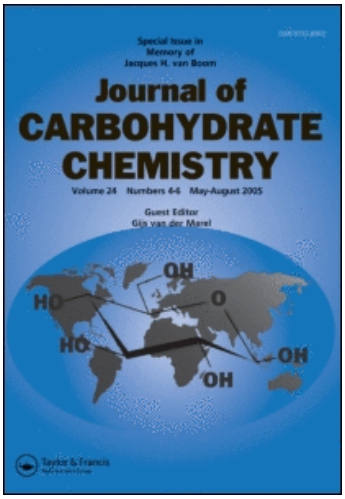

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COMMUNICATION

APPLICABILITY OF THE MOSHER MPTA-ESTER METHODOLOGY TO MONOSACCHARIDES

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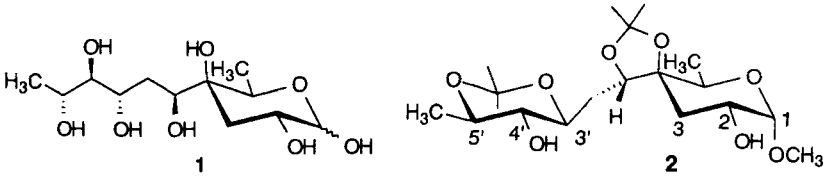
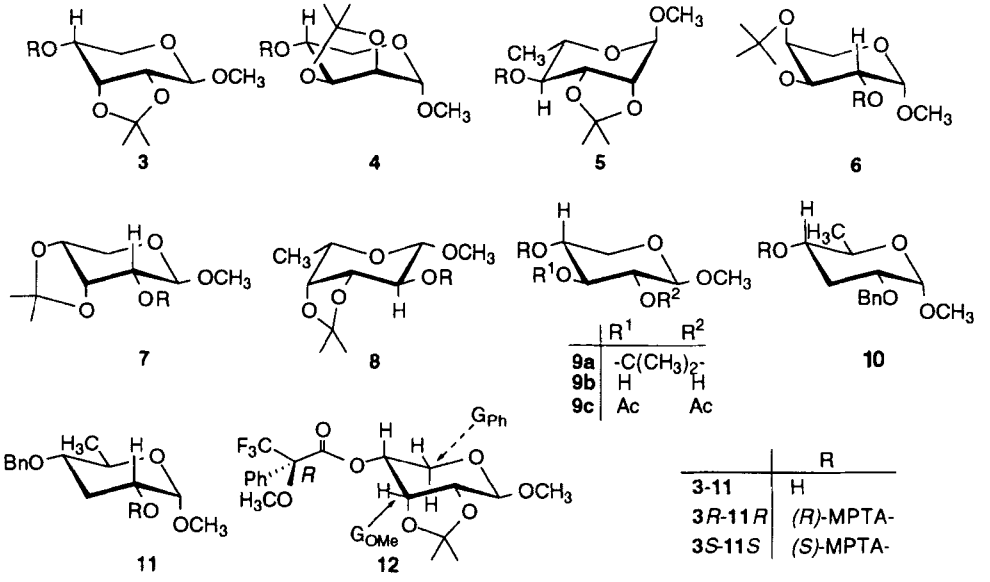
Caryophyllose **1** is a novel twelve carbon 4-C-branched monosaccharide and a component of the polysaccharide chains found in the lypopolysaccharide fraction from *Pseudomonas caryophylli* bacterium.[1] Its absolute stereochemistry was elucidated[2] by applying the exciton chiral coupling method to two fragments obtained by $NaIO_4$ oxidation of the polysaccharide chain. The absolute configuration of a chiral secondary alcohol can be defined by Mosher's method.[3] It analyzes the signs of the differences between the chemical shifts of the protons vicinal to the chiral center in the (*S*)- and (*R*)-α-methoxy-α-trifluoromethylphenylacetate (MPTA) esters obtained from the compound. However, the Mosher ester methodology failed to give completely reliable results when applied to the bisisopropylidene derivative **2** of caryophyllose. In fact, whereas $\Delta\delta_H(\delta_R-\delta_S)$ was positive for 3'-H and negative for 5'-H, indicating *R* configuration for the 4' chiral centre, it was positive for 1-H but of opposite sign for the two protons at C-3 (negative for 3_{eq} and positive for 3_{ax}), failing to indicate the configuration at C-2. This result, however, was in line with Mosher's warning[3] about circumspection in applying his correlation to molecules which "contain additional chiral centres, possess heteroatoms, or show unusual conformational restraints". It also prompted us to an investigation of applicability of Mosher arguments to sugar MPTA esters, in view of our interest in carbohydrate structure elucidation.



To this aim, we prepared a series of (*S*)- and (*R*)-MPTA esters of derivatives with only one esterifiable hydroxyl group of sugars of known absolute configuration. Here we present ^{1}H NMR data showing that chemical shift differences between the protons in proximity of MPTA-esterified carbinol chiral centres of a sugar can be utilized for absolute configurational assignment.



	R^1	R^2
9a	$-C(CH_3)_2-$	
9b	H	H
9c	Ac	Ac

	R
3-11	H
3*R*-11*R*	*(R)*-MPTA-
3*S*-11*S*	*(S)*-MPTA-

EXPERIMENTAL

General. ^{1}H NMR spectra were obtained at 400 MHz with a Bruker AM 400 spectrometer equipped with dual probe, in the FT mode. The ^{1}H chemical shifts were measured in C_6D_6 (δ 7.24).

Preparation of (*R*) and (*S*)-MPTA esters of 3-9a. Isopropylidene derivatives **3**,[4] **4**,[5] **5**,[6] **6**,[7] **7**,[4] **8**,[8] and **9a**[9] of methyl β-D-ribopyranoside, α-D-lyxopyranoside, α-L-rhamnopyranoside, β-L-arabinopyranoside, β-D-ribopyranoside, β-L-fucopyranoside, and β-D-xylopyranoside, respectively, were each converted to both (*S*)- and (*R*)-MPTA esters by the Mosher procedure.[3] ^{1}H NMR data for (*R*)- and (*S*)-MPTA esters (**3*R*-9a*R*** and **3*S*-9a*S***, resp.) are reported in Table 1.

TABLE 1. Proton chemical shifts of compounds **3*R*-11*R*** and **3*S*-11*S*** (400 MHz, C_6D_6)[a]

	3*R*	**3*S***	**4*R***	**4*S***	**5*R***	**5*S***	**6*R***	**6*S***	**7*R***	**7*S***	**8*R***	**8*S***
1	4.51	4.60	4.83	4.76	4.92	4.90	4.85	4.85	4.92	4.80	3.76	3.92
2	4.04	4.02	4.09	4.06	4.11	4.13	5.50	5.48	5.22	5.24	5.59	5.59
3	4.47	4.28	4.16	4.12	4.13	4.16	4.27	4.31	4.44	4.38	3.87	3.80
4	5.52	5.36	5.55	5.50	5.42	5.45	3.74	3.75	3.68	3.67	3.53	3.51
5	3.82 ax	3.86 ax	3.62 eq	3.59 eq	3.73	3.56	3.87	3.89	3.50	3.48	3.23	3.25
	3.66 eq	3.71 eq	3.38 ax	3.57 ax			3.55	3.54	3.40	3.38		
6					1.26	1.13					1.37	1.38
1-OCH_3	3.16	3.17	2.99	3.09	3.03	2.99	3.01	2.93	3.21	3.14	3.23	3.29
Others:												
OCH_3	3.60	3.54	3.53	3.44	3.47	3.66	3.57	3.64	3.60	3.66	3.72	3.66
CH_3	1.16	1.12	1.22	1.19	1.67	1.66	1.22	1.24	1.15	1.18	1.55	1.62
CH_3	1.48	1.36	1.57	1.56	1.24	1.25	1.57	1.56	1.46	1.54	1.25	1.26

	9a*R*	**9a*S***	**9b*R***	**9b*S***	**9c*R***	**9c*S***	**10*R***	**10*S***	**11*R***	**11*S***
1	4.36	4.45	3.82	4.03	4.03	4.17	4.60	4.60	5.04	4.85
2	3.55	3.58	3.27	3.34	5.23	5.21	3.42	3.44	4.93	4.97
3	3.70	3.74	3.56	3.57	5.39	5.32	2.28 ax	2.17 ax	2.12 ax	2.15 ax
							2.52 eq	2.53 eq	2.12 eq	2.28 eq
4	5.29	5.30	5.15	5.12	5.14	5.10	4.83	4.80	2.96	3.01
5	3.97 eq	3.93 eq	3.88 eq	3.85 eq	3.87 eq	3.93 eq	3.81	3.86	3.82	3.84
	3.13 ax	3.30 ax	2.92 ax	3.15 ax	2.86 ax	3.02 ax				
6							1.07	1.22	1.35	1.36
1-OCH_3	3.23	3.25	3.12	3.09	3.20	3.21	3.13	3.13	3.10	3.04
Others:										
OCH_3	3.54	3.43	3.55	3.44	3.47	3.43	3.46	3.41	3.63	3.51
CH_3	1.33	1.33								
CH_3	1.33	1.30								
-O-CH_2-Ph							4.35	4.34	4.29	4.37
							4.30	4.29	4.08	4.16
-$OCOCH_3$					1.72	1.63				
					1.77	1.73				

a. Signals were assigned on the basis of decoupling experiments, values of coupling constants (not reported) and, if necessary, NOE experiments.

Preparation of (*R*) and (*S*)-MPTA esters of Methyl 2-*O*-benzyl-α-D-paratopyranoside (10) and of 4-*O*-benzyl-α-D-paratopyranoside (11). Methyl α-D-paratopyranoside[10] was converted into a mixture of **10** and **11** *via* tributylstannylation with $(Bu_3Sn)_2O$ (0.75 mol, toluene) and treatment with benzyl bromide (3 mol)/tetrabutylammonium bromide (0.5 mol).[11] PLC (silica gel, 7:3 hexane-Et_2O, 2 runs) gave two pure compounds. ^1H NMR of the (*R*) and (*S*)-MPTA esters of the Rf_+ compound showed that the esterification occurred at the 4-position (Table 1, $\delta_{H\text{-}4}$ 4.83 and 4.80 for (*R*) and (*S*)-MPTA ester, resp.), indicating that it was compound **10**. The Rf_- compound was analogously shown to be compound **11** (Table 1, $\delta_{H\text{-}2}$ 4.93 and 4.97 for (*R*) and (*S*)-MPTA ester, resp.).

DISCUSSION

In Table 2 $\Delta\delta_H(\delta_R\text{-}\delta_S)$ values are listed for the protons that are vicinal to the esterified hydroxyl group, each proton being marked G_{Ph} or G_{OMe} depending on its being close to the phenyl group or to the methoxy group in the (*R*)-MPTA ester. The proximity of these groups is based upon a conformation with the CF_3 and the carbonyl groups of the MPTA moiety and the carbinyl hydrogen in a more or less eclipsed arrangement, as assumed by Mosher in his model representation.[3] (See model **12** for compound **3**, as an example.) By applying Mosher's arguments to the sugar derivatives here investigated, $\Delta\delta_H(\delta_R\text{–}\delta_S)$ values should be negative for G_{Ph} protons, which in the *R*-MPTA ester should be shifted to higher field than in the *S*-MPTA ester, and positive for G_{OMe} protons, which in the *R*-MPTA ester should be shifted to lower field than in the *S*-MPTA ester. Actually this is completely true only for compounds **3**, **5**, **6**, **8**, and **11**. Compounds **4**, **7**, and **10** do not fully meet that expectation, since $\Delta\delta_H(\delta_R\text{–}\delta_S)$ is positive for the G_{Ph} proton of compounds **4** and **7** (0.03 and 0.06, respectively) and negative for the G_{OMe} proton of compound **10** (-0.01). However, a more careful inspection of the data in Table 2 shows that for all three compounds, $\Delta\delta_H(\delta_R\text{–}\delta_S)$ for G_{Ph} protons ($\Delta\delta_H^{GPh}(\delta_R-\delta_S)$) is still less positive or more negative than $\Delta\delta_H(\delta_R\text{–}\delta_S)$ for G_{OMe} protons ($\Delta\delta_H^{GOMe}(\delta_R-\delta_S)$). In other words, $\Delta\delta_H^{GPh}(\delta_R-\delta_S)-\Delta\delta_H^{GOMe}(\delta_R-\delta_S)$ is negative not only for **3**, **5**, **6**, **8**, and **11** but also for **4**, **7**, and **10** (see Table 2).

Compound **9a** does not seem to conform even to the statement outlined just above. However, $\Delta\delta_H^{GPh}(\delta_R-\delta_S)-\Delta\delta_H^{GOMe}(\delta_R-\delta_S)$ values are of opposite sign for the two 5-protons (-0.13 and +0.08 for 5-H_{ax} and 5-H_{eq}, respectively) and this precludes us from drawing an incorrect conclusion. On the other hand, the deformation of the pyranoside ring of **9a**, due to *trans* fusion with the isopropylidene ring, constitutes one of the above-mentioned causes of inapplicability of the Mosher method. However, even when the isopropylidene protecting group of **9a** was removed (Amberlite-IR120(H^+), $CHCl_3$) to give **9b**, the observed discrepancy remained. That discrepancy was suppressed only when both 2- and 3-hydroxyl groups were acetylated (Ac_2O, C_5H_5N, 1 h, rt) to give **9c** in order to prevent the free hydroxyl group at the 3-position from distorting by hydrogen bonding the eclipsed arrangement assumed for the MPTA-ester groups. The MPTA-esters of **9c** fully accomplish the Mosher correlation.

In conclusion, the data above seem to indicate that the Mosher correlation can be applied to sugars and, presumably, to other molecules containing several chiral centres or/and heteroatoms on the condition that relative, in place of absolute, shifts of the relevant lines in the NMR spectra of the MPTA-ester pair are considered. The $\Delta\delta_H^{GPh}(\delta_R-\delta_S)-\Delta\delta_H^{GOMe}(\delta_R-\delta_S)$ calculated for **9a** and **9b**, although not leading to erroneous results, warn that conformational restraints as indicated by Mosher must be considered.

TABLE 2. $\Delta\delta_H(\delta_R-\delta_S)$ and $\Delta\delta_H^{GPh}(\delta_R-\delta_S)-\Delta\delta_H^{GOMe}(\delta_R-\delta_S)$ values for protons vicinal to the MPTA-ester groups of compounds **3***R*-**11***R* and **3***S*-**11***S*.

	3		**4**		**5**		**6**	
	proton	$\Delta\delta_H(\delta_R-\delta_S)$	proton	$\Delta\delta_H(\delta_R-\delta_S)$	proton	$\Delta\delta_H(\delta_R-\delta_S)$	proton	$\Delta\delta_H(\delta_R-\delta_S)$
G_{OMe}[a]	3	0.19	3	0.04	5	0.17	1-OCH_3	0.08
					6	0.13	1	0.00
G_{Ph}[a]	5_{ax}	-0.04	5_{ax}	-0.19	3	-0.03	3	-0.04
	5_{eq}	-0.05	5_{eq}	0.03				
$\Delta\delta_H^{GPh}(\delta_R-\delta_S)-\Delta\delta_H^{GOMe}(\delta_R-\delta_S)$	-0.23, -0.24		-0.23, -0.01		-0.20, -0.16		-0.12, -0.04	

	7		**8**		**9a**		**9b**	
	proton	$\Delta\delta_H(\delta_R-\delta_S)$	proton	$\Delta\delta_H(\delta_R-\delta_S)$	proton	$\Delta\delta_H(\delta_R-\delta_S)$	proton	$\Delta\delta_H(\delta_R-\delta_S)$
G_{OMe}[a]	1-OCH_3	0.07	3	0.07	3	-0.04	3	-0.01
	1	0.12						
G_{Ph}[a]	3	0.06	1-OCH_3	-0.06	5_{ax}	-0.17	5_{ax}	-0.23
			1	-0.16	5_{eq}	0.04	5_{eq}	0.03
$\Delta\delta_H^{GPh}(\delta_R-\delta_S)-\Delta\delta_H^{GOMe}(\delta_R-\delta_S)$	-0.01, -0.06		-0.13, -0.23		-0.13, +0.08		-0.22, +0.04	

	9c		**10**		**11**	
	proton	$\Delta\delta_H(\delta_R-\delta_S)$	proton	$\Delta\delta_H(\delta_R-\delta_S)$	proton	$\Delta\delta_H(\delta_R-\delta_S)$
G_{OMe}[a]	3	0.07	3_{ax}	0.11	1-OCH_3	0.06
			3_{eq}	-0.01	1	0.19
G_{Ph}[a]	5_{ax}	-0.16	5	-0.05	3_{ax}	-0.03
	5_{eq}	-0.06	6	-0.15	3_{eq}	-0.16
$\Delta\delta_H^{GPh}(\delta_R-\delta_S)-\Delta\delta_H^{GOMe}(\delta_R-\delta_S)$	-0.20, -0.13		-0.16, -0.04 -0.26, -0.14		-0.09, -0.22 -0.22, -0.35	

a. See text.

In this light, the behaviour of the bisisopropylidene derivative **2** of caryophyllose might be ascribed to the interference between the two ester MPTA-ester groups present in the same molecule.

From the data in Table 1, it could be also observed that the chemical shift differences, for each MPTA-ester pair, between protons farther from the esterified hydroxyl group than those at vicinal groupings cannot provide significant indications about the

absolute configuration of the investigated sugar molecules, probably because the cyclic structure implies a special location in the space of those protons with respect to the function responsible of the differential shifts, not necessarily present in linear molecules. However, our results offer a contribution to the reliability of the Mosher method as one of the most popular procedures for assigning absolute configuration of secondary alcohols.

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