Journal of the Serbian Chemical Society
JSCS@tmf.bg.ac.rs • www.shd.org.rs/JSCS
J. Serb. Chem. Soc. *89* (1) 1–11 (2024)
JSCS–5701
Original scientific paper
Published 12 February 2024

Assignment of NMR spectral data of diastereomeric tetrahydrofuranyl acetals directly from their mixture by spectral simulation

MILAN S. NEŠIĆ, MILICA D. NEŠIĆ and NIKO S. RADULOVIĆ*#

Department of Chemistry, Faculty of Science and Mathematics, University of Niš, Višegradska 33, 18000 Niš, Serbia

(Received 14 June, revised 3 August, accepted 27 August 2023)

Abstract: In this study, an NMR spectral analysis of the mixture of diastereomeric acetals, synthesized from 2,3-dihydrofurane and a racemic mixture of citronellol, was performed. ^{1}H-NMR full spin analysis was achieved by manually adjusting δ_H and J values (previously calculated using the Spartan software) to fit the experimentally available values, followed by further optimization using MestreNova software. The simulated ^{1}H- and ^{13}C-NMR spectra of individual diastereomers, as well as their superimposed and summed spectra, were compared with the obtained experimental spectra. Spin simulation of proton signals was particularly useful for the assignment of the diastereotopic protons of tetrahydrofuranyl moiety and diastereomer discrimination. The NMR spectral data of individual diastereomers – chemical shifts, coupling constants, HMBC and NOESY interactions were systematized in appropriate tables and schemes. To the best of our knowledge, this is for the first time that the complete assignment of tetrahydrofuranyl moiety was performed, and the data obtained herein may be of great importance for the utilization of this protecting group in the future.

Keywords: tetrahydrofuran; citronellol; spectral assignment; spin simulation; diastereomers; mixture.

INTRODUCTION

The acetal moiety can be found in many natural, as well as synthetic, organic compounds, thus a lot of research is focused on the development of synthetic procedures for the conversion of alcohols and aldehydes into acetals.[1–3] In addition to being protective groups for alcohols and aldehydes, acetals can also be transformed into a range of other functionalities, making them valuable synthetic intermediates. They can be allylated,[4] undergo substitution,[5–7] and other trans-

* Corresponding author. E-mail: nikoradulovic@yahoo.com
# Serbian Chemical Society member.
https://doi.org/10.2298/JSC230614054N

formations,[8,9] and some, such as tetrahydrofuranyl (THF) and tetrahydropyranyl (THP) acetals,[10–12] can undergo reductive ring cleavage,[13] a synthetically very useful transformation.

Tetrahydrofuranyl (THF) and tetrahydropyranyl (THP) acetals exhibit remarkable stability in the presence of strong bases (*e.g.*, LDA, *terc*-BuOK, HMDS), reducing agents (*e.g.*, H_2/Rh, H_2/Ni, H_2/Pd; $NaBH_4$, $LiAlH_4$, Na/NH_3), organometallics (*e.g.*, RLi, RMgX, RCuLi), certain electrophilic reagents (*e.g.*, RCHO, RX) and specific oxidizing reagents (*e.g.*, $KMnO_4$, OsO_4).[1,2] One of the main advantages of THF and THP acetals, unlike the other alcohol-protecting groups, is their great stability under basic and neutral conditions combined with very easy deprotection under mildly acidic conditions, such as diluted acetic acid in aqueous tetrahydrofuran.[14,15] These can be selectively removed in the presence of other alcohol-protecting groups, such as benzyl ethers, various esters and *t*-butyldiphenylsilyl ethers, which can also be selectively removed using H_2,Pd/C or Na/NH_3,[16,17] basic conditions[1,18] and fluoride-containing reagents,[1,18,19] respectively, the conditions under which THF and THP acetals are stable.[1] These acetals display different reactivity compared to other acetals, such as benzylidene acetals used for diol protection, which can be selectively removed using H_2/ /$Pd(OH)_2$,[16] and dimethyl acetals, which exhibit slightly higher stability under mildly acidic conditions.[20,21] THF acetals also find utility in protecting other functional groups, such as amine and thiol groups in peptides.[22,23] Subtle distinctions in the stability of THP and THF acetals indicate the potential for THF acetals to be hydrolyzed under slightly gentler conditions compared to THP acetals.[14]

Citronellol (**1**, Fig. 1) is an acyclic monoterpene alcohol known for its distinctive rose-like scent, found in the essential oils of various plant species, and valued for its diverse pharmacological activities.[24] It is widely used as a fragrance ingredient in the perfume industry and in formulations targeting mosquito repellency.[25] Derivatives of citronellol, including rose-oxide (**2**, Fig. 1) with a herbal-floral odor, obtained through the photooxidation of citronellol,[26] and acetaldehyde methyl-citronellyl acetal (**3**, Fig. 1) with a refreshing floral-citrus fragrance, obtained through the transacetalization of acetaldehyde dimethyl acetal with citronellol,[27] have also found significant applications in the fragrance industry.

The tetrahydrofuranyl acetal of citronellol is characterized by an intense, warm, floral-honey fragrance reminiscent of the fragrance of linden bee honey.[27] Due to its attractive smell, simplicity of preparation, and stability in neutral and elevated pH environments,[1,2] it can find practical use as a component of a fragrance composition intended for perfuming soaps, detergents, and cosmetics.[27]

Despite such great application and convenience in synthesis and industry, THP and THF acetals are less preferred or even avoided in some cases. One of

the reasons may be that the NMR spectra of these acetals are very complex, especially the part of the spectrum originating from the THF or THP group, which is difficult to analyze. Also, considering that the chemical shifts are around 2 and 4 ppm in the ^{1}H-NMR, and in the range of 20–70 ppm in the ^{13}C-NMR spectrum, they can overlap (^{1}H-NMR) or be very close (^{13}C-NMR) to the signals originating from the rest of the molecule which can make the spectral assignment of these acetals uncertain. In addition, commercially available monoterpene alcohols often represent a mixture of enantiomers, thus the obtained tetrahydrofuranyl acetals of these alcohols will represent a mixture of chromatographically difficult-to-separate diastereomers, due to the newly formed chiral center on the tetrahydrofuran moiety. In order to address primarily the difficulties in the NMR assignment of THF acetals, more specifically those of compound **4** (Fig 1), directly from a mixture of diastereomers, herein we performed a detailed analysis of the corresponding NMR spectra of **4**, and utilizing molecular modeling and spectral simulation tools, this resulted in the complete assignment of ^{1}H- and ^{13}C--NMR spectra of **4**. The data provided could be generally used for the assignments of other THF acetals, significantly facilitating future work on this protecting group.

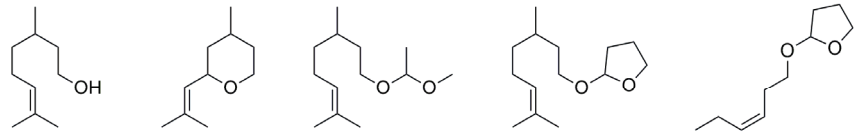

Fig. 1. Citronellol (**1**) and its derivatives: rose oxide (**2**), acetaldehyde methyl-citronellyl acetal (**3**), tetrahydrofuranyl acetal of citronellol (**4**) and tetrahydrofuranyl acetal of *cis*-3-hexen-1-ol (**5**).

EXPERIMENTAL

General procedures

All herein used reagents (citronellol, 2,3-dihydrofuran, *cis*-3-hexen-1-ol, *p*-toluenesulfonic acid) and solvents (hexane and diethyl-ether) were obtained from commercial sources (Sigma–Aldrich; Merck; Carl Roth, Karlsruhe, Germany) and used as received.

Gas chromatography/mass spectrometry (GC/MS) analysis was performed on a Hewlett––Packard 6890N gas chromatograph equipped with a fused silica capillary column DB-5MS (5 % polydiphenylsiloxane, 95 % polydimethylsiloxane, 30 m×0.25 mm, film thickness 0.25 μm; Agilent Technologies, Santa Clara, CA, USA) and coupled with a 5975B mass selective detector from the same company. The injector and interface were operated at 250 and 320 °C, respectively. The oven temperature was raised from 70 to 315 °C at a heating rate of 5 °C/min and then isothermally held for 30 min. As a carrier gas helium was used with a flow of 1.0 ml/min. The samples, 1 μl of the sample solutions in diethyl ether (10 mg dissolved in 1 ml), were injected in a split mode (split ratio 40:1). Mass selective detector was operated at the ionization energy of 70 eV, in the 35–850 amu range and scanning speed of 0.34 s. The relat-

ive abundance of the reaction mixture components was calculated from the peak areas without the use of correction factors. Retention indices (*RI*s) were determined using a mixture of *n*-alkanes from C8−C40. Analytical TLC separations were done on coated Al silica gel plates (Kieselgel 60 F254, 0.2 mm, Merck, Darmstadt, Germany). TLC plates were initially visualized by UV light (254 nm) and then sprayed with 50 mass % aqueous H_2SO_4 followed by heating. Infrared (IR) measurements (attenuated total reflectance) were carried out using a Thermo Nicolet 6700 FTIR spectrometer (Thermo Fisher Scientific, Waltham, MA, USA). Microanalysis of carbon and hydrogen were carried out on a Carlo Erba 1106 microanalyzer (Carlo Erba Strumentazione, Italy). High-resolution mass spectrometry (HRMS) analysis was performed using an MStation JMS-700 mass spectrometer (JEOL, Peabody, MA, USA) with an ionization energy of 70 eV, an ionization trap current of 300 μA, and a source temperature of 230 °C.

The ^{1}H- and ^{13}C-NMR spectra were recorded on a Bruker Avance III 400 MHz NMR spectrometer (Fällanden, Switzerland; ^{1}H at 400 MHz, ^{13}C at 100.6 MHz), equipped with a 5 mm dual ^{13}C/^{1}H probe head. All NMR spectra were recorded at 20 °C in deuterated chloroform with TMS as the internal standard. Chemical shifts (δ) are reported in ppm and referenced to TMS (δ_H = 0.00 ppm) in ^{1}H- and to the (residual) solvent signal in ^{13}C-NMR and heteronuclear 2D spectra (residual $CHCl_3$ δ_H = 7.26 ppm and $^{13}CDCl_3$ δ_C = 77.16 ppm). Scalar couplings are reported in Hz. The sample (30 mg of the acetal mixture) was dissolved in 1 mL of deuterated chloroform, and 0.7 mL of the solution was transferred into a 5 mm Wilmad, 528-TR-7 NMR tube.

Analytical and spectral data of the compounds are given in Supplementary material to this paper.

Synthetic procedure

*Preparation of 2-((3,7-dimethyloct-6-en-1-yl)oxy)tetrahydrofuran (**4**)*. In a flask equipped with a stirrer and a thermometer, 5 g (32 mmol) of citronellol 40 ml methylene chloride, and 0.025 g (0.145 mmol) of *p*-toluenesulfonic acid were added. Then, 2.4 g (35 mmol) of 2,3-dihydrofuran was added dropwise, and stirring was continued for 3 h at room temperature. The reaction mixture was basified with an aqueous solution of Na_2CO_3 and washed with water to pH 8. After drying with anhydrous $MgSO_4$ and removing the solvent under *vacuum*, the residue of 7.5 g (containing about 88 % of **4**, GC–MS analysis) was subjected to purification by silica gel column chromatography using a mixture of hexane and diethyl ether as the eluent. 4.5 g (62 %) of a colorless product was obtained, containing 99 % (GC analysis) of compound **4**, characterized by an intense, warm, floral-honey fragrance.

*Preparation of (Z)-2-(hex-3-en-1-yloxy)tetrahydrofuran (**5**)*. The same procedure was used as described for the preparation of **4**. 3.2 g of *cis*-3-hexen-1-ol was used, and 3.49 g (64 %) of **5** was obtained.

Quantum-mechanical calculations

Conformational search, geometry optimization, and NMR calculation details. Searches for the lowest energy conformers of THF acetals and calculation of the coupling constant were performed using a multi-step conformation method incorporated in Wavefunction's Spartan '20 software. Initially, a maximum number of meaningful conformers are considered, and their energies are calculated using the MM2 force field method (over 4000, in the case of **4**). Then, in subsequent steps, which included the energy calculation and geometry optimization, the energy window was narrowed, leading to a reduction in the number of conformers. Simultaneously, the level of theory is elevated, also using a more complex basis set, and with it the

precision of the calculation increased, ensuring more accurate results (for more details see Supplementary material, Figs. S-14–S-17). The final energy calculations were performed employing WB97X-V density functional with 6-311+G(2DF,2P)[6-311G*] basis set on the pool of around 50 conformers, making up the 99.99 % Boltzmann population. In the first case, referred to as "Spartan-NMR", the energy calculation, geometry optimization, and calculation of coupling constants using the method incorporated in Wavefunction's Spartan 20 software did not account for solvent effects. In the second case, referred to as "Spartan–Karplus" the solvent effects were considered through energy calculations and geometry optimizations, utilizing a method implemented within the software. However, the calculation of coupling constants involved the utilization of a dihedral angle and the incorporation of substituent effects through the modified Karplus equation.[32-34] The copies of the reports from this software, including the Cartesian coordinates for the lowest energy conformers (one per compound), are provided in the Supplementary material (Figs. S-14–S-17). The obtained 3D structures were used in the appropriate figures within the manuscript.

^{1}H-NMR full spin analysis

^{1}H-NMR full spin analysis of tetrahydrofuranyl acetal of citronellol was performed by manually adjusting δ_H and J values to fit the experimentally available values and further optimized using MestReNova 11.0.3 software (tools/spin simulation). This procedure led to a systematic refinement of all calculated NMR parameters until the simulation outcome was in excellent agreement (*NRMSD* < 0.05 %) with the experimental data of the synthesized compounds.

RESULTS AND DISCUSSION

Tetrahydrofuranyl acetal of citronellol (**4**, Fig. 1) was obtained by a modified procedure described in Patent PL224652.[27] The target acetal contains two chiral centers giving rise to 4 possible stereoisomers, two pairs of enantiomers (Fig. 2). The TIC chromatogram, obtained by GC–MS analysis of the isolated product (Supplementary material, Figs. S-7 and S-8), contained two almost completely overlapping peaks – each corresponding to one of the enantiomeric pairs, with a relative ratio of 1:1, based on TIC peak integration. A combination of 1D- and 2D-NMR experiments (Supplementary material, Figs. S-3–S-6), homonuclear selective decoupling experiments were initially employed to perform an approximate assignment of ^{1}H- and ^{13}C-NMR spectra directly from the mixture without any separation.

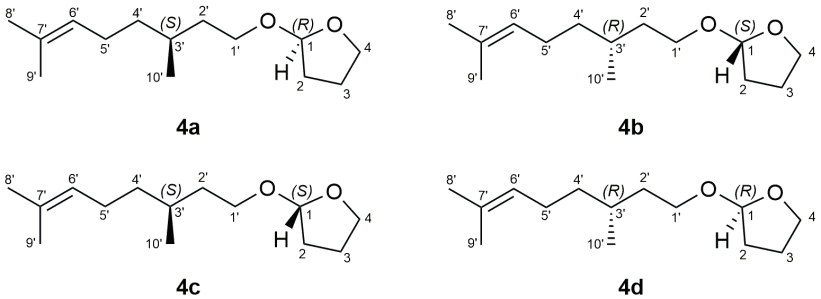

Fig 2. Structures of diastereomeric tetrahydrofuranyl acetals of citronellol.

Calculation of coupling constants and chemical shifts from 3D models has found application in the stereochemical assignment of molecules having complex NMR spectra, or higher order multiplets.[28–31] Unfortunately, the straightforward application is limited to conformationally rigid molecules, due to the fact that in these cases all parameters can be usually calculated based on only one structure/ /conformer. In order to apply such an approach to conformationally flexible molecules, an additional parameter had to be considered - the energy of the conformers, and thus their Boltzmann population, under the assumption that these are in fast equilibrium (see Experimental). Based on these parameters, numerous conformers were selected for each diastereomer, comprising well over 99 % of the total population. Coupling constants were then calculated for these conformers using two different methods. The first method utilized the built-in functionality of Wavefunction's Spartan 20 software (Table I, Spartan-NMR columns), while the second method employed a modified Karplus equation (Table I,

TABLE I. The comparison of the calculated coupling constants of **4** and **5**, and the ones obtained by spin simulation; designations "r" and "s" of hydrogen atoms refer to the prochirality of these hydrogens

J_{H-H}	Tetrahydrofuranyl group (from **5**)			Tetrahydrofuranyl acetal of citronellol (**4**)					
	Spartan--NMR	Spartan–Karplus	Spin simulation	Spartan-NMR		Spartan–Karplus		Spin simulation	
				SS(RR)	SR(RS)	SS(RR)	SR(RS)	SS(RR)	SR(RS)
1 - 2r	6.6	4.5	5	4.7	5.3	4.9	5.7	5.3	5.3
1 - 2s	0.8	1.5	1.5	1.2	0.7	1.3	1.9	0.9	0.9
2r - 3r	12.1	7.8	8.3	13.1	12.6	11.2	7.9	8.3	8.3
2r - 3s	6.2	5.9	10	8	7.3	7.1	8.1	10	10
2s - 3r	2.3	7.6	8.5	7.7	7.7	7.4	8.3	8.5	8.5
2s - 3s	12.2	7.6	4	0	0.5	2.0	4.4	4	4
3r - 4r	10.2	5.8	7.3	10.8	9.4	9.2	8.7	7.3	7.3
3r - 4s	2.2	4.3	5.6	10.3	9.4	9.1	6.1	5.6	5.6
3s - 4r	7.8	5.2	6.2	0.7	1.1	2.4	5.7	6.2	6.2
3s - 4s	9	6.0	7.5	7.6	7.8	9.0	8.8	7.5	7.5
1'r - 2'r	–	–	–	6.1	3.9	6.8	8.2	6.2	7.9
1'r - 2's	–	–	–	1.1	2.2	5.9	3.6	7.9	5.5
1's - 2'r	–	–	–	13.1	12	3.9	4.7	6.2	7.7
1's - 2's	–	–	–	3.8	1.6	6.9	8.1	7.9	6.9
2'r - 3'	–	–	–	4.1	1.5	11.4	8.0	8.5	6.5
2's - 3'	–	–	–	11.4	12.4	4.6	7.2	6.5	8.5
3' - 4'r	–	–	–	12	12.3	10.5	6.0	9.2	6.0
3' - 4's	–	–	–	4	1.7	4.8	7.0	5	6.2
4'r - 5'r	–	–	–	3.5	3.6	4.0	3.9	2.3	5.9
4'r - 5's	–	–	–	4.4	3.2	11.2	11.0	7.6	9.8
4's - 5'r	–	–	–	4.6	3.2	11.2	11.0	7.4	8.1
4's - 5's	–	–	–	13.5	13.1	4.1	4.4	5.6	4.2
5'r - 6'	–	–	–	11.6	4.1	8.2	7.5	7.6	7.6
5's - 6'	–	–	–	5	11.4	8.2	8.0	6.6	6.6

Spartan–Karplus columns).[32–34] In the latter approach, the calculation was based on the dihedral angle obtained from the Spartan software, as well as the attached substituents. The resulting coupling constants were multiplied by the relative abundance of each conformer and summed.

These parameters were employed in the initial spin simulation, which was followed by manual iterative adjustments to accurately reproduce the original ^{1}H--NMR spectrum. However, achieving a complete spin simulation proved challenging due to signal overlap in the ^{1}H-NMR spectrum of compound **4** (protons in positions 3 and 5'). To overcome this, a tetrahydrofuranyl acetal of a non--chiral alcohol, *cis*-3-hexen-1-ol, was synthesized and used for proton assignment of the tetrahydrofuranyl moiety, as in this case, appropriate signals do not overlap (Supplementary material, Figs. S-9–S-13, Table S-II). The chemical shifts and coupling constants, obtained from the spin simulation (Table I and Fig. 3) of ^{1}H--NMR spectrum of this acetal were then utilized in the spin simulation of the tetrahydrofuranyl acetal of citronellol. The coupling constants derived from the calculations were compared to the coupling constants obtained after the iterative adjustments and are presented in Table I.

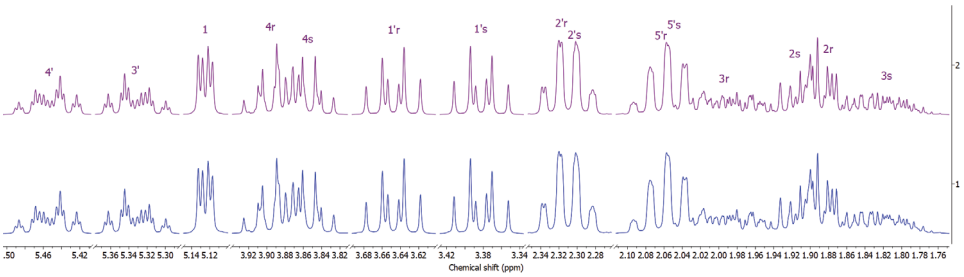

Fig. 3. Upper trace: simulated ^{1}H-NMR (400 MHz) spectrum of **5**; lower trace: ^{1}H-NMR (400 MHz, $CDCl_3$) spectrum of **5**.

Table S-I of the Supplementary material provides the assigned NMR chemical shifts of ^{1}H signals for the tetrahydrofuranyl acetals of citronellol, along with an interpretation of the couplings. The NMR chemical shifts ^{13}C signals, HMBC and NOESY interactions relevant to the assignment are summarized in Table S-I (Supplementary material), while Fig. S-2 (Supplementary material) highlights the key interactions used in the assignment process. The final result of the simulation of ^{1}H-NMR spectrum of the sample confirmed that it consisted of an equimolar mixture of stereoisomers **4a**–**d**.

The differences in chemical shifts and coupling constants between the analogous hydrogens of diastereomers of **4** are small but can be brought into connection with the spatial arrangement of the groups within these molecules. Fig. 4 shows important coupling constants between hydrogens in positions 1' to 5', as well as the appearance of signals of 1' and 4'. The differences in the dihedral

angles between these hydrogens in the highest abundant conformers of each diastereomer (shown in Fig. 4) are in agreement with the value of the couplings obtained by simulation.

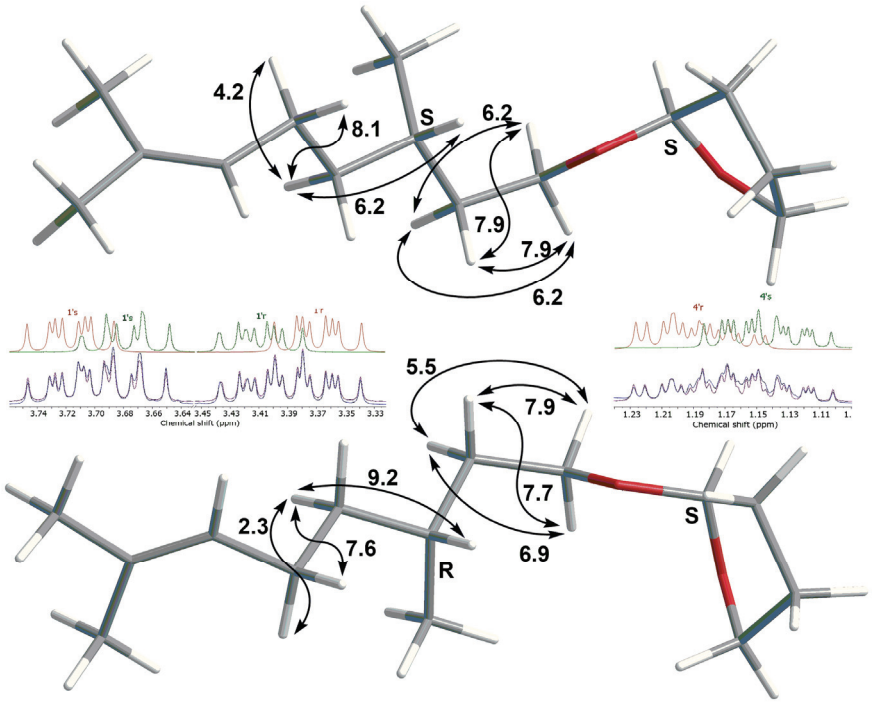

Fig. 4. The most stable conformers of the diastereomerers of **4**. Important coupling constants between hydrogens in positions 1' to 5', and the appearance of signals of 1' and 4'. Upper spectra represent spin simulations, while the bottom ones represent a comparison of the added simulated spectrum and the experimental one.

CONCLUSION

In conclusion, this study successfully performed an NMR spectral analysis of diastereomeric acetals derived from 2,3-dihydrofurane and a racemic mixture of citronellol, as well as corresponding acetal of *cis*-3-hexen-1-ol. Conformational analysis and calculation of coupling constants were done using Spartan software and Karplus equation, followed by manual adjustments to correspond to experimental values, using MestreNova software. Spin simulation of proton signals allowed the assignment of the diastereotopic protons of tetrahydrofuranyl moiety and diastereomer discrimination. The assignment of the tetrahydrofuranyl moiety was achieved for the first time, providing valuable data for the future utilization of this protecting group.

SUPPLEMENTARY MATERIAL

Additional data and information are available electronically at the pages of journal website: https://www.shd-pub.org.rs/index.php/JSCS/article/view/12436, or from the corresponding author on request.

Acknowledgments. This work was supported by the Ministry of Science, Technological Development and Innovation of Serbia (Grant No. 451-03-47/2023-01/200124). This work is a part of the Ph.D. dissertation of Milan S. Nešić under the supervision of Niko Radulović.

ИЗВОД

АСИГНАЦИЈА NMR СПЕКТРАЛНИХ ПОДАТАКА ДИЈАСТЕРЕОМЕРНИХ ТЕТРАХИДРОФУРАНИЛ-АЦЕТАЛА СПЕКТРАЛНОМ СИМУЛАЦИЈОМ ДИРЕКТНО ИЗ ЊИХОВЕ СМЕШЕ

МИЛАН С. НЕШИЋ, МИЛИЦА Д. НЕШИЋ и НИКО С. РАДУЛОВИЋ

Департман за хемију, Природно-математички факултет, Универзитет у Нишу, Вишеградска 33, 18000 Ниш

У овом раду извршена је НМР спектрална анализа смеше дијастереомерних тетрахидрофуранил-ацетала синтетисаних из 2,3-дихидрофурана и рацемске смеше цитронелола. Потпуна ^{1}H-NMR спинска анализа је остварена итеративним подешавањем вредности δ_H и J (израчунатих помоћу софтвера Spartan) до поклапања са експерименталним вредностима коришћењем софтвера MestreNova. Извршено је поређење симулираних ^{1}H-NMR спектара сваког дијастереомера понаособ, као и њихових преклопљених и сумираних спектара са експериментално добијеним спектрима. Спинска симулација сигнала водоника омогућила је асигнацију протона тетрахидрофуранил-групе, као и одређивање релативне конфигурације хиралних центара. Хемијска померања, константе купловања, HMBC и NOESY интеракције систематизовани су у одговарајућим табелама и шемама. Ово је први пут да је извршена потпуна асигнација протона на тетрахидрофуранил-групи, а добијени резултати могу бити од великог значаја за већу будућу примену ове заштитне групе.

(Примљено 14. јуна, ревидирано 3. августа. прихваћено 27. августа 2023)

REFERENCES

1. P. G. M. Wuts, T. W. Greene, *Greene's Protective Groups in Organic Synthesis*, John Wiley & Sons, Inc., Hoboken, NJ, 2006 (https://dx.doi.org/10.1002/0470053488)
2. B. Kumar, M. A. Aga, A. Rouf, B. A. Shah, S. C. Taneja, *RSC Adv.* **4** (2014) 21121 (https://dx.doi.org/10.1039/c4ra02093f)
3. N. S. Radulović, M. S. Nešić, *RSC Adv.* **6** (2016) 93068 (https://dx.doi.org/10.1039/C6RA19980A)
4. M. Barbero, S. Bazzi, S. Cadamuro, S. Dughera, C. Piccinini, *Synthesis* **2** (2010) 315 (https://dx.doi.org/10.1055/s-0029-1217093)
5. H. Fujioka, T. Okitsu, T. Ohnaka, R. Li, O. Kubo, K. Okamoto, Y. Sawama, Y. Kita, *J. Org. Chem.* **72** (2007) 7898 (https://dx.doi.org/10.1021/jo071187g)
6. C. V. T. Vo, T. A. Mitchell, J. W. Bode, *J. Am. Chem. Soc.* **133** (2011) 14082 (https://dx.doi.org/10.1021/ja205174c)
7. L. S. Li, S. Das, S. C. Sinha, *Org. Lett*. **6** (2004) 127 (https://dx.doi.org/10.1021/ol030108u)

8. S. Yoshioka, M. Oshita, M. Tobisu, N. Chatani, *Org. Lett.* **7** (2005) 3697 (https://dx.doi.org/10.1021/ol0513138)
9. L. Lemiègre, R. L. Stevens, J. C. Combret, J. Maddaluno, *Org. Biomol. Chem.* **3** (2005) 1308 (https://dx.doi.org/10.1039/B419381D)
10. A. Fürstner, T. Gastner, *Org. Lett.* **2** (2000) 2467 (https://dx.doi.org/10.1021/ol0061236)
11. A. Robinson, V. K. Aggarwal, *Angew. Chem. Int. Ed.* **49** (2010) 6673 (https://dx.doi.org/10.1002/anie.201003236)
12. N. Hama, T. Matsuda, T. Sato, N. Chida, *Org. Lett.* **11** (2009) 2687 (https://dx.doi.org/10.1021/ol900799e)
13. E. L. Eliel, B. E. Nowak, R. A. Daignault, V. G. Badding, *J. Org. Chem.* **30** (1962) 2441 (https://dx.doi.org/10.1021/jo01018a082)
14. L. J. Lambert, M. J. Miller, P. W. Huber, *Org. Biomol. Chem.* **13** (2015) 2341 (https://dx.doi.org/10.1039/C4OB02212B)
15. E. J. Corey, N. M. Weinshenker, T. K. Schaaf, W. Huber, *J. Am. Chem. Soc.* **91** (1969) 5675 (https://dx.doi.org/10.1021/ja01048a062)
16. H. Kusama, R. Hara, S. Kawahara, T. Nishimori, H. Kashima, N. Nakamura, K. Morihira, I. Kuwajima, *J. Am. Chem. Soc.* **122** (2000) 3811 (https://dx.doi.org/10.1021/ja9939439)
17. T. Mukaiyama, I. Shiina, H. Iwadare, M. Saitoh, T. Nishimura, N. Ohkawa, H. Sakoh, K. Nishimura, Y.-I. Tani, M. Hasegawa, K. Yamada, K. Saitoh, *Chem. Eur. J.* **5** (1991) 121 (https://dx.doi.org/10.1002/(SICI)1521-3765(19990104)5:1<121::AID-CHEM121>3.0.CO;2-O)
18. J. D. Winkler, M. B. Rouse, M. F. Greaney, S. J. Harrison, Y. T. Jeon, *J. Am. Chem. Soc.* **124** (2002) 9726 (https://dx.doi.org/10.1021/ja026600a)
19. G. Stork, A. Yamashita, J. Adams, G. R. Schulte, R. Chesworth, Y. Miyazaki, J. J. Farmer, *J. Am. Chem. Soc.* **131** (2009) 11402 (https://dx.doi.org/10.1021/ja9038505)
20. B. Liu, S. Thayumanavan, *J. Am. Chem. Soc.* **139** (2017) 2306 (https://dx.doi.org/10.1021/jacs.6b11181)
21. S. J. Danishefsky, J. J. Masters, W. B. Young, J. T. Link, L. B. Snyder, T. V Magee, D. K. Jung, R. C. A. Isaacs, W. G. Bornmann, C. A. Alaimo, C. A. Coburn, M. J. di Grandi, *J. Am. Chem. Soc.* **118** (1996) 2843 (https://dx.doi.org/10.1021/ja952692a)
22. I. Ramos-Tomillero, H. Rodriguez, F. Albericio, *Org. Lett.* **17** (2015) 1680 (https://dx.doi.org/10.1021/acs.orglett.5b00444)
23. 23. A. Sharma, I. Ramos-Tomillero, A. El-Faham, E. Nicolas, H. Rodriguez, B. G. de la Torre, F. Albericio, *ChemistryOpen* **6** (2017) 168 (https://dx.doi.org/10.1002/open.201600156)
24. P. L. Santos, J. P. S. C. F. Matos, L. Picot, J. R. G. S. Almeida, J. S. S. Quintans, L. J. Quintans-Júnior, *Food Chem. Toxicol.* **123** (2019) 459 (https://dx.doi.org/10.1016/j.fct.2018.11.030)
25. W. S. Hsu, J. H. Yen, Y. S. Wang, *J. Environ. Sci. Health., B* **48** (2013) 1014 (https://dx.doi.org/10.1080/03601234.2013.816613)
26. N. Monnerie, J. Ortner, *J. Sol. Energy Eng.* **123** (2001) 171 (https://dx.doi.org/10.1115/1.1354996)
27. Jozef Kula, Aleksandra Wojciechowska, PL224652 (2017)
28. N. S. Radulović, S. I. Filipović, M. S. Nešić, N. M. Stojanović, K. V. Mitić, M. Z. Mladenović, V. N. Randelović, *J. Nat. Prod.* **83** (2020) 3554 (https://dx.doi.org/10.1021/acs.jnatprod.0c00585)

29. N. S. Radulović, M. Z. Mladenović, N. M. Stojanović, P. J. Randjelović, P. D. Blagojević, *J. Nat. Prod.* **82** (2019) 1874 (https://dx.doi.org/10.1021/acs.jnatprod.9b00120)
30. N. Radulović, M. Stevanović, M. Nešić, N. Stojanović, P. Ranelović, V. Ranelović, *J. Nat. Prod.* **83** (2020) 2902 (https://dx.doi.org/10.1021/acs.jnatprod.0c00437)
31. M. Nesic, N. Radulovic, *Facta Univ., Ser.: Phys., Chem. Technol.* **19** (2021) 69 (https://dx.doi.org/10.2298/FUPCT2102069N)
32. H. Gunther, *NMR Spectroscopy; Basic Principles, Concepts and Application in Chemistry Third Edition*, Wiley-VCH, Weinheim, 2013 (ISBN: 978-3-527-33000-3)
33. C. A. G. Haasnoot, F. A. A. M. de Leeuw, C. Altona, *Tetrahedron* **36** (1980) 2783 (https://dx.doi.org/10.1016/0040-4020(80)80155-4)
34. L. A. Donders, F. A. A. M. De Leeuwt, C. Altonaz, *Magn. Reson. Chem.* **27** (1989) 556 (https://dx.doi.org/10.1002/mrc.1260270608).