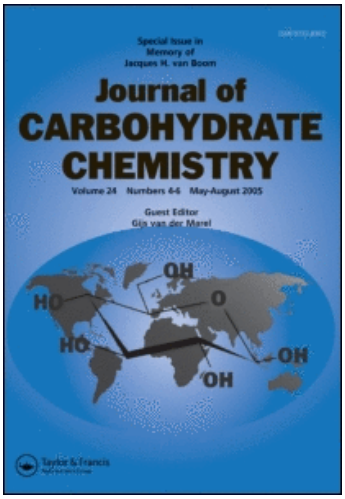

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DIMERIZATION BY HETERO DIELS-ALDER REACTION OF METHYL 4,6-*O*-BENZYLIDENE-3-DEOXY-3-*C*-METHYLENE-α-D-*ERYTHRO*-HEXOPYRANOSID-2-ULOSE

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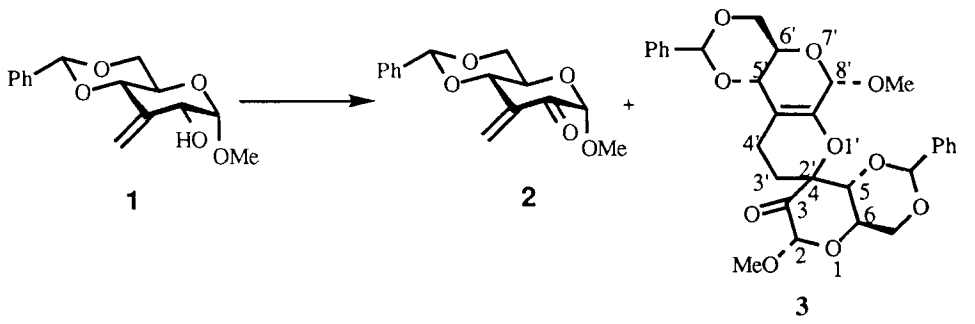
ABSTRACT

The dimerization by hetero Diels-Alder reaction of methyl 4,6-*O*-benzylidene-3-deoxy-3-*C*-methylene-α-D-*erythro*-hexopyranosid-2-ulose was found to be regio and stereospecific. The structure of the cycloadduct was assigned from NMR spectrographic and X-ray crystallographic results. These results indicated that this cycloaddition occurred by a concerted hetero Diels-Alder reaction with inverse electron demand.

INTRODUCTION

In the course of our research program devoted to methylene-linked disaccharide analogues (C-disaccharides), methyl 4,6-*O*-benzylidene-3-deoxy-3-*C*-methylene-α-D-*erythro*-hexopyranosid-2-ulose (**2**) was needed as a Michael acceptor of activated sugar derivatives. Surprisingly, oxidation of allylic alcohol **1**[1] with pyridinium dichromate (PDC) in the presence of acetic acid and 3 Å molecular sieves[2] did not afford enone **2**



Scheme 1

in good yield, although equatorial allylic alcohols derived from carbohydrates were readily oxidized with this reagent.[3] Chromatography on silica gel of the reaction mixture afforded **2** in low yield (34%). As indicated by TLC and ^{1}H NMR, enone **2** was contaminated by another compound which was identified later as the dimer **3** (Scheme 1).

Other oxidizing systems were evaluated, such as 4-methylmorpholine *N*-oxide (NMO) in the presence of tetra-*n*-propylammonium perruthenate (TPAP),[4] palladium acetate,[5] manganese dioxide[6] and dimethyl sulfoxide-acetic anhydride (DMSO/Ac_2O).[7] The reaction was taken to completion only with the latter one. Compound **3** was isolated in good yield (88%) after filtration on silica gel to eliminate excess DMSO.

The dimeric nature of **3** was determined by mass spectroscopy (see experimental) and was confirmed by ^{1}H NMR. The ^{1}H NMR spectrum of **3** exhibited the signals of two nonequivalent pyranose residues: *inter alia* two methoxy (3.39 and 3.41 ppm), two benzylidene H-C (5.46 and 5.51 ppm) and two anomeric protons (4.69 and 4.79 ppm). Two complex signals (4H) observed at 1.61 and 2.42 ppm could be assigned to two CH_2 groups (3' and 4'). Further structure confirmation was obtained from ^{1}H/^{1}H correlation (COSY 45), ^{13}C NMR spectroscopy and ^{1}H/^{13}C correlation.

Compound **3** could be the result of a (4+2) cyclization of enone **2** formed *in situ* behaving as a diene and dienophile. The regioselectivity of cycloaddition was determined by the displacement of quaternary C-4 at 82.4 ppm and two coupled methylene groups (3' and 4') at 14.6 and 21.0 ppm in the ^{13}C NMR spectra.

Finally, the structure of compound **3** was confirmed by X-ray diffraction analysis.[8] The crystal structure was solved by direct methods. Final non-hydrogen

atom coordinates and equivalent isotropic displacement parameters are listed in Table 1. A view of the solid-state conformation is provided in Figure 1. Both lengths and angles are close to accepted values. This allowed to establish as *S* the absolute configuration at C-4. The steric course of this cycloaddition can be rationalised by attack of the enone **2** on the *Si*-face of the C=C double bond of another enone.

This easy dimerization is quite surprising because it is well known that self-condensation of enones by hetero Diels-Alder reactions is rather difficult and that moderate yields are obtained even under harsh conditions.[9] In contrast, in our experiments, **3** was obtained in 88% yield at room temperature. Consequently, we decided to carry out some experiments in order to try to explain this unusual behavior and we report herein our results.

RESULTS AND DISCUSSION

Compound **3** could be obtained from **1** by two different pathways (Scheme 2).

Pathway A involves addition of enone **2** formed *in situ* to allylic alcohol **1** to give the adduct **4** which could be further oxidized to the final product **3**. However, whatever the reaction conditions were, only three spots corresponding to compounds **1**, **2** and **3** were observed by analytical thin-layer chromatography of the reaction mixture before completion of the reaction. If a hindered secondary alcohol such as **4** would have been formed as a transitory intermediate, a slower oxidation rate would have been expected for this compound as compared to **1**, since it is well known that oxidation of equatorially oriented cyclic allylic alcohols is easy.[3] Futhermore, no condensation occurred when alcohol **1** was treated with an excess of 3-buten-2-one even under reflux. Consequently pathway A is not very likely.

The other possibility (pathway B) is a direct dimerization of enone **2** as soon as it is formed. This dimerization could be a concerted reaction or a stepwise reaction catalyzed by any acid present. When alcohol **1** was oxidized with NMO in the presence of TPAP (non-acidic conditions), a mixture of **1** (64 %), **2** (13 %) and **3** (23 %) were obtained as indicated from ^{1}H NMR spectral data in $CDCl_3$, so a concerted Diels-Alder type reaction is possible but rather slow under these conditions. Oxidation of **1** with $DMSO/Ac_2O$ afforded a mixture of **2** (74 %) and **3** (26 %) before filtration on silica gel. When this mixture was dissolved in $CDCl_3$ or C_6D_6, examination of its ^{1}H NMR spectrum indicated diminution of signals corresponding to **2** with concomittant augmentation of those corresponding to **3**. The rate of transformation of **2** into **3** is

Table 1. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for **3**. U_{eq} is defined as one third of the trace of the orthogonalized U_{ij} tensor.

Atom	x	y	z	U_{eq}
O(1)	3914 (3)	9252 (8)	5640 (4)	575
C(2)	3724 (4)	9200 (1)	4646 (7)	483
O(2)	3093 (3)	9363 (8)	4215 (5)	634
O(3)	4208 (3)	7645 (8)	3806 (4)	649
C(3)	3912 (3)	7650 (1)	4315 (6)	460
C(4)	3729 (4)	6130 (1)	4717 (6)	410
O(5)	3845 (2)	5097 (7)	6282 (3)	443
C(5)	3985 (4)	6400 (1)	5787 (6)	454
C(6)	3727 (4)	7910 (1)	6045 (6)	524
O(7)	3892 (3)	6687 (9)	7564 (4)	653
C(7)	3985 (5)	8100 (1)	7103 (7)	661
C(8)	4133 (4)	5350 (1)	7265 (4)	519
C(9)	4031 (4)	3960 (1)	7803 (6)	530
C(10)	4512 (5)	2960 (2)	8227 (7)	742
C(11)	4459 (6)	1660 (2)	8749 (8)	893
C(12)	3919 (7)	1380 (1)	8860 (7)	789
C(13)	3432 (5)	2350 (2)	8461 (8)	747
C(14)	3494 (4)	3630 (1)	7919 (7)	687
C(21)	2909 (6)	10960 (1)	4150 (1)	878
O(1)'	4074 (2)	4843 (7)	4519 (3)	442
C(3)'	3067 (4)	5760 (1)	4327 (6)	462
C(4)'	2855 (3)	5570 (1)	3255 (5)	431
C(5)'	3206 (3)	4288(9)	1972(5)	353
O(5)'	2590 (2)	3782 (6)	1500 (3)	432
C(6)'	3617 (3)	2979 (9)	1878 (5)	386
O(7)'	4230 (2)	3458 (7)	2359 (3)	451
C(8)'	4365 (3)	3540 (1)	3351 (5)	399
O(8)'	4427 (2)	2052 (7)	3760 (4)	463
C(9)'	3863 (3)	4382 (9)	3580 (5)	374
C(10)'	3321 (3)	4688 (8)	2978 (5)	331
O(11)'	2883 (3)	2299 (7)	415 (4)	509
C(11)'	3515 (4)	2690 (1)	852 (5)	488
C(12)'	2495 (4)	3510 (1)	532 (5)	426
C(13)'	1851 (4)	3040 (1)	33 (5)	418
C(14)'	1570 (4)	3410 (1)	-890 (6)	581
C(15)'	971 (5)	2960 (1)	-1364 (6)	672
C(16)'	669 (4)	2190 (2)	-872 (8)	777
C(17)'	936 (4)	1800 (1)	35 (7)	734
C(18)'	1536 (4)	2240 (1)	494 (6)	574
C(81)'	4967 (4)	1290 (1)	3763 (6)	615

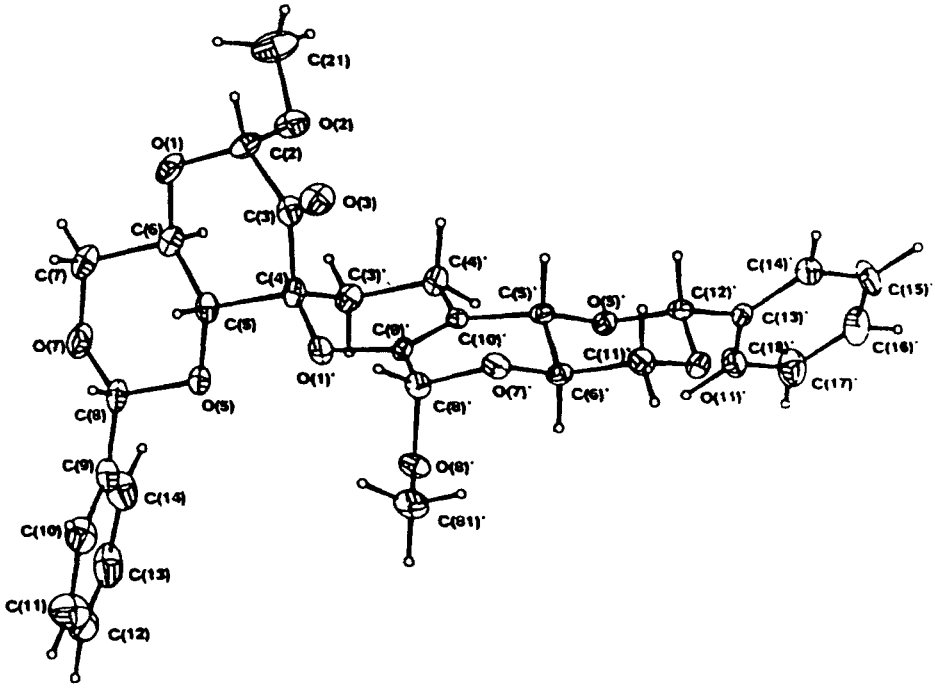
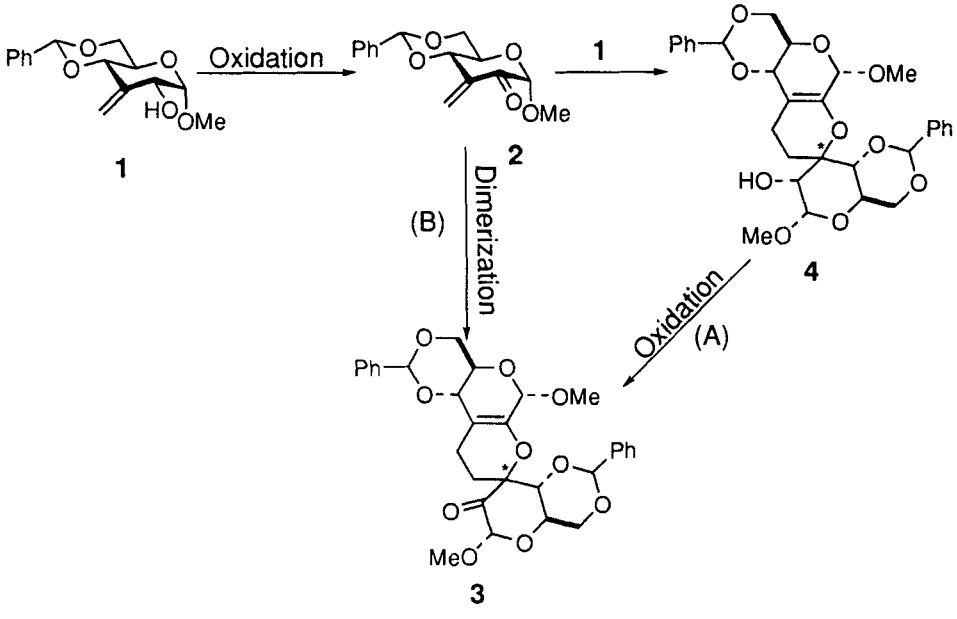
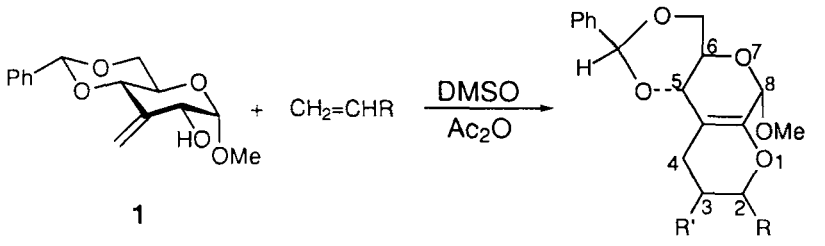


Figure 1. ORTEP diagram of the molecular structure of 3.



Scheme 2



5 R=COOEt, R'=H
5' R=H, R'=COOEt
6 R=OEt, R'=H
6' R=H, R'=OEt

Scheme 3

effectively increased under acidic conditions (for example, filtration on silica gel) or under ultrasonic conditions. These results rule out pathway A and confirm the propensity of self-condensation of **2** by a concerted mechanism which could be accelerated by acidic catalysis.

However, employing 1-oxabutadienes in Diels-Alder reactions proceeds usually with inverse electron demand.[10] Logically, the self condensation of enone **2** should be rather difficult, as enone is usually electron deficient. When oxidation of **1** was carried out with DMSO/Ac_2O in the presence of 10 equiv of an electron deficient double bond compound (ethyl acrylate) at room temperature (Scheme 3, R = COOEt), ^1H NMR data of the crude reaction mixture indicated absence of compound **5** or **5'** and a mixture of enone **2** (65%) and dimer **3** (35%) were observed. The same reaction held at 60 °C afforded exclusively the dimer **3**. In contrast, when the oxidation was carried out in the presence of an electron rich double bond compound such as vinyl ether (Scheme 3, R = OEt, 20 equiv), only 3.6% of dimer **3** was obtained. The single cross-coupling product **6** was isolated (69%) and characterized.

The structure of **6** was confirmed by the presence of the two acetal protons : H-8 at 4.63 ppm as a singlet and H-2 at 5.04 ppm as a triplet ($J_{2,3}$ = 2.8 Hz) in its ^1H NMR spectrum. The two CH_2 groups (3 and 4) were equally observed at relatively high magnetic field (1.83 to 2.21 ppm in ^1H NMR, 25.6 and 13.7 ppm in ^{13}C NMR). As in the case of compound **3**, only one stereoisomer of **6** was obtained. The observed small coupling constant $J_{2,3}$ indicated an equatorial orientation of H-2 and an *S* configuration is attributed to C-2 by comparison of $J_{2,3}$ values with analogous compounds in the literature.[11,12]

These two quenching experiments indicated that the cycloaddition with enone **2** proceeded with inverse electron demand. The regioselectivity of cycloaddition with vinyl ether is logical owing to LUMO-HOMO interactions between the carbonyl group and the vinyl ether as reported by numerous authors.[13,14]

Recently, such a spontaneous dimerization of carbohydrate-derived α-alkoxy-enone was described.[15] This unusual propensity to dimerization may be due to some special structural feature of these enones which is not present in very closely related enones which did not spontaneously dimerize.[14,16] More work, including molecular mechanics calculations, is needed to rationalize these observations.

In summary, our study of dimerization of enone **2**, formed *in situ* during the oxidation of the corresponding allylic alcohol **1**, confirmed that this dimerization proceeds through a concerted hetero Diels-Alder reaction with inverse electron demand. The regio- and stereospecificities observed in the cycloaddition of this pyranosidic enone indicated an absolute addition preference of enone to dienophile. This reaction can be used as a new pathway for pyranosidic homologation and for the synthesis of long chain multichiral arrays present in a number of natural products.

EXPERIMENTAL

General methods Melting points were measured with a Thomas-Hoover apparatus and are uncorrected. IR spectra were recorded with a Unicam spectrometer. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker AGH 250 spectrometer. Optical rotations were measured using a Perkin-Elmer 141 polarimeter and a 10-cm cell. Analytical TLC were performed on Merck aluminum precoated plates of silica gel 60 F-254 with detection by UV and by spraying with 6N H_2SO_4 and heating about 2 min at 300 °C. For flash chromatography, Merck silica gel 60 (230-400 mesh) was employed. Merck silica gel 600 PF-254 was used for preparative layer chromatography. Solvents were evaporated under reduced pressure in a rotary evaporator below 35 °C.

Microanalyses were performed at the Service de Microanalyse de l'Université Pierre et Marie Curie.

Methyl 4,6-*O*-benzylidene-3-deoxy-3-*C*-methylene-α-D-*erythro*-hexopyranosid-2-ulose (2). Freshly ground pyridinium dichromate (126 mg, 0.34 mmol) was added in one batch to a stirred solution of **1** (82 mg, 0.29 mmol) in CH_2Cl_2 containing anhydrous AcOH (22 μL, 0.39 mmol) and molecular sieves (3 Å, 179 mg). After

stirring at rt (19 h), ether (5 mL) was added in order to precipitate most of the chromium salts. The mixture was filtered through a layer of Celite and the filtrate concentrated under reduced pressure. The residue was filtered through silica gel with CH_2Cl_2 to give **2** (27 mg, 34%) which contains 12.5% of dimer **3**: Solid, R_f 0.62 ($CHCl_3$/EtOAc 9/1), IR 1730 cm^{-1}, ^1H NMR δ 7.48-7.50 (m, 5H, H-Ar), 6.20 (m, 1H, CH=), 5.79 (m, 1H, CH=); 5.65 (s, 1H, CH-Ph), 4.75 (s, 1H, H-1), 4.43 (dd, 1H, J = 10.4, 4.7 Hz, H-6), 4.44 (m, 1H, H-4), 4.14 (td, 1H, J = 9.8, 4.7 Hz, H-5), 3.85 (dd, 1H, J = 10.4, 9.8 Hz, H-6'), 3.51 (s, 3H, OMe).

(2*S*, 4*S*, 5*R*, 6*R*, 5'*S*, 6'*R*, 8'*S*) 5,6; 5',6'-bis-*O*-benzylidene-5,5'-dihydroxy-6,6'-bis(hydroxymethyl)-2,8'-dimethoxyspiro [tetrahydropyran-4,2'-(3',4',5',6'-tetrahydro-2H-pyrano[3,4-b]pyran)-3-one (3). A solution of **1** (278 mg, 1 mmol) in a mixture (8 mL) of DMSO-Ac_2O (5 : 3, v/v) was stirred at rt overnight. After addition of a saturated solution of $NaHCO_3$ (10 mL), the mixture was extracted with CH_2Cl_2 (3 x 10 mL). The organic layer was washed with H_2O (3 x 10 mL) and dried ($MgSO_4$). After solvent evaporation, the residue was filtered through a column of silica gel. Elution with CH_2Cl_2 afforded dimer **3**: 245 mg (88%), solid, mp 208-210 °C, R_f 0.38 ($CHCl_3$/EtOAc, 9/1); $[\alpha]_D$ +61.0 (*c* 0.35, CH_2Cl_2), IR 1750 cm^{-1}, ^1H NMR ($CDCl_3$) δ 7.27-7.42 (m, 10H, H-Ar), 5.51(s, 1H, CH-Ph), 5.46 (s, 1H, CH-Ph), 4.79 (d, 1 H, J = 1.5 Hz, H-8'), 4.69 (s, 1H, H-2), 4.35 (dd, 1H, J = 10.2, 5.0 Hz, CH-O), 4.22 (ddd, 1H, J = 9.8, 9.6, 5.0 Hz, H-6'), 4.19 (dd, 1H, J = 9.8, 4.3 Hz, CH-O), 4.08 (d, 1H, J = 8.8 Hz, H-5), 3.92 (ddd, 1H, J = 10.2, 8.8, 4.3 Hz, H-6), 3.87 (d, 1H, J = 9.8 Hz, H-5'); 3.74 (m, 2H, 2xCH-O), 3.41 (s, 3H, OMe), 3.39 (s, 3H, OMe), 2.42 (m, 3H, 2xH-4', H-3'), 1.61 (m, 1H, H-3'); ^{13}C NMR ($CDCl_3$) δ 195.2 (CO), 143.9 (C=), 136.7, 135.8, 128.1, 127.9, 127.2, 127.2, 125.2 (Ar), 107.0 (C=), 101.4 (C-2), 100.6, 100.2 (C-Ph), 95.1 (C-8'), 82.4 (C-4), 81.6 (C-5), 75.2 (C-5'), 68.0, 67.9 (CH_2-O), 63.9 (C-6'), 60.3 (C-6), 55.1 (OMe), 54.7 (OMe), 21.0 (C-4'), 14.6 (C-3'); CIMS : m/z 570 (54, $[m + NH_4]^+$), 553 (6.5, $[m + H]^+$).

Anal. Calcd for $C_{30}H_{32}O_{10}$: C, 65.21; H, 5.84. Found: C, 65.14; H, 5.84.

X-Ray Structure determination of compound 3. The X-ray data were measured on Philips PW100 diffractometer (MoKα-radiation, the ω/2θ scan technique). The space group of **3** crystals is C2, z = 4. The cell dimentions are a = 23.480 (4) Å, b = 8.484 (7) Å, c = 15.079 (3) Å, α = γ = 90 deg., β = 109.92 (1) deg., V = 2824 (14) $Å^3$. The structure was solved by a direct method and refined by the full-matrix least squares with anisotropic approximation for nonhydrogen atoms. The hydrogen atoms were located in their calculated positions and not refined. The final value of R factors was 0.044 for 1361 independant reflections (R_w = 0.045, w = 1.0).

(2*S*, 5*S*, 6*R*, 8*S*) 5,6-*O*-Benzylidene-2-ethoxy-6-(hydroxymethyl)-8-methoxy-3,4,5,6-tetrahydro-2H-pyrano [3,4-b] pyran (6). A solution of **1** (28 mg, 0.1 mmol) and ethyl vinyl ether (204 µL, 2 mmols) in a mixture (0.8 mL) of DMSO-Ac_2O (5 : 3, v/v) was stirred at rt overnight. After the same treatment as for dimer **3**, the crude product was purified by preparative layer chromatography using CH_2Cl_2 as eluent to give **3** (1 mg, 3.6%) and **6** (24 mg, 69%) : solid, mp 138-140 °C, Rf 0.47 (Et_2O/hexane, 1/1), $[\alpha]_D$ -62.5 (*c* 0.40, CH_2Cl_2), ^1H NMR ($CDCl_3$): δ 7.30-7.41 (m, 5H, H-Ar), 5.50 (s, 1H, CH-Ph), 5.04 (t, 1H, J = 2.8 Hz, H-2), 4.63 (s, 1H, H-8), 4.21 (dd, 1H, J = 9.9, 4.5 Hz, CH-C_6), 4.13 (d, 1H, J = 8.7 Hz, H-5), 3.94 (ddd, 1H, J = 10.1, 8.7, 4.5 Hz, H-6), 3.77 (qd, 1H, J = 9.8, 7.1 Hz, CH-C_6), 3.75 (t, 1H, J = 10.1 Hz, CH), 3.55 (qd, 1H, J = 9.8, 7.1 Hz, CH), 3.42 (s, 3H, OMe), 2.21 (td, 1H, J = 16.7, 5.0 Hz, H-4), 2.00 (m, 1H, H-4), 1.83 (m, 2H, H-3), 1.15 (t, 3H, J = 7.1 Hz, Me); ^{13}C NMR ($CDCl_3$, assignments verified by ^1H /^{13}C correlation) δ 141.5, 137.0, 128.4, 127.7, 125.7 (Ar), 109.0 (C=), 101.1 (C-Ph), 96.5, 95.6 (C-2, 8), 76.0 (C-5), 68.5 (CH_2-O), 64.4 (C-6), 63.4 (CH_2 ethyl), 55.3 (OMe), 25.6 (C-4), 14.6 (Me), 13.7 (C-3).

Anal. Calcd for $C_{19}H_{24}O_6$: C, 65.50; H, 6.94. Found : C, 65.45; H, 6.99.

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