Supplementary Material (ESI) for Chemical Communications


# Electronic Supplementary Information (ESI)

## *In Tube* Determination of the Absolute Configuration of α and β-Hydroxy Acids by NMR *via* Chiral BINOL Borates

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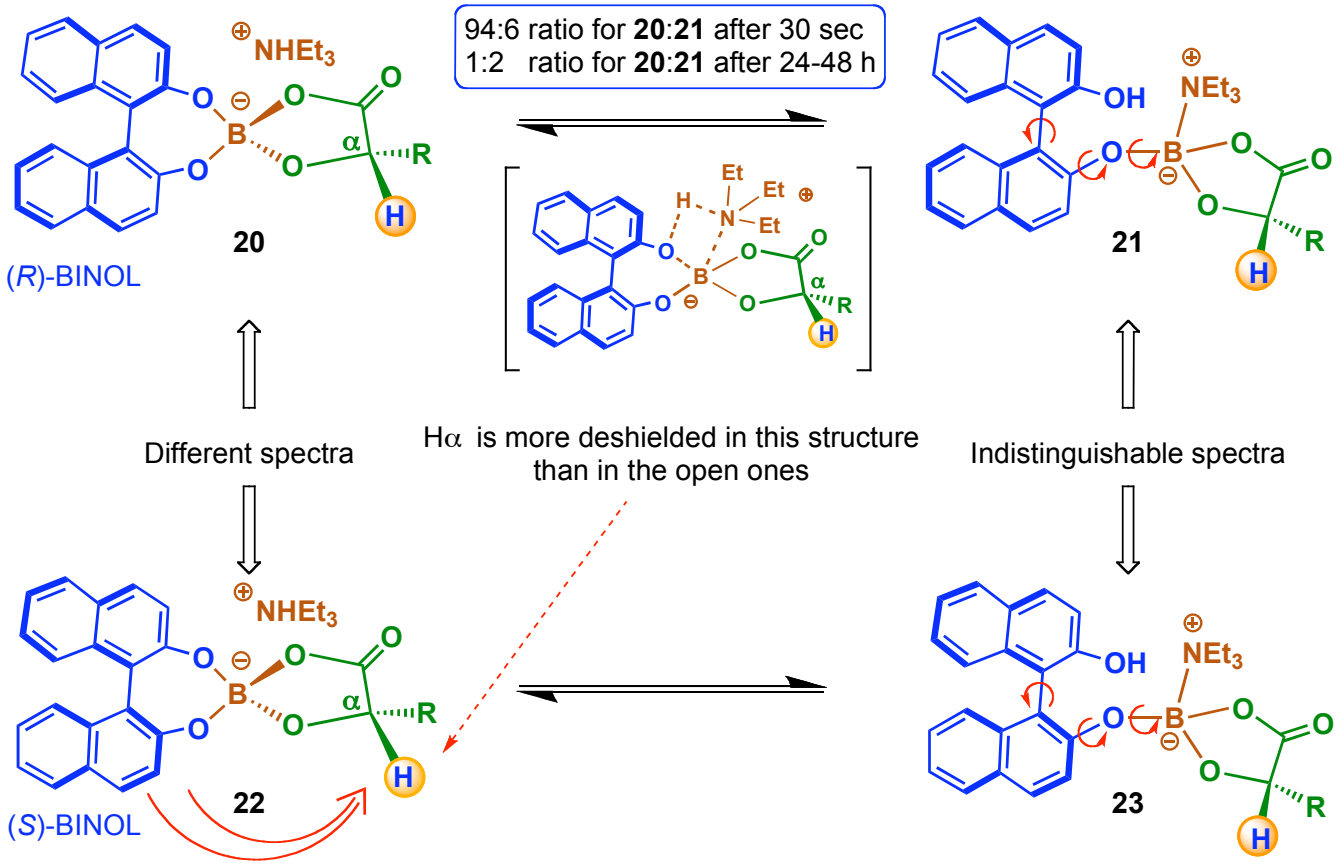
## Time evolution of the BINOL borate complexes

***Scheme 1S.*** Evolution of chiral BINOL borates from kinetic to thermodynamic products.




An interesting aspect of this methodology is the requirement to get the NMR spectrum immediately after addition of the amine. After longer reaction times (equilibration at 24-48 h), the cyclic mixed borates **20** (**22**) (kinetic products) evolve to the "open" borates **21** (**23**) (thermodynamic products) by replacement of one of the naphthol groups by the amine (Scheme 1S). Two diastereomeric "open" derivatives are formed in each case (two for **21** and two for **23**) depending on which naphthol moiety acts as leaving group. In fact, two signals for Hα are visible in the $^{1}$H-NMR spectra when the evolution is monitorized (Figures 1S and 2S). Both types of hydroxy acids (α and β) show this behavior.

The possibility of the carboxylic group acting as leaving group is ruled out on the basis of: a) UV monitoring of the reaction showing the appearance of a free naphthol chromophore;[1] b) CD and c) coupling constants ($^3$J) studies (see below).

Although the equilibrium is in favor of the "open" complexes, NMR monitoring shows that after 30 s approximately, 94% of the compound is still in the cyclic form and only about 4% in the open aminoborates.

Not unexpectedly, the $^1$H-NMR spectra of the open aminoborate complexes **21** and **23** with the (*R*) and (*S*)-BINOL are practically identical and worthless for assignment. In the case of glycolic acid (**13**), the two signals of the diastereotopic methylene group, in the cyclic borate, collapse in a singlet in the "open" form. $^{11}$B-NMR reflects this evolution and shows a small upfield shift from 6.8 to 6.2 ppm pointing to the replacement of one of the oxy substituents by the amine (Figures 1S and 2S).

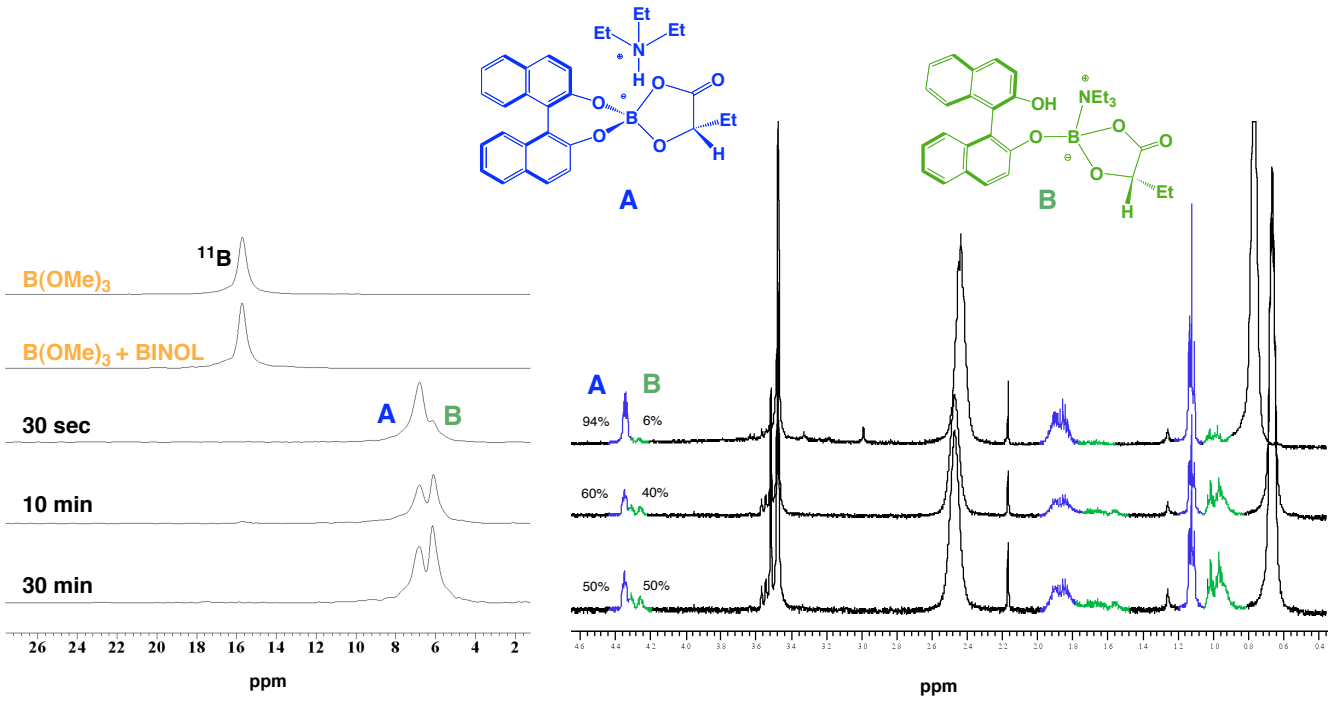



***Figure 1S.*** $^{11}$B and $^1$H-NMR monitoring of the time evolution of the (*R*)-BINOL borate of (*S*)-2-hydroxybutanoic acid (**1**).

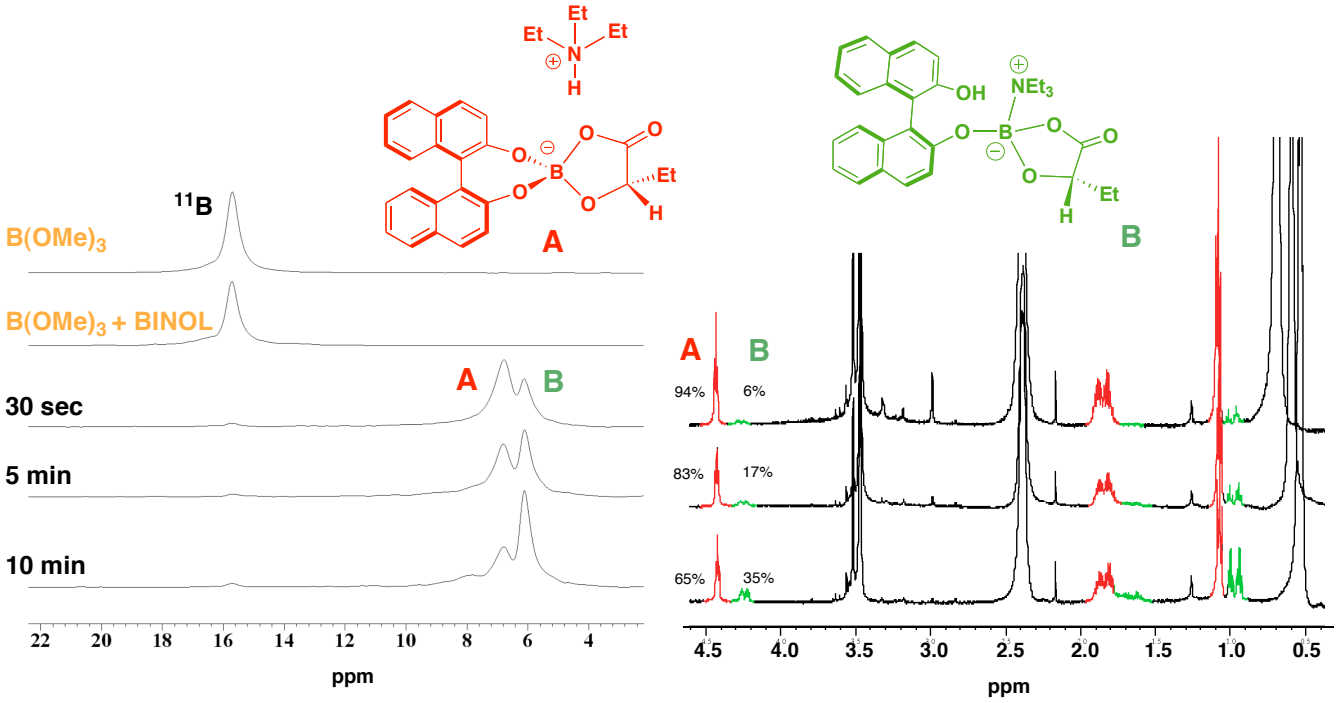



***Figure 2S.*** $^{11}$B and $^{1}$H-NMR monitoring of the time evolution of the (*S*)-BINOL borate of (*S*)-2-hydroxybutanoic acid (**1**).

## CD studies

BINOL[2] and related chiral derivatives of 1,1′-binaphthalene are characterized by strong exciton Cotton effects in the 220–240 nm region, due to the coupling of the naphthalene $^{1}B_b$ electric dipole allowed transitions.

Several spectral parameters, such as the amplitude, the magnitude of the long-wavelength Cotton effect or the wavelength splitting of the exciton Cotton effect are known to be related to the dihedral angle defined by the planes of the two naphthalene chromophores. When formation of boron complexes from BINOL and $B(OMe)_3$ are monitorized by CD, the naphthol band the moves to smaller wavelength and the CD spectrum obtained is similar to that of the reaction of those components together with the hydroxy acid and the amine after 30 s, indicating that BINOL is still attached to the boron atom with similar angles between the naphthyl groups. After 30 min, a new band appears due to the formation of new species that present a different angle between the naphthyl groups, in agreement with the proposed "open" forms (Figures 3S and 4S).

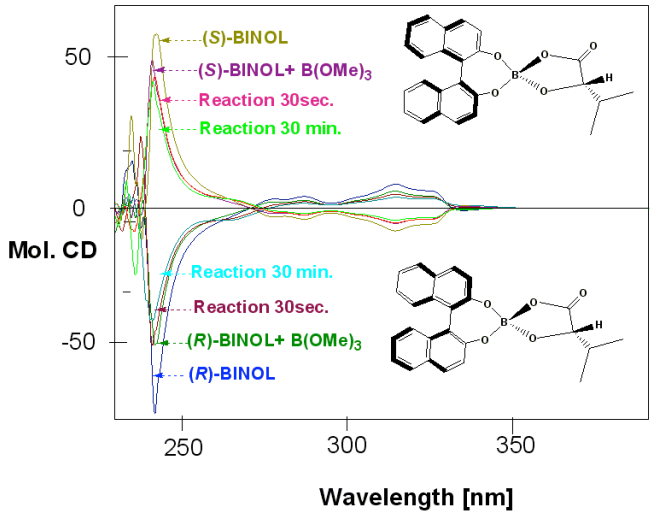



**Figure 3S.** CD monitoring of the BINOL borates of (*S*)-2-hydroxy-3-methylbutanoic acid (**3**).

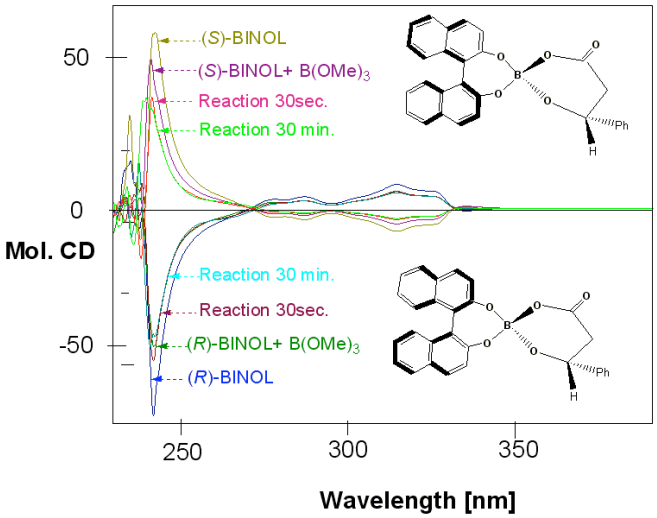



**Figure 4S.** CD monitoring of the BINOL borates of (*R*)-3-hydroxy-3-phenylpropanoic acid (**14**).

## Coupling constants ($^3$J) studies

The coupling constants of β-hydroxy acids ($^3$J) give also information on the evolution of the mixed borates. When the hydroxy acid forms the mixed BINOL borate, the $^3$J values among the methine (Hβ) and the methylene (Hα/Hα') are characteristic for a six member ring. The values are similar in all cases despite the different structures of the R groups, reinforcing the fact that the ring is quite rigid and correspondingly, the diagnostic methine protons are always placed in a fixed spatial location

(independent of R) in relation to the naphthyl rings, thus making this a truthful method in order to assign the configuration (Figure 5S). Models, build using this information, predict anisotropic effects that match the experimental NMR behavior.

In addition, when the kinetic ("close") borates evolve to the thermodynamic ("open" forms), the $^3J$ values keep the same order of magnitude, implying that the hydroxy acid is still part of the ring, thus giving further evidence on the fact that BINOL is the leaving group (Figure 6S).

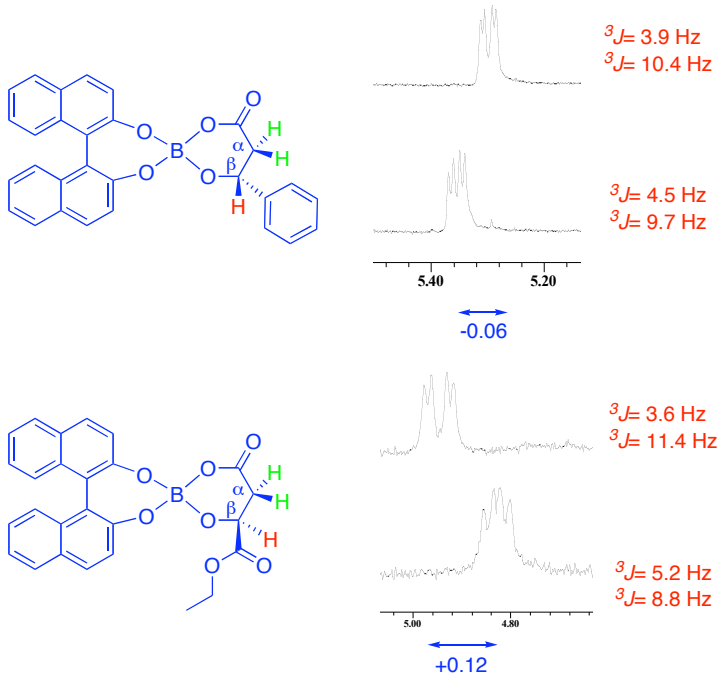



***Figure 5S.*** $^3$J values for the mixed (*R*) and (*S*)-BINOL borates (up and down respectively) of β-hydroxy acids **14** and **18**.

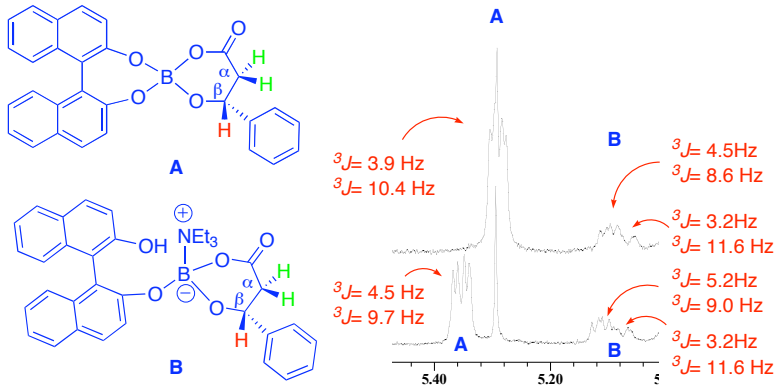



***Figure 6S.*** $^3$J values for the "close" (**A**) and "open" (**B**) forms (left and right respectively) of the mixed (*R*) and (*S*)-BINOL borates (up and down respectively) of β-hydroxy acid **14**.

## Bases tested in this study

The bases tested were triethylamine; pyridine; 2,6-dimethylpyridine; *N*,*N*-dimethylpyridin-4-amine; *N*,*N*-dimethylpyridin-4-amine; 1*H*-pyrrole and bicarbonate. Triethylamine was the base of choice because it gave the best yields of the mixed borates.

## NMR spectroscopy

NMR spectra were recorded at 250 and 500 MHz spectrometers. $^{1}H$ chemical shifts are internally referenced to the TMS signal (0.00 ppm). $^{11}B$ chemical shifts are internally referenced to $B(OMe)_3$ ($BF_3$-$Et_2O$ was not chosen as internal standard because it could interfere with the reaction). *J* values are recorded in Hz. All the compounds reported in this communication are commercially available.

## Notes and references

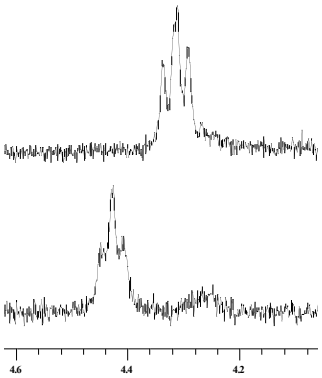
(1) In a complementary set of experiments, a standard NMR sample was submitted to UV monitoring. When a saturated THF solution of t-BuOK was added, the original 270 and 338 nm bands showed a batochromic shift to 344 and 372 nm indicative of the formation of a naphtholate moiety.

(2) (a) L. Di Bari, G. Pesticelli, P. Salvadori, *J. Am. Chem. Soc*. 1999, **121**, 7998. (b) C. Rosini, S. Superchi, H. W. I. Peerlings,E. W. Meijer, *Eur. J. Org. Chem*. 2000, 61.

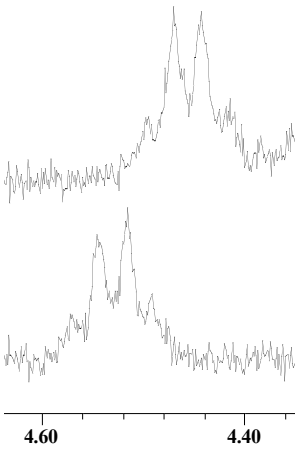
## NMR spectra of complexes of compounds 1-19

Compound number ($\Delta\delta^{RS}$); (*R*)-BINOL complex (up); (*S*)-BINOL complex (down)

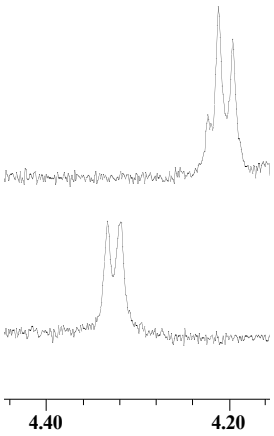
Compound 1 (-0.11)



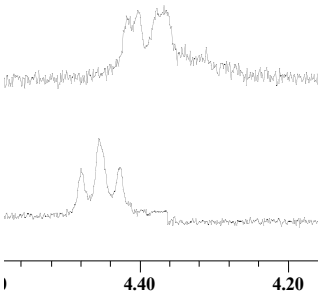

Compound 2 (-0.07)



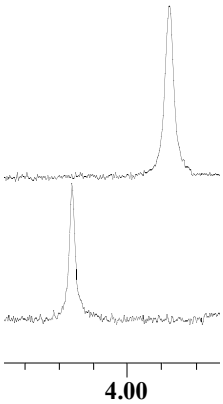
Compound 3 (-0.12)



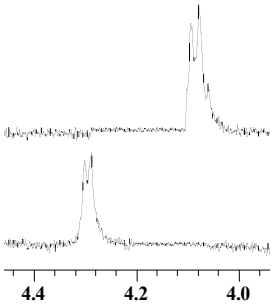

Compound 4 (-0.08)



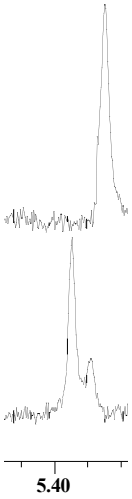

Compound 5 (-0.11)



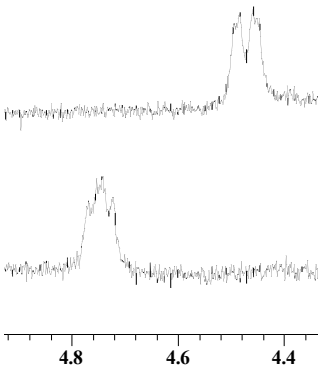
Compound 6 (-0.18)



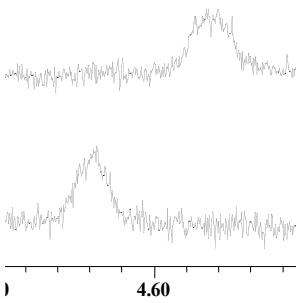

Compound 7 (-0.04)



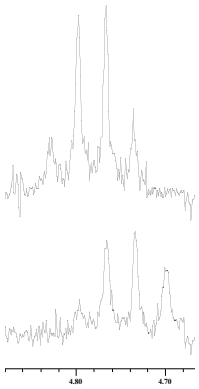

Compound 8 (-0.27)



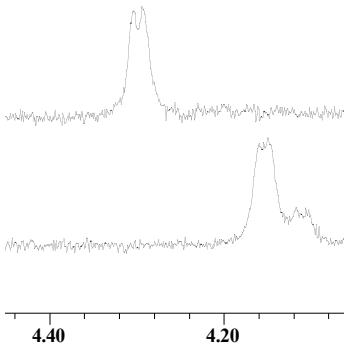
Compound 9 (-0.14)



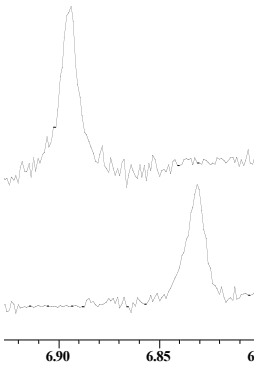

Compound 10 (+0.04)



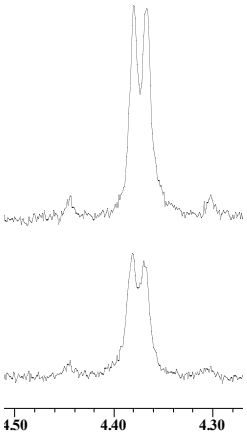

Compound 11 (+0.18)



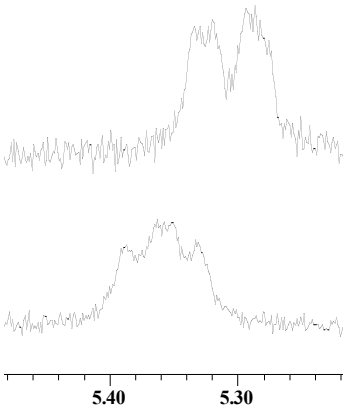
Compound 12 (+0.07)




Compound 13 ( 0.08)




Compound 14 (-0.06)



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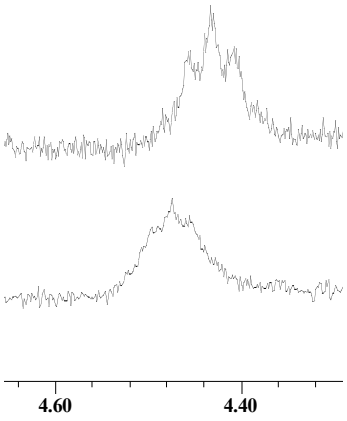


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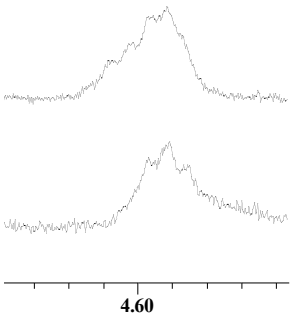
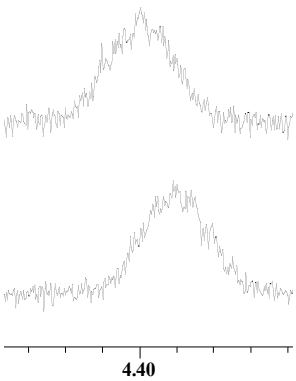
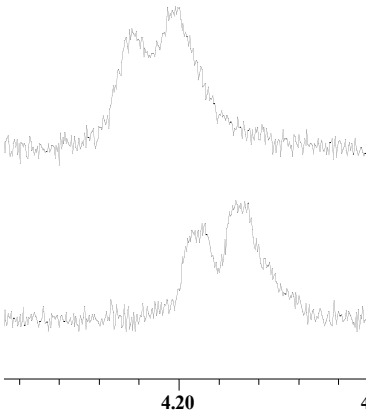



Compound 17 (+0.05)



Compound 18 (+0.12)




Compound 19 (+0.06)