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^{19}F NMR determination of the C^{20} absolute configuration of C^{21}-fluorinated arylthevinols

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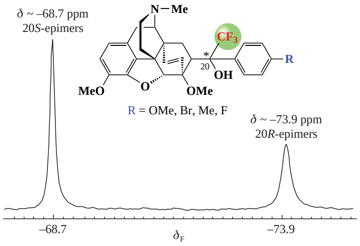
21,21,21-Trifluoro(aryl)thevinols were synthesized by the reaction of 21,21,21-trifluorothevinone with aryl Grignard reagents. The absolute configuration at C^{20} atom in these CF$_3$-substituted alcohols can be easily determined by one-dimensional ^{19}F NMR spectroscopy that was verified by X-ray diffraction studies.



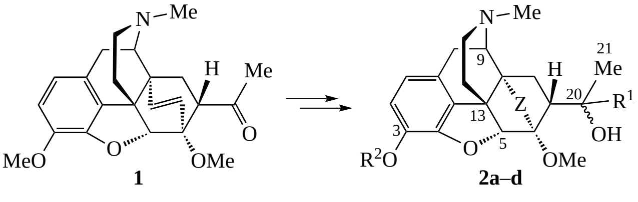
Keywords: thevinone, thevinols, orvinols, alkaloids, organofluorine compounds, Grignard reaction, absolute configuration, ^{19}F NMR.

Thevinone **1**, the Diels–Alder adduct of natural alkaloid thebaine and methyl vinyl ketone,[1] is a key intermediate for preparations of the corresponding alcohols, thevinols **2a**,**b**, and their 3-*O*-demethylated derivatives, orvinols **2c**,**d** (Scheme 1). Several drugs widely used in human and veterinary medicine (buprenorphine, dihydroethorphine, etorphine, diprenophine) are the thevinone derivatives.[2–4]

Organofluorine compounds are gaining increasing importance in various fields of chemistry and material science,[5] one of which is medicinal chemistry. A substitution of fluorine for hydrogen atoms in physiologically active compounds is known to affect both the profile of activity and their efficacy due to the changes in lipophilicity, metabolism, conformational and other properties of the molecules.[6] Therefore, the design of appropriately fluorinated analogues of physiologically active compounds for studying a structure–activity relationship is an important field in medicinal chemistry.

Fluorinated derivatives of thevinols and orvinols have been investigated only sporadically up to date.[7] The situation changed when 21,21,21-trifluorothevinone **3** was prepared.[8] This ketone seems to be promising for the syntheses of the corresponding fluorinated thevinols and their subsequent transformation into the related fluorinated orvinols (*cf*. Scheme 1).

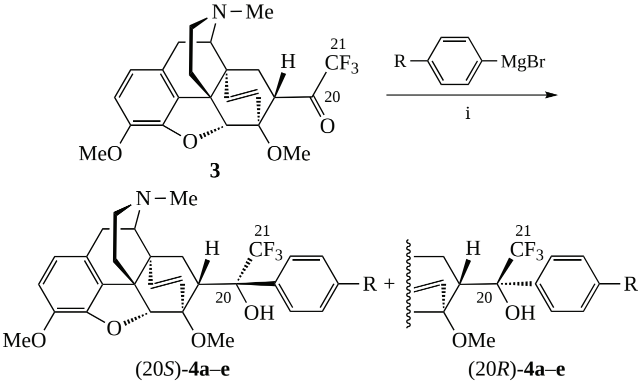
Herein, we report on the preparation of a series of 21,21,21-trifluoro(aryl)thevinols (for the nomenclature, see ref. 9) by the reactions of 21,21,21-trifluorothevinone **3** with 4-RC$_6$H$_4$MgBr (Scheme 2).[†] As one could expect,[2] alcohols **4a**–**d** were formed as 20*S*- and 20*R*-epimer mixtures. The ratios of the epimers were determined from the ratios of the integral intensities of the peaks of the CF$_3$ groups in ^{19}F NMR spectra of the reaction mixtures (Table 1). The major epimers of alcohols **4a**–**e** were isolated by crystallization from methanol in 28–40% yields. Their molecular structures were proved by ^{1}H, ^{13}C and ^{19}F NMR data, HRMS and elemental analysis. Along with the peaks of the morphinan hydrogen atoms exhibiting the characteristic chemical shifts and multiplicity, ^{1}H NMR spectra of compounds **4a**–**e** contained signals for the corresponding C^{20}-positioned 4-substituted aryl groups.



a R^2 = Me, Z = CH=CH
b R^2 = Me, Z = CH$_2$CH$_2$
c R^2 = H, Z = CH=CH
d R^2 = H, Z = CH$_2$CH$_2$

Scheme 1

It should be specially emphasized that the pharmacological activity profiles and the potencies of thevinols and orvinols are known to depend on the absolute configuration of the chiral



a R = OMe
b R = Br
c R = Me
d R = F
e R = H

Scheme 2 *Reagents and conditions*: i, ArMgBr, THF, room temperature, 2 h.

[†] For the synthesis procedures and characteristics of the prepared compounds, see Online Supplementary Materials.

Table 1 Outcome of the reaction between 21,21,21-trifluorothevinone **3** and arylmagnesium bromides.

Product	Yield of 20*S*-epimer (%)	20*S*:20*R* ratio[a]	Epimer δ(CF$_3$)/ ppm[b]		Hydrogen bond in 20*S*-epimer	
			20*S*	20*R*	OH···O/Å	O–H–O (°)
4a	37	4:3	–68.74	–73.98	1.91(5)	137(4)
4b	28	4:1	–68.67	–73.87	1.8635(17)	140.09(12)
4c	40	4:1	–68.63	–73.90	1.8576(15)	156.11(12)
4d	33	4:3	–68.71	–73.97	1.876(3)	138.00(19)
4e[9]	34	4:3	–68.50	–73.61	no data	no data

[a] From the integral intensities ratio of the CF$_3$ peaks in the ^{19}F NMR spectra. [b] Relative to CFCl$_3$.

centre at C^{20} (*cf.* refs. 2, 3, 10–12). Therefore, the determination of the absolute configuration at C^{20} in the epimers of fluorinated alcohols **4a–e** is of importance. The absolute configuration of all chiral centers in thevinols or orvinols can be unambiguously derived from single crystal X-ray diffraction study based on known absolute configuration of natural thebaine molecule. The determination of the absolute configuration at C^{20} in thevinols from NMR data, mainly by comparing ^{1}H–^{1}H coupling and homonuclear NOEs with the theoretical values of H–C–C–H dihedral angles and the interatomic distances calculated for energy minimized rotamers around the C^7–C^{20} bond has also been reported.[13] However, we discovered in this work that in the case of 21,21,21-trifluoro(aryl)thevinols, the absolute configuration at C^{20} can be unprecedentedly simply deduced from the data of conventional 1D ^{19}F NMR spectra. We were pleased to find out that the chemical shifts of the CF$_3$ groups in the ^{19}F NMR spectra of the major isomers of thevinols **4a**–**d** were very close to each other (about –68.7 ppm, see Table 1) and to the chemical shift of the CF$_3$ group in known compound (20*S*)-**4e** (–68.50 ppm) whose absolute configuration has been unequivocally elucidated by X-ray diffraction study.[8] This suggests that, in all these compounds, the CF$_3$ group is in an extremely similar steric environment despite the proximity of the highly anisotropic, in terms of NMR, aryl group and the presence of varying *para*-substituents in it. This is the strong evidence that the 20*S*-epimer of alcohol **4e** and major products **4a–d** have the same absolute configuration of the chiral center at C^{20}. Indeed, the X-ray diffraction study of major epimers of alcohols **4a–d** (Figure 1)[‡] showed that all of them as well as compound (20*S*)-**4e** are 20*S*-epimers. The substituent R at the *para*-position of the aryl group at C^{20} in thevinols **4a–d** has no significant effect on the steric environment of the adjacent CF$_3$ group. In all compounds, the hydroxy group at C^{20} is hydrogen bonded to the oxygen atom of the 6-MeO group, thus fixing the identical conformation of this fragment in the molecules and providing a very similar spatial environment of the CF$_3$ group. The parameters of the hydrogen bonds are given in Table 1. The very close values of the chemical shifts of the CF$_3$ groups in the ^{19}F NMR spectra of compounds **4a–e** indicate that conformations of their molecules are also similar in solution and, therefore, the hydrogen bonds mentioned above are probably retained.

In a similar way, the peaks with chemical shift at about –73.9 ppm in the ^{19}F NMR spectra (see Table 1) are referred to 20*R*-epimers of the alcohols **4a–d**.

In conclusion, the reactions of 21,21,21-trifluorotevinone **3** with aryl Grignard reagents deliver 21,21,21-trifluoro(aryl)-thevinols as the mixtures of C^{20}-epimers enriched with 20*S*-configured ones. An absolute configuration of the chiral center at C^{20} in these compounds can be unprecedented easily deduced from the chemical shift value of the CF$_3$ group in conventional 1D ^{19}F NMR spectrum, which is about –68.7 ppm for the 20*S*-isomers and about –73.9 ppm for the 20*R*-isomers. This situation is profoundly differ from the determination of an absolute configuration of chiral alcohols or amines using Mosher acid (MTPA), PhC(CF$_3$)(OMe)COOH.[14] The Mosher's method

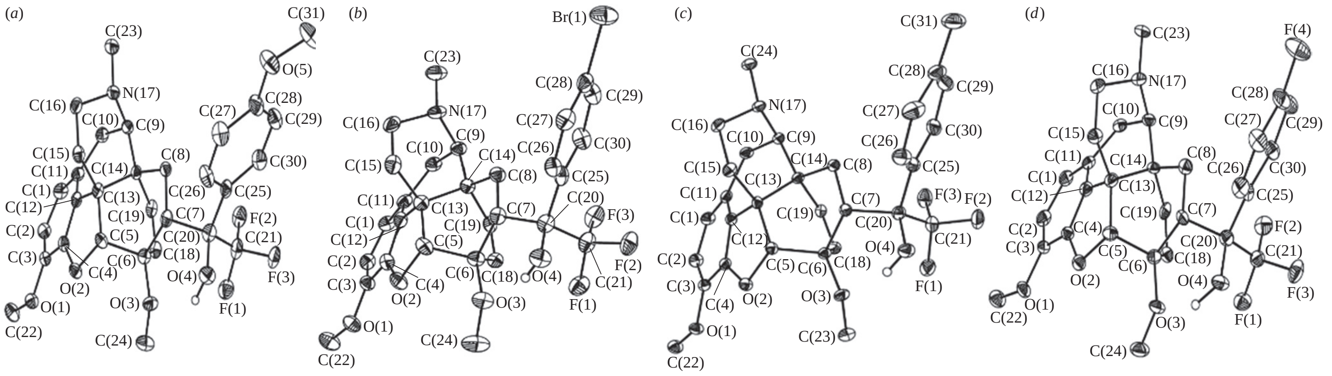


Figure 1 Molecular structures of compounds (*a*) (20*S*)-**4a**, (*b*) (20*S*)-**4b**, (*c*) (20*S*)-**4c**, and (*d*) (20*S*)-**4d**. Thermal ellipsoids are given with 50% probability.

[‡] *Crystal data for* (20*S*)-**4a**. C$_{30}$H$_{32}$F$_3$NO$_5$, *M* = 543.56, monoclinic, space group *P*2$_1$, 120 K: *a* = 8.914(14), *b* = 12.336(18) and *c* = 11.692(16) Å, β = 93.03(4)°, *Z* = 2, *V* = 1284(3) Å^3, μ = 1.09 mm^{-1}, d_{calc} = 1.406 g cm^{-3}, 16383 reflections measured, 7497 independent reflections were used for the structure solution and refinement. Final *R* factors: R_1 = 0.0545 [4029 reflections with $I > 2\sigma(I)$], wR_2 = 0.1069 (all reflections), GOF = 0.939.

Crystal data for (20*S*)-**4b**. C$_{29}$H$_{29}$BrF$_3$NO$_4$, *M* = 592.44, orthorhombic, space group *P*2$_1$2$_1$2$_1$, 120 K: *a* = 9.1057(2), *b* = 11.4867(3) and *c* = 24.5136(5) Å, *Z* = 4, *V* = 2563.99(10) Å^3, μ = 27.00 mm^{-1}, d_{calc} = 1.535 g cm^{-3}, 35878 reflections measured, 4329 independent reflections were used for the structure solution and refinement. Final *R* factors: R_1 = 0.0201 [4292 reflections with $I > 2\sigma(I)$], wR_2 = 0.0564 (all reflections), GOF = 1.068.

Crystal data for (20*S*)-**4c**. C$_{30}$H$_{32}$F$_3$NO$_4$, *M* = 527.56, triclinic, space group *P*1, 120 K: *a* = 7.3665(7), *b* = 8.0075(11) and *c* = 11.3133(11) Å, α = 87.794(3)°, β = 84.653(2)°, γ = 70.923(2)°, *Z* = 1, *V* = 627.92(12) Å^3, μ = 1.07 mm^{-1}, d_{calc} = 1.395 g cm^{-3}, 13492 reflections measured, 7384 independent reflections were used for the structure solution and refinement. Final *R* factors: R_1 = 0.0428 [6574 reflections with $I > 2\sigma(I)$], wR_2 = 0.1069 (all reflections), GOF = 1.035.

Crystal data for (20*S*)-**4d**. C$_{29}$H$_{29}$F$_4$NO$_4$, *M* = 531.53, orthorhombic, space group *P*2$_1$2$_1$2$_1$, 120 K: *a* = 8.8127(14), *b* = 11.8505(18) and *c* = 23.497(4) Å, *Z* = 4, *V* = 2454.0(7) Å^3, μ = 1.15 mm^{-1}, d_{calc} = 1.439 g cm^{-3}, 33139 reflections measured, 7392 independent reflections were used for the structure solution and refinement. Final *R* factors: R_1 = 0.0699 [4197 reflections with $I > 2\sigma(I)$], wR_2 = 0.1385 (all reflections), GOF = 0.978.

CCDC 2088140–2088143 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.

needs the preparations of the esters or amides from an alcohol or amine under investigation and each enantiomer of MTPA. The absolute configuration of the examined molecule is deduced from the positive or negative value of $\Delta\delta = \delta_S - \delta_R$, the difference in chemical shifts between the peaks obtained for the (*S*)- and (*R*)-MTPA esters (amides) in ^{1}H or ^{19}F NMR spectra. In addition, the Mosher's method using ^{19}F NMR lacks in reliability.[15,16] Alternatively, the chemical shifts of the CF_3 groups in epimeric thevinols, theoretically, can be calculated by computational methods. However, computations of ^{19}F NMR parameters are still a challenge because of wide range of ^{19}F chemical shifts and sensitivity to subtle differences in local and electronic environments.[17] As a result, the difference between the calculated and experimental ^{19}F NMR chemical shifts can be 5–6 ppm (see ref. 17). So, the finding reported herein will be useful for a determination of the absolute configuration of C^{20}-substituted 21,21,21-trifluorothevinols and 21,21,21-trifluoroorvinols without using 2D NMR spectroscopy or X-ray diffraction studies.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2022.01.031.

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