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SYNTHESIS OF 1-METHOXY-1*H*-INDOLES WITH A HETEROCYCLIC MOIETY VIA UNSTABLE INDOLE ISOTHIOCYANATE BY USING ENZYME FROM *BRASSICACEAE* PLANT

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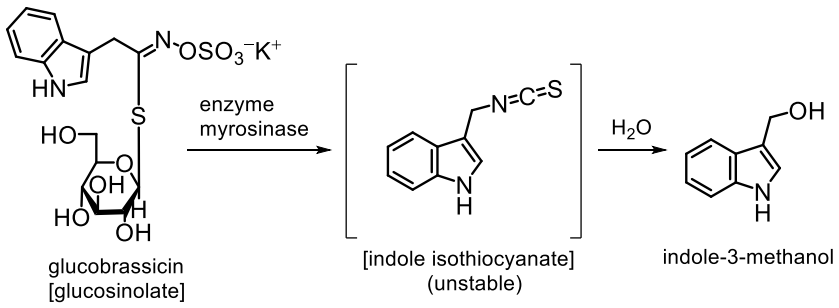
Abstract — A synthesis of five 1-methoxy-1*H*-indole derivatives with imidazole, pyrazole, 1*H*-1,2,3-triazole, and 1*H*-1,2,4-triazole moieties was achieved by focusing on the formation mechanism of plant constituents. The objective 1-methoxy-1*H*-indole derivatives were obtained *in situ* (in one step) through the reaction of an unstable 3-(isothiocyanatomethyl)-1-methoxy-1*H*-indole, which was derived from neoglucobrassicin and plant enzyme myrosinase, and a heterocyclic compound. We have great hopes that this method would be useful for the development of medicinal seeds.

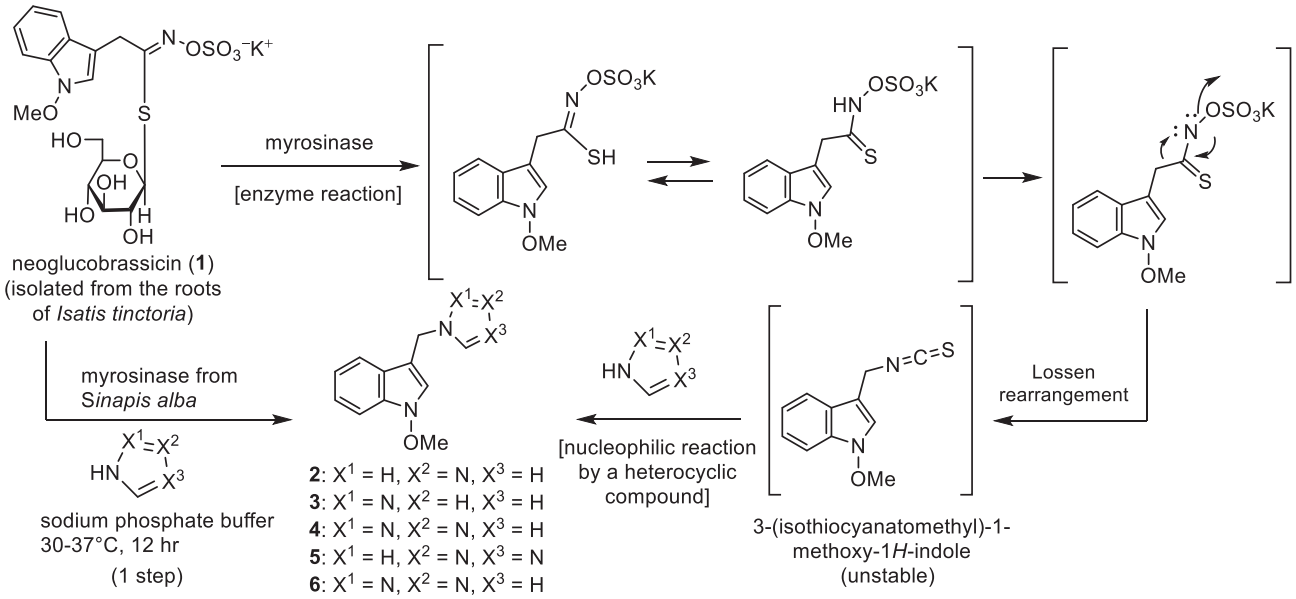
INTRODUCTION

Isothiocyanate is a well-known compound derived from *Brassicaceae* plants (e.g., broccoli, cabbage, etc.). Various isothiocyanates are produced by mixing glucosinolates (called mustard oil glycosides) and an enzyme, myrosinase, both of which stay in different parts of plants, when plant tissues are damaged.[1] Isothiocyanates are produced by the myrosinase-catalyzed deglucosidation of glucosinolates, followed by Lossen rearrangement. The stability of the obtained isothiocyanates differs by the type of glucosinolate. Aliphatic isothiocyanates are relatively stable, whereas 3-indolylmethyl isothiocyanates are



Scheme 1. Reaction of glucobrassicin catalyzed by enzyme myrosinase

extremely unstable.[2-4] For example, an 3-indolylmethyl isothiocyanate that is derived from an enzyme-catalyzed reaction of glucobrassicin glucosinolate is immediately transformed into indole-3-methanol (3-indolylcarbinol) by the reaction with water (Scheme 1).[5] Several indole derivatives were generated by the reaction of glucobrassicin and ascorbic acid or amino acids.[6-8] This reaction process in *Brassicaceae* plants will be useful for the construction of new bioactive indole derivatives. Several indole derivatives with heterocyclic moieties have an antifungal effect and an inhibitory effect to thromboxane synthetase.[9,10] Thus, indole derivatives are important for new drug development.

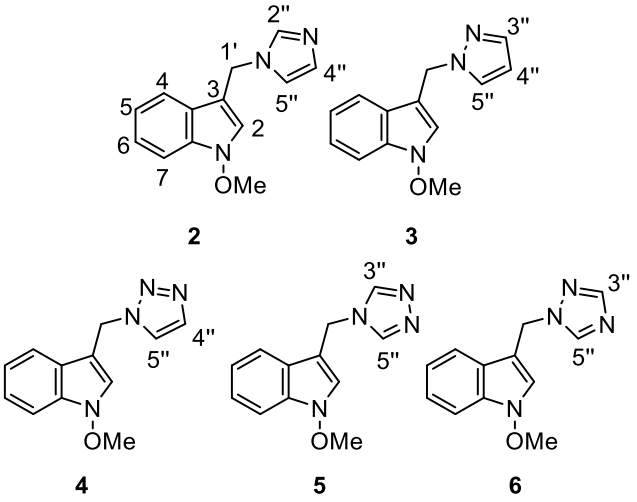


Scheme 2. Construction of 1-methoxyindoles with a heterocyclic moiety

In the present study, we envisioned harnessing unstable isothiocyanate 3-(isothiocyanatomethyl)-1-methoxy-1*H*-indole, which was obtained from neoglucobrassicin known as major compound from *Isatis tinctoria*,[9] for the construction of biofunctional 1-methoxyindoles with a heterocyclic moiety. We tried to obtain 3-(isothiocyanatomethyl)-1-methoxy-1*H*-indole *in situ* by a myrosinase-catalyzed deglucosidation reaction of neoglucobrassicin and Lossen rearrangement, followed by a nucleophilic reaction with a heterocyclic compound to obtain 1-methoxyindole with a heterocyclic moiety (Scheme 2). In general, several steps are needed to synthesize 1-methoxyindole derivatives with a heterocyclic moiety.[10-15] However, this method realizes the synthesis of objective compounds in one step without having to isolate unstable 3-(isothiocyanatomethyl)-1-methoxy-1*H*-indole. Herein, we demonstrate the syntheses of five 1-methoxyindoles with a heterocyclic moiety (Scheme 3).

RESULTS AND DISCUSSION

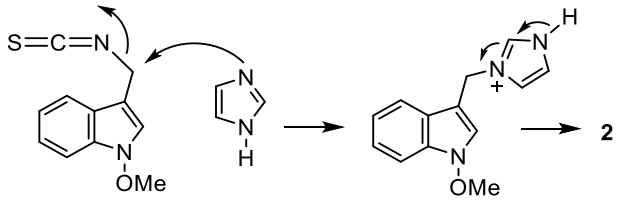
Neoglucobrassicin (**1**) was isolated from the roots of *I. tinctoria* (Brassicaceae) and used as the starting material for the syntheses of 1-methoxyindoles with a heterocyclic moiety. The dried roots of *I. tinctoria* were extracted with MeOH. The extract was subjected to HP-20 and normal-phase silica gel column chromatography to give neoglucobrassicin (**1**, 0.044% [isolation yield from dry plants]).[16] First, a blank experiment by using **1** was advanced. Namely, the incubation of neoglucobrassicin (**1**) and myrosinase as the plant enzyme was proceeded to confirm whether **1** was good substrate for commercially available myrosinase. As the result, 1-methoxyindole-3-methanol were generated by the reaction of the unstable isothiocyanate obtained by the enzyme reaction of **1** and water. The yield after 5 min and 3 h in the enzyme reaction was 1.0% and 2.9% by HPLC analysis, respectively. In addition, the generation of complex compounds by the polymerization of 1-methoxyindole-3-methanol were also confirmed by NMR spectrum. Furthermore, the yield of 1-methoxyindole-3-methanol after 24 h was little changed compared with that after 3 h and **1** was confirmed to be completely consumed by NMR analysis. From the above, the enzyme-catalyzed deglucosidation of **1** proceeded on a time-series basis and **1** was confirmed to be good substrate for myrosinase. Next, we tried to synthesize 3-(1*H*-imidazol-1-ylmethyl)-1-methoxy-1*H*-indole (**2**) from **1** by using a biochemical reaction in *Brassicaceae* plants (Scheme 2). Neoglucobrassicin (**1**) was incubated with myrosinase and imidazole as the nucleophilic agent in sodium phosphate buffer [pH 7.4] at 30–37 °C for 12 h. As expected, the reaction proceeded, and new compound **2** was afforded. In addition, the presence of 1-methoxyindole-3-methanol was confirmed by HPLC analysis although the accurate yield could not calculate. On the other hand, the adducts of imidazole to the isothiocyanate intermediate were not confirmed by HPLC analysis. Furthermore, the blank experiment by the incubation of **1** and imidazole without myrosinase was performed to confirm whether enzyme was required. As the result, the purpose compound **2** was not obtained at all by HPLC analysis. Therefore, enzyme was found to essential for this reaction. Compound **2** was obtained as a yellow oil and its molecular weight was determined to be $C_{13}H_{13}N_3O$ by ESIMS analysis and HRESIMS analysis. ^{1}H and ^{13}C-NMR (Table 1) spectra (CD_3OD) indicated that compound **2** contains an indole moiety [δ_H 7.06 (1H, dd, J = 8.3, 6.8 Hz, 5-H), 7.22 (1H, dd, J = 8.2, 6.8 Hz, 6-H), 7.43 (1H, d, J = 8.2 Hz, 7-H), 7.45 (1H, d, J = 8.3 Hz, 4-H), 7.55 (1H, s, 2-H)]; an imidazole moiety [δ_H 6.92 (1H, s like, 4"-H),



Scheme 3. Structure of compounds **2**-**6**

7.12 (1H, s like, 5"-H), 7.73 (1H, s, 2"-H)]; a methylene moiety bound to 3-position of the indole moiety [δ_H 5.34 (2H, s, 1'-H)]; and a methoxy moiety bound to nitrogen functionality [δ_H 4.09 (3H, s)]. The position of the imidazole moiety was characterized on the basis of an HMBC experiment in which long-range correlations were observed between 1'-H and 2, 3, 2"-C. Consequently, the chemical structure of compound **2** was determined as 3-(1*H*-imidazol-1-ylmethyl)-1-methoxy-1*H*-indole.

The plausible reaction mechanism for the synthesis of **2** is shown in Scheme 4. The objective compound was obtained by deprotonation of the imidazolium salt, which was produced by the reaction between 3-(isothiocyanatomethyl)-1-methoxy-1*H*-indole and imidazole. Next, we tried to synthesize various 1-methoxy-1*H*-indoles with pyrazole, 1*H*-1,2,3-triazole, or 1*H*-1,2,4-triazole instead of imidazole as the nucleophilic agent. Treatment of **1** and pyrazole, 1*H*-1,2,3-triazole, or 1*H*-1,2,4-triazole with myrosinase in sodium phosphate buffer [pH 7.4] at 30–37 °C for 12 h produced new compounds **3**–**6**, respectively (Scheme 3). Their chemical structures were determined from detailed analysis of ^{1}H-and ^{13}C-NMR spectra and 2D-NMR (DQF COSY, HMBC) spectra. Linkages between the indole moiety and the pyrazole or triazole moiety of compounds **3**–**6** were confirmed on the basis of HMBC or NOESY experiments, respectively. Long-range correlations in HMBC experiments of compounds **3**, **5**, and **6** were observed between 1'-H and 2, 3, 5"-C (compound **3**); 1'-H and 2, 3, 3", 5"-C (compound **5**); and 1'-H and 2, 3, 5"-C (compound **6**). On the other hand, NOE correlations in NOESY experiments of compound **4** were observed between 2-H and 5"-H, and 1'-H and 5"-H. Consequently, the chemical structures of compounds **3**–**6** were determined as 1-methoxy-3-(1*H*-pyrazol-1-ylmethyl)-1*H*-indole, 1-methoxy-3-(1*H*-1,2,3-triazol-1-ylmethyl)-1*H*-indole, 1-methoxy-3-(4*H*-1,2,4-triazol-4-ylmethyl)-1*H*-indole, and 1-methoxy-3-(1*H*-1,2,4-triazol-1-ylmethyl)-1*H*-indole, respectively. We also tried using pyrrole or propylamine instead of imidazole as the nucleophilic agent, but were unable to obtain the objective 1-methoxy-1*H*-indole derivatives. These results suggest that the nucleophilicity of the nucleophilic agent are related to the progress of the reaction.



Scheme 4. Plausible reaction mechanism for the synthesis of **2**

In conclusion, we have constructed five 1-methoxyindole derivatives with a heterocyclic moiety by focusing on the formation mechanism of plant constituents. This method has made it possible to synthesize objective unnatural compounds in one step by using complex reactions in plant biochemistry and organic chemistry. Previously, simple synthesis of several 3-alkylindoles such as dialkylaminoarylated indoles by multi-component reaction was reported.[17] In addition, synthesis of several 1-methoxyindoles were also reported.[18] These synthesis methods are useful for the construction of

indole derivatives. But, the oxidizing agents and metal reagents are needed for the reactions. In the present study, we have showed the construction method of 1-methoxyindole derivatives with a heterocyclic moiety by enzyme-triggered transformation of neoglucobrassicin. This method is important as the example of "green and sustainable chemistry". Although the yields of the objective compounds in this synthetic method need to be improved, we have great hopes that this method would be useful for the development of medicinal seeds.

EXPERIMENTAL

The following instruments were used to obtain physical data: IR spectra, JASCO FT/IR-4600 Fourier Transform Infrared Spectrometer; ESIMS and high-resolution ESIMS, Agilent Technologies Quadrupole LC/MS 6130 (ESIMS), SHIMADZU LCMS-IT-TOF (HRESIMS); ^{1}H-NMR spectra, JEOL ECA-600 (600 MHz) spectrometers; ^{13}C-NMR spectra, JEOL ECA-600 (150 MHz); LC/MS, LCMS-8040 tandem quadrupole mass spectrometer and a Nexera UHPLC system; HPLC detector, Shimadzu SPD-20AVP UV-VIS detector; and HPLC column, YMC triart C_{18} (250 x 4.6 mm i.d.) and (250 x 10 mm i.d.) columns were used for analytical and preparative purposes, respectively. The following experimental materials were used for chromatography: normal-phase silica gel column chromatography, Silica gel BW-200 (Fuji Silysia Chemical, Ltd., 150–350 mesh); reversed-phase silica gel column chromatography, Cosmosil140C_{18}-OPN (nacalaitesque); synthetic adsorbent, DIAION ion exchange Resin HP-20 (MISUBISHI CHEMICAL CORPORATION). TLC, precoated TLC plates with Silica gel 60F_{254} (Merck, 0.25 mm) (normal phase) and Silica gel RP-18 F_{254S} (Merck, 0.25 mm) (reversed phase); and detection was achieved by spraying with 1% $Ce(SO_4)_2$–10% aqueous H_2SO_4 followed by heating.

Plant Material

The dry roots of *I. tinctoria* (Banlangen) was purchased from Tochimoto Tenkaido Co., Ltd. (Osaka, Japan) in 2018. Myrosinase from *Sinapis alba* seeds was purchased from Sigma Aldrich (Steinheim, Germany).

Isolation of Constituent from the Roots of *I. tinctoria.*

The roots of dry *Isatis tinctoria* (5.0 kg) were extracted with MeOH three times. Evaporation of the filtrate under reduced pressure provided MeOH extract (540.1 g, 10.8%). The extract was subjected to HP-20 column chromatography to obtained 20% MeOH fraction (13.25 g, 0.27%). The 20% MeOH fraction (13.25 g) was subjected to normal phase silica gel column chromatography [$CHCl_3$-MeOH (1:0 →6:1→5:1→3:1, v/v)] to give four fractions. Fr. 4 (total 2.29 g, 0.046%) was subjected to normal phase

silica gel column chromatography [$CHCl_3$-MeOH (1:0→6:1→5:1→3:1, v/v)] to give neoglucobrassicin (**1**, 2.21 g, 0.044%).

Preparation of standard solution of 1-methoxyindole-3-methanol and constructing calibration curve

1-Methoxyindole-3-methanol (0.8 mg) was introduced into a 10 mL volumetric flask and made up to volume with MeOH. The solution was used as a stock standard solution (80 μg/mL). Several working solutions (3.2 μg/mL, 6.4 μg/mL, 16 μg/mL, 32 μg/mL) for constructing calibration curve were prepared by diluting of the standard solution. Each solution was subjected to HPLC analysis under the following conditions [HPLC column: YMC triart C_{18} (5 μm particle size, 250 × 4.6 mm i.d.); detection: UV (280 nm); mobile phase: MeOH–H_2O (50:50); flow rate: 1.0 mL/min; column temperature: 25 °C; injection volume: 10 μL.]. The regression equation of the calibration curve is described as follows: $y = 3929515x + 130$ [y is the peak area and x is the concentration of 1-methoxyindole-3-methanol (mg/mL)]. The calibration curve was linear in the range studied (3.2–32 μg/mL) and showed a correlation coefficient (R_2) was 0.9993.

Incubation of compound 1 and myrosinase without nucreophilic agent

Neoglucobrassicin (**1**, 50 mg, 0.11 mmol) was incubated with myrosinase (20-40 mU) in 5 mL sodium phosphate buffer (100 mM, pH 7.4) at 30–37 °C for 5 min, 3 h and 24 h, respectively. Each mixture was subjected to reversed-phase ODS column chromatography [H_2O (3 mL) → MeCN (6 mL)]. Compound **1** was confirmed to be completely consumed by myrosinase because the signal (7.75 ppm, d, J = 7.6 Hz) at 4-positon on the indole moiety of **1** was not detected on ^{1}H NMR spectra of the H_2O and MeCN layer. The MeCN layer was evaporated in vacuo and the residue was introduced into a 2 mL volumetric flask and made up to volume with MeOH. The solution was filtered by membrane filter (MILEX LH Filter Unit, 0.45 μM) and an aliquot of 200 μL of this solution was put into a 2 mL volumetric flask and made up to volume with MeOH. Finally, an aliquot of 10 μL of each solution was injected into the HPLC system. Each peak was assigned by comparison of their retention times with that of standard sample and each yield was calculated by the calibration curve. The yield after 5 min and 3 h in the enzyme reaction was 1.0% and 2.9% by HPLC analysis, respectively. (see supporting information)

Incubation of compound 1 and imidazole without myrosinase

Neoglucobrassicin (**1**, 6.6 mg, 0.014 mmol) was incubated with imidazole (0.14 mmol, 10.0 eq.) in 1.0 mL sodium phosphate buffer (100 mM, pH7.4) at 30–37 °C for 12 h. The resulting mixture was subjected

to reversed-phase ODS column chromatography [H_2O-MeCN (1:0→0:1, v/v)]. The MeCN layer was subjected to HPLC analysis under the following conditions [HPLC column: YMC triart C_{18} (5 μm particle size, 250 × 4.6 mm i.d.); detection: UV (220 nm); mobile phase: MeOH–H_2O (55:45); flow rate: 1.0 mL/min; column temperature: 25 °C]. Compound **2** was not obtained at all by HPLC analysis. (see supporting information)

General Procedure for the synthesis of 1-methoxy-1*H*-indole derivatives with nucleophilic agent

Neoglucobrassicin (**1**, 100-200 mg, 0.21-0.42 mmol, 1.0 eq) was incubated with nucleophilic agent [imdazole, pyrazole, 1*H*-1,2,3-triazole, or 1*H*-1,2,4-triazole] (2.1-4.2 mmol, 10 eq.) and myrosinase (20-40 mU) in 10-20 mL sodium phosphate buffer (100 mM, pH7.4) at 30–37 °C for 12 h. The resulting mixture was subjected to reversed-phase ODS column chromatography [H_2O-MeCN (1:0→0:1, v/v)]. The MeCN layer was subjected to HPLC analysis under the following conditions [HPLC column: YMC triart C_{18} (5 μm particle size, 250 × 4.6 mm i.d.); detection: UV (220 nm); mobile phase: MeOH–H_2O (55:45, v/v for compounds **2** and **3**, 50:50, v/v for compounds **4**, and 45:55, v/v for compounds **5** and **6**); flow rate: 1.0 mL/min; column temperature: 25 °C] to afford compounds **1**-**6**, respectively.

3-(1*H*-Imidazol-1-ylmethyl)-1-methoxy-1*H*-indole (2). 0.9 mg, 1.9% yield from compound **1** (100 mg, 0.21 mmol), yellow oil. IR (ATR) 1598, 1101, 739 cm^{-1}. ^{1}H-NMR (600 MHz, CD_3OD) δ_H: and ^{13}C NMR (150 MHz, CD_3OD) δ_C: given in Table 1. HRMS (ESI) *m/z* calcd for $C_{13}H_{13}N_3O$ $[M+H]^+$ 228.1131, found 228.1130. (see supporting information)

1-Methoxy-3-(1*H*-pyrazol-1-ylmethyl)-1*H*-indole (3). 1.2 mg, 2.5% yield from compound **1** (100 mg, 0.21 mmol), yellow oil. IR (ATR) 1581, 1087, 742 cm^{-1}. ^{1}H-NMR (600 MHz, CD_3OD) δ_H: and ^{13}C-NMR (150 MHz, CD_3OD) δ_C: given in Table 1. HRMS (ESI) *m/z* calcd for $C_{13}H_{13}N_3O$ $[M+Na]^+$ 250.0951, found 250.0947. (see supporting information)

1-Methoxy-3-(1*H*-1,2,3-triazol-1-ylmethyl)-1*H*-indole (4). 1.2 mg, 1.3% yield from compound **1** (200 mg, 0.21 mmol), yellow oil. IR (ATR) 1586, 1078, 746 cm^{-1}. ^{1}H-NMR (600 MHz, CD_3OD) δ_H: and ^{13}C-NMR (150 MHz, CD_3OD) δ_C: given in Table 1. HRMS (ESI) *m/z* calcd for $C_{12}H_{12}N_4O$ $[M+Na]^+$ 251.0903, found 251.0908. (see supporting information)

1-Methoxy-3-(4*H*-1,2,4-triazol-4-ylmethyl)-1*H*-indole (5). 0.7 mg, 0.7% yield from compound **1** (200 mg, 0.21 mmol), yellow oil. IR (ATR) 1592, 1103, 741 cm^{-1}. ^{1}H-NMR (600 MHz, CD_3OD) δ_H: and ^{13}C-NMR (150 MHz, CD_3OD) δ_C: given in Table 1. HRMS (ESI) *m/z* calcd for $C_{12}H_{12}N_4O$ $[M+Na]^+$ 251.0903, found 251.0907. (see supporting information)

1-Methoxy-3-(1*H*-1,2,4-triazol-1-ylmethyl)-1*H*-indole (6). 0.7 mg, 0.7% yield from compound **1** (200 mg, 0.21 mmol), yellow oil. IR (ATR) 1580, 1101, 742 cm^{-1}. ^{1}H-NMR (600 MHz, CD_3OD) δ_H: and ^{13}C-NMR (150 MHz, CD_3OD) δ_C: given in Table 1. HRMS (ESI) *m/z* calcd for $C_{12}H_{12}N_4O$ $[M+Na]^+$ 251.0903, found 251.0900. (see supporting information)

Table 1. ^{1}H-NMR and ^{13}C-NMR data for **2-6**

Compound	**2**		**3**		**4**		**5**		**6**	
Position	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C
2	7.55 (s)	123.5	7.41(s)	125.2	7.64 (s)	124.6	7.65 (s)	124.1	7.60 (s)	124.7
3		107.5		109.1		106.6		105.8		106.4
3a		123.5		125.3		124.1		123.2		124.1
4	7.45 (d, *J*=8.3)	119.1	7.34 (d, *J*=8.3)	120.9	7.50 (d, *J*=8.2)	119.7	7.51 (d, *J*=8.3)	118.8	7.54 (d, *J*=8.3)	119.7
5	7.06 (dd, *J*=8.3, 6.8)	120.8	6.94 (dd, *J*=8.3, 6.8)	122.3	7.06 (dd, *J*=8.2, 6.9)	121.5	7.10 (dd, *J*=8.3, 6.9)	121.2	7.08 (dd, *J*=8.3, 6.8)	121.5
6	7.22 (dd, *J*=8.2, 6.8)	123.4	7.11 (dd, *J*=8.2, 6.8)	124.9	7.22 (dd, *J*=8.3, 6.9)	124.1	7.25 (dd, *J*=8.2, 6.9)	123.7	7.23 (dd, *J*=8.3, 6.8)	124.0
7	7.43 (d, *J*=8.2)	108.9	7.32 (d, *J*=8.2)	110.4	7.43 (d, *J*=8.3)	109.5	7.46 (d, *J*=8.2)	109.1	7.43 (d, *J*=8.3)	109.5
7a		133.3		134.9		133.7		133.2		133.7
OCH_3	4.09 (s)	65.9	3.99 (s)	67.5	4.09 (s)	66.6	4.11 (s)	66.1	4.09 (s)	66.6
1'	5.34 (s)	42.5	5.37 (s)	49.7	5.76 (s)	46.4	5.46 (s)	41.0	5.55 (s)	46.0
2"	7.73 (s)	137.6					8.55 (s)	144.0		
3"			7.38 (d, *J*=1.4)	140.9					7.95 (s)	151.9
4"	6.92 (s like)	128.4	6.16 (dd, *J*=2.0, 1.4)	107.7	7.66 (s like)	134.5	8.55 (s)	144.0		
5"	7.12 (s like)	120.1	7.50 (d, *J*=2.0)	131.9	7.87 (s like)	125.4			8.44 (s)	144.5

Measured in CD_3OD

ACKNOWLEDGMENTS

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