Pergamon

Tetrahedron, Vol. 52, No. 32, pp. 10785-10798, 1996

0040-4020/96 $15.00 + 0.00

PII: S0040-4020(96)00600-X

An Efficient Approach to Partially O-Methylated α-D-Mannopyranosides Using Bis-*tert*-butyldiphenylsilyl Ethers as Intermediates

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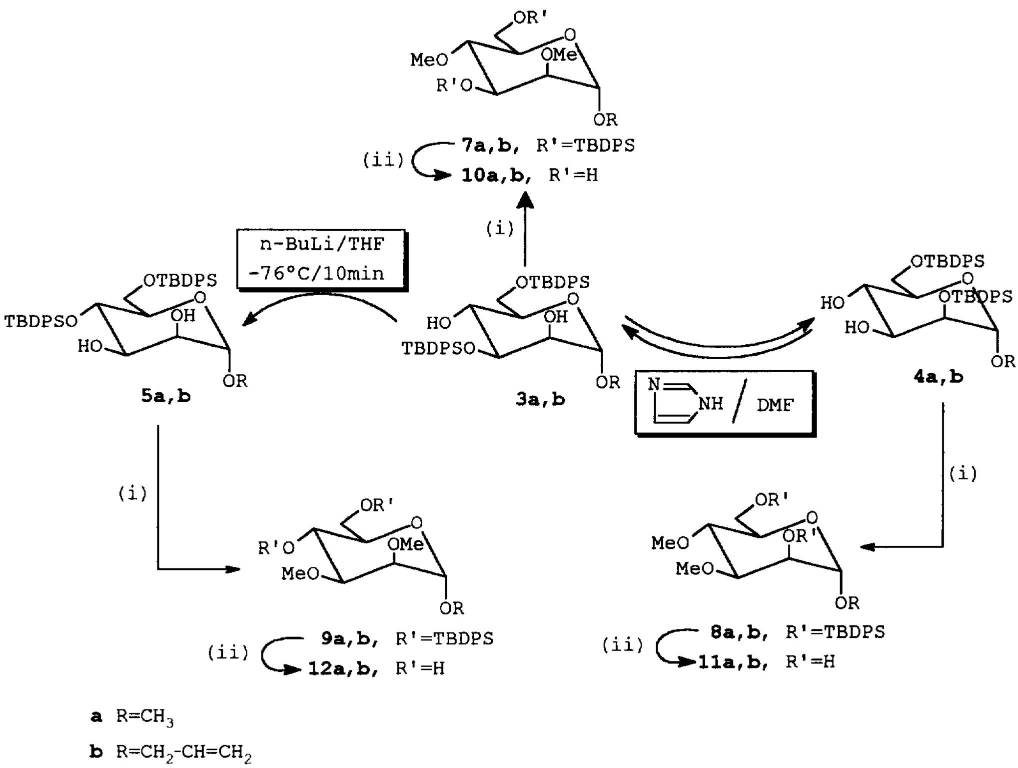
Abstract: Differential migratory aptitudes of secondary *tert*-butyldiphenylsilyl (TBDPS) groups have been observed for the bis-silylated derivatives of methyl and allyl α-D-mannopyranosides under several basic media. A remarkable variation of the selectivity in the migration of the TBDPS group at position 3 (O-3 → O-2 *versus* O-3 → O-4) was found by changing the hardness of the base and reaction conditions. This behaviour was directed towards the practical synthesis of the 3,6-, 2,6- and 4,6-bis-TBDPS ethers, **3-5a,b**, versatile intermediates for the preparation of other O-substituted derivatives. Their conversion into the methyl and allyl 2,4-, 3,4- and 2,3-di-O-methyl α-D-mannopyranosides (**10-12a,b**) was successfully achieved. Copyright © 1996 Elsevier Science Ltd

In the last years cell-wall glycolipids have been identified as specific antigens of many pathogenic mycobacteria.[1] Whatever the structure of the antigens, their epitope was delineated in the carbohydrate moiety and assigned, in most cases, to the distal mono or disaccharide residue. More precisely the species-specificity arises from the unique structure of this fragment containing partially O-methylated and/or O-acetylated monosaccharide units.[1] For example, 4-O and 2,4-di-O-methyl-α-D-mannopyranosyl are the distal monosaccharide units present in two phenolic glycolipid antigens isolated from *Mycobacterium kansasii*, an etiological agent of pulmonary diseases resembling tuberculosis.[1e] In order to facilitate mapping of the inmunodominant region, the development of selective strategies for the synthesis of the saccharide building blocks is of great importance and may also open the way to prepare fully synthetic specific antigens for early serodetection of mycobacterial infections.[1]

Among many useful protecting groups for the hydroxy functionality, *tert*-butyldimethylsilyl (TBDMS) and *tert*-butyldiphenylsilyl (TBDPS) groups are being widely applied.[2-6] Selective protection of secondary hydroxyl groups as TBDMS ethers has been extensively studied.[2,4-6] However, little systematic work has been reported for the more stable TBDPS ethers.[2,4]

It is known that TBDMS and TBDPS groups can migrate between suitably disposed hydroxyl groups under basic conditions.[2-6] The base-induced migrations were found to be strongly dependent on the base and/or the solvent employed. Thus, Ikegami *et al.*[4] reported a 1,5-migration of TBDMS and TBDPS groups under Wittig reaction conditions and by treatment with sodium hydride (NaH) in dimethyl sulfoxide (DMSO) or N,N-dimethylformamide (DMF), during the synthesis of prostaglandin derivatives. In these conditions, they observed a thermodynamically-equilibrated mixture of isomers, while the use of NaH or n-butyllithium (n-BuLi) in tetrahydrofuran (THF) or dimethoxyethane (DME) resulted in recovery of the starting silyl ether. Halmos and co-workers[5] described the migration of the TBDMS groups in partially protected derivatives of methyl α- and β-aldohexopyranosides promoted by imidazole or triethylamine in dipolar solvents. The authors postulated that these migrations occur only between vicinal *cis* positions. Stoddart *et al.*[6] reported a novel approach to the synthesis of some chemically-modified cyclodextrins which involves the TBDMS group migration during alkylation under strong basic conditions (NaH/THF). They found the migration of the silyl groups from the O-2 to the O-3 positions on all the D-glucopyranose residues.

As we have focused on synthetic and structural studies of some partially O-methylated saccharide units, present in antigenic glycolipids, we decided to explore the use of the *tert*-butyldiphenylsilyl chloride (TBDPSCl)-methyl trifluoromethanesulfonate (methyl triflate) tandem. The present paper describes a convenient synthetic methodology to afford methyl and allyl 2,3-, 2,4- and 3,4-di-O-methyl-α-D-mannopyranosides. (Scheme 1).



Scheme 1. Synthesis of the methyl and allyl 2,4-, 3,4- and 2,3-di-O-methyl-α-D-mannopyranosides **10-12 a,b**. Reagents: (i) $CF_3SO_3CH_3$/2,6-di-*tert*-butylpyridine/CH_2Cl_2; (ii) *n*-Bu_4N^+,F^-/THF.

Disilylation of methyl and allyl α-D-mannopyranosides (**1a,b**) using TBDPSCl with imidazole in dry DMF led to variable distribution of the 3,6- and 2,6-bis-silylated derivatives (**3** and **4a,b**), strongly influenced by the temperature and reaction times. Migrations of the secondary TBDPS groups were found in several basic media and, after further investigations, we observed that the TBDPS group at O-3 position, which bears two vicinal hydroxyl groups susceptible to participate in the rearrangement, exhibited the highest migratory aptitude. The selectivity in the migration of the TBDPS group -to vicinal O-2 or O-4 positions- was found to depend on the hardness of the base and reaction conditions. This behaviour offers a valuable approach to the practical synthesis of the 3,6-, 2,6- and 4,6-bis-*tert*-butyldiphenylsilyl ethers (**3-5a,b** Scheme 1), not reported previously and interesting intermediates for further derivatization processes. Their conversion into the methyl and allyl 2,4-, 3,4- and 2,3-di-O-methyl-α-D-mannopyranosides (**10-12a,b**, Scheme 1) was achieved through methylation with methyl triflate[7,8] followed by deprotection using tetra-*n*-butylammonium fluoride.[9] To our knowledge, this approach provides a significant improvement on the previous synthesis of these compounds involving more conventional protecting groups.[10]

RESULTS AND DISCUSSION

The silylation reactions of methyl and allyl α-D-mannopyranosides (**1a,b**) with TBDPSCl (2.2 equiv.) were carried out using imidazole (5 equiv.) in DMF at different temperatures and reaction times. The results obtained are summarized in Table 1. The starting product was always exhausted and the reaction exhibited the expected regioselectivity: the silylation of the primary hydroxyl group takes place readily while the secondary ones react smoothly and higher temperature and/or reaction times were necessary to obtain the optimun yield.[3,5] The order of reactivity of the secondary hydroxyl groups is as follows: 3-OH > 2-OH > 4-OH, in agreement with the accumulating evidence which demonstrates that 3,6-disubstituted derivatives can be obtained regioselectively in high yields from α-D-mannopyranosides.[5,11-13] Under these conditions, only traces of the 4,6-bis-TBDPS ethers, **5**, (<3%) were detected, showing clearly that the 4-OH group is the least reactive. The distribution of the 3,6- and 2,6-bis-TBDPS ethers, **3** and **4**, however, is strongly influenced by the temperature and reaction times. Thus, an increase of the times and/or temperature led to higher yields of the latter suggesting that the silylation reaction is accompanied by the migration of the TBDPS group from the O-3 to the O-2 positions. Moreover, the trisilylation of **1a** at 48°C during 70h afforded the methyl 2,4,6-tri-O-*tert*-butyldiphenylsilyl α-D-mannopyranoside (**6a**, 47%) and **4a** (34 %) as the major products. A similar behaviour was found in the preparation of the less stable TBDMS ethers of **1a** under the same reaction conditions.[5]

The silylation reaction of **1a** was used to compare the effectiveness of the imidazole with the Et_3N/DMAP system, which led to better yields in the preparation of the TBDMS ethers.[5] The use of Et_3N/DMAP raised the selectivity for the 3,6-isomer **3a**, but the overall conversion was lower at comparable temperature and/or reaction times (Table 1, entries 15-17 *vs.* 5-7). Therefore, the presence of imidazole increases the rate of both the silylation reaction and the rearrangement of the TBDPS groups. By this way, the 3,6- and 2,6-bis-TBDPS ethers **3** and **4** can be obtained in synthetically useful yields at 20°C by changing the reaction times from 8h -57% (**3a**), 70% (**3b**)- to 48h -64% (**4a**), 60% (**4b**)-.

Migration of the TBDPS groups between O-2 and O-3 positions could be verified by treatment of 3,6- and 2,6-bis-TBDPS ethers **3a** and **4a** with imidazole in DMF under the silylation reaction conditions (Figure 1; Table 2, entries 1-5). Interconversion between both isomers was observed and the 6-TBDPS ether **2a**, 4,6-bis-silylated derivative **5a** and/or other by-products were not detectable in yields higher than 2%. The rearrangement was faster at higher temperature (Table 2, entries 1 and 2, 4 and 5) and molar ratio

Table 1. Disilylation Reactions of Methyl and Allyl α-D-Mannopyranosides (**1a,b**) with *tert*-Butylchlorodiphenylsilane (TBDPSCl) in DMF[a].

Entry	Substrate	Temperature (°C)	Reaction time (h)	Disilylation[b,c] yield (%)	TBDPS ethers ratio[b,d] **2**	**3**	**4**
1	**1a**	0	8	38	62	33	4
2		4	8	54	46	47	5
3			24	65	25	55	18
4			48	81	19	45	33
5		20	8	80	20	57	20
6			24	90	8	42	46
7			48	92	5	26	64
8		48	4	72	28	32	37
9			8	81	17	25	53
10			24	88	8	19	66
11			48	89	5	19	67
12	**1b**	20	8	93	7	70	23
13			24	94	-	42	52
14			48	86	-	26	60
15	**1a**	20	8	25	75	20	5
16			24	46	54	35	11
17			48	58	42	44	14

[a] The reactions were carried out in presence of imidazole (molar ratio substrate:TBDPSCl: imidazole 1:2.2:5) except for entries 15-17, in which cases Et_3N/DMAP were used (molar ratio substrate:TBDPSCl:Et_3N:DMAP 1:2.2:2.4:0.08); [substrate]= 0.25M.

[b] Deduced by ^1H-NMR spectroscopy (±1%).

[c] This value also includes the small amount of the 4,6-bis-TBDPS ether (**5**) detected (≤3%).

[d] At 20 and 48°C it was observed the formation of the 2,4,6-tris-TBDPS ether, **6**, in low yield, entries 6(2), 7(3), 10(4), 11(6), 13(6) and 14 (14%).

base:substrate (Table 2, entries 2 and 3). The results from control experiments indicated that at 20°C **3a** and **4a** afford to a similar products ratio, **3a**:**4a**, of ca. 1:3, which remained almost unchanged with longer reaction times (-4, 6, 8h-, Figure 1). Moreover, when the imidazole was not removed from the reaction mixture in the quenching, the isomerization continued during the workup till the same constant ratio. These observations suggest that the process may be an intramolecular base-induced 1,4-migration of the TBDPS group, resulting in the thermodynamically equilibrated mixture of **3a** and **4a**.

From the 4,6-bis-TBDPS ether **5a** a mixture of the three possible isomers was found, with a ratio of **3a**:**4a** also near to 1:3 (Table 2, entry 6). Although the extent of the migration is low, this trend may be related to the fact that the directing effect comes from the great thermodynamic stability of the 2,6-isomer **4a**. Since its formation from **5a** should take place by means of two consecutive migrations (O-4 → O-3 → O-2) through the less stable derivative **3a**, higher time and/or temperature should be need to afford a similar result.

In order to gain additional evidence for the silyl group migration, the stability of the bis-TBDPS ethers

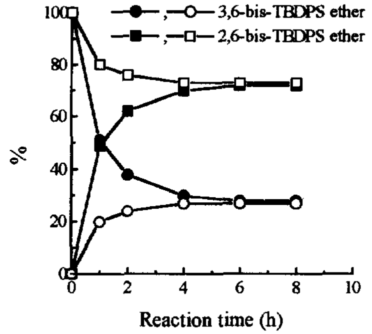


Figure 1. Isomerization of 3,6- and 2,6-bis-TBDPS ethers **3a** and **4a** with imidazole in DMF at 20°C using a molar ratio substrate:imidazole 1:5; ●/■ and ○/□ represent the yields of **3a**/**4a** obtained from **3a** and **4a** respectively.

Table 2. Base-Induced Migrations of the Secondary TBDPS Groups[a].

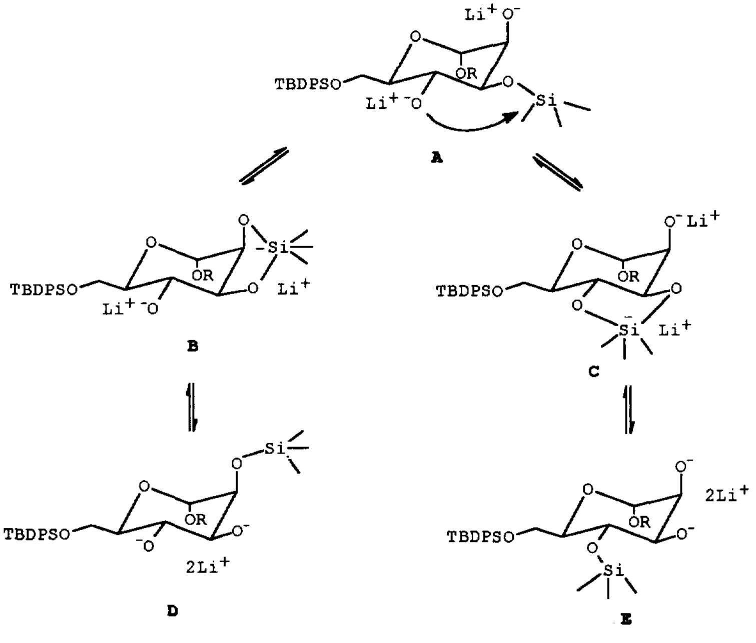
Entry	Substrate bis-TBDPS ether	Base/solvent	Temperature(°C)/ Time	TBDPS ratio[b] 3	4	5
1	**3a** (3,6-)	Imidazole/DMF	4 / 8 h	68	32	-
2			20 / 8 h	28	72	-
3			20 / 8 h	65	35	-
4	**4a** (2,6-)		4 / 8 h	21	79	-
5			20 / 8 h	27	73	-
6	**5a** (4,6-)		20 / 8 h	10	24	66
7	**3a** (3,6-)	Imidazole/THF	20 / 8 h	20	69	11
8		Et_3N/DMAP/DMF	20 / 8 h	56	44	-
9		Pyridine-H_2O (5%)	20 / 8 h	25	71	4
10		n-BuLi/THF	-76 / 10 min (1h)	6	20	73
11			20 / 10 min (1h)	5	25	64
12			20 /24 h	7	57	27
13	**4a** (2,6-)		-76 / 10 min (1h)	7	85	2
14			20 / 10 min (1h)	-	99	-
15	**5a** (4,6-)		-76 / 10 min (1h)	1	3	95
16	**3b** (3,6-)		-76 / 10 min	19	28	52

[a] Molar ratios: substrate:imidazole 1:5 for entries 1,2 and 4-7, 1:1 for entry 3; substrate: Et_3N/DMAP 1:2.4:0.08 (entry 8); substrate: n-BuLi 1:2.2 (entries 10-16). [substrate]= 0.09M (entries 1-9) and 0.06M (entries 10-16).

[b] Determined by ^1H-NMR spectroscopy (±1%). For entries 10-16 difference fron 100% corresponds to 6-O-TBDPS ether.

was checked in other basic media (Table 2). An analogous behaviour was observed when **3a** was treated with imidazole/THF or pyridine/H_2O(5%), affording a mixture of **3a** and **4a** in a similar ratio along with a small amount of the 4,6-bis-TBDPS ether **5a** (Table 2, entries 7 and 9). In the presence of Et_3N/DMAP/DMF the silyl group migration became less important (Table 2, entry 8), according to the above considerations for the silylation reaction performed under these conditions. On the other hand, isomerization was not detected for the three isomers in dry DMF, pyridine or 2,6-di-*tert*-butylpyridine/CH_2Cl_2.

By contrast, a remarkable change in the migration selectivity was found by treating **3a** with n-BuLi in dry THF. The preferential migration of the TBDPS group from the O-3 to the O-4 positions was observed under strong basic conditions using low temperatures and reaction times. Nevertheless, the TBDPS group remained practically intact in the case of the silyl ethers **4a** and **5a**. In all cases, the 6-TBDPS ether **2a** was detected in low yield indicating that the desilylation of the secondary TBDPS groups is not an important limitation even when strong bases are employed. These results may be justified on the basis of the proposed mechanism for related systems under similar conditions.[4,6] Now, the migration of the silyl protecting groups must take place in the dialkoxide dianion, generated by the action of the strong base, through an intramolecular process which probably involves a five-membered ring intermediate containing a pentacovalent silicon atom (Scheme 2).



Scheme 2

The observed selectivity may be explained as a consequence of the different reactivity of the electronegative atoms in the dianion intermediate **A**. Since O-4 should be more reactive than O-2 as a result of less steric hindrance, the TBDPS group will tend to migrate to the former position in preference to O-2 under kinetic control conditions. Furthermore, 1,2-dialkoxides **D** and **E** seem to be less reactive than **A**, probably due to the feasible formation of more stable tightly associated ion pairs with the small lithium cations (chelated structures) in the ethereal solvent.[14] These assumptions agree with the very low isomerization detected for **4a** and **5a** in these conditions, and the greater temperatures and reaction times needed to shift the equilibrium towards the most stable species **D**.

Moderate bases, such as the Et_3N/DMAP system or imidazole, can not generated dianionic intermediates and a plausible mechanism for the intramolecular migration of the silyl group could involve a simultaneous acid and base catalysis. This possibility should explain the acceleration effect exerted by the imidazole or the water, suitable proton donors.[14]

On the other hand, it was confirmed that the primary TBDPS group at position 6 is stable in all the conditions employed.

The methylation of the bis-TBDPS ethers **3-5a,b** was accomplished using methyl triflate (Table 3), whose high reactivity make it a suitable reagent for alkylation under mild conditions.[7,8] The process has been usually performed in the presence of a strongly sterically hindered base such as 2,6-di-*tert*-butylpyridine and a large excess of the alkylating reagent and the expensive base are needed.[8] Alternatively, it has been reported that the use of n-BuLi as a base can provide an economic alternative for the alkylation step.[15] Accordingly, **4a,b** were treated with n-BuLi in THF (Method A) and methylated to furnish the 3,4-di-O-methyl (**8a,b**) and 4-O-methyl-2,6-di-O-TBDPS-α-D-mannopyranosides in ca. 40% and 30% yields respectively, along with 10% of the 4-O-methyl-3,6-di-O-TBDPS derivative. The application of a similar protocol to **3a,b** afforded complex mixtures in which all possible O-methylated derivatives of **3-5a,b** were present, being the 2,3-di-O-methyl

Table 3. Methylation Reactions of the bis-TBDPS ethers **3-5** with $CF_3SO_3CH_3$.

Entry	Substrate bis-TBDPS ether	Method[a]	Reaction time (h)	% Di-O-methylation[b] (Product)[c]
1	**4a** (2,6-)	A	24	43 (**8a**)[d]
2	**4b** (2,6-)	A	24	37 (**8b**)[d]
3	**3a** (3,6-)	B	8	36 (**7a**)[e]
4	**3a** (3,6-)	B	36	100 (**7a**)
5	**3b** (3,6-)	B	24	68 (**7b**)[e]
6	**4a** (2,6-)	B	8	79 (**8a**)[e]
7	**5a** (4,6-)	B	8	77 (**9a**)[e]
8	**5a** (4,6-)	B	36	100 (**9a**)

[a] Reaction conditions : Method A: n-BuLi in THF, molar ratio substrate:base:$CF_3SO_3CH_3$ 1:2.2:2.2, 25°C; Method B: 2,6-di-*tert*-butylpyridine in CH_2Cl_2 molar ratio substrate:base:$CF_3SO_3CH_3$ 1:20:10, 80°C.

[b] Deduced by ^{1}H-NMR spectroscopy (±1%) except for entries 1 and 2, which corresponds to isolated products.

[c] **7**: 2,4-di-O-methyl-3,6-bis-TBDPS ether; **8**: 3,4-di-O-methyl-2,6-bis-TBDPS ether; **9**: 2,3-di-O-methyl-4,6-bis-TBDPS ether.

[d] 4-O-methyl-2,6-bis-TBDPS and 4-O-methyl-3,6-bis-TBDPS ethers (25 and 9%, entry 1; 35 and 13%, entry 2) were also obtained.

[e] Difference fron 100% corresponds to the expected mono-O-methylated derivatives except for entry 3 in which case the starting product, **3a**, was also found (19%).

(**9a,b**) and the 3-O-methyl-4,6-di-O-TBDPS-α-D-mannopyranosides the major products. In light of this situation, the process was achieved with 2,6-di-*tert*-butylpyridine in dichloromethane (Method B), in which case the expected di-O-methylated derivatives were obtained in high yields (Table 3). Once again, these results confirm the different behaviour of the bis-TBDPS ethers **3-5a,b** under basic conditions and point out the special usefulness of method B for their methylation, remarkably free of migration and/or desilylation products. Finally, cleavage of the silyl groups from **7-9a,b** using tetra-*n*-butylammonium fluoride in THF,[9] proceeded in very high yields.

The structure of all the compounds was confirmed by ^{1}H and ^{13}C NMR spectroscopy.[16-19] The unambiguous assignment of proton and carbon resonances for the mannopyranoside moiety was achieved through the combined use of 2D NMR techniques (COSY and ^{1}H-^{13}C correlation spectra) and double-resonance experiments. The substitution patterns were established on the basis of the proton signals strongly shifted to lower field in the ^{1}H NMR spectra of the corresponding O-acetylated derivatives.[18] The assignment of the α - anomeric configuration was carried out taking into account the value of the ^{13}C-^{1}H direct coupling constants for the C-1 carbon, $^1J_{CH}$. These coupling constants exhibit a value of 169±2Hz in all cases, in agreement with an equatorial disposition of the H-1 proton.[19] The experimental values of the vicinal coupling constants for the protons of the mannopyranoside ring indicate that all the derivatives are almost completely in the $^4C_1$ conformation.[16]

CONCLUSIONS

The different migratory aptitude of the *tert*-butyldiphenylsilyl (TBDPS) groups and selectivity of the rearrangement under basic conditions have proved to be an useful alternative to prepare some partially O-substituted α-D-mannopyranosides. The migration of the TBDPS group from the O-3 to the O-2 positions appears to be favoured by moderate bases (imidazole), aprotic highly dipolar solvents (DMF), proton donors and the formation of the most stable isomer, 2,6-bis-TBDPS ether, is the result of a thermodynamically controlled process. Therefore, the 3,6- and 2,6-bis-TBDPS ethers **3** and **4a,b** can be obtained in synthetically useful yields by silylation of methyl and allyl α-D-mannopyranosides (**1a,b**) with the imidazole/DMF system by changing the temperature and/or the reaction times. Nevertheless O-3 → O-4 migration seems to be promoted by much stronger bases (n-BuLi) in aprotic dipolar solvents (dry THF) under kinetic control conditions and provides an unexpected choice to obtain the 4,6-bis-TBDPS ethers **5a,b**, no avaible by direct silylation. This methodology has been applied for the synthesis of the methyl and allyl 2,4-, 3,4- and 2,3-di-O-methyl-α-D-mannopyranosides with good overall yield.

EXPERIMENTAL

All NMR spectra (^{1}H, ^{13}C, double resonance experiments, COSY-45 and XHCORD) were recorded on a Varian Unity-300 spectrometer in $CDCl_3$ at 298°K; resolution enhancement was applied to deduce the proton magnetic parameters. Solvents were purified and dried using standard methods. Allyl α-D-mannopyranoside (**1b**) was prepared and purified as described previously.[20] Acetylation reactions were performed with an excess of acetic anhydride in pyridine at room temperature for 24 h. All reactions were conducted under a nitrogen atmosphere. Anhydrous Na_2SO_4 was used to dry the organic solutions during workups, and the removal of the solvents was done under vacuum with a rotoevaporator. The composition of the reaction mixtures was determined by ^{1}H NMR spectroscopy. In all cases, yields obtained from isolated products were in good agreement with those determined by ^{1}H NMR spectroscopy. Thin-layer chromatography (TLC) was performed on precoated kieselgel 60F$_{254}$; detection was first by UV and then charring with a 0.2% solution of anthrone in 85% sulfuric acid. Column chromatography was carried out on silica gel .

General Method for Silylation Reactions. To a stirred solution of methyl or allyl α-D-mannopyranoside (**1a,b**, 5 mmol) in dry N,N-dimethylformamide (20 ml) at the selected temperature were added imidazole (25 mmol) -or triethylamine (12 mmol)/4-(dimethylamino)pyridine (0.4 mmol)- and *tert*-butylchlorodiphenylsilane (11 mmol). The resultant solution was stirred for the appropiate reaction time (Table 1). The reaction mixture was quenched with a saturated solution of NH_4Cl and diluted with Et_2O. The organic layer was separated and the aqueous phase extrated several times with Et_2O. The combined organic fractions were washed with water and brine, dried and the solvent evaporated to yield the crude product mixture.

General Method for Isomerization Reactions. Control Experiments with moderate bases. A solution of the TBDPS ether (0.5 mmol) and the base (imidazole or Et_3N/DMAP; molar ratios substrate: imidazole 1:5 or 1:1, substrate:Et_3N:DMAP 1:2.4:0.08) in dry DMF (or THF) (5.5 ml, [substrate]= 0.09M) was stirred at the selected temperature for the appropiate reaction time (Table 2). The reaction was quenched and worked up as described for the silylation process. Proofs in dry DMF, pyridine, pyridine-DMF (1:1), 2,6-di-*tert*-butylpyridine/CH_2Cl_2 (molar ratio substrate:base 1:20) or pyridine-H_2O (5%) were performed according to a similar method.

Control Experiments using n-Butyllithium. To a solution of the TBDPS ether (0.5 mmol) in THF (carefully dried because traces of water change the migration selectivity) at -76 or 20°C was added n-butyllithium (1.6M in hexane, 1.1 mmol) ([substrate]= 0.06M) and the mixture was stirred for the reaction time (Table 2). After hydrolysis with water, the reaction mixture was worked up as just described.

General Procedure for Methylation Reactions. Method A. To a stirred solution of the bis-TBDPS ether (1 mmol) in dry THF (10 ml) at -78°C was added n-butyllithium (1.6 M in hexane, 2.2 mmol). The mixture was stirred for 10 min. to produce the dilithium dialkoxide and methyl triflate (2.2 mmol) was then added. The reaction mixture was allowed to reach 25°C and stirring was maintained for 24 h. After hydrolysis with water the aqueous phase was extrated three times with Et_2O. The ethereal extracts were washed with water and brine, dried and the solvent was removed.

Method B. To a solution of the bis-TBDPS ether (1 mmol) in dry dichloromethane (15 ml) was successively added 2,6-di-*tert*-butylpyridine (20 mmol) and methyl triflate (10 mmol). The homogeneous solution was stirred at 80°C for the reaction time (Table 3). The reaction was then quenched and worked up as described above.

General Procedure for Desilylation Reactions. To a solution of the dimethyl disilyl derivative (**7**, **8** or **9a,b**) in dry THF (3 ml/mmol) was added the tetra-*n*-butylammonium fluoride (1 M in THF, 3 ml/mmol) and the mixture was kept at room temperature with stirring for 24 h. The reaction mixture was diluted with CH_2Cl_2 and dried. Solvents were removed and the residue was purified by flash chromatography.

Methyl and allyl 3,6-di-O-*tert*-butyldiphenylsilyl-α-D-mannopyranosides (3a,b). The title compounds were prepared by the general method from **1a,b** (20 mmol, 4 g (**1a**), 4.4 g (**1b**)) at 20°C for 8 h followed by flash chromatography. Elution was started with hexane-EtOAc, 95:5 to separate the 2,4,6-tris-TBDPS ethers **6** and a by-product (Bu^tPh_2SiOH) coming from the hydrolysis of the reagent; elution then with hexane-EtOAc, 85:15 afforded the 3,6-bis-TBDPS ethers **3** as syrups (**3a**, 7.4 g, 55%; **3b**, 9.5 g, 68%) and the silyl derivatives **4** as white solids (**4a**, 2.4 g, 18%; **4b**, 2.9 g, 21%); for elution of monosilyl derivatives **2a,b** hexane-EtOAc, 4:6 was empoyed. TLC (hexane-EtOAc, 7:3) R_f 0.72(**6a**), 0.57(**3a**), 0.45(**4a**), 0.37(**5a**), 0.05(**2a**), 0.74(**6b**), 0.59(**3b**), 0.47(**4b**), 0.41(**5b**), 0.06(**2b**).

Methyl and allyl 2,6-di-O-*tert*-butyldiphenylsilyl-α-D-mannopyranosides (4a,b). Application of the general procedure for the silylation of **1a,b** (20 mmol, 4 g (**1a**), 4.4 g (**1b**)) at 20°C for 48 h gave after flash chromatography in the conditions described above the 2,6-bis-TBDPS ethers **4** (**4a**, 8.3 g, 62%; **4b**, 8.1 g, 58%) along with the silyl derivatives **3** (**3a**, 3.2 g, ; **3b**, 3.3 g, 24%).

These compounds were also prepared by rearrangement of **3a,b** (3 mmol, 2 g) with imidazole (molar ratio substratre:imidazole 1:5) in dry DMF at 20°C for 8 h as described above. Purification of the reaction mixtures by flash chromatography (hexane-EtOAc, 85:15) afforded recovered **3a,b** (540 mg, 27%) and the silyl derivatives **4** (**4a**, 1.4 g, ; **4b**, 1.5 g, 70%).

Methyl and allyl 4,6-di-O-*tert*-butyldiphenylsilyl-α-D-mannopyranosides (5a,b). Silyl derivatives **3a,b** (3 mmol, 2 g) were subjected to isomerization in the presence of n-butyllithium at -76°C for 1 h according to the general method. A careful column chromatography (hexane-EtOAc, 9:1) of the reaction mixture led to the isolation of the 4,6-bis-TBDPS ethers **5a,b** as syrups (**5a**, 1.4 g, 68%; **5b**, 970 mg, 48%) and the above described silylated compounds **3** and **4**.

All TBDPS ethers afforded ^{1}H and ^{13}C spectral data in accordance with their structures (selected parameters for **2-5a,b** are collected in Tables 4-6) as well as satisfactory analytical data.

Methyl 6-O-*tert*-butyldiphenylsilyl-α-D-mannopyranoside (2a). Anal. Found: C, 63.78; H, 7.59%. Calcd. for $C_{23}H_{32}O_6Si$: C, 63.86; H, 7.46%.

Allyl 6-O-*tert*-butyldiphenylsilyl-α-D-mannopyranoside (2b). Anal. Found: C, 65.39; H, 7.31%. Calcd. for $C_{25}H_{34}O_6Si$: C, 65.47; H, 7.48%.

Methyl 3,6-, 2,6- and 4,6-di-O-*tert*-Butyldiphenylsilyl-α-D-mannopyranosides. Anal. Found: **3a**: C, 69.71; H, 7.42%; **4a**: C, 69.65; H, 7.71%; **5a**: C, 69.66; H, 7.39%. Calcd. for $C_{39}H_{50}O_6Si_2$: C, 69.82; H, 7.52%.

Allyl 3,6-, 2,6- and 4,6-di-O-*tert*-Butyldiphenylsilyl-α-D-mannopyranosides. Anal. Found: **3b**: C, 70.51; H, 7.41%; **4b**: C, 70.81; H, 7.64%; **5b**: C, 70.82; H, 7.42%. Calcd. for $C_{41}H_{52}O_6Si_2$: C, 70.66; H, 7.53%.

Methyl 2,4,6-tri-O-*tert*-Butyldiphenylsilyl-α-D-mannopyranoside (6a). ^{1}H NMR: δ= 0.79, 0.92, 1.05 (each 9H, s, t-Bu), 1.41 (1H, d, J=10.2 Hz, OH), 3.12 (3H, s, OMe), 3.73 (1H, m, J= 10.2, 3.3, 8.8 Hz, H-3), 3.75 (1H, m, J= 9.5, 5.9, 1.5 Hz, H-5), 3.79 (1H, dd, J=1.5, 3.3 Hz, H-2), 3.84 (1H, dd, J= 5.9, -10.6 Hz, H-6), 3.93 (1H, ap.t, J= 8.8, 9.5 Hz, H-4), 4.09 (1H, dd, J= 1.5, -10.6 Hz, H-6'), 4.30 (1H, d, J=1.5 Hz, H-1), 7.25-7.76(30H, m, Ph). ^{13}C NMR: δ= 19.25 (2), 19.80 ($C(CH_3)_3$), 26.85 (2), 27.03 ($C(CH_3)_3$), 54.43 (OMe), 63.85 (C-6), 70.76 (C-4), 72.38 (C-2), 73.06 (C-3), 73.59 (C-5), 99.81 (C-1, $J_{C1\text{-}H1}$= 167 Hz). Anal Found: C, 72.44; H, 7.61%. Calcd. for $C_{55}H_{68}O_6Si_3$: C, 72.65; H, 7.54%.

Dimethyl disilyl derivatives (7-9a,b). Application of the method A for the methylation of **4a,b** (1mmol) afforded after flash chromatography (hexane-EtOAc, 98:2) **8a,b** (43 and 37%). By this procedure **3a,b** led to complex mixtures in which all possible O-methylated derivatives of **3-5a,b** were present, being the 2,3-di-O-methyl (**9a,b**) and the 3-O-methyl-4,6-di-O-TBDPS ethers the major products. In these cases only **9b** was isolated by column chromatography (hexane-EtOAc, 98:2).

Bis TBDPS ethers **3a,b**, **4a** and **5a** (1 mmol) were subjeted to the general methylation conditions according to method B (Table 3). The products **7-9a,b** and **7b** were isolated by flash chromatography (hexane-EtOAc, 98:2). TLC (hexane-EtOAc, 8:2) R_f 0.59(**7a**), 0.55(**8a**), 0.43(**9a**); (hexane-EtOAc, 9:1) R_f 0.47(**7b**), 0.44(**8b**), 0.32(**9b**).

All compounds afforded ^{1}H and ^{13}C spectral data in accordance with their structures (selected parameters are given in Tables 4-6) as well as satisfactory analytical data.

Anal. Found: **7a**: C, 70.39; H, 7.89%; **8a**: C, 70.58; H, 7.61%; **9a**: C, 70.65; H, 7.91%. Calcd. for $C_{41}H_{54}O_6Si_2$: C, 70.45; H,9%. Anal. Found: **7b**: C, 71.09; H, 7.92%; **8b**: C, 71.45; H, 7.61%; **9b**: C, 71.04; H, 7.95%. Calcd. for $C_{43}H_{56}O_6Si_2$: C, 71.24; H, 7.79%.

Table 4. ^{1}H Chemical Shifts for Methyl and Allyl α-D-Mannopyranoside Derivatives **2-5a,b** and **7-9a,b**.

δ(ppm)[a]	**2a**	**3a**	**4a**	**5a**	**7a**	**8a**	**9a**
H-1 (d)	4.66	4.66	4.36	4.64	4.53	4.52	4.73
H-2 (dd)	3.87	3.68	3.95	3.76	2.87	3.93	3.53
H-3 (dd)	3.78	3.95	3.70	3.82	4.17	3.32	3.40
H-4 (ap.t)	3.77	3.84	4.01	3.67	3.43	3.82	3.84
H-5 (m)	3.59	3.47	3.56	3.80	3.49	3.50	3.82
H-6 (dd)	3.87	3.81	3.95[b]	3.68	3.84	3.89	3.59
H-6'(dd)	3.91	3.89	3.95[b]	3.99	3.88	3.93	3.93
H-7(CH_3)(s)	3.28	3.23	3.07	3.40	3.17	3.16	3.43
$C(CH_3)_3$ (s)	1.05	1.09	1.08	1.01	1.09	1.08	0.99
		1.04	1.08	0.92	1.05	1.08	0.91
2-O-CH_3 (s)					3.21		3.32
3-O-CH_3 (s)						3.14	2.77
4-O-CH_3 (s)					3.35	3.52	

δ(ppm)[a]	**2b**	**3b**	**4b**	**5b**	**7b**	**8b**	**9b**
H-1 (d)	4.82	4.81	4.50	4.80	4.67	4.66	4.90
H-2 (dd)	3.92	3.70	3.98	3.78	2.88	3.97	3.56
H-3 (dd)	3.85	3.98	3.74	3.85	4.19	3.38	3.44
H-4 (ap.t)	3.80	3.85	4.00	3.68	3.47	3.83	3.85
H-5 (m)	3.65	3.52	3.61	3.85	3.49	3.55	3.85
H-6 (dd)	3.89[b]	3.81	3.93[b]	3.69	3.82	3.89	3.58
H-6'(dd)	3.89[b]	3.89	3.93[b]	3.98[c]	3.86	3.95	3.93[c]
H-7 (m)	3.91	3.85	3.65	4.02	3.78	3.78	4.04
H-7'(m)	4.10	4.07	3.91	4.25	4.06	4.01	4.29
H-8 (m)	5.84	5.77	5.59	5.92	5.73	5.68	5.97
H-9 (m)	5.16	5.08	4.99	5.21	5.03	5.04	5.22
H-9'(m)	5.23	5.10	5.01	5.29	5.03	5.08	5.30
$C(CH_3)_3$ (s)	1.05	1.12	1.07	1.02	1.10	1.08	1.00
		1.04	1.07	0.93	1.04	1.08	0.92
2-O-CH_3 (s)					3.19		3.33
3-O-CH_3 (s)						3.17	2.79
4-O-CH_3 (s)					3.38	3.53	

[a] Aromatic protons appear as complex multiplets between ca. 7.84 and 7.18 ppm.

[b] H-6, H-6' and H-5 protons absorb as a three-spin A_2M system.

[c] Apparent doublet.

Methyl and allyl 2,4-, 3,4- and 2,3-di-O-methyl-α-D-mannopyranosides (10-12a,b). Dimethyl disilyl derivatives **7-9a,b** (0.5 mmol) were submitted to the standard conditions of desilylation to afford after flash chromatography (hexane-acetone, 1:1) the di-O-methyl derivatives **10-12a,b** in high yields (≥85%). TLC (hexane-acetone, 1:2) R_f 0.43(**10a**), 0.34(**11a**), 0.40(**12a**); (hexane-acetone 1:1) R_f 0.31(**10b**), 0.23(**11b**), 0.29(**12b**).

Physical data of the methyl 2,4-, 3,4- and 2,3-di-O-methyl-α-D-mannopyranosides (**10-12a**) are in agreement with those reported in the literature.[10]

Table 5. Vicinal ^{1}H-^{1}H Coupling Constants for Methyl and Allyl α-D-Mannopyranoside Derivatives **2-5a,b** and **7-9a,b**.

J (Hz)	2a	3a	4a	5a	7a	8a	9a
H-1-H2	1.48	1.59	1.59	1.65	2.20	1.95	2.56
H-2-H3		3.54	3.36	3.48	3.30	2.99	3.02
H-3-H4	9.16	8.85	9.34	8.42	8.06	9.34	7.60
H-4-H5	9.52	9.52	9.40	9.34	9.70	9.83	9.15
H-5-H6	5.01	5.37	4.52	6.41	2.56	2.14	6.65
H-5-H6'	5.55	3.66	4.52	1.74	4.58	4.11	1.83

J (Hz)	2b	3b	4b	5b	7b	8b	9b
H-1-H2	1.59	1.65	1.59	1.60	2.01	1.98	2.44
H-2-H3	3.54	3.54	3.36	3.54	3.11	2.98	3.17
H-3-H4	9.03	8.85	9.34	8.52	8.61	9.38	7.93
H-4-H5	8.79	9.53	9.40	9.34	9.89	9.73	
H-5-H6	5.33	5.60	4.51	6.64	< 2.0	1.98	6.84
H-5-H6'	5.33	3.60	4.51	< 2.0	4.50	4.12	< 2.0
H-7-H8	6.22	5.86	6.23	6.54	5.49	5.04	6.47
H-7'-H8	5.13	4.76	5.01	5.15	4.58	5.04	5.19
H-8-H9	10.38	9.94	10.38	10.30	10.16	10.30	10.32
H-8-H9'	17.21	17.70	17.21	17.25	17.76	17.32	17.21

Allyl 2,4-di-O-methyl-α-D-mannopyranoside (10b). ^{1}H NMR: δ= 3.31 (1H, ap.t, J= 9.3, 9.9 Hz, H-4), 3.46 (3H, s, 2-OMe), 3.47 (1H, dd, J= 1.7, 3.7 Hz, H-2), 3.51 (1H, m, J= 9.9, 4.4, 2.9 Hz, H-5), 3.56 (3H, s, 4-OMe), 3.73 (1H, dd, J= 4.4, -11.7 Hz, H-6), 3.81 (1H, dd, J= 2.9, -11.7 Hz, H-6'), 3.89 (1H, dd, J= 3.7, 9.3 Hz, H-3), 3.94 (1H, m, J= 6.0, -13.0 Hz, H-7), 4.15 (1H, m, J= 5.1, -13.0 Hz, H-7'), 4.91 (1H, d, J= 1.7 Hz, H-1), 5.17 (1H, m, J= 10.4, 2.0 Hz, H-9), 5.26 (1H, m, J= 17.2, 2.0 Hz, H-9'), 5.86 (1H, m, J= 6.0, 5.1, 10.4, 17.2 Hz, H-8). ^{13}C NMR: δ= 58.73 (2-OMe), 60.68 (4-OMe), 62.31 (C-6), 68.07 (C-7), 71.46, 71.49 (C-3 and C-5), 78.13 (C-4), 80.51 (C-2), 95.61 (C-1, $J_{C1\text{-}H1}$= 167 Hz), 117.62 (C-9), 133.56 (C-8). Anal. Found: C, 53.35; H, 8.04%. Calcd. for $C_{11}H_{20}O_6$: C, 53.20; H, 8.12%.

Allyl 3,4-di-O-methyl-α-D-mannopyranoside (11b). ^{1}H NMR: δ= 3.44 (1H, ap.t, J= 9.2, 9.5 Hz, H-4), 3.48 (3H, s, 3-OMe), 3.51 (1H, dd, J= 3.2, 9.2 Hz, H-3), 3.53 (3H, s, 4-OMe), 3.56 (1H, m, J= 9.5, 4.1, 3.0 Hz, H-5), 3.74 (1H, dd, J= 4.1, -11.8 Hz, H-6), 3.82 (1H, dd, J= 3.0, -11.8 Hz, H-6'), 3.96 (1H, m, J= 6.2, -12.8 Hz, H-7), 4.03 (1H, dd, J= 1.7, 3.2 Hz, H-2), 4.15 (1H, m, J= 5.3, -12.8 Hz, H-7'), 4.89 (1H, d, J= 1.7 Hz, H-1), 5.19 (1H, m, J= 10.3, 1.9 Hz, H-9), 5.26 (1H, m, J= 17.2, 1.9 Hz, H-9'), 5.87 (1H, m, J= 6.2, 5.3, 10.3, 17.2 Hz, H-8). ^{13}C NMR: δ= 57.41 (3-OMe), 60.68 (4-OMe), 61.86 (C-6), 67.75 (C-2), 68.02 (C-7), 71.51 (C-5), 75.70 (C-4), 81.35 (C-3), 98.36 (C-1, $J_{C1\text{-}H1}$= 169 Hz), 117.62 (C-9), 133.55 (C-8). Anal. Found: C, 53.09; H, 8.25%.

Allyl 2,3-di-O-methyl-α-D-mannopyranoside (12b). ^{1}H NMR: δ= 3.46 (3H, s, 2-OMe), 3.47 (3H, s, 3-OMe), 3.48 (1H, dd, J= 3.2, 9.5 Hz, H-3), 3.61 (1H, m, J= 9.8, 5.0, 3.8 Hz, H-5), 3.63 (1H, dd, J= 1.7, 3.2 Hz, H-2), 3.78 (1H, dd, J= 5.0, -11.7 Hz, H-6), 3.85 (1H, dd, J= 3.8, -11.7 Hz, H-6'), 3.85 (1H, ap.t, J= 9.5,

Table 6. Selected ^{13}C Chemical Shifts for Methyl and Allyl α-D-Mannopyranoside Derivatives **2-5a,b** and **7-9a,b**.

δ(ppm)[a]	**2a**	**3a**	**4a**	**5a**	**7a**	**8a**	**9a**
C-1	100.62	100.16	100.44	100.13	97.85	101.00	98.42
C-2	70.34	70.82	72.40	71.03	79.91	69.38	75.79
C-3	71.69	74.42	72.17	72.11	73.04	81.91	80.97
C-4	70.40	69.25	69.88	70.95	78.18	75.86	68.87
C-5	70.64	71.59	71.52	73.31	73.30	72.88	74.73
C-6	65.24	64.47	64.60	63.84	63.97	63.45	64.19
C-7	54.87	54.62	54.61	54.73	54.51	54.47	54.73
$C(CH_3)_3$	19.19	19.41	19.46	19.56	19.37	19.45	19.63
		19.26	19.25	19.28	19.37	19.33	19.26
$C(CH_3)_3$	26.84	27.05	27.00	27.04	27.11	26.89	27.03
		26.83	26.84	26.82	26.79	26.17	26.72
2-O-CH_3					58.02		58.46
3-O-CH_3						57.08	55.26
4-O-CH_3					60.50	60.38	

δ(ppm)[a]	**2b**	**3b**	**4b**	**5b**	**7b**	**8b**	**9b**
C-1	98.62	98.12	98.20	98.22	95.88	98.81	96.57
C-2	70.42	70.96	72.51	71.24	80.06	69.47	76.00
C-3	71.69	74.44	72.18	72.28	73.20	81.87	81.14
C-4	70.55	69.15	69.93	71.16	77.97	75.96	69.09
C-5	70.72	71.89	71.75	73.55	73.54	73.07	75.00
C-6	65.25	64.39	64.61	63.95	63.88	63.43	64.33
C-7	67.98	67.39	67.41	67.93	67.29	67.33	67.83
C-8	133.61	133.74	133.51	133.84	134.10	133.87	134.23
C-9	117.49	116.68	117.17	117.51	115.96	117.14	117.41
$C(CH_3)_3$	19.28	19.39	19.47	19.58	19.42	19.52	19.66
		19.25	19.25	19.29	19.37	19.32	19.28
$C(CH_3)_3$	26.85	27.05	27.00	27.12	27.08	26.96	27.11
		26.83	26.84	26.91	26.79	26.89	26.81
2-O-CH_3					58.00		58.51
3-O-CH_3						57.13	55.26
4-O-CH_3					60.57	60.40	

9.8 Hz, H-4), 3.97 (1H, m, J= 6.2, -12.8 Hz, H-7), 4.18 (1H, m, J= 5.3, -12.8 Hz, H-7'), 4.95 (1H, d, J= 1.7 Hz, H-1), 5.20 (1H, m, J= 10.4, 2.0 Hz, H-9), 5.28 (1H, m, J= 17.2, 2.0 Hz, H-9'), 5.89 (1H, m, J= 6.2, 5.3, 10.4, 17.2 Hz, H-8). ^{13}C NMR: δ= 57.15 (3-OMe), 59.11 (2-OMe), 62.92 (C-6), 67.38 (C-4), 68.19 (C-7), 72.21 (C-5), 75.95 (C-2), 81.14 (C-3), 96.74 (C-1, J_{C1-H1}= 168 Hz), 117.66 (C-9), 133.63 (C-8). Anal. Found: C, 53.33; H, 8.29%.

Acknowledgements. This work was supported by the University of Alcalá. We thank Professor G. Puzo of the Centre de Recherche de Biochemie et de Génétique Cellulaires du CNRS (Toulouse, France) for several helpful comments and suggestions.

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(*Received in UK* 21 *May* 1996; *revised* 24 *June* 1996; *accepted* 26 *June* 1996)