Synthesis of a Novel Coumarin C-Riboside as a Photophysical Probe of Oligonucleotide Dynamics

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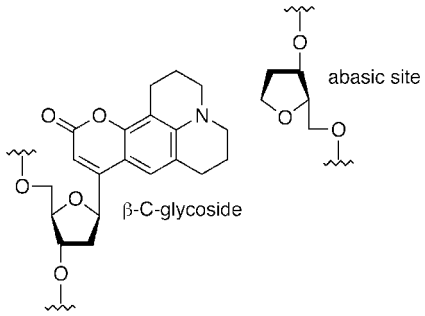
Introduction

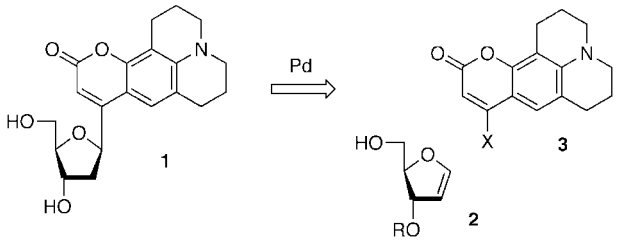
The examination of local dynamics within the DNA double helix can provide information about the flexibility and structure of oligonucleotides that are relevant to understanding function.[1] It is well recognized that many features of DNA and RNA are sequence-dependent, and the time-dependent description of oligonucleotide conformation is important in this regard.[2] It is our goal to design probe molecules with which we can gain an understanding of the sequence dependent conformation of the DNA double helix on an ultrafast time scale. Although there are many studies of DNA conformational and translational movements on a slow time scale,[2,3] because of a lack of appropriate chromophores in native DNA, recent advances in picosecond spectroscopic techniques[4] have not yet been used to examine dynamics on the individual nucleotide scale. Very recently, Murphy and Berg have reported studies on the dynamic properties of the interior of the DNA duplex by measuring Stokes shifts of intercalated dyes.[5] These studies would be significantly augmented by the availability of more suitable photophysical probes. Herein, we describe the synthesis of a structurally novel photophysical probe designed for use in studies of ultrafast DNA dynamics.

Incorporation of reporter molecules into a DNA double helix that are designed for such studies should optimally meet three conditions: (1) the probe must minimally distort the DNA duplex; (2) the orientation of the probe relative to the helix axis must be fixed and known; and (3) the photophysical properties of the probe must be appropriate for the spectroscopic technique to be used. A consideration of these design criteria, including the additional constraint of synthetic accessibility, led to the design of the coumarin 2′-deoxy-C-riboside **1** as a potential photophysical probe. The coumarin nucleus is frequently used in solvation dynamic studies because it exhibits a large Stokes shift.[6]



Molecular modeling of this C-glycoside system positioned opposite to an abasic model[7] within canonical B-DNA convincingly demonstrated the first condition, and because the coumarin ring system is effectively intercalated only while in the anti conformation, the second condition is also met. The parent coumarin is well studied spectroscopically, and we felt comfortable that our system would exhibit useful photophysical properties, thereby satisfying the third condition.

The design elements of **1** that led us to its consideration were complemented by the potential to apply demonstratedly effective methodology for the synthesis of C-glycosides. Coumarin C-riboside **1** could be obtained by the palladium-catalyzed Heck coupling of suitably protected glycal **2** with a halocoumarin **3** (X = I, OSO_2CF_3) following the strategy developed by Daves[8] and Cabri.[9] Herein, we report an effective synthesis of the target coumarin β-C-riboside **1** following the basic strategy shown.



Results and Discussion

Glycals **2a** and **2b** were prepared from D-(+)-ribono-γ-lactone following the sequence originally described by Ireland and co-workers,[10] as modified by Daves.[11] We had initially selected a *tert*-butyldiphenylsilyl ether (**2a)** for protection of the 3′ hydroxyl position, but we found that this group inhibited the subsequent Heck coupling reaction by virtue of its size (vida infra). We subse-

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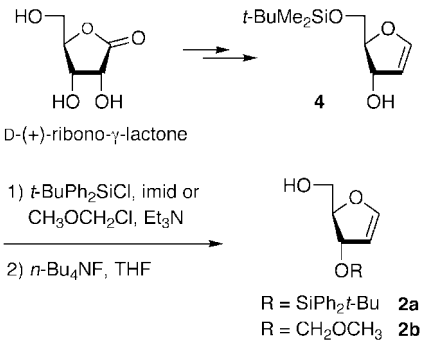
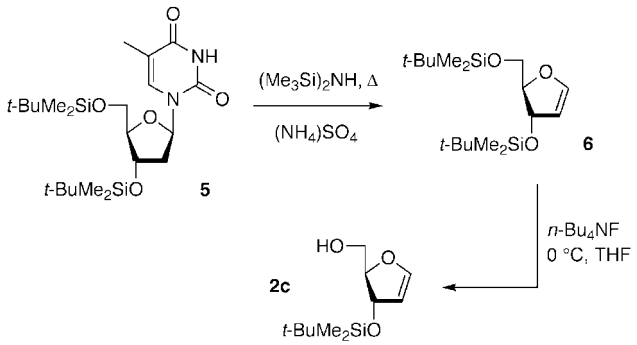
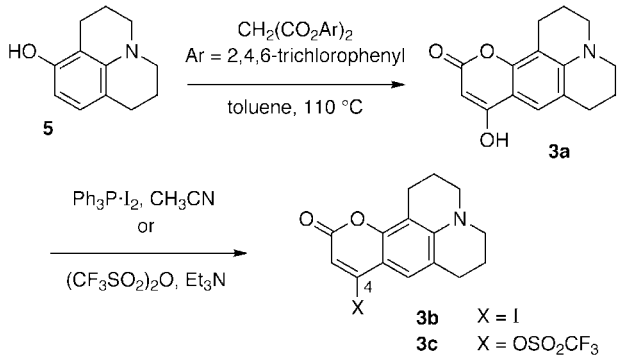
quently opted for the smaller methoxymethyl acetal for protection of this position. In the event, this sequence of reactions worked smoothly to produce known glycals **2a** and **2b**.



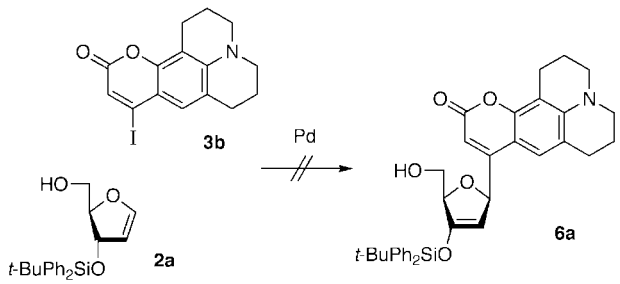
During the course of this work, Hammer and co-workers reported a highly effective synthesis of furanoid glycals by pyrolysis of thymidine in the presence of hexamethyldisilazane,[12] based on the earlier report by Pederson and co-workers.[13] In our hands this protocol worked well and greatly simplified the synthesis of the glycal systems of interest. Specifically for the construction of selectively protected glycals **2**, we found the bis-(*tert*-butyldimethylsilyl) ether of thymidine (**5**) to undergo fragmentation at elevated temperatures in the presence of hexamethyldisilazane to produce bis-silyl ether **6**. Selective desilylation of the primary ether of **6** occurred smoothly by treatment with 1 equiv of *n*-Bu_4NF (THF, 0 °C, 2 h) to afford coupling partner **2c** in 60% overall yield from **5** after silica gel chromatography. In the end, this sequence of reactions was considerably more effectual for the synthesis of glycal systems such as **2c** and significantly shortened the synthetic route to the desired C-riboside target.



Coumarin **3a** (X = OH) was prepared from 8-hydroxyjulolidine (**5**) following literature procedures.[14] Reaction of **5** with bis(2,4,6-trichlorophenyl) malonate in refluxing toluene effected annulation of the α-pyrone ring system to afford **3a** in excellent yields (94%). The hydroxyl group of **3a** could be transformed to the iodide by treatment with a preformed complex of triphenylphosphine and iodine (Ph_3P, I_2, CH_3CN, 82 °C).[15] Alternatively, the hydroxyl group could be acylated with trifluoromethanesulfonic anhydride (Tf_2O, Et_3N, CH_2Cl_2, 0 °C)[16] to afford triflate **3c** in 87% yield. These systems were examined in the Heck coupling reaction with glycals **2a** and **2b**.



Our initial experiments on palladium-catalyzed coupling of vinylic iodide **3b** with *t*-$BuPh_2Si$ protected glycal **2a** were unsuccessful in providing any of the coupled product **6a** under a variety of reaction conditions.[17] The predominate product formed under these conditions was the corresponding reduced coumarin (**3d**, X = H), and on occasion a dimeric product. The glycal **2a** was always recovered unchanged. These results indicated that we were forming the requisite palladium Ar−I insertion product from reaction with **3b**, but that this was taking an unproductive pathway (e.g., reduction or dimerization) in preference to reacting with the sterically encumbered, electron-rich glycal **2a**. This is consistent with Cabri's mechanistic insights where dissociation of the strong Pd−I bond must occur prior to coordination of the Pd with an electron-rich alkene.[9c]



As a result of these unsuccessful experiments, two variables in this coupling reaction were changed: (1) the iodide of **3b** was changed to the more reactive trifluoromethanesulfonate **3c**, accompanied by the introduction of the chelating phosphine 1,3-(diphenylphosphino)propane (dppp); and (2) the more bulky *t*-$BuPh_2Si$ ether of **2a** was changed to the smaller methoxymethyl acetal of **2b**. In this instance, reaction of triflate **3c** with glycal

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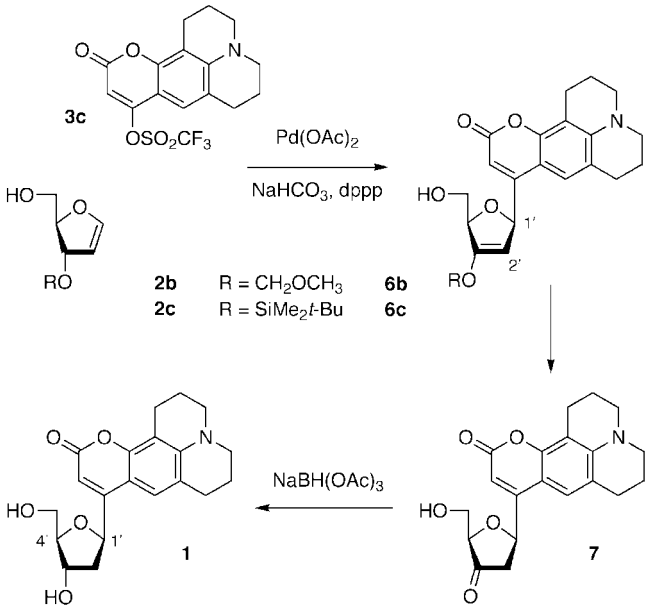
(17) Examples of unsuccessful reaction conditions for the coupling of TBDPS glycal **2a** with iodide **3b** include the following: $Pd(OAc)_2$ (0.1 equiv), Bu_3N (0.2 equiv), NaOAc (1 equiv), DMF, 16 h, 60 °C; $Pd(OAc)_2$ (0.1 equiv), Ph_3P (0.2 equiv), Et3N (1.1 equiv), DMF, 40 h, 60 °C; $Pd(OAc)_2$ (0.1 equiv), dppp (0.2 equiv), Et_3N (1.2 equiv), DMF, 24 h, 60 °C; $Pd(dba)_2$ (0.1 equiv), As_3P (0.2 equiv), Bu_3N (2 equiv), DMF, 24 h, 60 °C. An example of unsuccessful reaction conditions for the coupling of MOM glycal **2b** with iodide **3b** include the following: $Pd(OAc)_2$ (0.1 equiv), Ph_3P (0.2 equiv), Na_2CO_3 (3 equiv), CH_3CN, 16 h, 60 °C. An example of unsuccessful reaction conditions for the coupling of MOM glycal **2b** with triflate **3c** include the folowing: $Pd(OAc)_2$ (0.1 equiv), dppp (0.2 equiv), Et_3N or *i*-Pr_2NEt (3 equiv), CH_3CN or DMF, 24 h, 80 °C.

2b in the presence of $Pd(OAc)_2$ (5−10 mol %), dppp, and $NaHCO_3$[18] afforded the desired Heck product **6b**, although in low yield. Coupling conversions were substantially improved by performing the reaction by sequential addition of aliquots of $Pd(OAc)_2$ as the reaction progressed.[19] In the end, we found optimal reaction conditions for this system to be 40 mol % $Pd(OAc)_2$, 5 mol % dppp, and 3 equiv $NaHCO_3$ in CH_3CN at reflux, and under these conditions, Heck product **6b** was produced in 75% yield. Under these conditions, dissociation of the Pd−OTf bond in the oxidative insertion product to form an intermediate cationic palladium species facilitates coordination to the electron-rich olefin of glycal **2b**.[9c]



Hydrolysis of the enol acetal of **6b** under acidic conditions (HCl, CH_3OH, 25 °C) afforded the corresponding dimethylacetal of ketone **7**, and this difficulty combined with the lengthy preparation of **2b** from D-ribono-γ-lactone led us to an additional tactical change. *tert*-Butyldimethylsilyl ether **2c** is easily available using the recently detailed protocol of Hammer and co-workers,[12] and when **2c** was used as the glycal partner in the Heck coupling reaction, silyl enol ether **6c** could be produced in 79% yield. Fluoride-promoted cleavage of the silyl ether (HF/pyridine) afforded ketone **7** in excellent yields. The carbonyl group of **7** could be reduced stereoselectively to the *ribo*-glycoside **1** with sodium triacetoxyborohydride following literature conditions.[20] This sequence of reactions starting from **2c** and **3c** proceeded to afford **1** in 66% overall yield.

The stereochemistry around the dihydrofuran ring of **6b** and **6c** was determined to exist as shown by observation of the expected coupling constant between C1′-H and C2′-H (J = 3.7 Hz).[21] Ultimately the stereochemistry of the C1′ glycosidic center of **1** was confirmed by the observation of a nuclear Overhauser enhancement of the C4′-H when C1′-H was irradiated (300 MHz, $CDCl_3$).

Coumarin C-riboside **1** was designed to serve as a surrogate for the normal purine/pyrimidine base pair in order to maintain the normal helical parameters when incorporated opposite to an abasic site analogue. The photophysical properties of **1** will be critical to its proposed role as a probe of DNA dynamics. Studies on the incorporation of coumarin β-C-riboside **1** into synthetic oligonucleotides are in progress, and we will report separately on these and future photophysical studies.

Experimental Section

4-Hydroxycoumarin 3a. 8-Hydroxyjulolidine (3.7 g, 19.5 mmol) and bis(2,4,6-tricholorophenyl) malonate (9.05 g, 19.5 mmol, 1 equiv) were dissolved in dry toluene (60 mL), and the reaction mixture was warmed at reflux for 2 h. The light brown suspension was cooled and filtered, and the solids were washed with hexanes (3 × 30 mL) to afford **3a** as a light brown solid (4.7 g, 94%) that was used without further purification: mp 278−279 °C; ^{1}H NMR (250 MHz, DMSO-d_6) δ 11.70 (br s, 1H), 7.17 (s, 1H), 5.24 (s, 1H), 3.24 (m, 4H), 2.72 (m, 4H), 1.90 (m, 4H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 166.8, 163.1, 151.1, 146.2, 120.0, 117.5, 105.5, 103.2, 101.5, 85.9, 49.4, 48.8, 27.1, 21.1, 20.2; EI−HRMS, m/z calcd for $C_{15}H_{15}NO_3$, 257.1052; found, 257.1048.

4-Iodocoumarin 3b. A solution of I_2 (1.12 g, 4.4 mmol, 1.1 equiv) in dry CH_3CN (50 mL) under argon was treated with Ph_3P (1.15 g, 4.4 mmol, 1.1 equiv), and the resulting yellow precipitate of Ph_3P/I_2 was stirred at 24 °C for 15 min. Triethylamine (0.6 mL, 4.4 mmol, 1.1 equiv) and 4-hydroxycoumarin **3a** (1.03 g, 4.0 mmol) were added, and the reaction mixture was heated at reflux for 15 h. Evaporation of the volatiles in vacuo and purification of the residue by flash chromatography (silica gel, 7:3 hexane/acetone) afforded **3b** as a yellow solid (885 mg, 60%): mp 258−259 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.00 (s, 1H), 6.71 (s, 1H), 3.28 (m, 4H), 2.83 (m, 4H), 1.97 (m, 4H); EI−HRMS m/z calcd for $C_{15}H_{14}NO_2I$, 367.0069, found, 367.0091.

4-Trifluoromethylsulfonyl Coumarin 3c. 4-Hydroxycoumarin **3a** (257 mg, 1 mmol) and triethylamine (0.2 mL, 1.45 mmol, 1.45 equiv) were dissolved in dry CH_2Cl_2 (10 mL) under N_2. The mixture was cooled to −10 °C (acetone/ice bath), and trifluoromethanesulfonic anhydride (0.22 mL, 1.3 mmol, 1.3 equiv) was added dropwise via syringe. The dark green reaction mixture was stirred at −10 °C for 1 h and was diluted with a mixture of ether and hexane (1:1, 30 mL). The reaction was passed through a silica column (4 × 10 cm), and the bright yellow product was washed from the column with 1:1 ether/hexane until the solvent came out colorless. The combined effluant was concentrated in vacuo to afford **3c** as a bright yellow solid (338 mg, 87%) that was used without further purification: mp 97−99 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.01 (s, 1H), 5.99 (s, 1H), 3.30 (m, 4H), 2.86 (m, 2H), 2.78 (m, 2H), 1.96 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.6, 158.3, 151.2, 147.6, 120.6, 119.2, 116.4, 106.7, 101.7, 97.6, 50.0, 49.6, 27.7, 21.0, 20.4, 20.2; IR (neat) ν_{max} 2943, 2856, 1720, 1616, 1523, 1430, 1404, 1365, 1310 cm^{-1}; EI−HRMS, m/z calcd for $C_{16}H_{14}NO_5F_3S$, 389.0545; found, 389.0558.

C-Riboside 6b. A solution of triflate **3c** (262 mg, 0.725 mmol) in dry CH_3CN (15 mL) in a Teflon-capped vial was treated with glycal **2b** (348 mg, 2.18 mmol, 3 equiv), $Pd(OAc)_2$ (64 mg, 0.29 mmol, 0.4 equiv), 1,3-bis(diphenylphosphino)propane (14 mg, 0.036 mmol, 0.05 equiv), and $NaHCO_3$ (153 mg, 2.175 mmol, 3 equiv). The reaction mixture was stirred for 3 h at 24 °C. The mixture was concentrated in vacuo, and the residue was purified by flash chromatography (silica gel, ether) to afford **6b** as a yellow oil (227 mg, 79%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.02 (s, 1H), 6.20 (s, 1H), 6.00 (m, 1H), 5.08 (app t, J = 1.7 Hz, 1H), 5.01 (m, 2H), 4.82 (m, 1H), 3.78 (ddd, J = 12.0, 4.6, 3.0 Hz, 2H), 3.44 (s, 3H), 3.25 (m, 4H), 2.88 (m, 2H), 2.78 (m, 2H), 1.97 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.1, 155.6, 153.4, 151.5, 145.8, 121.1, 118.2, 107.0, 106.4, 104.5, 95.8, 83.0, 80.4, 63.5, 56.5, 49.9, 49.5, 33.4, 30.6, 22.7, 20.6, 20.5; IR (neat) ν_{max} 3442,

(18) Triethylamine was completely ineffective as a base in these coupling reactions.

(19) We can offer no rationale for the requirement of 0.4 equiv of Pd for effective conversion to product. The Heck coupling reaction was accompanied by the formation of a metallic deposit on the walls of the reaction flask, and this deposition was not affected by additional 1,3-(diphenylphosphino)propane.

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(21) Cheng, J. C.-Y.; Hacksell, U.; Daves, G. D., Jr. *J. Org. Chem.* **1986**, *51*, 3093.

2932, 2856, 1700, 1662, 1601, 1556, 1518, 1431, 1370, 1311 cm^{-1}; EI−HRMS, *m/z* calcd for $C_{22}H_{25}NO_6$, 399.1682, found, 399.1696.

C-Riboside 6c. A solution of triflate **3c** (375 mg, 1 mmol) in dry CH_3CN (20 mL) in a Teflon-capped vial was treated with glycal **2c** (700 mg, 3 mmol, 3 equiv), $Pd(OAc)_2$ (90 mg, 0.4 mmol, 0.4 equiv), 1,3-bis(diphenylphosphino)propane (20.6 mg, 0.050 mmol, 0.05 equiv), and $NaHCO_3$ (252 mg, 3 mmol, 3 equiv). The reaction mixture was stirred for 5 h at 24 °C. A metallic deposit was observed to develop on the walls of the reaction flask during the course of the reaction. The mixture was concentrated in vacuo, and the residue was purified by flash chromatography (silica gel, 4:1 ether/hexane) to afford **6c** as a yellow oil (227 mg, 79%): ^1H NMR (250 MHz, $CDCl_3$) δ 7.06 (s, 1H), 6.14 (s, 1H), 5.95 (d, J = 3.7 Hz, 1H), 4.87 (dd, J = 2.0, 1.7 Hz, 1H), 4.66 (m, 1H), 3.72 (m, 2H), 3.25 (m, 4H), 2.86 (m, 2H), 2.78 (m, 2H), 1.97 (m, 4H), 0.93 (s, 9H), 0.11 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.0, 155.6, 152.3, 151.4, 145.7, 121.2, 118.1, 106.9, 106.6, 104.8, 98.3, 83.6, 79.7, 63.4, 49.8, 49.4, 27.7, 25.3, 21.4, 20.5, 20.4, 17.9, −4.9, −5.1; IR (neat) ν_{max} 3444, 2932, 2856, 1703, 1654, 1600, 1556, 1518, 1431, 1370, 1311 cm^{-1}; EI−HRMS, *m/z* calcd for $C_{26}H_{35}NO_5Si$, 469.2284; found, 469.2284.

3′-Keto-2′-deoxy C−Riboside 7. Enol ether **6c** (740 mg, 1.58 mmol) was dissolved in dry THF (40 mL) under argon and was treated with HF/pyridine (70% HF by weight, 0.75 mL, 17 equiv). The reaction mixture was stirred for 14 h at 24 °C. Concentration in vacuo and purification of the residue by flash chromatography (silica gel, ether) afforded **7** as a bright yellow solid (500 mg, 89%): ^1H NMR (300 MHz, $CDCl_3$) δ 6.79 (s, 1H), 6.43 (s, 1H), 5.36 (dd, J = 11.0, 6.1 Hz, 1H), 4.08 (dd, J = 3.4, 3.3 Hz, 1H), 3.94 (m, 2H), 3.20 (m, 4H), 2.97 (dd, J = 18.0, 6.1 Hz, 1H), 2.81 (m, 2H), 2.70 (m, 2H), 2.38 (dd, J = 18.0, 11.0 Hz, 1H), 1.91 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.2, 162.9, 154.3, 151.1, 145.8, 120.5, 118.3, 106.8, 105.5, 103.6, 82.2, 72.6, 61.3, 49.7, 49.3, 44.4, 27.6, 21.3, 20.4, 20.3; IR (neat) ν_{max} 3412, 2921, 2845, 1758, 1698, 1616, 1600, 1556, 1518, 1436, 1311 cm^{-1}; EI−HRMS, *m/z* calcd for $C_{20}H_{21}NO_5$, 355.1420, found, 355.1429.

2′-Deoxy C-Riboside 1. Ketone **7** (500 mg, 1.42 mmol) was dissolved in dry CH_3CN (30 mL) and glacial CH_3COOH (30 mL) under argon. The reaction mixture was cooled to 0 °C, and sodium triacetoxyborohydride (392 mg, 1.85 mmol, 1.3 equiv) was added. After 10 min at 0 °C, the volatiles were removed in vacuo and the orange-brown residue was purified by flash chromatography (silica gel, 4:1 $CHCl_3$/MeOH) to afford **1** as a yellow solid (475 mg, 94%): mp 195−197 °C (dec); ^1H NMR (250 MHz, $CDCl_3$) δ 6.92 (s, 1H), 6.29 (s, 1H), 5.36 (dd, J = 9.6, 6.1 Hz, 1H), 4.44 (m, 1H), 4.08 (m 1H), 3.80 (m, 2H), 3.23 (m, 4H), 2.85 (m, 2H), 2.73 (m, 2H), 2.46 (ddd, J = 13.2, 6.1, 2.4 Hz, 1H), 1.94 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.4, 156.7, 151.2, 145.8, 120.9, 118.3, 106.9, 106.1, 102.8, 87.2, 75.2, 73.2, 63.1, 49.9, 49.5, 42.6, 27.7, 21.5, 20.6, 20.4; IR (neat) ν_{max} 3401, 2943, 2556, 1687, 1605, 1551, 1519, 1438, 1301 cm^{-1}; EI−HRMS, *m/z* calcd for $C_{20}H_{23}NO_5$, 357.1576, found, 357.1568.

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Supporting Information Available: ^1H and ^{13}C NMR spectra for **1**, **3a**, **3c**, **6b**, **6c**, and **7** (13 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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