

19F NMR FOR THE STEREOCHEMISTRY ASSIGNMENT OF NEW β -FLUORINATED γ -BUTYROLACTONE DERIVATIVES

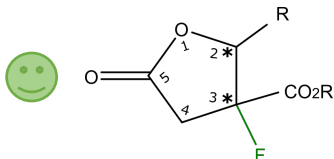
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biologically active molecule



R = n -C₅H₁₁

a: R' = Me

b: R' = Et

paraconic acids

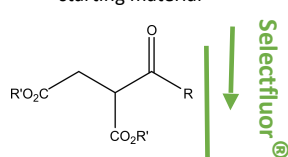
antitumor, antibiotic, antifungal, antibacterial



β -fluorinated paraconic acid derivatives
biological activity under testing

new, easy synthetic route [1]

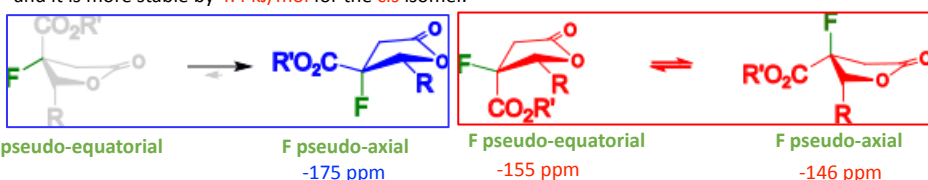
starting material



Selectfluor[®]

Conformational flexibility:

Owing to the rigidity of the ester lactone moiety: two possible envelope conformers for the ring [2] RDKit open access quick conformation generation and MM (MMFF force field) energy minimization [3]: the ring conformations with F pseudo-axial are more stable by 9 kJ/mol (trans) and 0.7 kJ/mol (cis). After DFT geometry optimization the F pseudo axial ring conformer is the only stable one for the trans and it is more stable by 4.4 kJ/mol for the cis isomer.



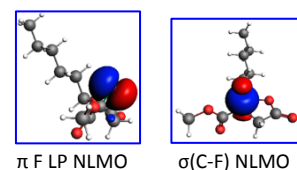
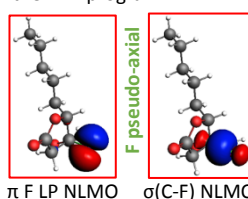
19F shielding calculations

By means of two-component relativistic DFT based on the ZORA Hamiltonian and gauge-including basis functions (GIAOs) implemented in the ADF program

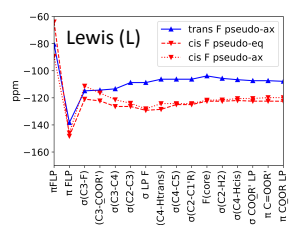
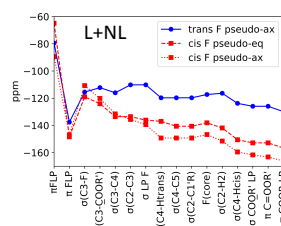
NBO/NLMO analysis of computed 19F nuclear shielding constants [6]

σ_{dia} , as well as the main contributions to σ_{p+SO} , assigned to the F π LP and σ (C-F) orbitals, do not discriminate the cis and trans isomers

At variance with $^3J(F,H)$, of three being only one different, the ^{19}F shift responds sensitively to the relative arrangement (either cis or trans) of R and CO₂R' [5]

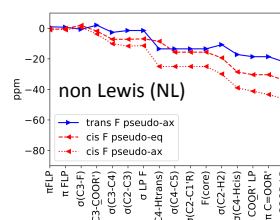


Incremental sums of the various orbital contributions to shielding

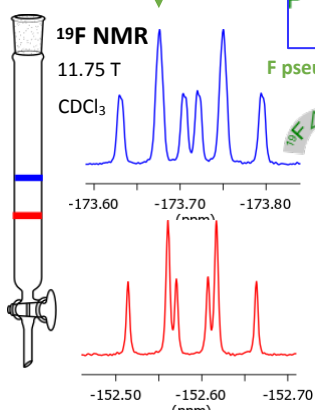


As an overall the ^{19}F nucleus is less shielded in the cis isomer, due to the summing up of a manifold of, both Lewis (L) and non Lewis (NL), minor contributions, with lower magnitudes in the cis than in the trans isomer.

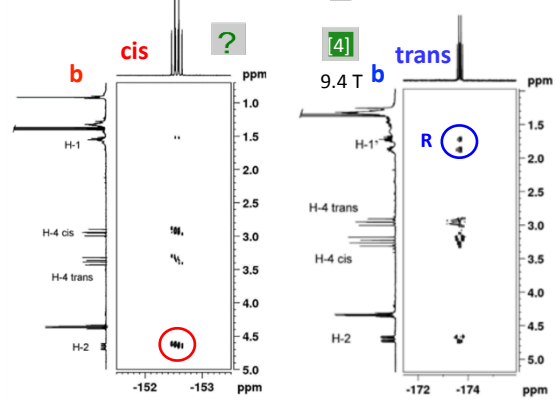
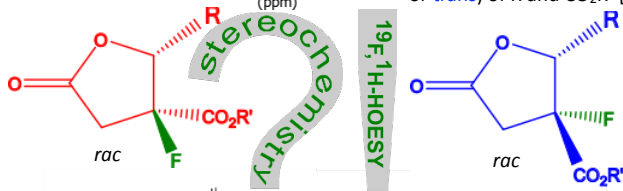
The more delocalized NL ones are sensitive to the ring conformation.



separation of diastereomers by column chromatography



DFT calc



References

[1] F. Asaro, S. Drioli, P. Martinuzzi, P. Nitti, D. Toffoli, S. Zago, and D. Zuccaccia *J. Fluor. Chem.* in press.

[2] C.A. Stortz, and M.S. Maier *J. Chem. Soc. Perkin Trans. 2*, 1832–1836 (2000)

[3] <https://www.rdkit.org>

[4] A. Macchioni, A. Magistrato, I. Orabona, F. Ruffo, U. Rothlisberger, and C. Zuccaccia *New J. Chem.* **27**, 455–458 (2003)

[5] G. Saielli, R. Bini, and A. Bagno *RSC Adv.* **4**, 41605–41611 (2014)

[6] J. A. Bohmann, F. Weinhold, and T. C. Farrar *J. Chem. Phys.* **107**, 1173–1184 (1997)