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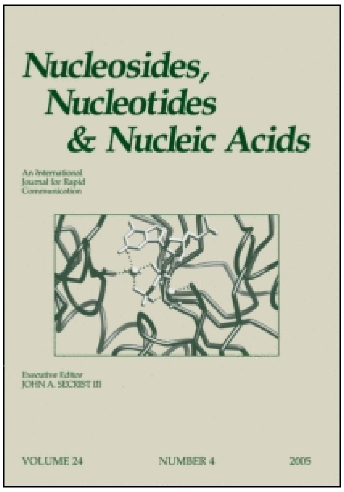

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Intramolecular Glycosylation to Form 4-Methoxy-2,6-Dioxopyrimidine Nucleosides *via* O^6,5'-Cyclonucleosides

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NUCLEOSIDES & NUCLEOTIDES, 18(11&12), 2415–2423 (1999)

INTRAMOLECULAR GLYCOSYLATION TO FORM 4-METHOXY-2,6-DIOXOPYRIMIDINE NUCLEOSIDES *VIA* O^6,5'-CYCLONUCLEOSIDES

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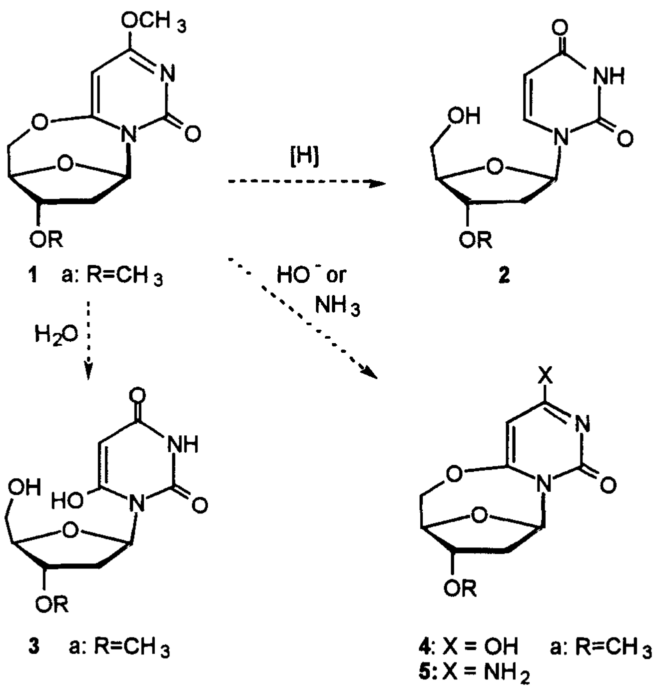
ABSTRACT: Lewis-acid promoted intramolecular *N*1 glycosylation to form the novel O^6,5'-cyclonucleoside **1a** occurs in high yield from the corresponding acyclic thiophenylglycoside **12**. The relative stability of the O^6,5' tether compared with O^2,5' and O^2,3' tethers is reported. Cleavage of the anhydro bond was effected with aqueous base to yield the 4-methoxybarbituric acid nucleoside analogue **14**.

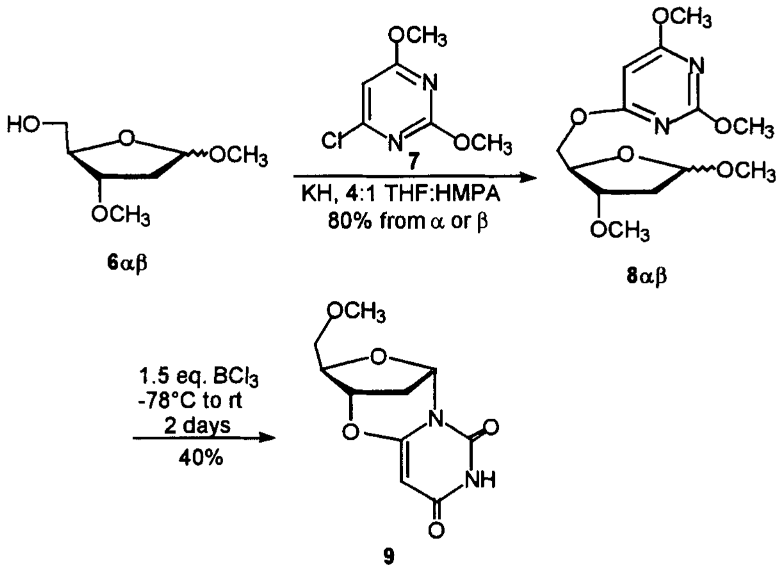
One of the major problems in the synthesis of modified nucleosides is the coupling of the purine or pyrimidine base to the modified sugar to give the desired β-anomer of the nucleoside. This is especially true for 2'-deoxy analogues where the normal anchimeric directing effect of the 2'-α-acyloxy group is absent. Recently, we[1] and others[2] have reported the use of intramolecular N-glycosylation reactions to synthesize important modified β-nucleosides. This approach, using an oxygen tether to deliver the base to the anomeric center, has yielded several biologically active β-nucleosides,[2b,2d] all limited however to the 2,4-dioxopyrimidine derivatives.[3] We now report the application of this methodology to the synthesis of 2'-deoxy-4-methoxy-3'-*O*-methyl-O^6,5'-cyclouridine (**1**) (Scheme 1). Cyclonucleosides like **1** are potentially versatile compounds since they might be useful precursors for not only the traditional 2,4-dioxopyrimidine β-nucleosides **2**, but also the novel 6-hydroxyuridines **3**.[4] Moreover, displacement of the pyrimidyl methoxy group in **1** by hydroxide or ammonia would permit access to *anti*-restricted nucleosides, namely 3'-*O*-alkyl-2'-deoxy-4-hydroxy-O^6,5'-cyclouridine (**4**) and its cytidine analogue **5**, which are useful conformational probes.[4,5]



Scheme 1

As shown in Scheme 2, our initial O^6,5'-bridged cyclization precursor **8**, easily prepared from commercially available 6-chloro-2,4-dimethoxypyrimidine (**7**) and the methyl ribosides **6**,[6] did not produce the desired cyclonucleoside **1a** upon treatment with several Lewis acids (TMSOTf, TBSOTf, $SnCl_4$, $TiCl_4$, Et_2AlCl). Prolonged exposure to these reagents either hydrolyzed the methyl acetal of **8** or decomposed the starting material by cleaving the O^6,5'-tether to yield the free base and the carbohydrate. However, treatment of **8** with boron trichloride yielded the unexpected adduct **9** in 40% yield (80% based on recovered starting material).[6] As we reported previously, the formation of **9** is reasonable based on intramolecular glycosylation occurring after pyrimidyl base transfer from C5 to O3.[6]

In order to circumvent the formation of this novel anhydro adduct, other modes of activating the anomeric center to nucleophilic attack by N1 of the pyrimidine base were considered. Since thiophenyl glycosides have been used extensively in glycosylation reactions, we hoped to convert **8** into its corresponding thioglycoside using trimethylsilyl triflate (TMSOTf) and trimethyl(thiophenyl)silane (TMSSPh).[7] This approach would require fewer steps than the alternative of initial preparation of the

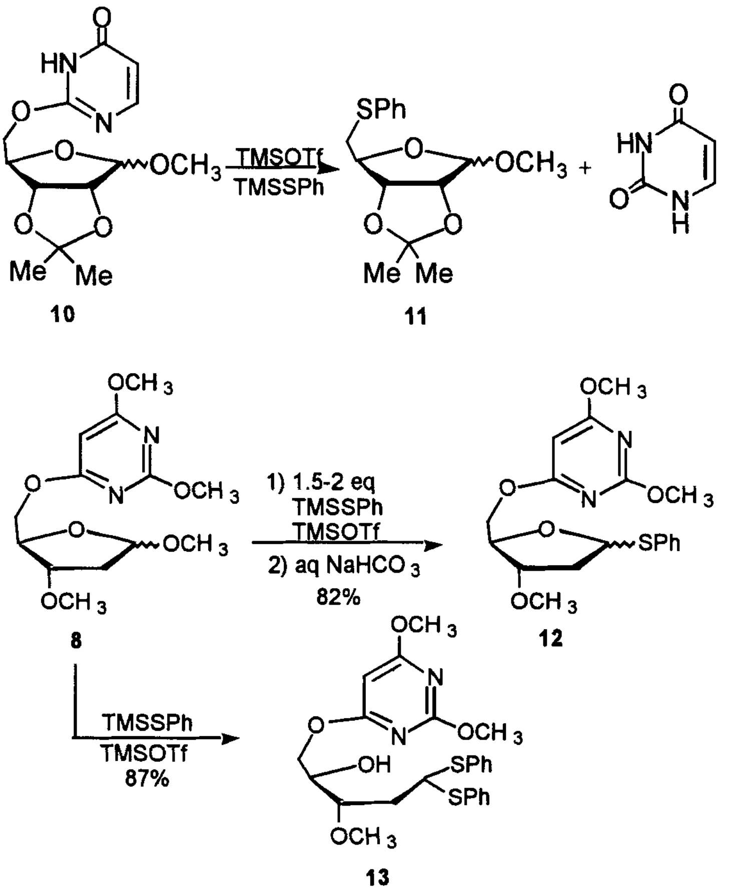


Scheme 2

thiophenyl glycoside and its subsequent coupling with the chloropyrimidine 7. Of concern, however, was that the conditions used to install the thiophenyl group might cleave the tether, since previous work in our laboratories had shown that systems with an O^2,5' linkage are very sensitive to nuc-leophilic attack.[8] For example, compound **10** was rapidly converted to the corresponding 5-deoxy-5-phenylthioriboside **11** and free uracil upon exposure to TMSSPh and TMSOTf (Scheme 3).

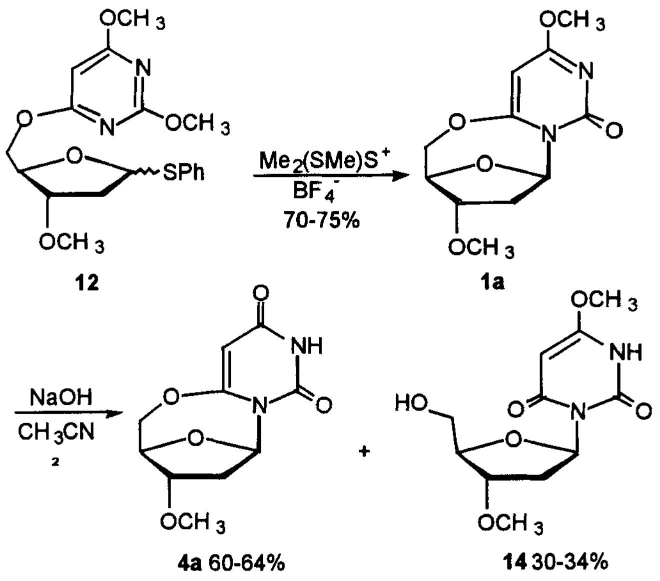
Fortunately, the O^6,5' tether proved to be more stable than the O^2,5' linkage, and an anomeric mixture of thiophenyl glycoside **12** was prepared from **8** in good yield (Scheme 3). It would appear that the greater stability ofthis type of linkage makes compounds such as **8** easier to manipulate than the corresponding O^2,5' systems. However, if the aqueous basic work-up step is omitted in the formation of **12**, only the thioketal **13** is isolated. This is unexpected since bis(thiophenyl) acetals of carbohydrates are rare, although the corresponding bis(thioalkyl) compounds are common.[9]

The critical cyclization step (Scheme 4) was successfully accomplished using dimethyl(methylthio)sulfonium tetrafluoroborate as the activating agent, the Lewis acid used extensively by Sugimura's group in their intramolecular glycosylation reactions.[2a,b] The cyclized adduct **1a** formed in good yield with dichloromethane as the solvent; the only other product isolated (10-15%) was starting material hydrolyzed at the anomeric center. This cyclization reaction proved to be very sensitive to the solvent used. In



Scheme 3

acetonitrile, only trace amounts of the desired product were identified by TLC, a result which differs from those of the Sugimura group since in their systems cyclization was much more effective in acetonitrile. In addition, Sugimura has suggested that the amount of hydrolyzed starting material recovered is minimized when a 3'-substituent is present.[2b] The appearance of hydrolyzed adduct in our case seems to suggest that the role of the 3'-substituent is not as significant as the role of the solvent. To return to the synthesis of the nucleosides, removal of the pyrimidyl methoxy group was accomplished with aqueous base under rather vigorous conditions (1M sodium hydroxide in refluxing acetonitrile)[10] to give the desired O^6,5'-cyclouridine **4a** in 60-64% yield along with the 2'-deoxy-4-methoxy-2,6-dioxopyrimidine **14** in 30-34% yield.



Scheme 4

That N1 cyclization had occurred was evident from the large downfield shift of H1' from the acyclic precursor **12** (5.6-5.8 ppm, α or β anomer) to the cyclic product **1** (7.1 ppm). Moreover, the two H5' protons showed the characteristic shifts and splitting pattern typical of O^6,5'-cyclopyrimidine nucleosides (two doublets of doublets with one large and one small coupling constant: $J = 12.5$ and 1 Hz at δ 4.43 and $J = 12.5$ and 1.2 Hz at δ 3.97 ppm).[11] Finally, the high resolution mass spectrometry for both **1a** and **4a** showed a cleavage pattern similar to those reported for other O^6,5'-cyclonucleosides.[12] The isolation and characterization of **1a** is especially noteworthy because it represents the first synthesis of an anhydronucleoside *via* this route in high yield. While the Lipshutz group has studied O^6,5'-tethers to a 5,6-dihydro-5-bromopyrimidine, ring closures have been problematic with yields less than 50%.[2c] Reports using O^2,3' or O^2,5' tethers to deliver the aglycone propose the existence of a cycloadduct based on the isolation of the β-nucleoside after aqueous work-up.[2a,b,d] In our earlier work, the anhydro adduct was isolated but only in modest yield (<20%).[1]

In conclusion, O^6,5'-cyclonucleosides and β-barbituric acid nucleosides should be readily accessible using the intramolecular glycosylation approach. We have shown that this method can be used to synthesize both the 2'-deoxy-O^6,5'-cyclouridines **1a** and **4a** and 2'-deoxy-4-methoxy-2,6-dioxopyrimidine nucleoside **14**. Furthermore, we believe that the greater stability of the O^6,5' tether makes these sugar-base hybrid compounds much more useful than systems having an O^2,5' bridge.

Experimental

General: ^1H (at 400MHz) and ^{13}C NMR (at 100 MHz) were recorded on a Bruker DPX-400 spectrometer (δ in ppm, *J* in Hz). Infrared spectra were obtained using a 6020 Galaxy FT-IR or MIDAC Corporation Prospect-IR spectrometer. High resolution mass spectra were obtained from the Mass Spectrometry Facility at the University of California, San Francisco. Samples were analyzed by electron impact (EI) using a VG 7OSE mass spectrometer. Melting points were obtained using a Mel-Temp apparatus and are uncorrected. TLC was carried out on Baker Si250F TLC precoated glass plate silica gel, 0.25mm layer thickness. Acetonitrile and dichloromethane were distilled over calcium hydride. Tetrahydrofuran (THF) was distilled from Na/benzophenone ketyl prior to use. Other solvents were used without further purification. Flash column chromatography with silica gel was carried out according to the method of Still.[13] All reactions were carried out under an inert nitrogen or argon atmosphere.

Phenyl 2-deoxy-5-*O*-(2,6-dimethoxypyrimidin-4-yl)-3-*O*-methyl-1-thio-α,β-D-*erythro*-pentofuranoside (12). (Phenylthio)trimethylsilane (0.39 mL, 2.1 mmol) and trimethylsilyl trifluoromethanesulfonate (TMSOTf, 0.32 mL, 1.6 mmol) were added slowly *via* syringe to a solution of **8** (0.41 g, 1.4 mmol) in dichloromethane (60 mL) at 0° C. After stirring for 5 h, the reaction mixture washed twice with saturated $NaHCO_3$ solution and once with saturated NaCl solution. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The resulting residue was purified by flash chromatography (2:1 hexane/EtOAc) to yield an anomeric mixture of **12** (0.34 g, 82%) as an oil; R_f 0.6 (2:1 hexane/EtOAc). ^1H NMR ($CDCl_3$): δ 7.51 (m, 2H, H-Ph), 7.27 (m, 3H, H-Ph), 5.76 (s, 0.55 H, 5-H), 5.75 (s, 0.45 H, 5-H). 5.74 (m, 0.55H, 1'-H), 5.61 (dd, *J* = 8.1, 6.2, 0.45 H, 1'-H), 4.53-4.36 (m, 4 H, 3'-H, 4'-H, 2 x 5'-H), 3.97 (s, 3 H, OCH_3), 3.94 (s, 3 H, OCH_3), 3.39 (s, 1.6 H, OCH_3), 3.33 (s, 1.4 H, OCH_3), 2.69 (ddd, *J* = 13.8, 7.4, 7.4, 0.55 H, 2'-H), 2.45 (ddd, *J* = 13.8, 6.2, 2.7, 0.45 H, 2'-H), 2.17 (m, 1 H, 2'-H). ^{13}C NMR ($CDCl_3$): δ 172.77, 171.94, 171.79, 164.66, 135.76, 134.10, 131.62, 130.76, 128.72, 127.17, 126.78, 87.15, 85.94, 83.73, 82.80, 82.07, 80.95, 80.88, 66.56, 65.89, 58.21, 57.46, 54.61, 53.98, 38.59, 37.82 (several lines unresolved). IR (neat): 3055, 2988, 2939, 2901, 1598, 1465, 1396, 1267, 1204, 1170, 1106, 1059 cm^{-1}. HRMS: calcd for $C_{18}H_{23}N_2O_5S$ (MH^+) 379.1328, found 379.1329.

2-Deoxy-5-*O*-(2,6-dimethoxypyrimidin-4-yl)-3-*O*-methyl-D-*erythro*-pentose diphenyl dithioacetal (13). The same procedure described above for the preparation of **12** was used to prepare the thioacetal **13** with one variation, namely, the aqueous work-up steps were omitted. Instead, the reaction mixture was concentrated *in vacuo* and purified *via* flash chromatography (2:1 hexane:EtOAc) to yield a pale yellow syrup (87%); R_f 0.5 (2:1 hexane/EtOAc). ^{1}H NMR ($CDCl_3$): δ 7.49 (m, 4H, H-Ph), 7.23 (m, 6H, H-Ph), 5.76 (s, 1H, 5-H), 4.72 (dd, *J* = 9.7, 4.6, 1H, 1'-H), 4.37 (dd, *J* = 11.4, 4.0, 1H, 5'-H), 4.33 (dd, *J* = 11.4, 6.2, 1H, 5'-H), 4.07 (ddd, *J* = 6.2, 4.5, 4.0, 1H, 4'-H), 3.96 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 3.77 (ddd, *J* = 8.6, 4.6, 4.6, 1H, 3'-H), 3.40 (s, 3H, OCH_3), 3.10 (br s, 1H, OH), 2.27 (ddd, *J* = 13.6, 9.1, 4.6, 1H, 2'-H), 1.99 (ddd, *J* = 13.6, 9.7, 3.4, 1H, 2'-H). ^{13}C NMR ($CDCl_3$): δ 173.36, 172.43, 165.13, 135.18, 134.03, 133.36, 132.80, 129.35, 129.32, 128.24, 128.03, 84.33, 79.21, 71.22, 68.33, 58.73, 55.19, 54.81, 54.57, 37.19. IR (neat): 3421, 2947, 1594, 1461, 1363, 1169, 1108 cm^{-1}. HRMS: calcd for $C_{24}H_{28}N_2O_5S_2$ 488.1440, found 488.1442.

3,4,5,6-Tetrahydro-4,10-dimethoxy-3,6-epoxy-2*H*,8*H*-pyrimido[6,1-*b*][1,3]oxazocin-8-one (1a). A solution of the thiosugar **12** (0.12 g, 0.31 mmol) in dichloromethane (70 mL) was added to activated molecular sieves (4Å, 5 g) at 25 °C. The reaction mixture was cooled to –20 °C and stirred for 20 min, after which dimethyl(methylthio)sulfonium tetrafluoroborate (0.075 g, 0.38 mmol) was introduced. After further stirring for 1 h and 40 min, the reaction was quenched with 1M NaOH (4 mL). The organic layer was washed with saturated $NaHCO_3$, saturated NaCl, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by flash chromatography (2:1 hexane/EtOAc-EtOAc, gradient elution). **1a** was isolated as a white solid (0.057 g, 70%); R_f 0.5 (EtOAc), mp 142-143 °C. ^{1}H NMR ($CDCl_3$): δ 7.08 (dd, *J* = 8.4, 1.8, 1H, 1'-H), 5.46 (s, 1H, 5-H), 4.44 (s, 1H, 4'-H), 4.43 (dd, *J* = 12.5, 1, 1H, 5'-H), 4.16 (dd, *J* = 6.8, 0.7, 1H, 3'-H), 3.97 (dd, *J* = 12.5, 1.2, 1H, 5'-H), 3.86 (s, 3H, 4-OCH_3), 3.28 (s, 3H, 3'-OCH_3), 2.46 (dd, *J* = 14.7, 8.4, 1H, 2'-H), 2.26 (ddd, *J* = 14.7, 6.8, 1.8, 1H, 2'-H). ^{13}C NMR ($CDCl_3$): δ 172.56, 163.83, 155.97, 85.58, 85.15 (2C), 82.39, 77.52, 56.46, 54.47, 39.51. IR: 2953, 1674, 1622, 1537, 1387, 1194, 1182, 1135 cm^{-1}. HRMS: calcd for $C_{11}H_{14}N_2O_5$ 254.0902, found 254.0897.

3,4,5,6-Tetrahydro-4-methoxy-3,6-epoxy-2*H*,8*H*-pyrimido[6,1-*b*][1,3]oxazocin-8,10(9*H*)-dione (4a) and 2'-deoxy-4-methoxy-3-*O*-methyl-2,6-dioxouridine (14). To a solution of **1a** (0.015 g, 0.059 mmol) in acetonitrile (2 mL) at 25 °C was added 1M NaOH (0.35 mL). After refluxing for 72 h, the solution was subjected to flash chromatography (ethyl acetate) to yield both **4a** (0.009 g, 64%, mp 180-185 °C) and **14** (0.005 g, 32%, mp 110-114 °C) as white solids . Compound **4a:** ^{1}H NMR ($CDCl_3$): δ 8.20 (br s, 1H, NH), 6.94 (dd, *J* = 8.4, 2, 1H, 1'-H), 5.40 (s, 1H, 5-H), 4.52 (app s, 1H, 4'-H), 4.50 (dd, *J* = 13.2, 1.4, 1H, 5'-H), 4.24 (dd, *J* = 6.6, 1, 1H, 3'-H), 4.05 (dd, *J* = 13.2, 1.6, 1H, 5'-H), 3.37 (s, 3H, OCH_3), 2.55 (ddd, *J* = 14.9, 8.4, 1, 1H, 2'-H), 2.41 (ddd, *J* = 14.9, 6.7, 2, 1H, 2'-H). ^{13}C NMR ($CDCl_3$): δ 162.09, 149.47, 149.40, 90.78, 84.68, 82.44, 82.38, 77.92, 56.58, 39.46. IR: 3185, 3071, 2944, 2827, 1728, 1682, 1624, 1537, 1461, 1387, 1183, 1088 cm^{-1}. HRMS: calcd for $C_{10}H_{12}N_2O_5$ 240.0746, found 240.0745. Compound **14:** ^{1}H NMR (acetone-d_6): δ 6.64 (dd, *J* = 8.2, 7.2, 1H, 1'-H), 6.11 (br s, 1H, NH), 5.09 (s, 1H, 5-H), 4.14 (ddd, *J* = 6.6, 2.6, 2.6, 1H, 3'-H), 3.98 (app q, *J* = 2.9, 1H, 4'-H), 3.93 (s, 3H, 4-OCH_3), 3.73 (dd, *J* = 11.9, 3, 1H, 5'-H), 3.59 (dd, *J* = 11.9, 3, 1H, 5'-H), 3.33 (s, 3H, 3'-OCH_3), 2.87 (br s, 1H, OH), 2.85 (ddd, *J* = 13.1, 8.3, 6.7, 1H, 2'-H), 2.10 (m, 1H, 2'-H). ^{13}C NMR ($CDCl_3$): δ 164.37, 162.40, 150.75, 85.86, 82.77, 82.49, 77.52, 63.47, 56.72, 56.35, 33.91. IR (KBr): 3469, 3118, 2947, 2865, 1728, 1634, 1520, 1429, 1250, 1097, 1066 cm^{-1}.

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