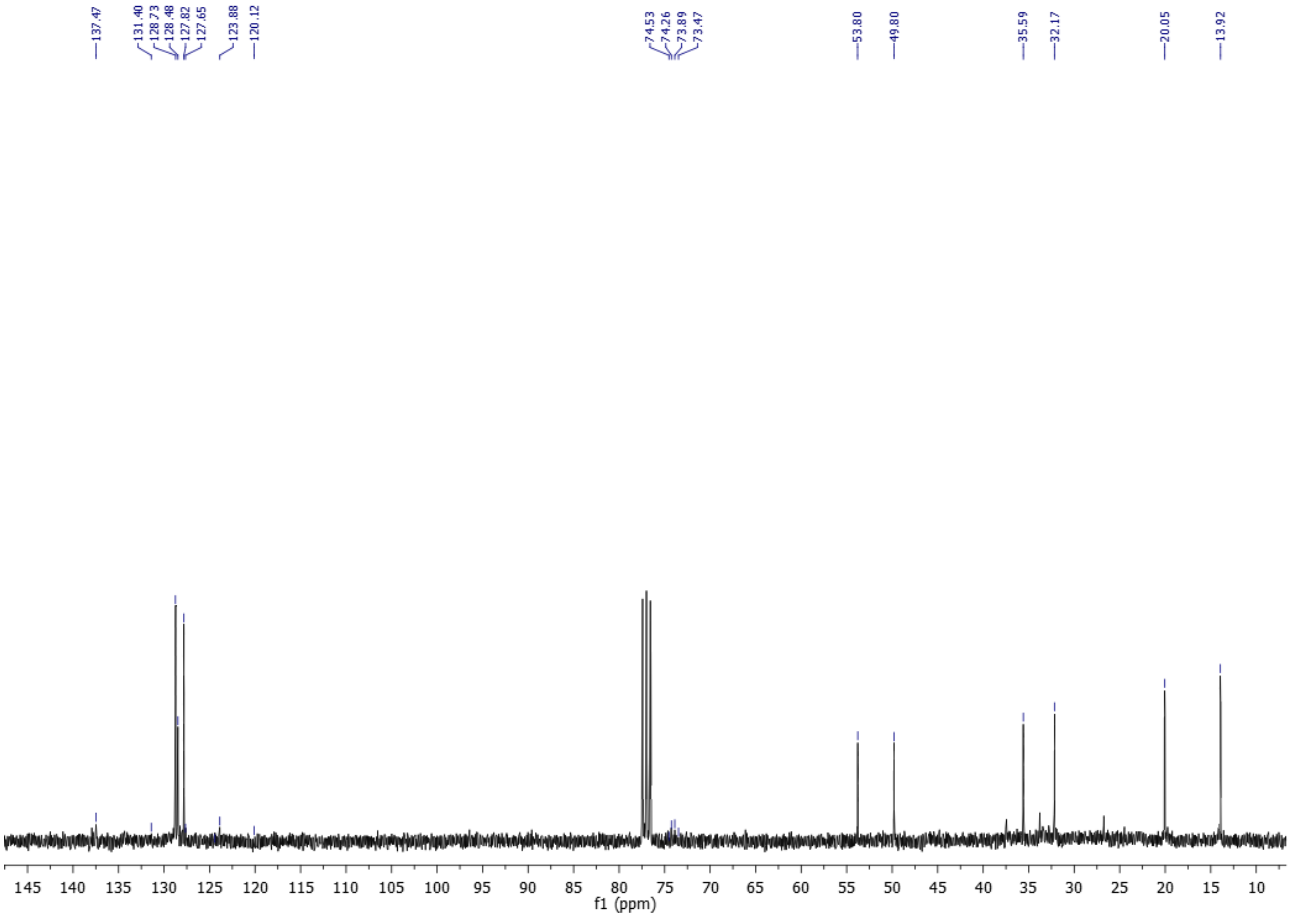
(2*R)-2-[(1*R**)-1-(Benzylamino)-2,2,2-trifluoroethyl]pentan-1-ol (*syn*-3a)**



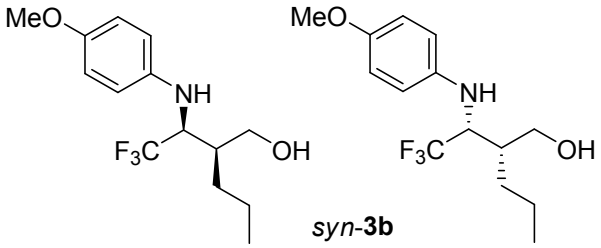
syn-**3a**



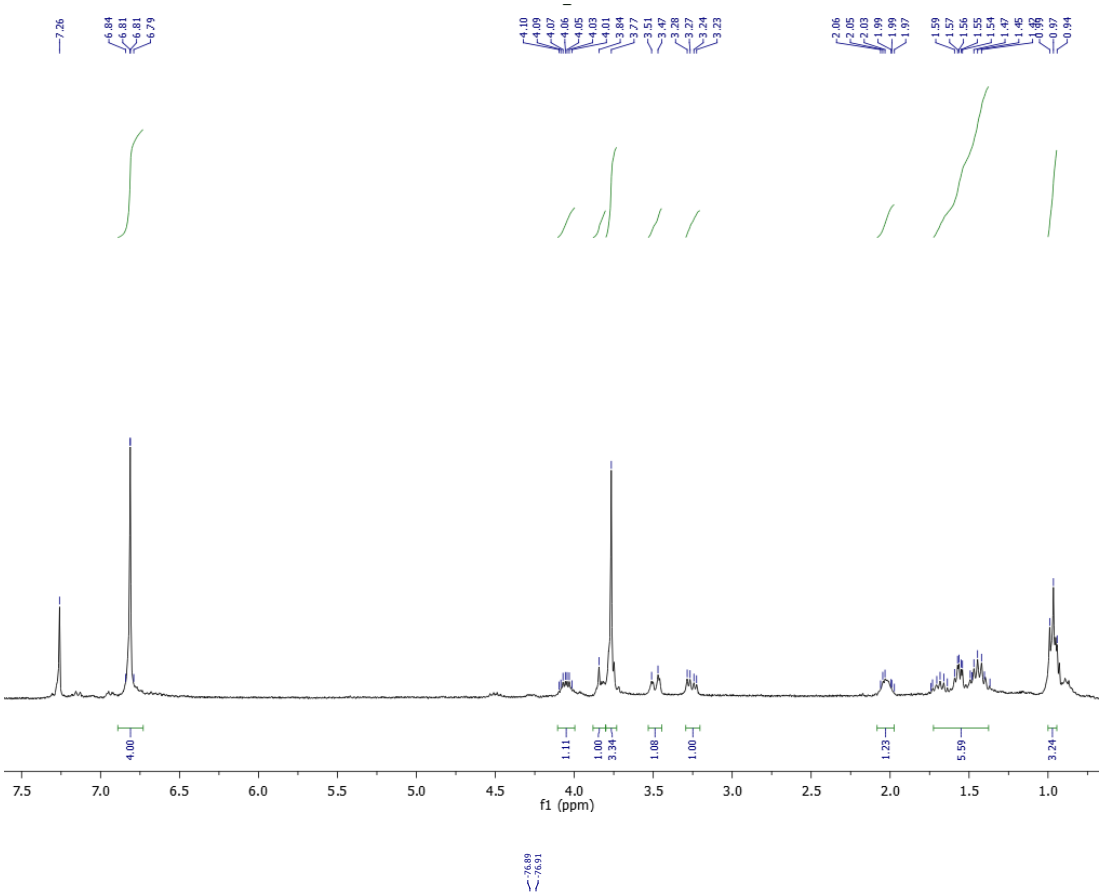


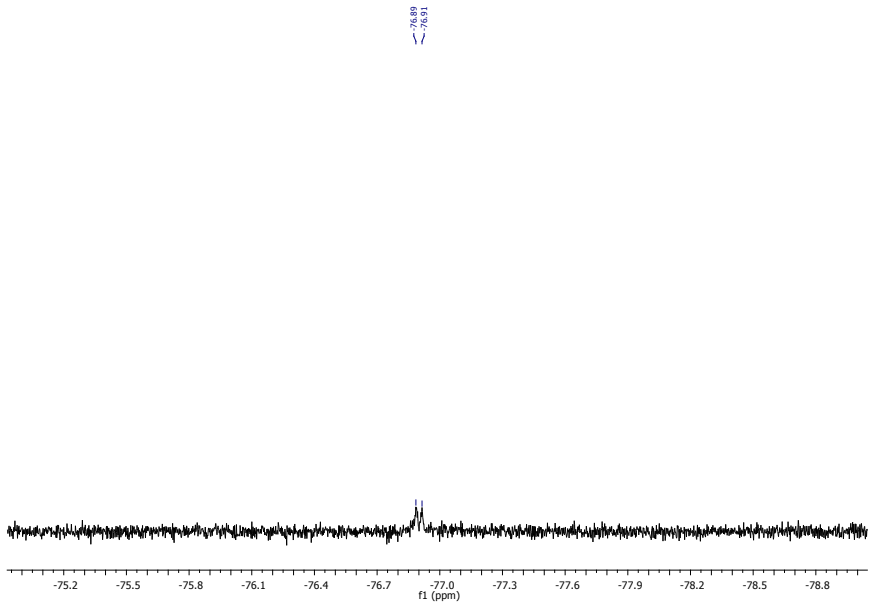


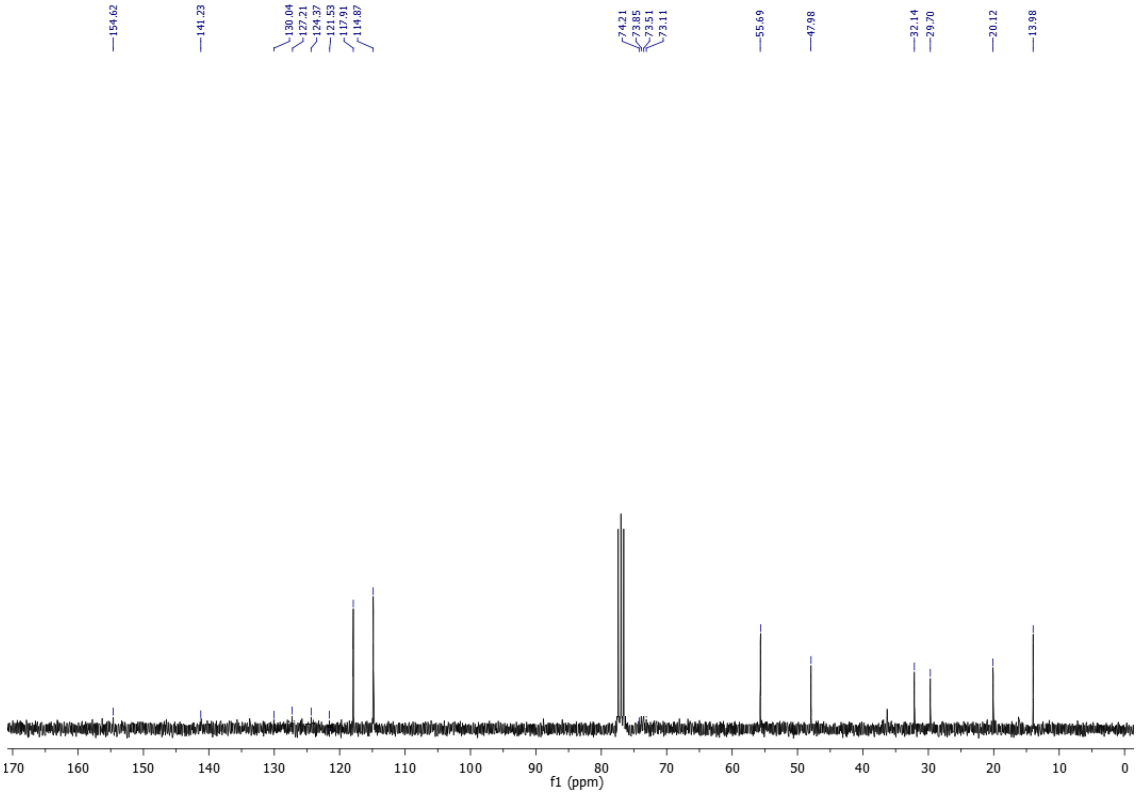
(2*R)-2-[(1*R**)-(2,2,2-Trifluoro)-1-(4-methoxyphenylamino)ethyl]pentan-1-ol (*syn*-3b)**



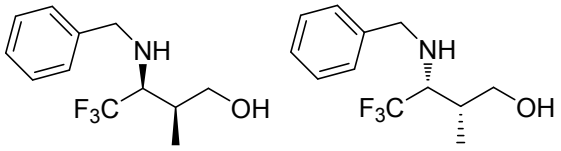
syn-**3b**



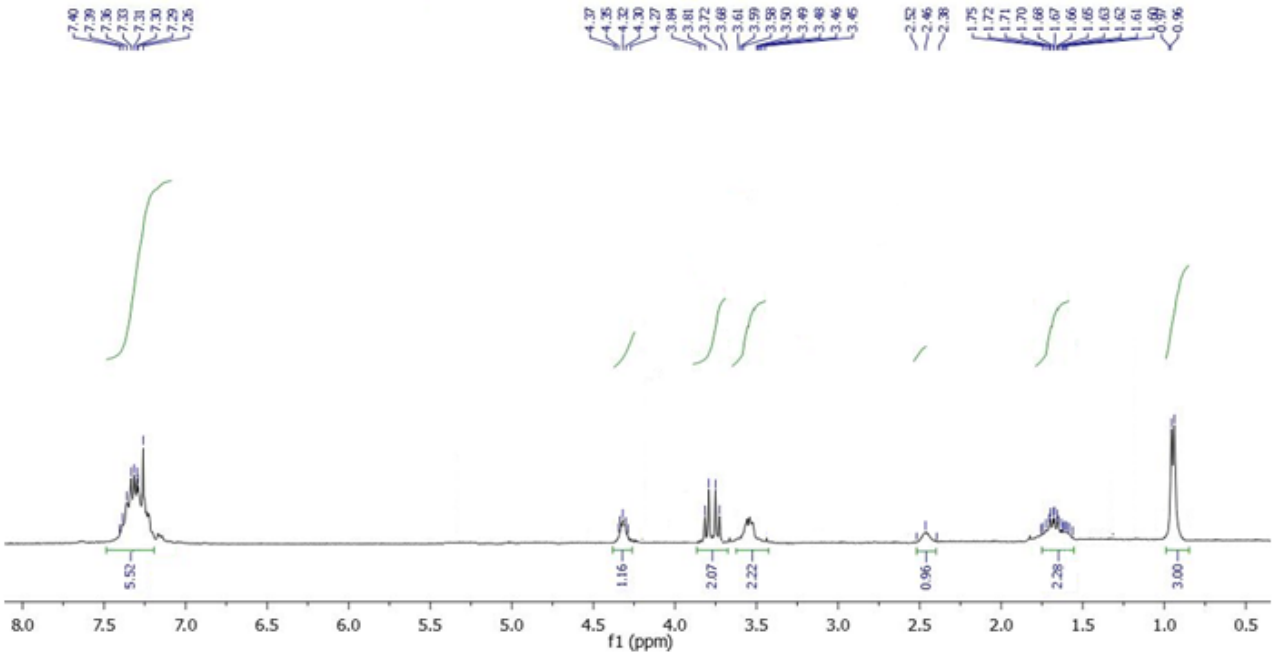


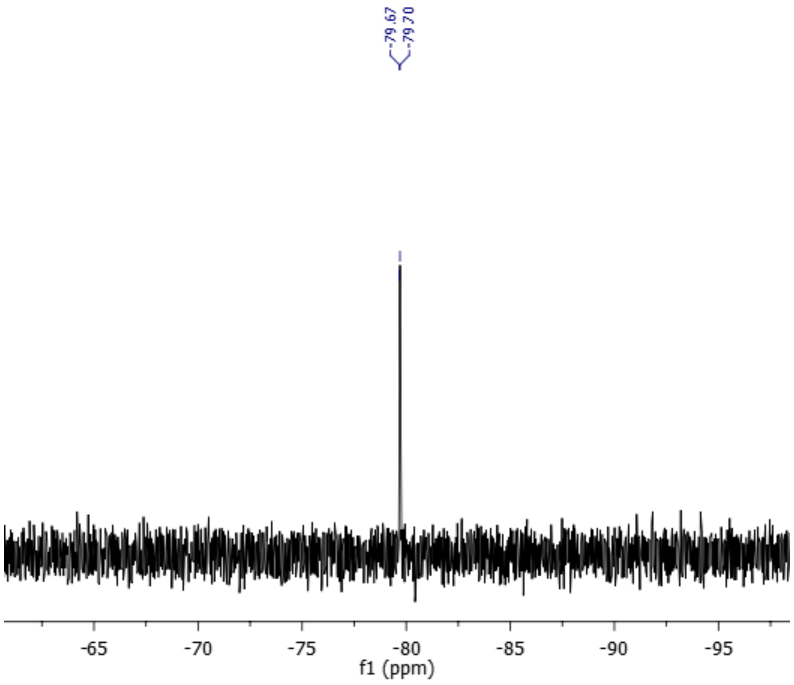


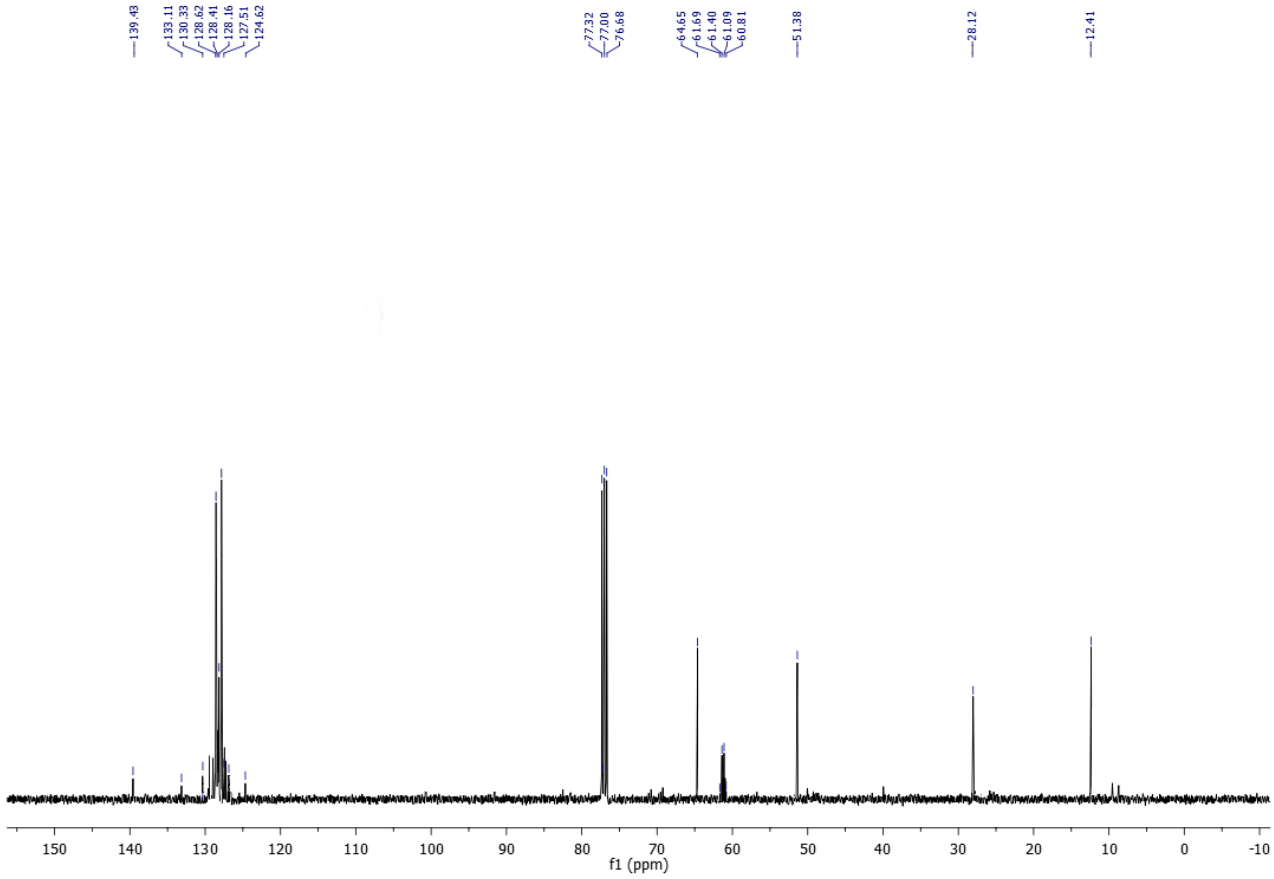
(2*R,3*R**)-3-(Benzylamino)-4,4,4-trifluoro-2-methylbutan-1-ol (*syn*-4a)**



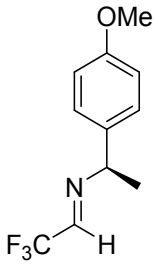
syn-**4a**



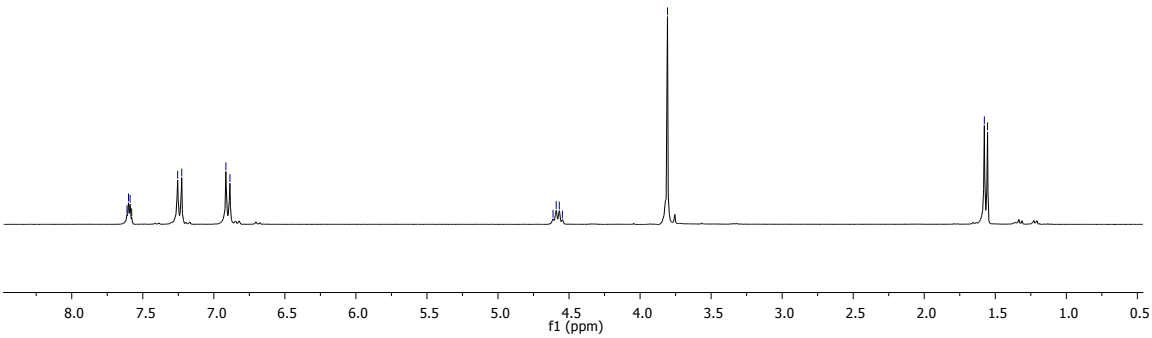


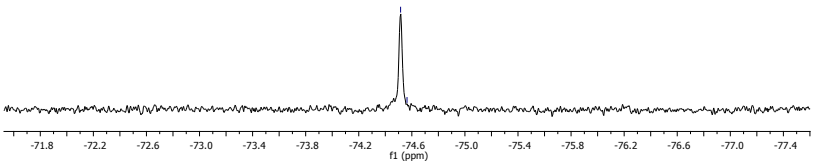


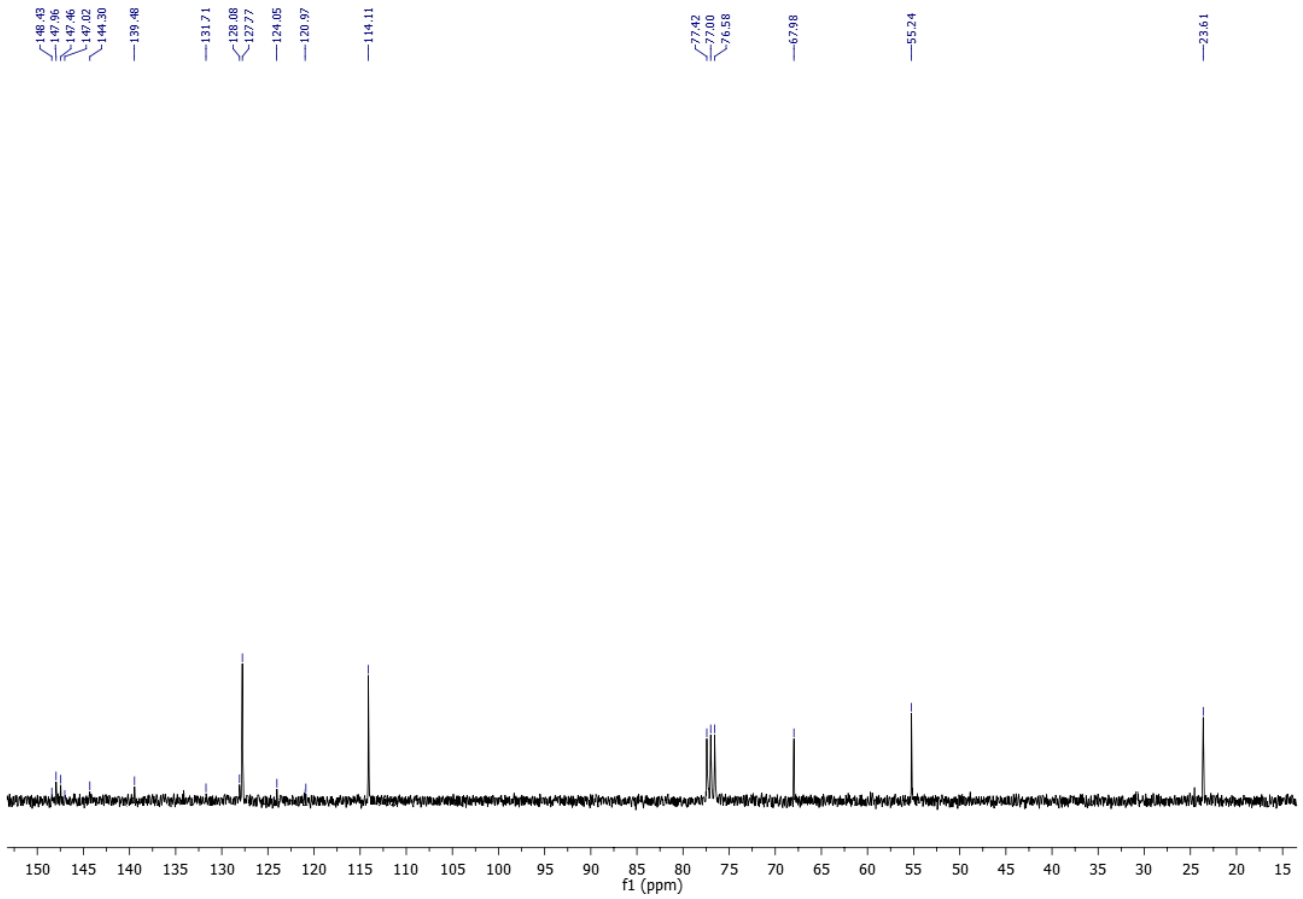
(*R*,*E*)-1-(4-Methoxyphenyl)-*N*-(2,2,2-trifluoroethylidene)ethanamine (6b)



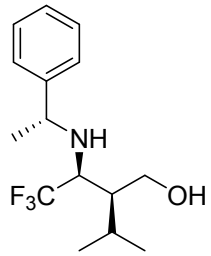
(*R*,*E*)-**6b**



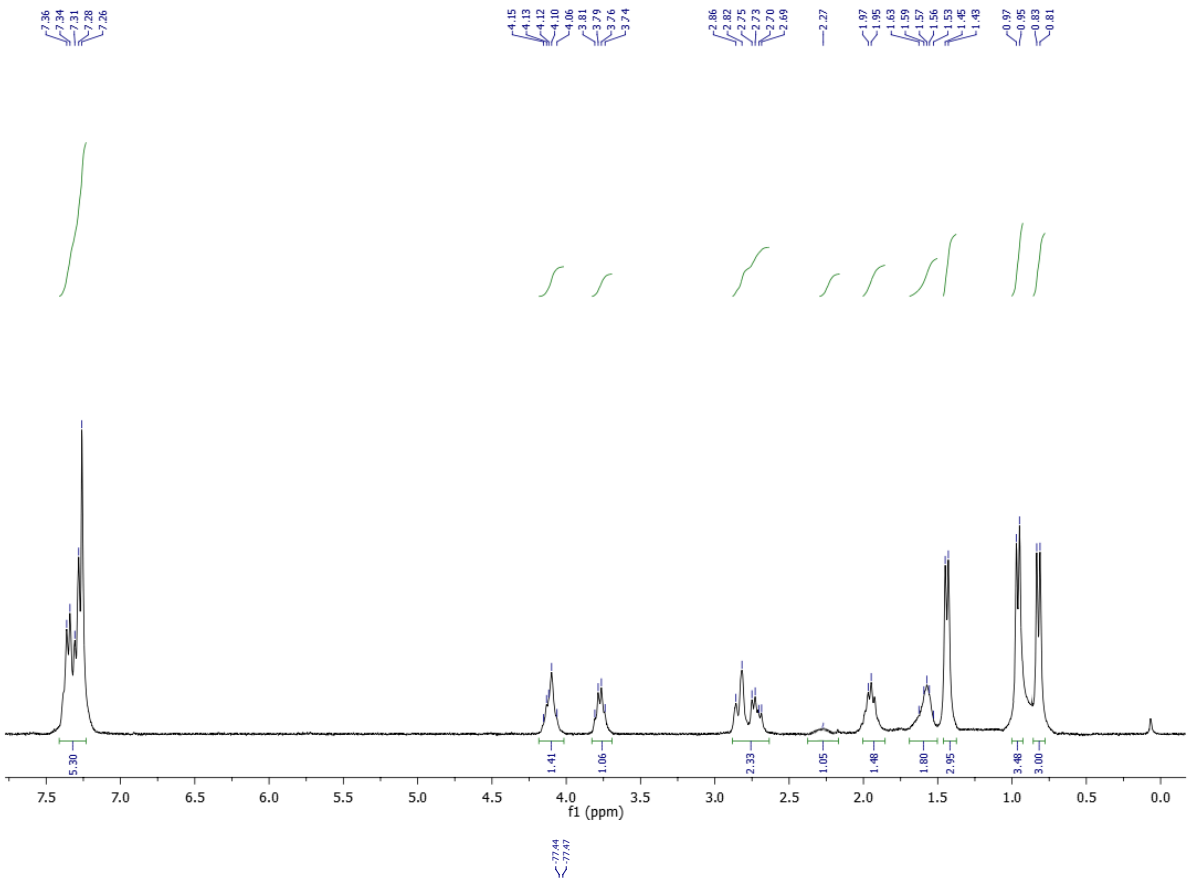


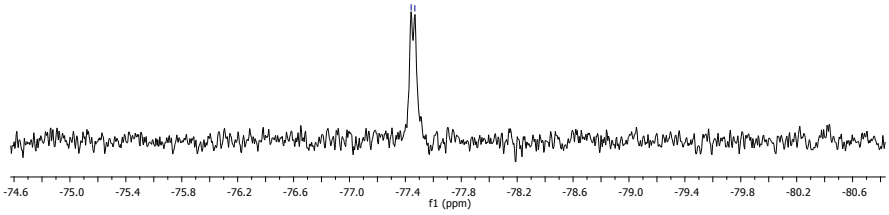


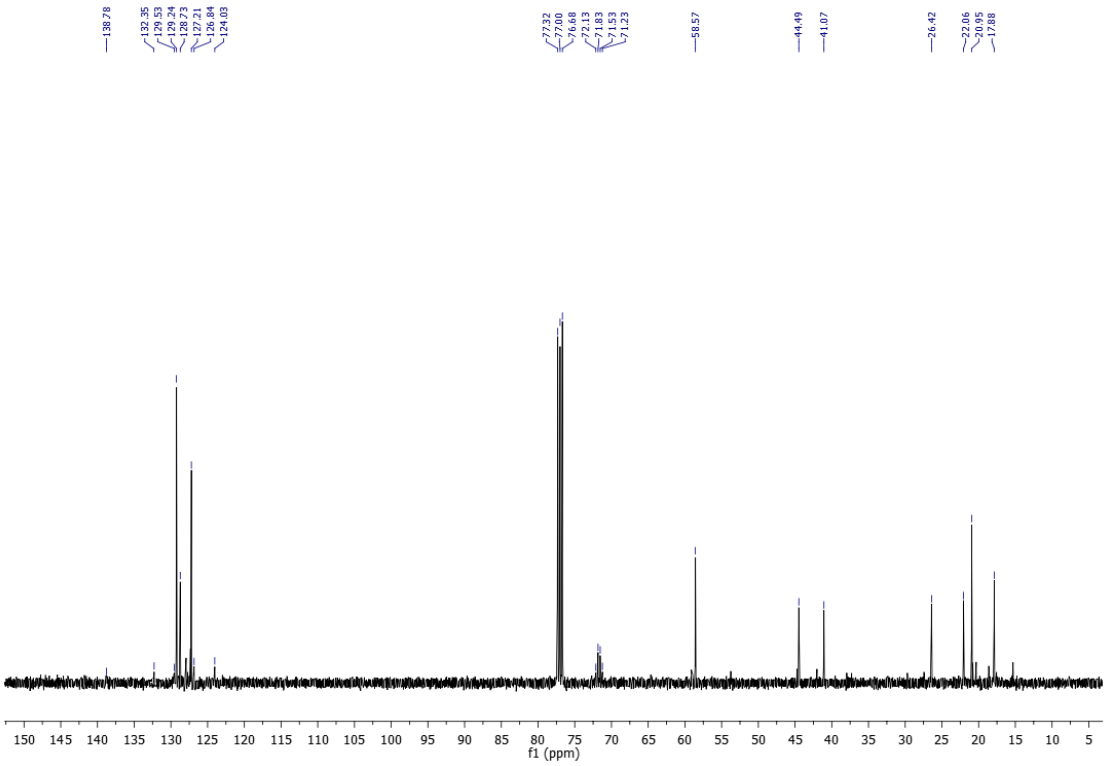
(2*S*,3*S*)-4,4,4-Trifluoro-2-isopropyl-3-[(*R*)-1-phenylethylamino]butan-1-ol (*syn*-7a)



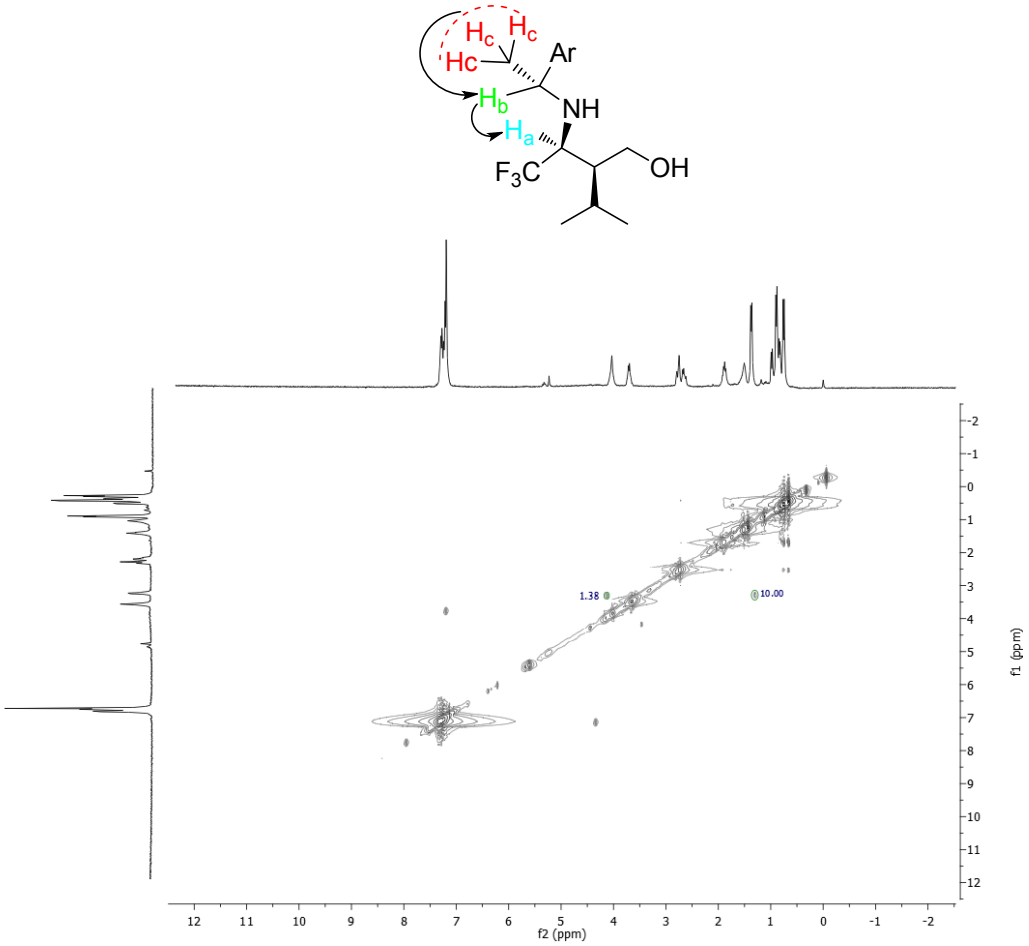
(*S*,*S*,*R*)-**7a**



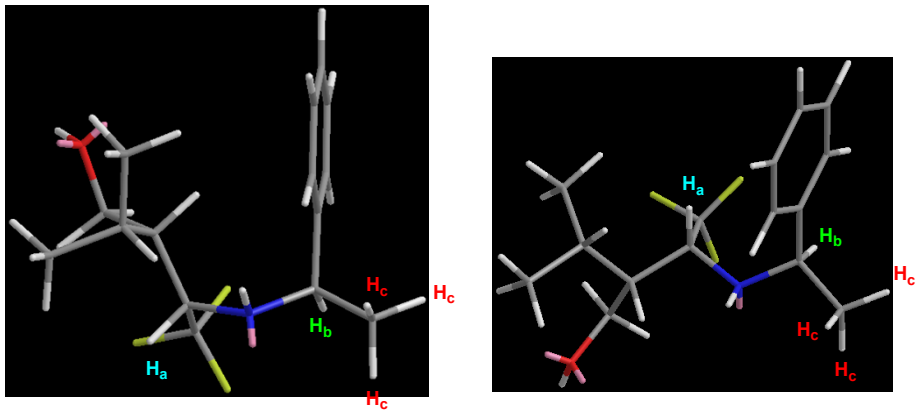




NOESY spectrum of (*S*,*S*,*R*)-7a



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.



H_a/H_b : 3.675 Å

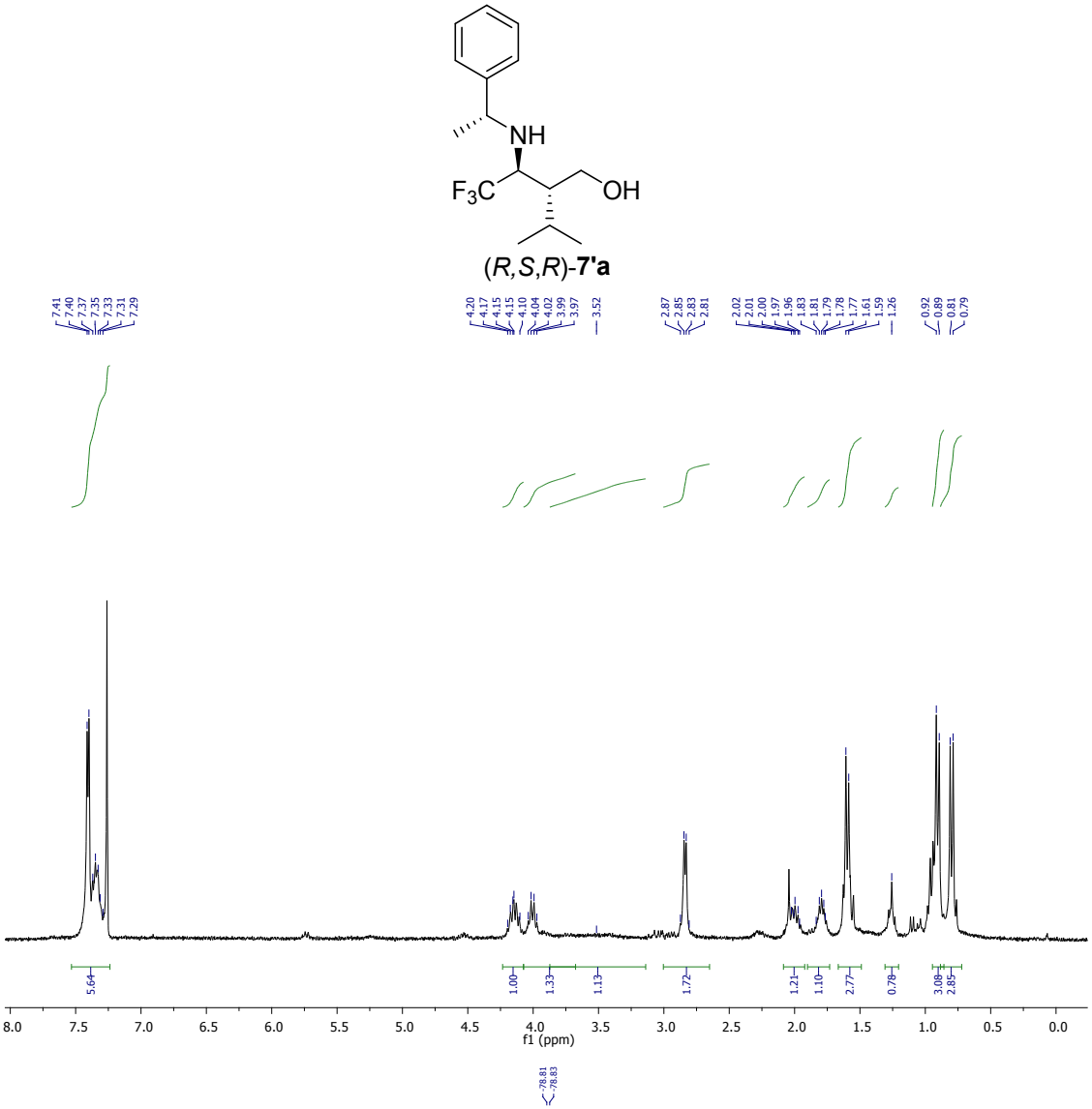
(*S*,*S*,*R*)-**7a**

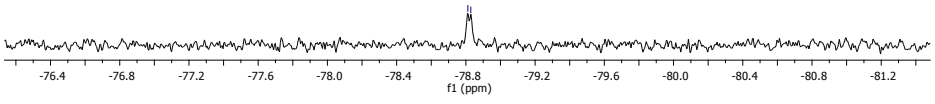
H_a/H_b : 3.202 Å

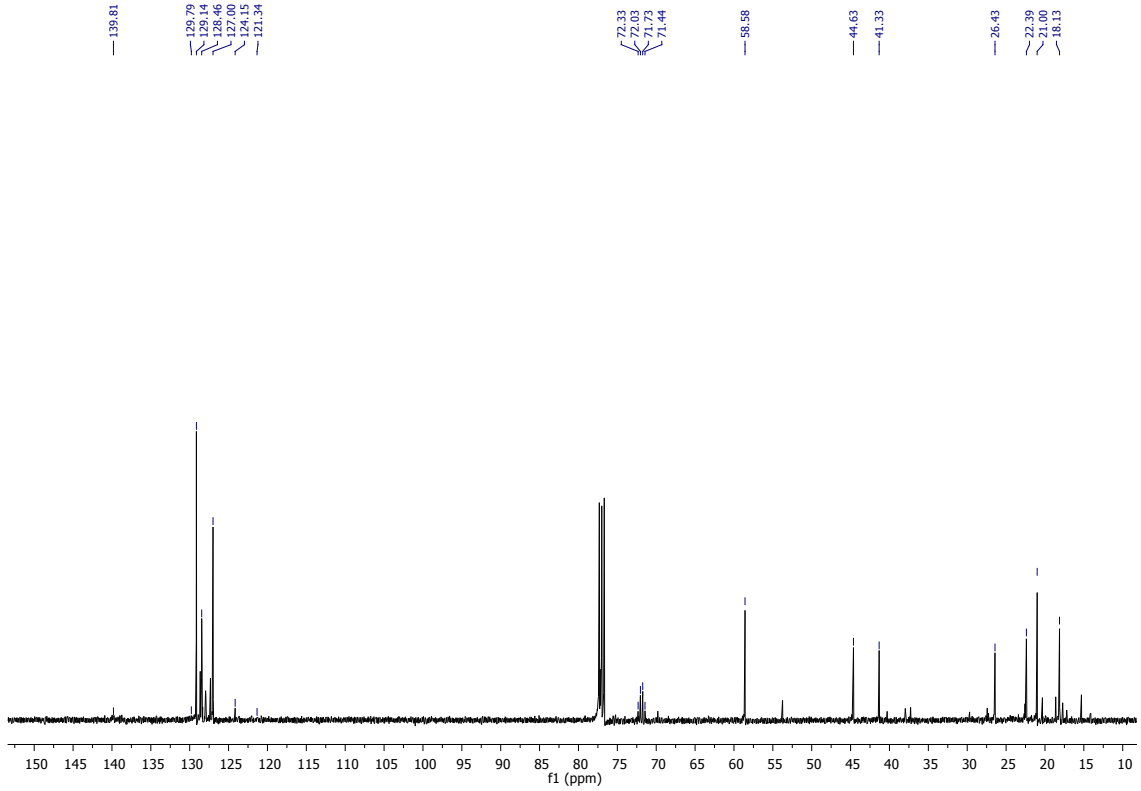
(*R*,*R*,*R*)

Fig. 1. Optimized geometries of (*S*,*S*,*R*)-**7a** and of its possible diastereomer (*R*,*R*,*R*)

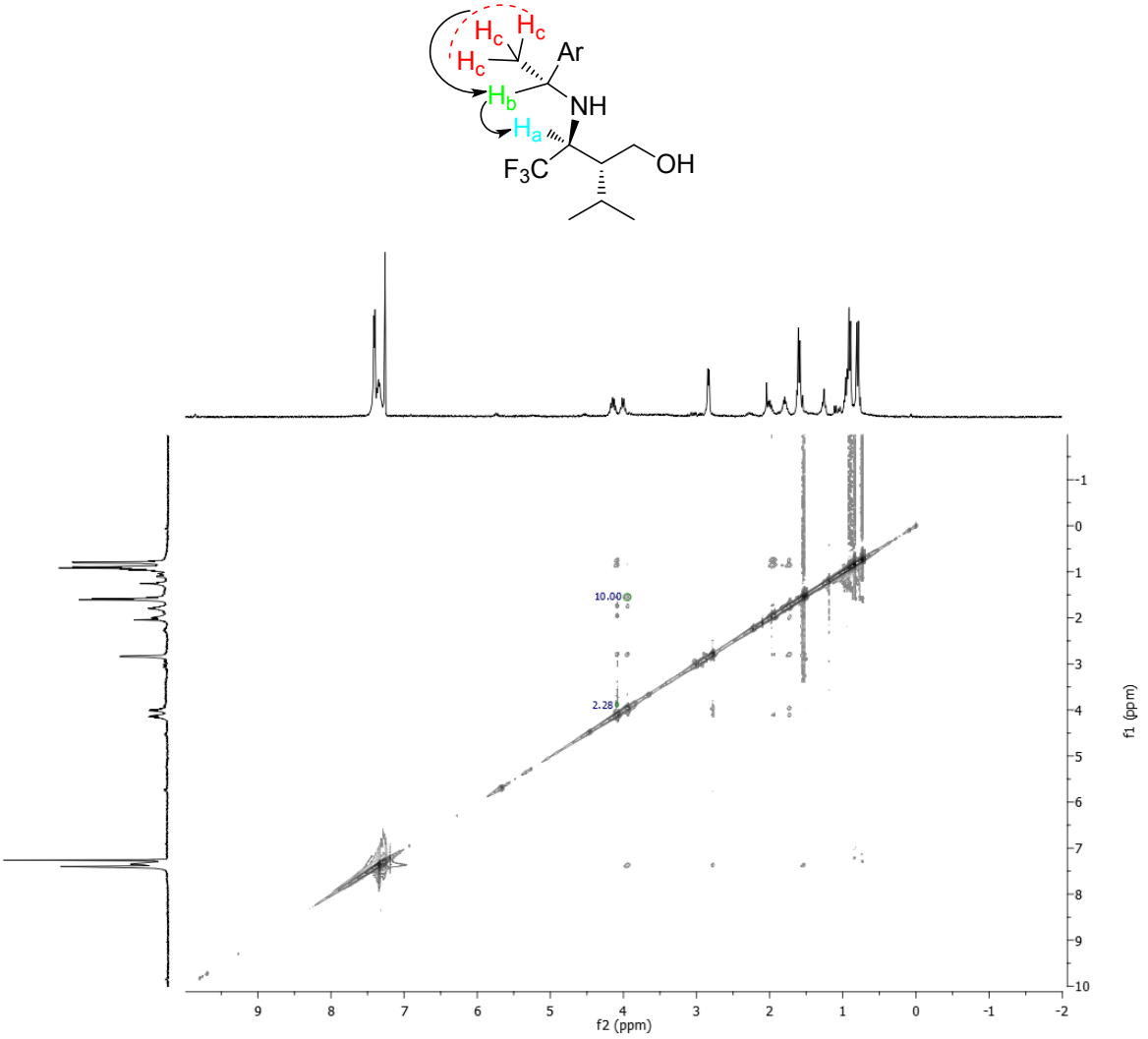
(2*R*,3*S*)-4,4,4-Trifluoro-2-isopropyl-3-[(*R*)-1-phenylethylamino]butan-1-ol (*anti*-7'a)







NOESY spectrum of (*R*,*S*,*R*)-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.

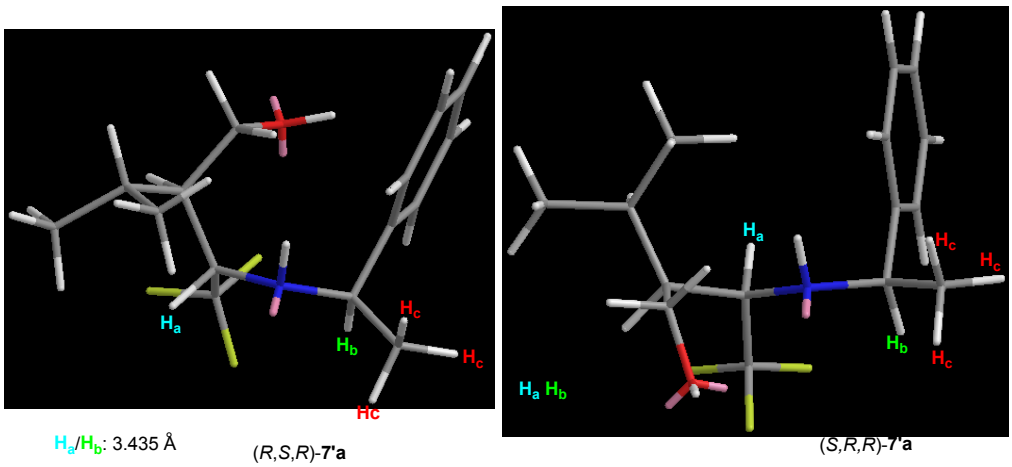
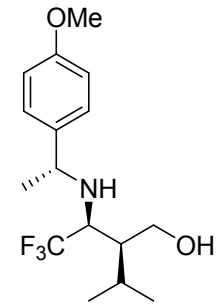
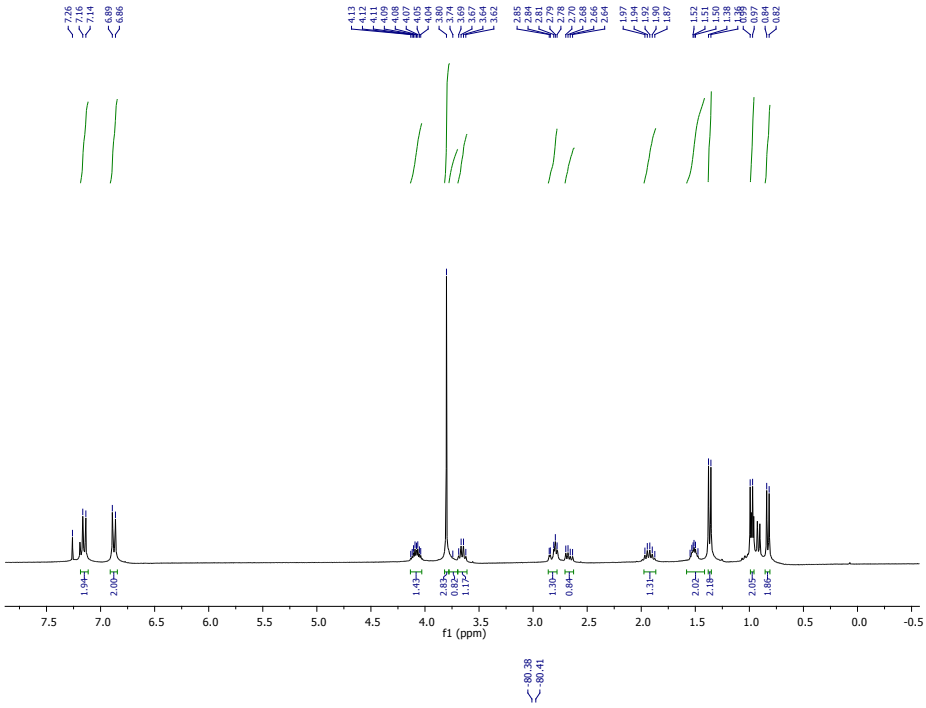


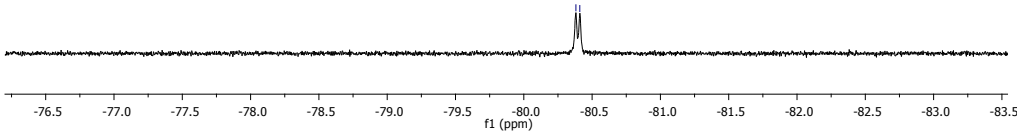
Fig. 2. Optimized geometries of (*R*,*S*,*R*)-**7'a** and of its possible diastereomer (*S*,*R*,*R*)

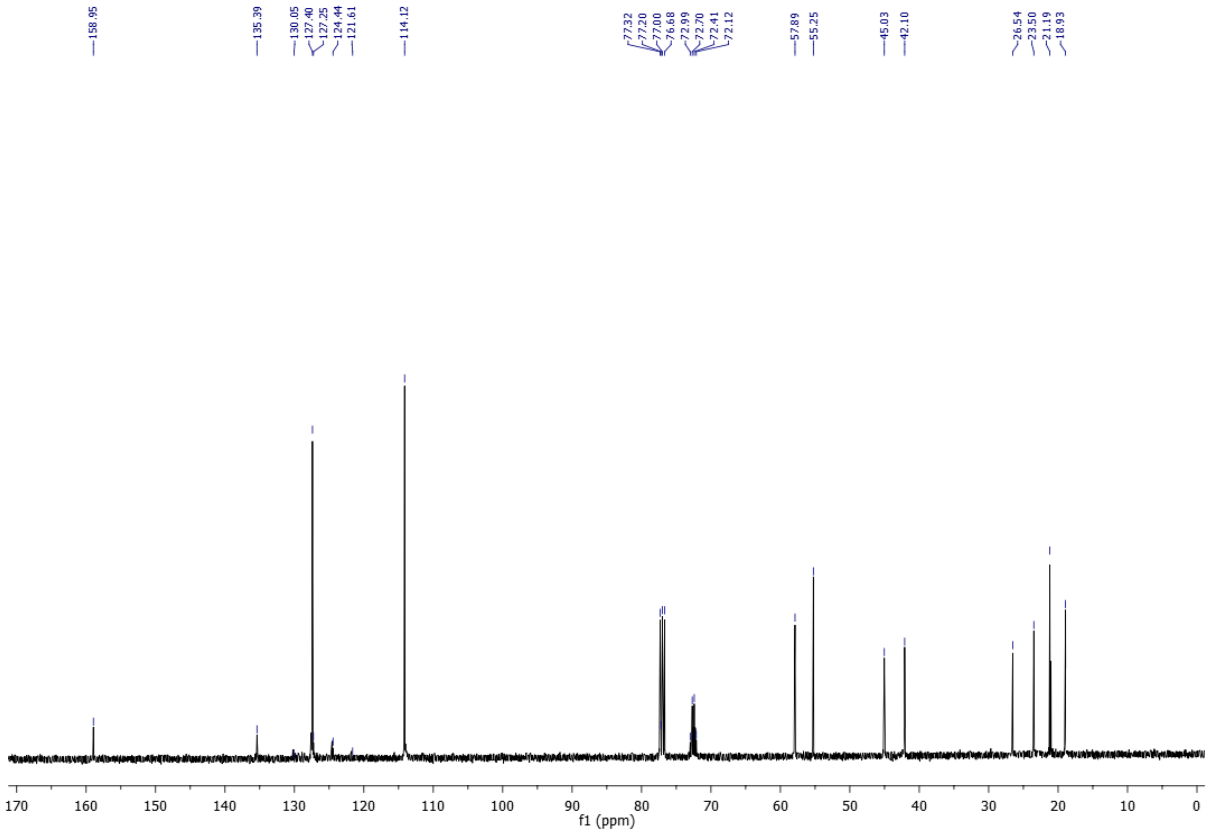
(2*S*,3*S*)-4,4,4-Trifluoro-2-isopropyl-3-[(*R*)-1-(4-methoxyphenyl)ethylamino]butan-1-ol (*syn*-7b)



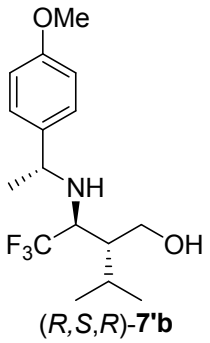
(*S*,*S*,*R*)-**7b**



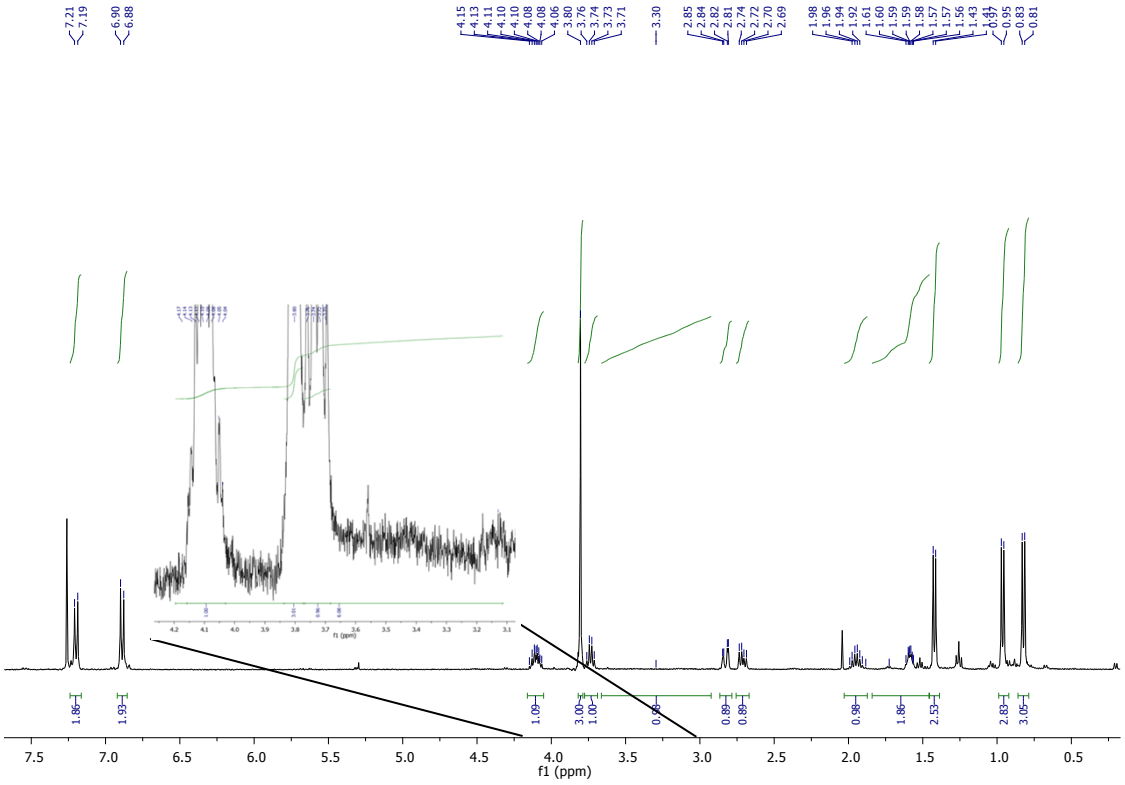


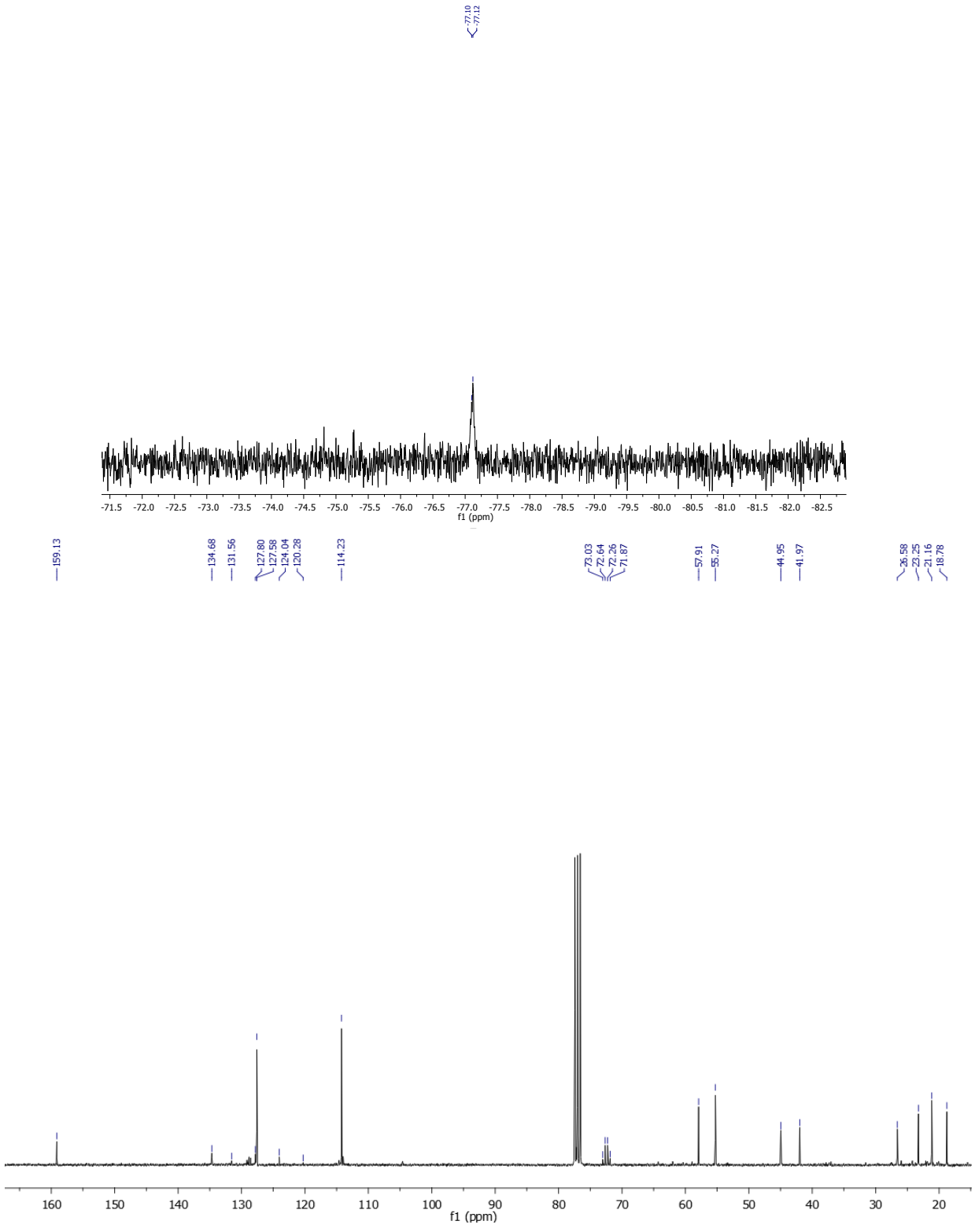


(2*R*,3*S*)-4,4,4-Trifluoro-2-isopropyl-3-[(*R*)-1-(4-methoxyphenyl)ethylamino]butan-1-ol (*anti*-7'b)

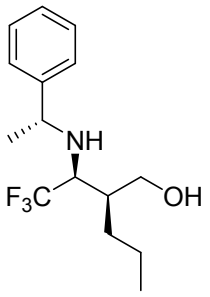


(*R*,*S*,*R*)-**7'b**

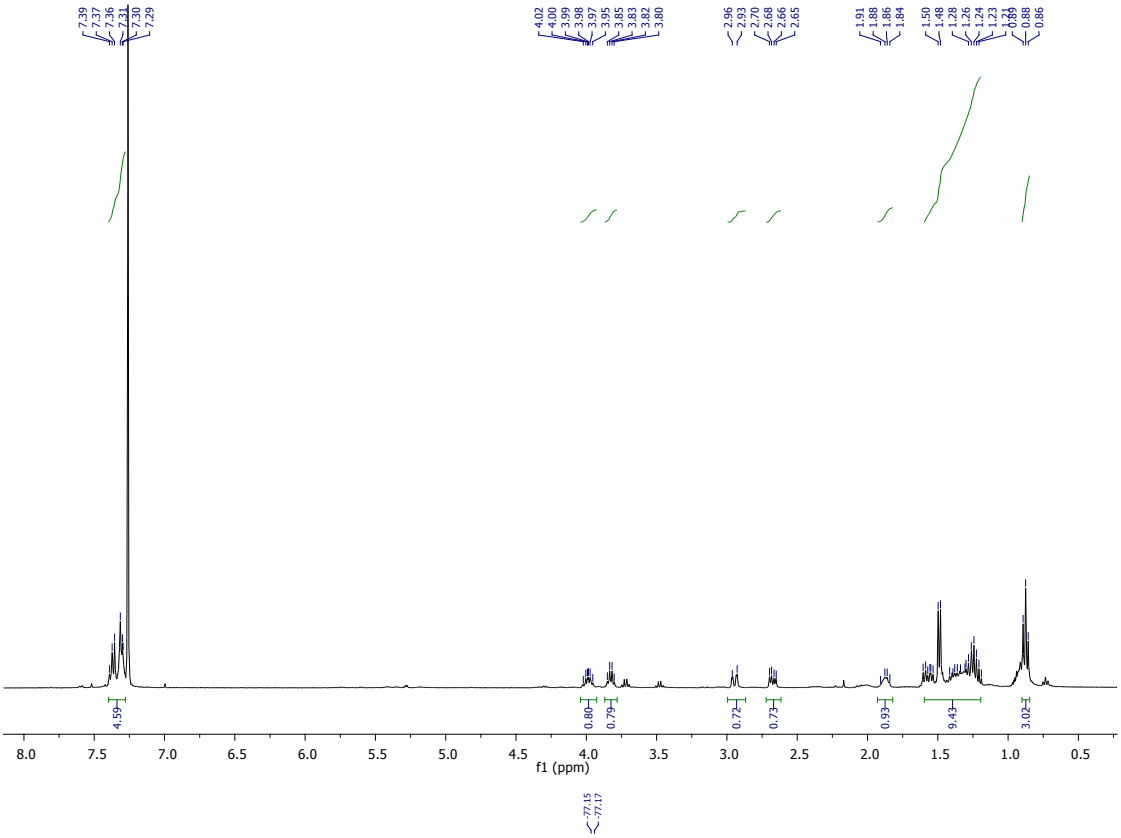


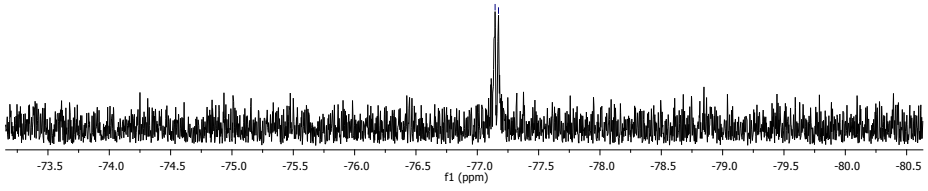


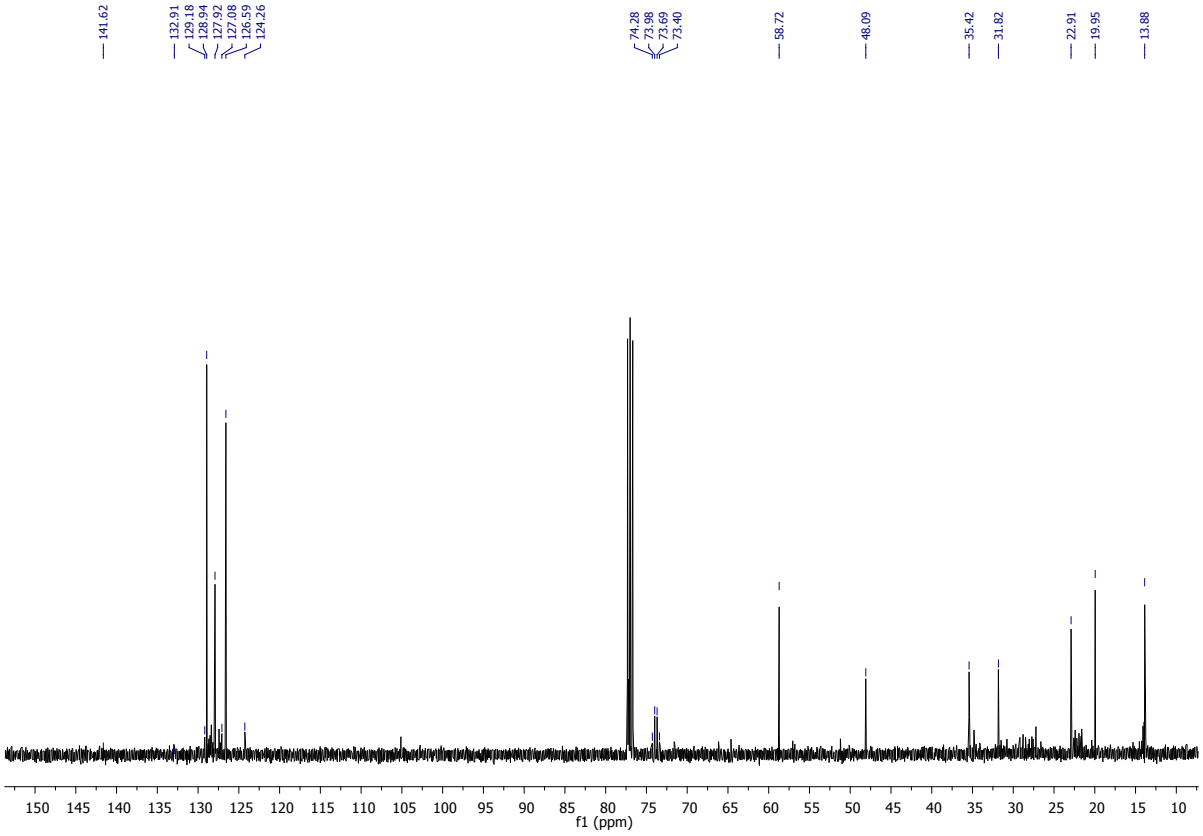
(2*S*)-2-[(1*S*)-2,2,2-Trifluoro-1-{[(1*R*)-1-phenylethyl]amino}ethyl]pentan-1-ol (*syn*-8a)



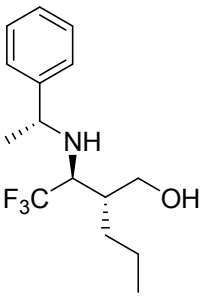
(*S*,*S*,*R*)-**8a**



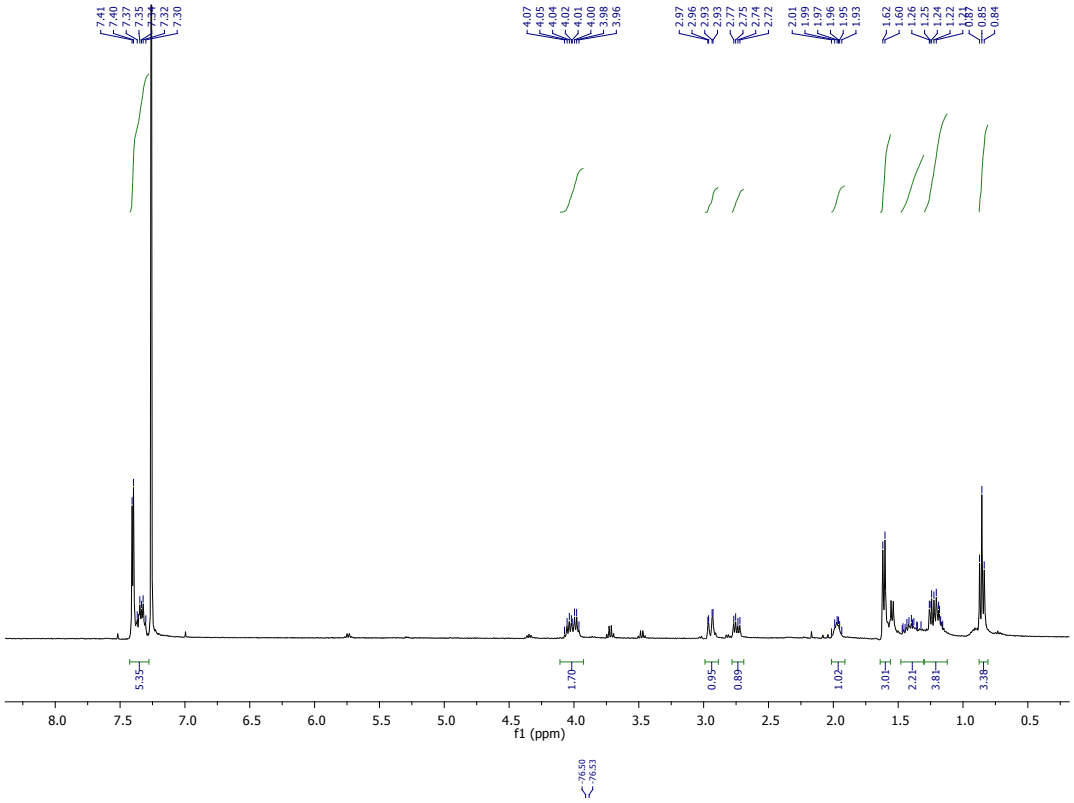


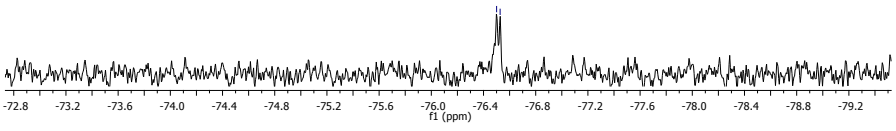


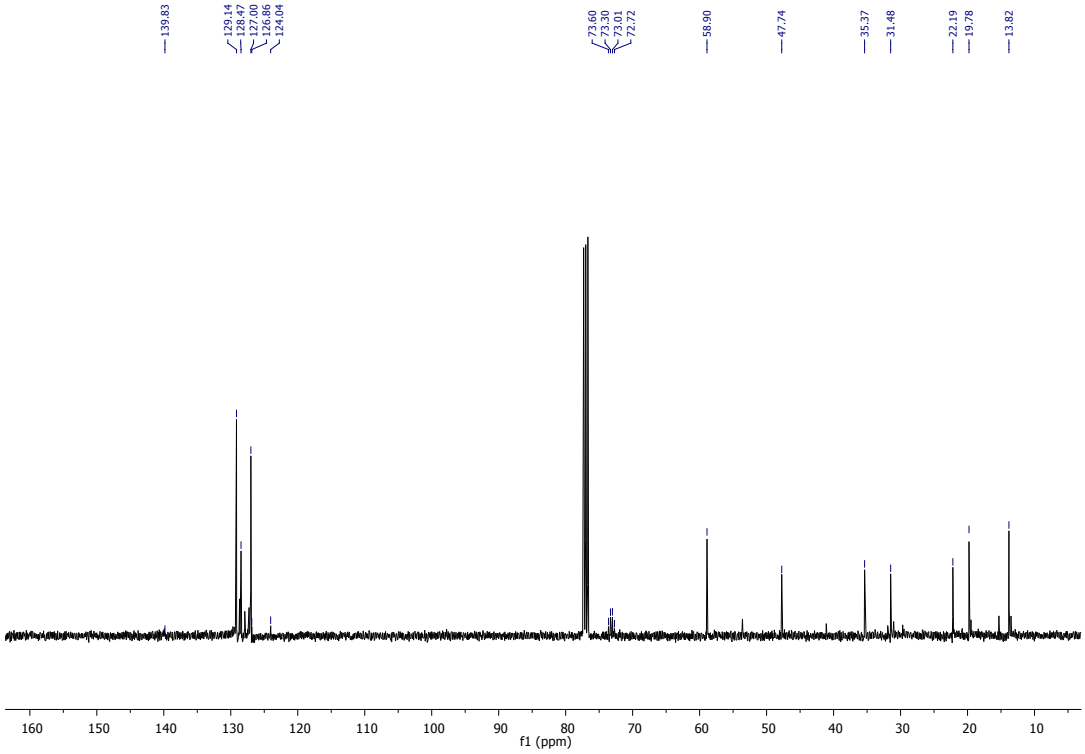
(2*R*)-2-[(1*S*)-2,2,2-Trifluoro-1-{[(1*R*)-1-phenylethyl]amino}ethyl]pentan-1-ol (*anti*-8′a)



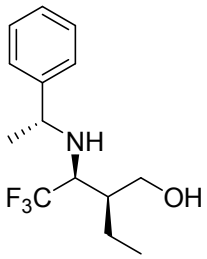
(*R*,*S*,*R*)-**8'a**



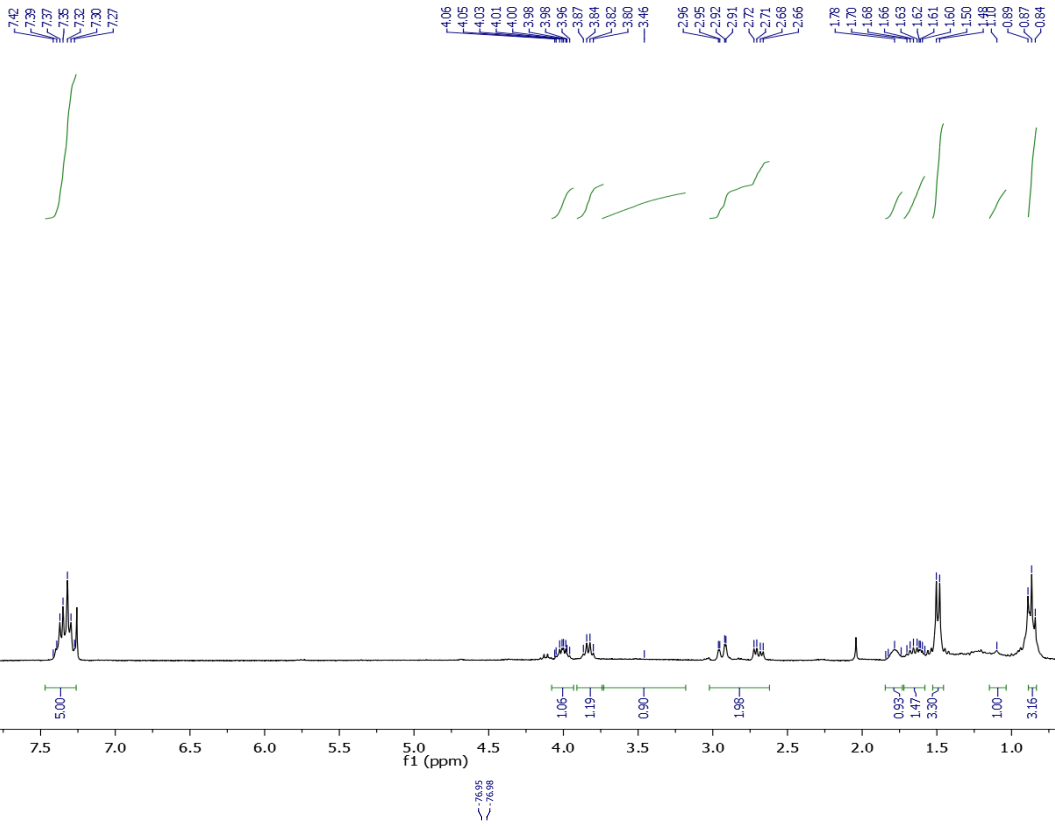


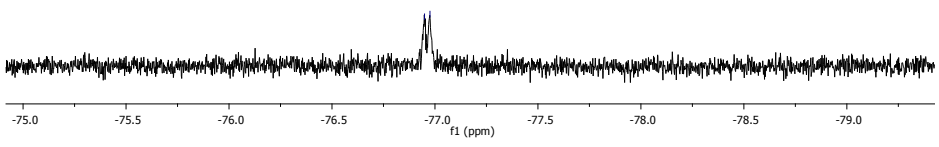


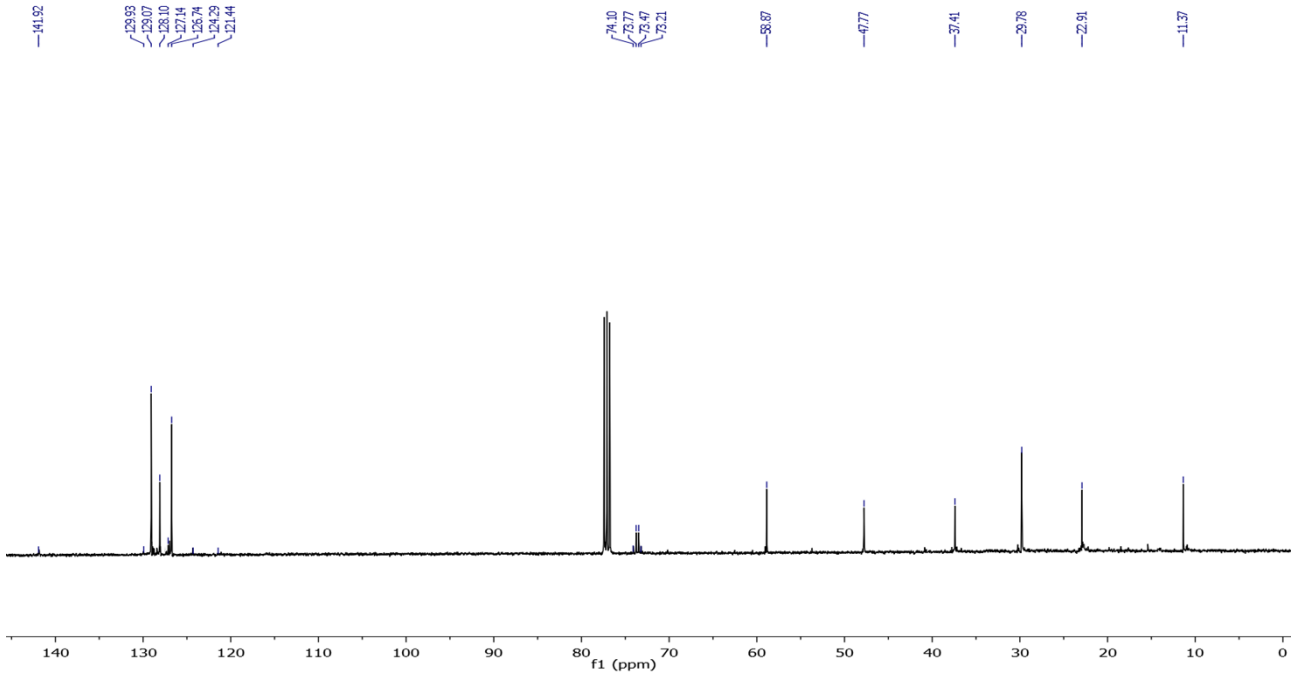
(2*S*,3*S*)-2-Ethyl-4,4,4-trifluoro-3-{[(1*R*)-1-phenylethyl]amino}butan-1-ol (*syn*-9a)



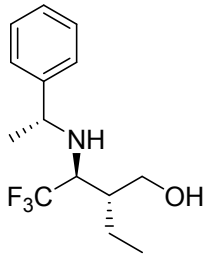
(*S*,*S*,*R*)-**9a**







(2*R*,3*S*)-2-Ethyl-4,4,4-trifluoro-3-((1*R*)-1-phenylethylamino)butan-1-ol (*anti*-9′a)



(*R*,*S*,*R*)-**9'a**