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Application of $[Mo_2(OAc)_4]$ for Determination of Absolute Configuration of Pyranoid and Furanoid *vic*-Diols by Circular Dichroism

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Abstract: The in situ complexes of $[Mo_2(OAc)_4]$ with vic-diols obtained from monosaccharides gave CD spectra suitable for determination of absolute configuration in this group. Positive (negative) torsional angle in the O-C-C-O moiety leads to a positive (negative) Cotton effect at around 300 nm. This rule was also extended to vic-diols containing an amino group in the same molecule. Protection of the amino group as a carbamate inhibits the formation of a chiral complex with the NH_2 moiety and enables determination of absolute configuration of the diol fragment.

A circular dichroism (CD) spectrum is tightly connected with absorption of light. Thus, alcohols, amines, aminoalcohols, ethers etc. can not be investigated by CD because no absorption appears in the accessible spectral range down to 220 nm. One of the possibilities for analysing these compounds is to introduce a suitable chromophore by complexing with a metal cluster. This technique was established some years ago[1] with transition metal complexes of general formula $[M_2(O_2CR)_4]$ which can serve as chromophores capable of manifesting the chirality of optically active molecules added to a metal core. These complexes can either exchange their achiral ligand(s) for chiral one(s) or add the chiral molecule(s) to the axial position of the metal cluster. This addition or exchange of ligands gives rise to circular dichroism within the absorption bands of the metal core and the CD obtained depends on the chirality of the ligand applied. For this purpose dimolybdenum tetraacetate $[Mo_2(OAc)_4]$ was first employed[1,2]. It was found that $[Mo_2(OAc)_4]$, due to its low acceptor strength in the axial position[3], forms optically active complexes only by ligand exchange reactions with bidentate ligands such as carboxylic acids, diols, aminoalcohols, and others[4]. The great advantage of this bidentate bonding is that flexible molecules like e.g. aliphatic ones will form only single conformers which often have a large Cotton effect facilitating the interpretation of the CD spectra.

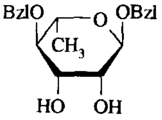
The molybdenum *in situ* complexes with *vic*-diols show several Cotton effects (CE's) between 650 and 250 nm. Among them the most suitable for the absolute configuration determination appear around 400 (band II), 350 (band III) and 300 (band IV). As has been shown with many *vic*-glycols of rigid conformation[4] positive (negative) torsional angle in the O-C-C-O moiety leads to a positive (negative) CE at around 300 nm in the instance when the absolute value of this angle is ca ±60°. The same rule was successfully applied for diols in the sugar pyranoside series[5].

In order to assess the scope and limitation of the aforementioned rule we decided to explore some other examples of *vic*-diols. In this paper we describe the chiroptical properties of *in-situ* complexes formed from [$Mo_2(OAc)_4$] and sugar glycols with pyranose as well as furanose ring forms. Moreover, some derivatives of pyranose are substituted with halogen which influence the electronic transitions. Furthemore, in order to prove the applicability of the *in situ* method to *vic*-diols having an additional group or groups capable to form complexes with the Mo-cluster, we have also examined several amino sugars.

Results and discussion

A. Pyranoside glycols.

The rhamnopyranoside *vic*-diol **1** in the presence of [$Mo_2(OAc)_4$] gives a strong positive Cotton effect around 310 nm (band IV), which is consistent with the positive sign of the torsional angle of the diol unit. The CE of the band II of about 25% of band I magnitude and the same positive sign is observed at around 380 nm. In this case a negative band III CE appearing in the spectrum at ca. 360 nm can only be seen as a very small positive minimum between two distinct maxima due to the presence of an axial RO group next to the glycol moiety (at C-1)[5]. The shape of the CD curve for **1** as well as its magnitude differs from that described earlier for L-rhamnopyranosides[5]. However, the positive sign of the band IV is consistent with the positive sign of the torsional angle of the diol unit und thereby fulfills the helicity rule proposed for *vic*-diols (**Fig. 1**).



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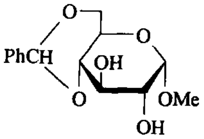

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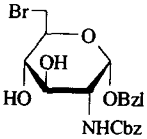

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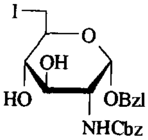

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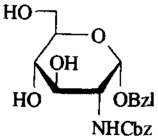

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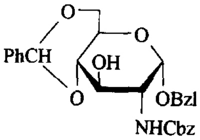

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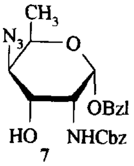

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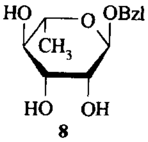

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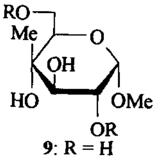


9: R = H
10: R = Bzl

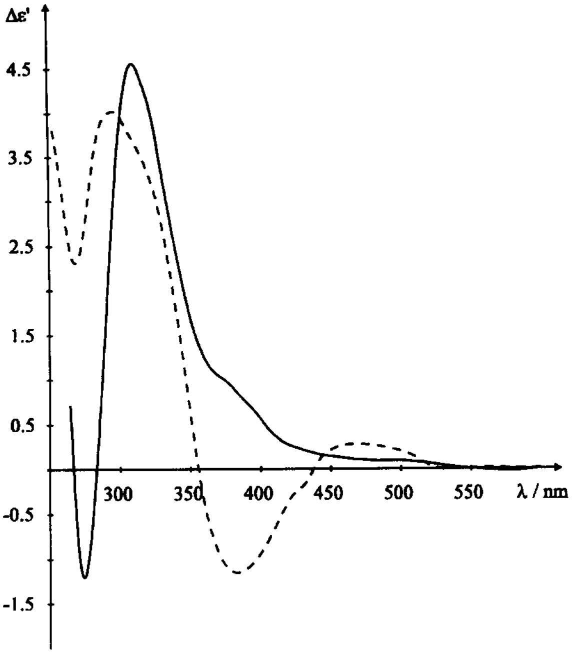


Fig. 1: CD spectra of *in situ* complexes of **1** (———) and **8** (– – – –) with [Mo$_2$(OAc)$_4$].

The CD of the compound **2** with diequatorial hydroxyl groups in the 2,3-diol unit is similar to that of **1** (**Fig.2**). The negative band III CE is only clearly visible as a positive minimum between two maxima present at around 380 (band II) and 310 nm (band IV). This is also in accord with the aforementioned regularity that with the presence of at least one axial C-O bond next to the glycol unit (at C-1) this band is too small to circumvent the positive contributions of the neighbouring bands and cannot be seen as a negative band. For **2**, the positive sign of the CE IV reflects correctly the helicity of the diol moiety again (**Fig. 2**).

The CD spectra of the related glucopyranosides: **3** and **4** with [Mo$_2$(OAc)$_4$] are anomalous (**Fig. 2**). In both cases only three CE's, one positive and two with a negative sign, are present: a very weak negative one at around 500 nm (band I), a strong negative one at around 310 nm (band IV) and a positive one at ca. 270 nm (band V). The CD spectrum of compound **5** exhibits a very weak negative CE at ca. 500 nm (band I), a stronger negative one at around 380 nm (band II), a strong negative one at around 310 nm (band IV) and a strong positive one at around 270 nm (band V). Band III CE is seen as a negative maximum at ca. 360 nm. The positive CE band V in compounds **3** - **5**, situated below 280 nm, cannot be taken as characteristic for the glycol complex and seems to be due to the presence of the benzenoid substituents in molecules. The negative sign of the band IV in compounds **3** - **5** is consistent with the negative sign of the torsional angle of the 3e,4e-diol unit present in all three compounds.

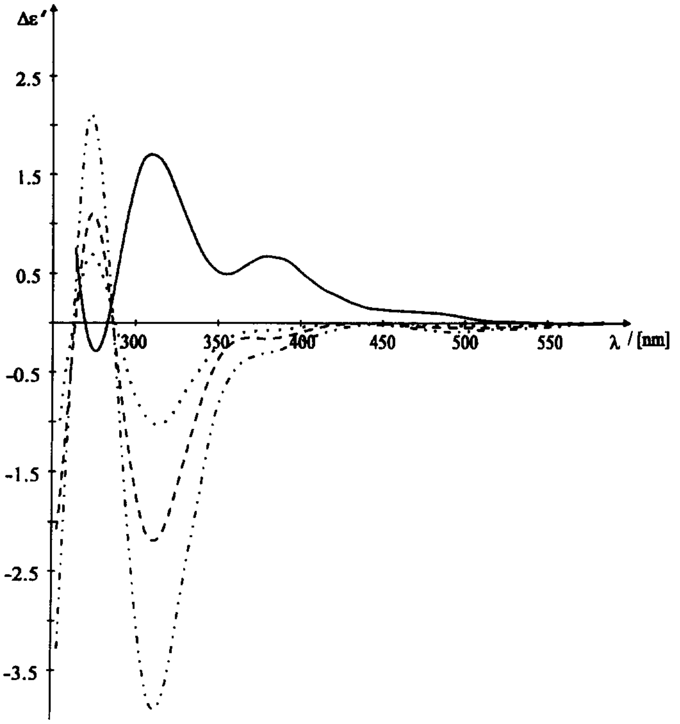


Fig. 2: CD spectra of *in situ* [Mo$_2$(OAc)$_4$] complexes of 2 (———), 3 (— ·· — ··), 4 (············), and 5 (– – – –).

However, in compounds **3** - **5** besides a glycol moiety, a *vic*-aminoalcohol grouping is also present. The amino group is protected as N-benzyloxycarbonyl derivative (Cbz) in order to avoid its complexation. To prove that a protected amino group cannot ligate the Mo-cluster, we have synthesized and investigated compounds **6** and **7** containing the Cbz-protected amino alcohol unit. In neither case did we obtain Cotton effects for the *in situ* Mo-complexes of these compounds. On the basis of this result we can conclude that in compounds **3** - **5** only the 1,2-diol unit ligates the metal core and the Cotton effects obtained reflect exclusively the chirality of the glycol moiety. Band IV with its inversed sign as compared to **1** and **2** is consistent with the expected negative torsion angle and in agreement with the sign predicted by the helicity rule. Bands II and III are no longer visible and thus cannot be assigned. This bad resolution may result from interaction of the chromophoric system with NHCbz or/and halogen-groups, present in **3** and **4**. However, comparing the shapes of the CD curves of compounds containing a halogen atom (**3** and **4**) and the one bearing a C6-OH group (**5**) shows, that the halogen substituent essentially does not influence the spectra (**Fig. 2**).

Since the CD spectra of compounds **3** and **4** measured in DMSO in the absence of the Mo-cluster do not show any CE's in the range 650 - 290 nm, we conclude that the halogen as well as NHCbz-group alone do not contribute to CD in this region.

On the other hand, it is well known that 1,3-diols can also form chiral *in situ* complexes with dimolybdenum tetraacetate[6,7]. However, the measured CD for these complexes are relatively small and thus in the presence of the 1,2-diol grouping the contributions of the 1,3-diol unit to the CD spectrum may be overlooked. This is indeed the case because no special differences in the shape or in the magnitude of the CD curve of compound **5** in comparison to **3** and **4** can be seen.

The rhamnopyranoside derivative **8** contains three hydroxyl groups which can be grouped into two 1,2-diol systems with a common hydroxyl group at C-3, i.e. 2a,3e and 3e,4e, capable of forming different chiral Mo-complexes. For that reason the CD curve obtained is a weighted sum of the CD with the different complex concentrations of all possible complexes formed. Therefore the CD spectrum of this compound can not be used for an unambiguous determination of the absolute configuration of particular pairs of hydroxyl groups, although the positive sign of band IV at 295 nm seems to reflect correctly the chirality of both diol units with positive torsional angles (**Fig. 1**).

In the case of compound **9**, the CD spectrum in the region of 400 - 300 nm exhibits two positive Cotton effects at 384 nm (band II) and 315 nm (band IV). Band III appears at ca 360 nm only as a positive minimum between two distinct maxima mentioned before. This is once again in accord with our finding, that in the pyranoside series the Cotton effect III is strong only for *vic*-glycols if no axial RO group is adjacent to the glycol moiety. In this compound, similarly as in case of **8**, two 1,2-diol units and additionally one 1,3-diol unit are present. All of them are able to form chiral complexes with [Mo_2O_8] core and thus contribute to the CD spectrum. For the 2e,3e-diol with a positive torsion angle, a positive band IV Cotton effect can be expected. For the 3e,4e-diol, due to its negative chirality, a negative band IV should appear. The contributions to the CD spectrum of 1,3-diol grouping may be weak and therefore can be neglected as mentioned before. The positive sign of band IV observed in the spectrum is consistent with the positive chirality of the 2e,3e-diol unit having both hydroxyl groups secondary. The 3e,4e-diol unit with negative torsional angle has a secondary C-3 hydroxyl group and a tertiary one at C-4 and therefore different Cotton effects could be expected in this case, most likely for steric reasons. In order to prove this assumption we have investigated compound **10** bearing a secondary hydroxyl group at C-3 and a tertiary one at C-4. Its CD spectrum, as expected, has a different shape of the CD curve than the *sec,sec*-diols. It shows two, very weak Cotton effects with opposite signs in the region 400 - 300 nm. Although the band IV CE at 308 nm is very weak, its negative sign reflects correctly the chirality of the diol moiety and confirms the helicity rule.

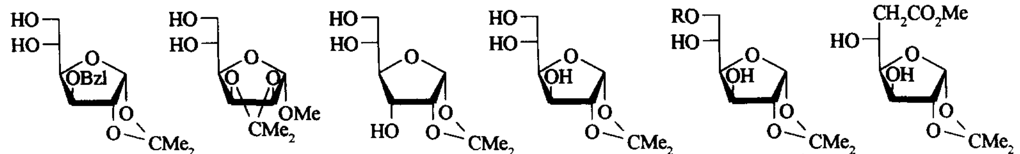
To conclude, one can assume that larger contributions to the CD spectrum in **9** originate from 2e,3e-diol system so that the sign of band IV is in agreement with the sign of the diol's torsional angle.

Table. CD data of the *in situ* complexes of 1,2-diols with $[Mo_2(OAc)_4]$ in DMSO. Values are given as Δε' (λ/nm).

Comp.	Band I λ [nm] (Δε')	Band II λ [nm] (Δε')	Band III λ [nm] (Δε')	Band IV λ [nm] (Δε')	Band V λ [nm] (Δε')
1		376.0 (+0.96)	positive min at ca. 360 nm	309.0 (+4.55)	273.0 (-1.20)
2	490.0 (+0.03)	375.0 (+0.12)	positive min at ca. 340 nm	308.0 (+0.31)	264.0 (+0.12)
3	500.0 (-0.10)			311.0 (-3.62)	272.0 (+2.61)
4	502.0 (-0.03)			312.5 (-0.95)	272.0 (+0.83)
5	499.0 (-0.09)	378.5 (-0.18)	negative max at ca. 355 nm	310.5 (-2.22)	273.0 (+1.14)
6	no Cotton effects				
7	no Cotton effects				
8	460.5 (+0.56)	382.0 (-0.761)		295.0 (+4.54)	
9	507.3 (+0.05)	383.6 (+0.11)	positive min. at ca. 360 nm	315.4 (+0.11)	
10		380.2 (+0.01)		308.2 (−0.07)	
11		373.0 (-0.06)		311.5 (+0.36)	283.0 (-0.21)
12	490.5 (-0.02)	394.0 (+0.05)	339.5 (-0.11)	288.0 (+0.15)	258.5 (+0.28)
13	476.0 (+0.13)	381.5 (-0.33)		307.5 (+0.59)	258.5 (-0.88)
14	464.0 (-0.29)	377.5 (+1.07)		320.5 (-1.02)	285.5 (-0.17)
15	no Cotton effects				
16	no Cotton effects				

B. Furanoside Glycols

The helicity rule correlating sign of the CE at ca. 300 nm with stereochemistry of the ligand can also be applied to *vic-prim,sec*-glycols. For steric reasons their conformation must be fixed so that the torsion angle of O-C6-C5-C4 moiety is about 180° and of O-C6-C5-O around ±60°. These conformational requirements assigned the positive torsional angle O-C6-C5-O for compounds **11** - **14** due to their *R* configuration at C-5. The positive Cotton effect IV obtained for **11** - **13** is in agreement with these assumptions (**Table**, **Fig. 3**). Compound **13** contains two glycol units in the molecule: 1,2-*prim,sec*- at C-5 and C-6 and 1,3-*sec,sec* one at C-3 and C-5. An inspection of Dreiding models as well as the MMX calculations[8] show that in this case hydroxyl groups in the 1,3-diol unit cannot attain *syn*-parallel orientation. For this reason the distance between two hydroxyl groups is too long for formation of a chiral complex and only 1,2-diol unit is responsible for the Cotton effects in the CD spectrum.



11 **12** **13** **14** **15**: R = Bzl **16**: R = Piv **17**

Compound **14** is the only exception in this series which exhibits a negative sign of the Cotton effect at around 300 nm (**Table, Fig. 3**). In this case, however, in accordance with our MMX calculations, the hydroxyl group at C-3 together with the hydroxyl group at C-5 can create a 1,3-diol unit capable of binding to Mo-core. For that reason the CD spectrum of this compound should reflect the contributions of both diol units: 1,2- and 1,3. As it was mentioned before, the contributions of 1,3-diol unit should be much weaker then these of *vic*-glycol. Therefore the CD spectrum of the chiral complex of **14** was expected to be similar to the spectrum of **11**, what was not the case. In order to determine the contributions of a 1,3-diol unit with Mo-core to CD we measured the CD spectra of compounds **15** and **16** containing hydroxyl groups at C-3 and C-5. In both cases, however, the Cotton effects were not observed. Also our earlier studies on this subject have demonstrated that the analogous 1,3-diol unit in another sugar derivative (compound **17**) did not show any Cotton effects[6].

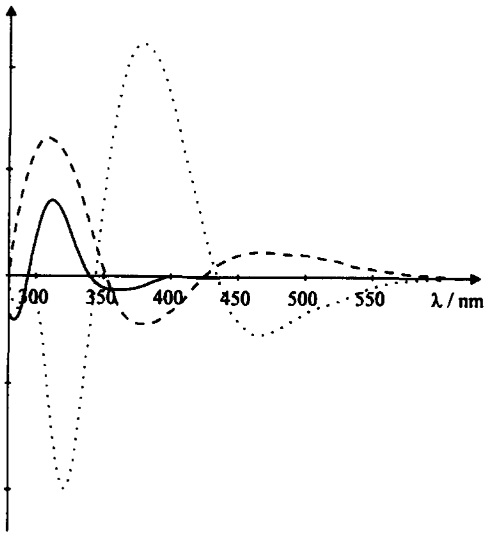


Fig. 3: CD spectra of *in situ* [$Mo_2(OAc)_4$] complexes of **11** (———), **13** (– – – – –), and **14** (· · · · · ·).

Apparently diversion of the sign of the CE IV in compound **14** originates from the specific orientation of hydroxyl groups in the triol system. The only structural difference between compound **13** and **14** is the opposite orientation of hydroxyl groups at C-3. This suggests that complexation between the Mo-core and 1,3-diol unit in **14** occurs. However, the latter is in contradiction to observation that compounds **15** and **16** as well as **17** do not show any CE. At present state we can not explain this discrepancy. Further investigation should be undertaken to explain these phenomena.

Conclusions

The results described here confirm the validity of the helicity rule connecting the sign of the 300 nm Cotton effect (band IV) with the stereochemistry of the *vic*-diols in application to *prim,sec-*, *sec,sec-* as well as to *sec,tert*-diols from pyranoside and furanoside series. Furthermore, the results are consistent with our earlier observation[5] that the 350 nm Cotton effect for the pyranoside series is manifested as a distinct band only in cases when no axial RO-group is present at the atom neighbouring to the glycol moiety. The presence of a halogen atom in the investigated glycol molecule does not influence significantly the CD curve thus making structural studies by this method possible.

Derivatization of an amino group with benzyloxycarbonyl carbamate (Cbz) inhibits the formation of a chiral complex with $[Mo_2(OAc)_4]$ of this group and therefore enables a selective determination of the absolute configuration of 1,2-diol group present in the same molecule.

The circular dichroism of *in situ* complexes of *vic*-diols is a very powerful tool for the determination of the stereochemistry of such systems especially useful when small amounts of the substance are available. An additional advantage of this *in situ* method is, that it allows to avoid derivatization, which is not facile particularly in case of tertiary hydroxyl groups.

Experimental

General methods. CD spectra were measured in DMSO between 650 and 250 nm at room temperature with a Jobin-Yvon ISA dichrograph Mark III or Aviv 62 DS. Data were collected on-line with a PDS-8/e computer (1 or 2 data points per nm), and curve smoothing making use of the Golay - Savitzky algorithm[8]. Depending on the S/N - ratio the λ-scan speed was 0.2 or 0.5 nm/s.

To a stock solution of $[Mo_2(OAc)_4]$ in DMSO, solid diol was added so that the molar ratio of the stock complex to the diol was about 1:0.5 to 1:0.9. As a true concentration of the individual optically active complexes are not known, apparent $\Delta\varepsilon'$ values are given, calculated for the total ligand concentration and assuming 100% complexation.

The solvents were purified and dried according to literature methods. TLC was performed on Silica Gel HF-254 and column chromatography on Silica Gel 230 - 400 mesh (Merck). ^{1}H NMR spectra were recorded with a Bruker AM-500 (500 MHz) and Varian AC-2C0 (200 MHz) spectrometers in dimethylsulfoxide-d_6 (DMSO-d_6) and deuterochloroform ($CDCl_3$) with Me_4Si as internal standard. High resolution mass spectra (HR-MS) were measured with AMD-604 mass spectrometer. Optical rotations were measured with a JASCO DIP-360 automatic polarimeter. Compounds **1**[10], **2**[11], **3**[12], **5**[13], **6**[14], **7**[12], **8**[15], **11**[16], **12**[17], **13**[18], **14**[19], and **15**[20] were obtained according to literature methods.

Benzyl 2-benzyloxycarbonylamino-2,6-dideoxy-6-iodo-α-D-glucopyranoside **4**

A mixture of triphenylphosphine (3.94 g, 15.0 mM), imidazole (2.04 g, 30.0 mM), **8** (4.03 g, 10.0 mM), and toluene (150 mL) was heated to 75°C, and iodine (3.56 g, 28.0 mM) was slowly added. The suspension was stirred for 4 h at the same temperature, cooled and filtered through Celite. The solvents were evaporated to dryness and the gummy residue was extracted with toluene. The combined organic extracts were concentrated. The product was purified by crystallization from ethanol yielding 945 mg (19%) of **4**. Mp. 189 - 190°C; $[\alpha]_D^{20}$ +113.0 (c 1.0, pyridine). ^{1}H NMR (DMSO-d_6), δ 5.34 (d, 1H, $J_{NH,2}$ 5.9 Hz, NH), 5.02 (s, 2H, NHCOOCH_2Ph), 4.80 (d, 1H, $J_{1,2}$ 3.5 Hz, H-1), 4.74 and 4.47 (ABq, 2H, J 12.3 Hz, PhCH$_2$), 5.56 (m, 2H, H-3,4), 3.45 (m, 1H, H-2), 3.05 (m, 1H, H-5), 2.50 (m, 2H, H-6,6'). HR-MS (EI): $C_{21}H_{25}INO_6$ (M+H)$^+$. Calc.: 514.0723. Found: 514.0727.

1,2-O-Isopropylidene-6-O-pivaloyl-α-D-glucofuranose **16**

A mixture of **2** (550 mg, 2.5 mM), pyridine (1 mL), CH_2Cl_2 (5 mL), and pivaloyl chloride (360 mg, 3.0 mM) was stirred at room temp. for 1 h. The solvents were evaporated to dryness. Column chromatography (hexane - ethyl acetate, 1 : 1) of the residue gave 555 mg (73%) of **16**. Mp. 146 - 147°C; $[\alpha]_D^{25}$ -5 (c 1, chloroform). ^{1}H NMR (CDCl$_3$), δ 5.96 (d, 1H, $J_{1,2}$ 3.6 Hz, H-1), 4.55 (d, 1H, H-2), 4.43 (dd, 1H, $J_{6,5}$ 5.3; $J_{6,6'}$ 14.0 Hz, H-6), 4.36 (d, 1H, $J_{3,4}$ 2.7 Hz, H-3), 4.20 - 4.30 (m, 2H, H-5,6'), 4.09 (dd, 1H, $J_{4,5}$ 6.0 Hz, H-4), 1.48 and 1.32 (2s, 6H, CMe$_2$), 1.23 (s, 9H, CMe$_3$). HR-MS (EI): $C_{13}H_{21}O_7$ (M-CH$_3$)$^+$. Calc.: 289.1287. Found: 289.1287.

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Literature

1. Snatzke, G.; Wagner, U.; Wolff, H.P. *Tetrahedron*, **1981,** *37*, 349-361.
2. Frelek, J.; Snatzke, G. *Fresenius J. Anal. Chem.*, **1983**, *316*, 261-264.
3. Cotton, F.A.; Watson, R.A. *Multiple Bonds Between Metal Atoms*, Clarenden Press - Oxford **1993**, pp.139 -243.
4. Frelek, J.; Perkowska, A.; Snatzke, G.; Tima, M.; Wagner, U.; Wolff, H.P. *Pure App. Chem.* **1985**, *57*, 441- 451.
5. Liptak, A.; Frelek, J.; Snatzke, G.; Vlahov, I. *Carbohydr Res.* **1987**, *164*, 149 - 159.
6. Frelek, J.; Pakulski, Z.; Zamojski, A. *J. Carbohydr. Chem.* **1993**, *12*, 625 - 639.
7. Frelek, J.; Snatzke, G.; Szczepek, W.J. *Fresenius J. Anal. Chem.* **1993**, *345*, 683 - 687.
8. PCModel, Serena Software, Bloomington, IN 47402-3076, USA.
9. Ziessow, D. *On-line Rechner in der Chemie*, de Gruyter, Berlin, **1977**, p. 345.
10. Haines, A.H. *Carbohydr. Res.*, **1965**, *1*, 214 - 228.

11. Chittenden, G.J.F. *Rec. Trav. Chim. Pays - Bas,* **1988**, *107*, 607 - 609.
12. Banaszek, A.; Pakulski, Z.; Zamojski, A. *Carbohydr. Res.*, **1995**, *279*, 173 - 182.
13. Heyns, K.; Paulsen, H. *Chem. Ber.*, **1955**, *88*, 188 - 195.
14. Gross, P.H.; Zimmerman Jr, H.K. *Liebigs Ann. Chem.*, **1964**, *674*, 211 - 218.
15. Brimacombe, J.S.; Cook, M.C.; Tucker, L.C.N. *J. Chem. Soc.*, **1965**, 2292 - 2294.
16. Bonini, C.; Di Fabio, R.; Sotgiu, G.; Cavagnero, S. *Tetrahedron,* **1989**, *45*, 2895 - 2904.
17. Evans, M.E.; Parrish, F.W. *Carbohydr. Res.*, **1973**, *28*, 359 - 364.
18. Szarek, W.A.; Zamojski, A.; Tiwari, K.N. Ison, E.R. *Tetrahedron Lett.*, **1986**, *27*, 3827 - 3830.
19. Schmidt, O.T. *Methods Carbohydr. Chem.*, **1963**, *2*, 322.
20. Lubineau, A.; Queneau, Y. *Tetrahedron,* **1989**, *45*, 6697 - 6712.

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