Regioselective ring openings in the 3,5-dioxa-8-azabicyclo-[5.2.0]nonane ring system

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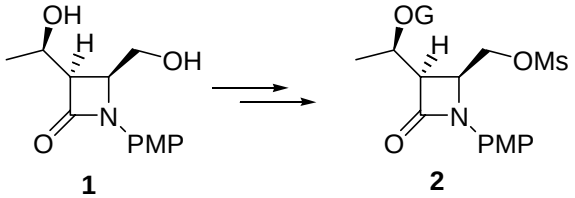
Abstract
In order to distinguish primary and secondary hydroxyl groups in the presence of a β-lactam moiety benzylidene acetal protection and reductive cleavage were used. When the reductive ring opening was carried out using diisobutylaluminium hydride, the benzylidene acetal group remained intact, while the β-lactam was reduced to the corresponding β-amino alcohol. The acetal cleavage with sodium cyanoborohydride was successful, resulting mainly in a β-lactam compound bearing the benzyloxy group on the secondary carbon atom.

Keywords: β-Lactam, benzylidene acetal, protecting group, reductive cleavage

Introduction

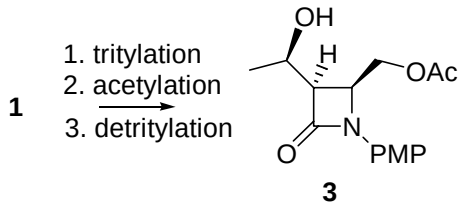
In the course of our work in the synthesis of 2-iso-oxacephems, we faced the problem of distinguishing between primary and secondary hydroxyl groups with an appropriate protecting group strategy.[1] We needed a compound having a protecting group (G), which is stable to acids and mild bases, on the secondary O, but contains a free primary hydroxyl group, which can be mesylated to give **2** (Scheme 1, PMP = *p*-methoxyphenyl).



Scheme 1

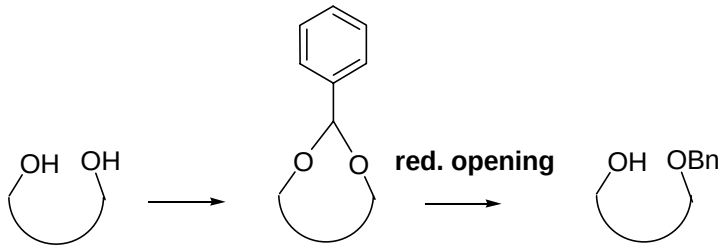
Similar problems were already successfully solved by the tritylation/acetylation/detritylation method. In the case of **1**, however, this method failed and surprisingly resulted exclusively in **3.**

This compound bears the acetoxy group on the primary carbon atom, presumably due to a transacetylation reaction occurring because of the spatial proximity of the two hydroxyl groups (Scheme 2).[1]



Scheme 2

After these unsuccessful attempts we tried to use the benzylidene acetal group, which is suitable for protecting diols and is widely used in the carbohydrate chemistry. It is reported that its regioselective reductive cleavage can be accomplished with DIBALH or alane ($LAH/AlCl_3$) to give the free hydroxyl group in the less hindered position and the benzyl ether moiety in the more hindered position (Scheme 3).[2]



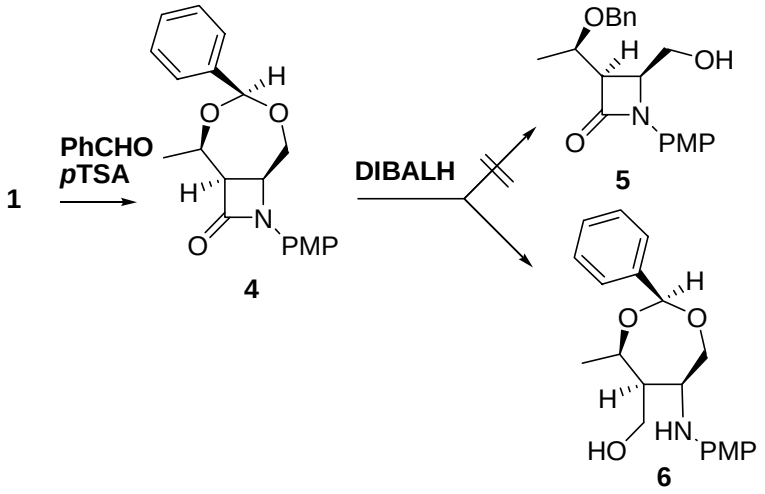
Scheme 3

Although the cleavage with alane cannot be taken into consideration in the presence of the lactam moiety, the usage of DIBALH seemed to be promising due to the fact that we have already used DIBALH in the course of our preliminary work to reduce an ester function without destroying the lactam function.[3] As far as we know, the usage of this protecting group strategy is unique among compounds containing a β-lactam function as well. It is also unique in the respect that we investigated these methods in a case of a 1,4-diol.

Results and Discussion

The benzylidene acetal group was built on **1** with benzaldehyde in the presence of a catalytic amount of *p*-toluenesulfonic acid. Compound **4** was formed in a diastereomerically pure form, the configuration of the new stereocenter was determined by 2D NOESY spectra. The reduction of **4** was carried out according to the common procedure to be found in the literature with

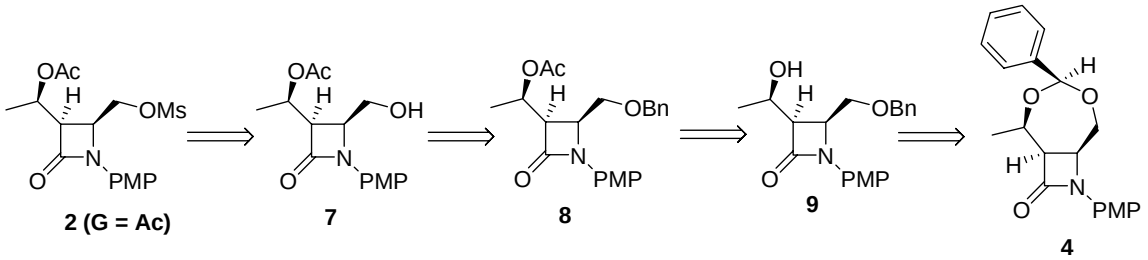
DIBALH in CH_2Cl_2 at 0°C. Surprisingly, the reaction resulted in **6** instead of the expected **5** along with many other minor products. The reaction was carried out also at -78 °C, resulting in the same main compound with a much better yield and fewer minor products. This means that the reactivity of the 7-membered benzylidene acetal moiety in that case is less than that of the β-lactam (Scheme 4). As far as we know it is unprecedented to reduce a β-lactam with DIBALH to β-amino alcohol, such reactions can be normally carried out with LAH or diborane. A possible explanation of this observation is the enhanced ring strain in the *cis*-annelated 4+7 ring system.



Scheme 4

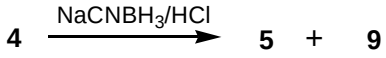
However, it is reported that *p*-methoxybenzylidene (PMB) acetals are more sensitive to reductive cleavage, and hence their reactivity might be higher than that of the β-lactam moiety. In this case this protecting group cannot be taken into consideration, because of the sensitivity of the resulting PMB ethers to oxidative circumstances that we must use later in our synthesis to remove the PMP protecting group.[4]

After these experiences, we decided to try to open the benzylidene acetal ring using $NaCNBH_3$/HCl. It has been reported that with that method a regioselective cleavage also takes place, but resulting mainly in a secondary alcohol.[5] Hence we planned the following retrosynthetic pathway (Scheme 5).



Scheme 5

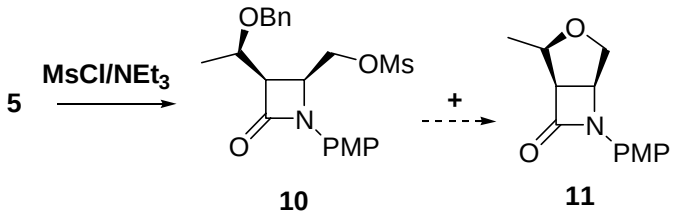
Contrary to the literature, we found that the main product of the reaction was **5** along with the by-product **9** (Scheme 6).



Scheme 6

The identification of the two regioisomers was based on 2D HMQC and NOESY spectra. Since the purification of the compounds from inorganic residues proved to be difficult and we also wanted to examine the question of selectivity, we tried to apply further reducing agents, namely $NaBH_4$ and $Na(AcO)_3BH$, but without any reaction taking place.

Compound **5** was mesylated to obtain **10** with methanesulfonyl chloride in the presence of NEt_3. When **5** contained inorganic impurities (presumably originated from the reagent $NaCNBH_3$) **11** was also formed in high quantity (Scheme 7). The structure of **11** was determined based on its spectra, which were the same as we previously reported.[1] Of note is that the NMR sample of **10** in $CDCl_3$ also transformed completely to **11** after a day of standing. These observations mean that the benzyl ether group in that compound is relatively unstable. Therefore the application of **10** for further synthesis demands increased caution.



Scheme 7

Conclusions

In this work we showed the possible utilization of the benzylidene acetal protecting group for distinguishing between primary and secondary hydroxyl groups in the presence of a β-lactam moiety. The 4+7 ring system could be cleaved regioselectively with DIBALH and $NaCNBH_3$ as well, in the first case the β-lactam ring was opened, in the second case the 1,3-dioxepane ring. For our purposes the reducing agent $NaCNBH_3$ proved to be suitable.

Experimental Section

General Procedures. Melting points were determined on a hot stage melting point apparatus and are uncorrected. Optical rotations (c = 1.0 g / 100 cm^3, CH_2Cl_2, unless stated otherwise) were taken on a Perkin–Elmer 241 polarimeter calibrated by measuring the optical rotations of both enantiomers of menthol. The ^1H and ^{13}C NMR spectra were obtained using a Bruker DRX 500 spectrometer (^1H 500.33 MHz, ^{13}C 125.75 MHz) or a Bruker 300 spectrometer (^1H 300.13, ^{13}C 75.48 MHz) at 298 K in $CDCl_3$ as a solvent, unless stated otherwise. The IR spectra were recorded on a Zeiss Specord M80 spectrophotometer. High resolution MS were measured on a Waters-Micromass LCT apparatus using ESI+ method (**6**) or on a Finnigan MAT 95XP mass spectrometer (**5**, **9**); perfluorotributyl amine was used as a reference compound (EI, 220°C source temperature, 70 eV). Elemental analyses (C, H, N, S) were conducted using the Elemental Analyser VARIO EL III (Elementar Analysensysteme Gmbh), their results were found to be in good agreement (±0.4 %) with the calculated values. Column and thin-layer chromatography were carried out on Merck Kieselgel 60 (0.063–0.2 mm) and Merck Kieselgel 60 F_{254} Alufolien, respectively. For preparative TLC Merck PSC ready-for-use plates (Kieselgel 60 F_{254}, 20 × 20 cm, 2 mm) were used. TLC spots were detected by UV, and/or phosphomolybdic acid (PMA). All solvents were distilled and dried before use.

(1*R*,2*R*,4*S*,7*S*)-8-(4-methoxyphenyl)-2-methyl-4-phenyl-3,5-dioxa-8-azabicyclo[5.2.0]nonan-9-one (4). Benzaldehyde (0.25 mL; 2.4 mmol) was added to a suspension of (3*R*,4*S*)-3-[(1*R*)-1-hydroxyethyl]-4-hydroxymethyl-1-(4-methoxyphenyl)azetidin-2-one (**1**)[1] (0.5 g; 2 mmol) in 0.05N *p*-toluenesulfonic acid/toluene (5 mL) and refluxed for 2 hours (TLC: CH_2Cl_2:EtOAc 10:1.5, UV, Rf_4 = 0.5). The solvent was removed under reduced pressure, the residue was dissolved in CH_2Cl_2, the insoluble materials were filtered off, and the filtrate was purified by flash chromatography (CH_2Cl_2) to give 0.47 g (70 %) of **4**. M.p.: 202 °C. $[\alpha]_D^{22.5}$ = –179.7 (c = 0.5). IR (KBr): ν 1728 (CON), 1516 (Ar), 1448, 1400, 1352, 1328, 1304, 1248, 1168, 1044, 960, 912, 832, 752, 736, 696 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): 1.64 (d, J = 6.5 Hz, 3 H, CH_3), 3.58 (d, J_{7H} = 5.5 Hz, 1 H, 1-H), 3.77 (s, 3 H, OCH_3), 4.00 (d, J_{gem} = 14.3 Hz, 1 H, 6-H_A), 4.22 (m, 1 H, 7-H), 4.25 (q, J_{CH3} = 6.5 Hz, 1 H, 2-H), 4.72 (dd, J_{gem} = 14.3 Hz, J_{7H} = 1.1 Hz, 1 H, 6-H_B), 5.35 (s, 1 H, 4-H), 6.86 (d, J_{ortho} = 8.8 Hz, 2 H, PMP-3',5'-H), 7.27–7.31 (m, 3 H, Ph-3',4',5'-H), 7.35 (d, J_{ortho} = 8.8 Hz, 2 H, PMP-2',6'-H), 7.43 (d, J_{ortho} = 7.3 Hz, 2 H, Ph-2',6'-H) ppm. ^{13}C

NMR (125 MHz, $CDCl_3$): 20.73 (CH_3), 55.73 (OCH_3), 56.02 (C-6), 59.41 (C-1), 67.27 (C-7), 74.95 (C-2), 108.02 (C-4), 114.71 (PMP-C-3',5'), 119.40 (PMP-C-2',6'), 126.39 (Ph-C-2',6'), 128.32 (Ph-C-3',5'), 128.77 (Ph-C-4'), 131.03 (PMP-C-1'), 139.09 (Ph-C-1'), 156.01 (PMP-C-4'), 164.22 (CON) ppm. $C_{20}H_{21}NO_4$ (339.38) calcd. C 70.78, H 6.24, N 4.13; found C 70.94, H 6.00, N 4.06.

Reduction of comp. *4* with DIBALH. 1N DIBALH/hexane (1 mL, 1 mmol) was added to a solution of **4** (0.17 g, 0.5 mmol) in abs. CH_2Cl_2 at –78 °C under N_2 atmosphere. After 1 hour of stirring at this temperature another 1 mL of DIBALH/hexane was added, because the reaction was not completed (TLC: CH_2Cl_2:EtOAc 10:1.5, UV, $Rf_{\mathbf{6}}$ = 0.3, $Rf_{\mathbf{4}}$ = 0.5). After 2 hours of stirring at –78 °C EtOH (2 mL) was added to the mixture, then it was allowed to warm up to 0 °C. Brine (4 mL) was added to it. The insoluble material was filtered off through a celite bed, which was washed with EtOAc several times. The 2 phases were separated, the organic phase was dried ($MgSO_4$) and the solvent evaporated under reduced pressure. It was purified with prep. TLC (CH_2Cl_2:EtOAc 10:2) to give 0.11 g (64 %) of **{(2*S*,4*R*,5*S*,6*S*)-6-[(4-methoxyphenyl)amino]-4-methyl-2-phenyl-1,3-dioxepan-5-yl}methanol (6)** as a beige solid, which was crystallized from EtOAC/hexane. M.p.: 95 °C. $[\alpha]_D^{27.5}$ = –50.7. IR (KBr): ν 3400 (br, OH, NH), 1516 (Ar), 1236, 1112, 1040, 824, 748, 704 cm^{-1}. ^1H NMR (500 MHz, DMSO): 1.30 (d, J = 6.6 Hz, 3 H, CH_3), 2.12 (m, 1 H, 5'-H), 3.65 (s, 3 H, OCH_3), 3.67 (dd, J_{gem} = 11.5 Hz, $J_{6'H}$ = 9.5 Hz, 1 H, 7'-H_A), 3.78 (dd, J_{gem} = 11.5 Hz, J = 4.5 Hz, 2 H, 7'-H_B + 1-H_A), 3.88 (dd, J_{gem} = 11 Hz, $J_{5'H}$ = 5 Hz, 1 H, 1-H_B), 3.97 (m, 1 H, 6'-H), 4.25 (qd, J_{CH3} = 6.5 Hz, $J_{5'H}$ = 2 Hz, 1 H, 4'-H), 4.58 (brs, 1 H, OH), 5.06 (brs, 1 H, NH), 5.77 (s, 1 H, 2'-H), 6.58 (d, J_{ortho} = 8.8 Hz, 2 H, PMP-3',5'-H), 6.73 (d, J_{ortho} = 8.8 Hz, 2 H, PMP-2',6'-H), 7.31–7.36 (m, 3 H, Ph-3',4',5'-H), 7.40 (d, J_{ortho} = 7.5 Hz, 2 H, Ph-2',6'-H) ppm. ^{13}C NMR (125 MHz, DMSO): 20.06 (CH_3), 48.12 (C-5'), 55.49 (OCH_3), 56.25 (C-6'), 57.44 (C-1), 66.37 (C-7'), 75.13 (C-4'), 99.68 (C-2'), 114.06 (PMP-C-3',5'), 114.95 (PMP-C-2',6'), 126.28 (Ph-C-2',6'), 128.11 (Ph-C-3',5'), 128.23 (Ph-C-4'), 140.32 (Ph-C-1'), 141.91 (PMP-C-1'), 151.06 (PMP-C-4') ppm. MS(EI) *m/z* 343 (63%, M^+), 325 (40%), 312 (45%), 254 (23%), 237 (9%), 206 (53%), 190 (25%), 176 (100%). HRMS: $C_{20}H_{25}NO_4$ calcd. 341.1778, found 343.1769.

Reduction of comp. *4* with $NaCNBH_3$. Molecular sieves 3Å (2 g) and $NaCNBH_3$ (2.5 g, 40 mmol) was added to a solution of **4** (0.9 g, 2.6 mmol) in abs. THF (10 mL) in a flame-dried flask under nitrogen atmosphere. Ether saturated with HCl gas was added to the mixture dropwise at 0 °C till no more gas elevation could be observed. After 1 hour of stirring (TLC: CH_2Cl_2:EtOAc 10:2, UV + PMA, $Rf_{\mathbf{4}}$ = 0.6, $Rf_{\mathbf{5}}$ = 0.45, $Rf_{\mathbf{7}}$ = 0.3) the insoluble precipitation was dissolved by adding water, the mixture was diluted with EtOAc, the phases were separated and the aqueous phase was extracted 3 times with EtOAc. The combined organic layers were washed with 1N HCl, sat. $NaHCO_3$ and brine. The solvent was evaporated under reduced pressure, the residue dissolved in EtOAc, and washed with water and brine again. It was dried ($MgSO_4$), the solvent removed, then purified by flash chromatography (CH_2Cl_2 → CH_2Cl_2:EtOAc 10:1) to give a fraction containing **5**, which was further purified with prep TLC (CH_2Cl_2:EtOAc 10:2) to give 0.38 g (42 %) of **5** as a white solid; and a fraction containing **9**, which was further purified with

prep. TLC (CH_2Cl_2:EtOAc 2:1) to give 0.18 g (20 %) of **9** as a colorless oil. Also 0.08 g (9 %) of **1** was recovered.

(3*R*,4*S*)-3-[(1*R*)-1-(benzyloxy)ethyl]-4-(hydroxymethyl)-1-(4-methoxyphenyl)azetidin-2-one (5). M.p.: 120–121 °C. $[\alpha]_D^{30}$ = –89.3. IR (KBr): ν 3416 (OH), 1712 (CON), 1512 (Ar), 1456, 1400, 1376, 1344, 1296, 1244, 1200, 1168, 1136, 1108, 1072, 1048, 1028, 844, 744 cm^{-1}. ^1H NMR (500 MHz): 1.53 (d, J = 6.5 Hz, 3 H, CH_3), 3.30 (brs, 1H, OH), 3.54 (dd, $J_{\alpha H}$ = 3.4 Hz, J_{4H} = 5.8 Hz, 1 H, 3-H), 3.77 (s, 3 H, OCH_3), 3.98–4.06 (m, 3 H, C*H*$_2$OH + α-H), 4.19 (td, J_{3H} = 5.8 Hz, J_{CH2} = 3.3 Hz, 1 H, 4-H), 4.49 + 4.73 (AB, J_{gem} = 12 Hz, 2 H, $PhCH_2$), 6.85 (d, J_{ortho} = 9 Hz, 2 H, Ar-3',5'-H), 7.28–7.34 (m, 5 H, Ph), 7.35 (d, J_{ortho} = 9 Hz, 2 H, Ar-2',6'-H) ppm. ^{13}C NMR (125 MHz): 18.28 (CH_3), 55.04 (OCH_3), 56.65 (C-4), 56.71 (C-3), 59.64 (CH_2OH), 69.75 (CH_2Ph), 70.94 (C-α), 113.80 (PMP-C-3',5'), 118.36 (PMP-C-2',6'), 127.09 (Ph-C-4'), 127.30 (Ph-C-2',6'), 127.93 (Ph-C-3',5'), 131.44 (PMP-C-1'), 138.18 (Ph-C-1'), 155.31 (PMP-C-4'), 164.71 (CON) ppm. $C_{20}H_{23}NO_4$ (341.40) calcd. C 70.36, H 6.79, N 4.10; found C 70.52, H 6.77, N 4.16.

(3*R*,4*S*)-3-[(1*R*)-1-hydroxyethyl]-4-[(benzyloxy)methyl]-1-(4-methoxyphenyl)azetidin-2-one (9). $[\alpha]_D^{31}$ = –85.1. IR (film): ν 3376 (OH), 1732 (CON), 1516 (Ar), 1456, 1400, 1304, 1248, 1104, 1032, 832 cm^{-1}. ^1H NMR (500 MHz, DMSO): 1.26 (d, J = 6.3 Hz, 3 H, CH_3), 3.38 (m, 1 H, 3-H), 3.72 (s, 3 H, OCH_3), 3.96 (d, J_{4H} = 4.9 Hz, 2 H, CH_2OBn), 4.03 (m, 1 H, α-H), 4.29 (q, J = 4.9 Hz, 1 H, 4-H), 4.49 + 4.55 (AB, J_{gem} = 12 Hz, 2 H, $PhCH_2$), 4.85 (d, $J_{\alpha H}$ = 4 Hz, 1 H, OH), 6.89 (d, J_{ortho} = 9 Hz, 2 H, Ar-3',5'-H), 7.28–7.36 (m, 5 H, Ph), 7.46 (d, J_{ortho} = 9 Hz, 2 H, Ar-2',6'-H) ppm. ^{13}C NMR (125 MHz, DMSO): 23.18 (CH_3), 54.90 (C-4), 55.42 (OCH_3), 57.76 (C-3), 62.82 (C-α), 69.25 (CH_2OBn), 72.64 (CH_2Ph), 114.28 (PMP-C-3',5'), 118.50 (PMP-C-2',6'), 127.49 (Ph-C-4'), 127.70 and 128.48 (Ph-C-2',3',5',6'), 131.73 (PMP-C-1'), 138.26 (Ph-C-1'), 155.42 (PMP-C-4'), 165.63 (CON) ppm. MS (EI) *m/z* 341 (90%, M^+), 206 (45%), 91 (100%). HRMS: $C_{20}H_{23}NO_4$ calcd. 341.16216, found 341.1623.

(3*R*,4*S*)-3-[(1*R*)-1-(benzyloxy)ethyl]-4-[(mesyloxy)methyl]-1-(4-methoxyphenyl)azetidin-2-one (10). Mesyl chloride (0.05 mL, 0.75 mmol) and NEt_3 (0.1 ml, 0.75 mmol) was added to a solution of **5** (0.16 g, 0.47 mmol) in THF (5 mL) under salt-ice cooling. After 1 hour of stirring (TLC: CH_2Cl_2:EtOAc 10:1, UV, $Rf_{\mathbf{5}}$ = 0.4, $Rf_{\mathbf{10}}$ = 0.75) the reaction was not completed, therefore another portion of mesyl chloride (0.05 mL) and NEt_3 (0.1 mL) was added. After 1 hour the reaction was completed. The solvent was evaporated under reduced pressure; the residue was dissolved in EtOAc and water. The phases were separated, the aqueous phase was washed with EtOAc, and the combined organic layers were washed with brine and dried ($MgSO_4$). The solvent was removed under reduced pressure, the residue triturated with ether to give 0.16 g (81 %) of **10** as a white solid. M.p.: 115–116 °C. $[\alpha]_D^{23}$ = –75.5. IR (KBr): ν 1728 (CON), 1520 (Ar), 1456, 1400, 1372, 1336 (Ms), 1296, 1256, 1208, 1176 (Ms), 1144, 1064, 1032, 952, 832, 744, 704, 552, 520 cm^{-1}. ^1H NMR (500 MHz): 1.57 (d, J = 6.5 Hz, 3 H, CH_3), 2.80 (s, 3 H, SCH_3), 3.56 (dd, $J_{\alpha H}$ = 2 Hz, J_{4H} = 6 Hz, 1 H, 3-H), 3.81 (s, 3 H, OCH_3), 3.99 (qd, J_{CH3} = 6.5 Hz, J_{3H} = 2 Hz, 1 H, α-H), 4.43 (m, 1 H, 4-H), 4.60 + 4.63 (dAB, J_{gem} = 11 Hz, $J_{4H,\ H\text{-}4.60}$ = 4.5 Hz, $J_{4H,\ H\text{-}4.63}$ = 6.5 Hz, 2 H, CH_2OS), 4.44 + 4.76 (dAB, J_{gem} = 11.5 Hz, 2 H, $PhCH_2$),

6.89 (d, J_{ortho} = 9 Hz, 2 H, Ar-3',5'-H), 7.28–7.38 (m, 5 H, Ph), 7.40 (d, J_{ortho} = 9 Hz, 2 H, Ar-2',6'-H) ppm. ^{13}C NMR (125 MHz): 17.94 (CH_3), 37.32 (SCH_3), 53.98, 55.72 and 57.63 (OCH_3, C-3, C-4), 69.47, 70.30 and 70.73 (C-α, CH_2S, CH_2Ph), 114.62 (PMP-C-3',5'), 119.25 (PMP-C-2',6'), 128.03 (Ph-C-4'), 128.33 and 128.73 (Ph-C-2',3',5',6'), 130.77 (PMP-C-1'), 137.87 (Ph-C-1'), 156.62 (PMP-C-4'), 164.17 (CON) ppm. $C_{21}H_{25}NO_6S$ (419.41) calcd. C 60.13, H 6.01, N 3.34, S 7.64; found C 60.06, H 6.07, N 3.16, S 7.83.

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