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SYNTHESIS OF 2-SUBSTITUTED 9,10-ANTHRAQUINONES

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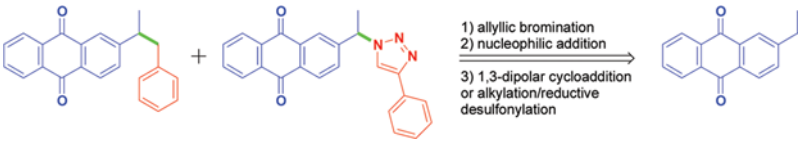
GRAPHICAL ABSTRACT



Abstract *A convenient preparation of racemic 2-substituted 9,10-anthraquinones that included 2-triazoylethyl skeleton* ***1*** *and 2-alkylethyl skeleton* ***6*** *is reported. The products were obtained in good yields by a three- or four-step synthetic route based on a sequence of N-bromosuccinimide (NBS)–mediated bromination of 2-ethyl-9,10-anthraquinone* ***2****, nucleophilic substitution, and CuI-catalyzed 1,3-dipolar cycloaddition or alkylation/reductive desulfonylation.*

[Supplementary materials are available for this article. Go to the publisher's online edition of Synthetic Communications® *for the following free supplemental resource(s): Full experimental and spectral details.]*

Keywords Alkynes; azides; dipolar cycloaddition; heterocycles; nucleophilic substitution

INTRODUCTION

Miscellaneous anthraquinone (anthracene-9,10-dione) derivatives are important condensed three-ring arenes in combinatorial drug discovery libraries; physcion, emodin, fallacinal, teloschistin, chrysophanol, and xanthorin abound in lichens and some plants, from which they can be easily isolated.[1] The functionalization of substituted anthraquinones has been restricted to a narrow choice of chemical transformations[2] due to the inertness of this skeleton to common electrophilic substitution reactions.[3] The reductive Claisen rearrangement reaction of allyloxyanthraquinones has become a standard method for introducing the alkyl groups onto the nucleus of this skeleton.[4] However, there is no example of structures containing both triazole and anthraquinone moieties. 1,2,3-Triazoles have received considerable attention in the search for new drugs in pharmacology, and

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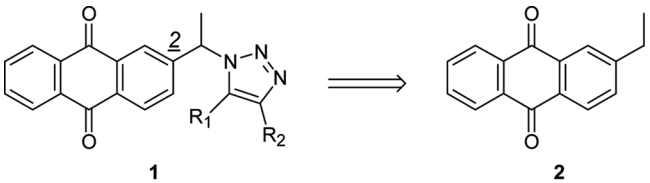
several efforts have been made to optimize methods for their preparation. Based on this reason, the synthesis of triazoles with the conjugated anthraquinone moieties was explored by the CuI-promoted 1,3-dipolar cycloaddition.[5,6]

DISCUSSION

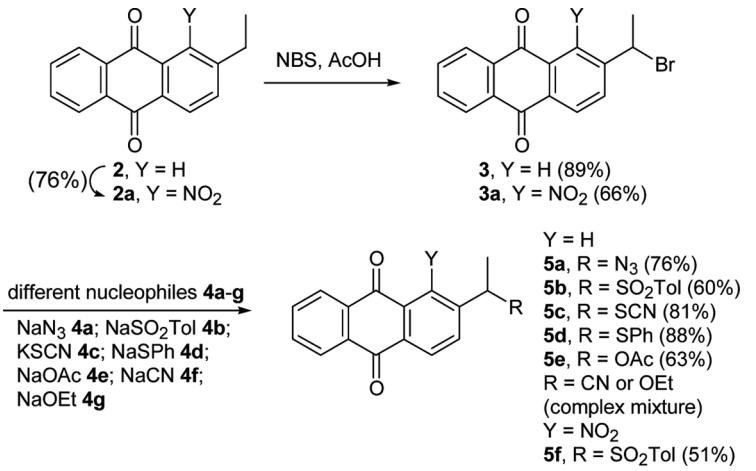
Herein, an easy and rapid synthetic route was investigated for preparing a series of racemic *N*-triazolyl-conjugated 2-ethyl-9,10-anthraquinones **1** (see Scheme 1). As shown in Scheme 2, a convenient three-step synthesis of skeleton **1** from 2-ethyl-9,10-anthraquinone **2** is described. It involves (i) α-bromination of compound **2** with N-bromosuccinimide (NBS) in AcOH; (ii) nucleophilic substitution of the benzylic bromide with NaN_3; and (iii) the regioselective CuI-catalyzed 1,3-dipolar cycloaddition reaction of the resulting azide with different alkynes.

First, NBS-mediated treatment of compound **2** or **2a** in boiling AcOH for 5 h provided a sole compound, **3** or **3a**, in 89% or 66% yield.[7] 1-Nitro-2-ethyl-9,10-anthraquinone could be provided by nitration of compound **2** with fuming HNO_3 and H_2SO_4 in 76% yield.[8] Nucleophilic substitution of bromine atom in compound **3** or **3a**, with different nucleophiles **4a**–**g**, was investigated subsequently. Initially, treatment of compound **3** with NaN_3 **4a** in acetone gave compound **5a** in 76% yield. When compound **3** was treated with NaCN **4f** or NaOEt **4g**, the complex mixture was observed to change with the reaction time, temperature, or solvent. By changing the nucleophile to sodium p-toluenesulfinic salt **4b**, compounds **5b** and **5f** were isolated in 60% and 51% yield when compound **3** or **3a** was used as a substrate. The expected 3-S-substituted compound **5c** or **5d** was obtained in good yield (NaSCN **4c**, ~81%; NaSPh **4d**, ~88%) by the abovementioned methodology. When compound **3** was treated with poorer nucleophile (NaOAc **4e**), compound **5e** was produced in 63% yield. We believed that a stronger nucleophile, such as NaCN **4f** or NaOEt **4g**, could not be easily introduced into the benzylic position of compound **3** via an intermolecular nucleophilic substitution as it might attack the carbonyl group to form labile adducts or abstract the proton to generate the dehydrobrominated olefinic products. The desired compounds **1a**–**h** were achieved via CuI-promoted 1,3-dipolar cycloaddition of compound **5a** with several alkynes **6a**–**h**. Eight commercially available alkynes **6a**–**h** were examined in the preparation of skeleton **1**, as shown in Table 1.



R_1 = H, R_2 =
a, Ph; **b**, $(CH_2)_3OH$; **c**, CO_2Et; **d**, COMe; **e**, 4-MePh; **f**, 3-HCCPh;
g, R_1 = Ph, R_2 = CO_2Me; **h**, R_1 = R_2 = CO_2Et

Scheme 1. Synthetic approach to the skeleton **1**.



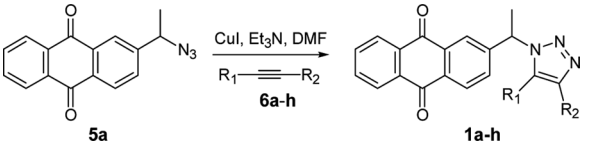
Scheme 2. Nucleophilic substitution of compound **2**.

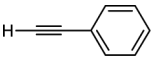
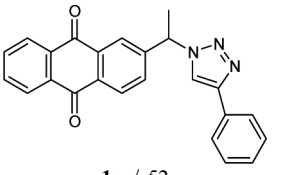
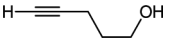
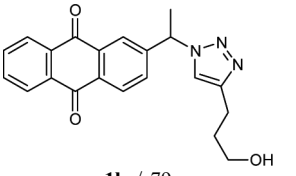
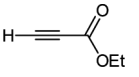
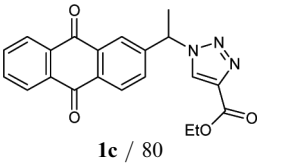
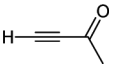
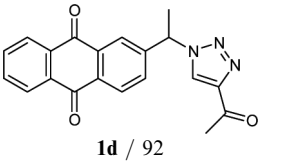
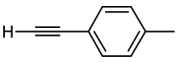
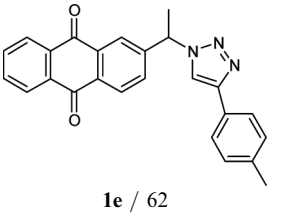
Based on the model of a cycloaddition reaction for the preparation of compound **1a**, we examined the reaction of compound **5a** and ethynylbenzene (**6a**) at 80 °C for 10 h in the presence of CuI without the addition of other reagents. Compound **1a** was obtained only in 35% yield. When 2.0 equivalents of Et_3N were added to the reaction mixture and the heating at 80 °C was continued for 2 h, the yield of product was increased to 52%. This result confirmed that the addition of Et_3N could increase the yield and cut the reaction time efficiently. In another experiment, when sodium ascorbate was added to the reaction mixture and the heating was continued at 80 °C for 4–6 h, the yield of product was increased to only 42%. Under the previously mentioned CuI-promoted reaction condition, the second regioisomer of triazole was not observed during the cycloaddition procedure. The possible reason might be that steric hindrance was a key factor affecting the regiochemical procedure. Based on these results, treatment of compound **5a** with different alkynes **6b**–**h** was further examined.

Compounds **1b**–**h** with 1-triazolylethyl group were obtained in good yields of 60–92% via the CuI-promoted the regioselective 1,3-cycloaddition of compound **5a** with the alkynes **6b**–**h** in the presence of Et_3N.[9] The yields of products and purity were determined after chromatographic purification. The structures of compounds **1a**–**h** were assigned on the basis of NMR spectroscopy. According to the synthetic experience, some variations on the carbon C2 of anthraquinone skeleton using the alkylation reaction of compound **5b** by different halogen derivatives **7a**–**e** in the presence of NaH was studied (Table 2).

In the first case, the *C*-allylation of compound **5b** with allyl bromide (**7a**) in the presence of 3.3 equivalents of NaH did not proceed in anhydrous tetrahydrofuran (THF) at rt for 10 h, and the starting material **5b** was recovered in its majority. When 3.3 equivalents of NaI were added to the reaction at rt and the reaction was carried out for 5 h, product **8a** was isolated in 60% yield. When the same reaction was performed at the reflux temperature, the yield of compound **8a** was increased to 88%. The results showed that the addition of excess amounts of NaI and the elevated

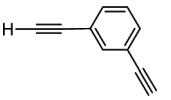
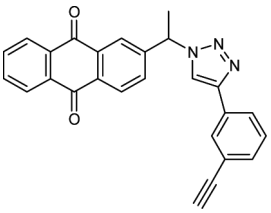
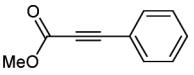
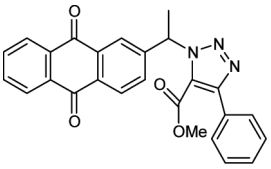
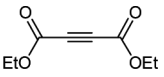
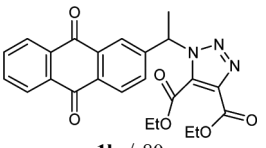
Table 1. Synthesis of triazolyl-conjugated anthraquinones 1a–h[a]



Entry	Alkyne **6**	Product **1** / yield (%)
1	 **6a**	 **1a** / 52
2	 **6b**	 **1b** / 79
3	 **6c**	 **1c** / 80
4	 **6d**	 **1d** / 92
5	 **6e**	 **1e** / 62

(*Continued*)

Table 1. Continued

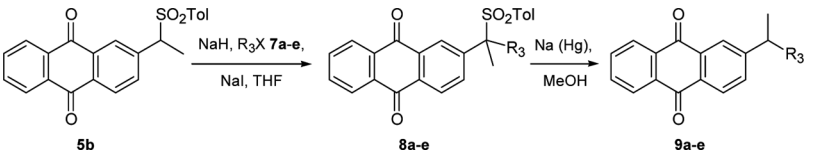
Entry	Alkyne **6**	Product **1** / yield (%)
6	 **6f**	 **1f** / 60
7	 **6g**	 **1g** / 79
8	 **6h**	 **1h** / 80

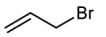
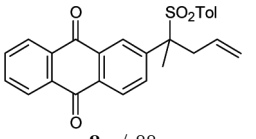
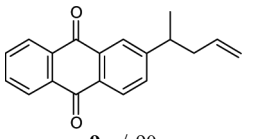
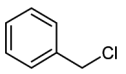
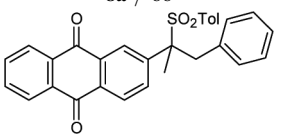
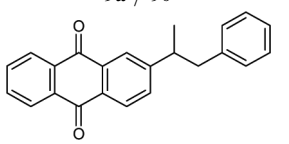
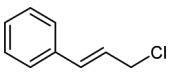
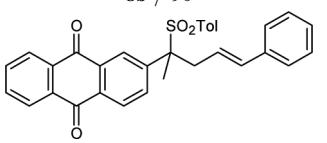
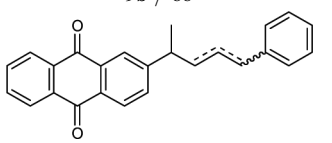
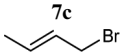
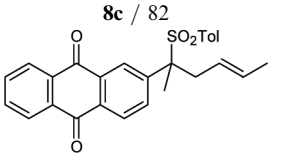
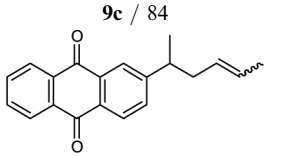
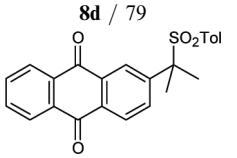
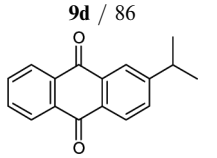
[a]The products **1a**–**h** were >95% pure as judged by ^{1}HNMR analysis.

reaction temperature could increase the yield and efficiently promote the S_N2-type alkylation reaction. With the results in hand, compounds **8b**–**e** could also be obtained in good yields of 79–90%. The attempts to extend this alkylation reaction to a secondary alkyl halide (e.g., isopropyl or isobutyl halide) were unsuccessful. To afford the derivatives of 2-substituted 9,10-anthraquinones **9a**–**e**, the reductive desulfonylation of compounds **8a**–**e** was carried out in boiling anhydrous MeOH using the freshly prepared sodium amalgam. The appropriate products **9a**–**e** were obtained in good yields (84–92%). In particular, compounds **9c** and **9d** were obtained as a mixture of *Z*- and *E*-isomers under the reductive desulfonylation conditions.[10] However, attempts to treat compound **5f** with NaH and MeI failed to yield the desired methylated product. We believed that the nitro group on the C1 position of compound **5f** should be a key factor in stabilizing the generated carbanion, so that the methylation was unsuccessful.

In summary, we have successfully presented a concise three- or four-step synthetic methodology for producing a series of novel racemic 2-triazoylethyl or 2-alkylethyl 9,10-anthraquinone derivatives **1a**–**h** and **9a**–**e** involving NBS-mediated benzylic bromination of 2-ethyl-9,10-anthraquinone **2**, nucleophilic substitution with NaN_3 or sodium *p*-toluenesulfinic salt, and the CuI-catalyzed 1,3-dipolar cycloaddition reaction or alkylation/reductive desulfonylation. More important, the overall prepared procedures are shorter, high-yielding, and more efficient for synthesizing the skeleton of triazolyl-conjugated anthraquinones.

Table 2. Synthesis of 2-substituted anthraquinones **9a**–**e**[a]



Entry	R_3X **7**	Product **8** / yield (%)	Product **9** / yield (%)
1	 **7a**	 **8a** / 88	 **9a** / 90
2	 **7b**	 **8b** / 90	 **9b** / 88
3	 **7c**	 **8c** / 82	 **9c** / 84
4	 **7d**	 **8d** / 79	 **9d** / 86
5	Me—I **7e**	 **8e** / 85	 **9e** / 92

[a]The products **8a**–**e** and **9a**–**e** were >95% pure as judged by ^{1}HNMR analysis.

EXPERIMENTAL

Synthesis of Skeleton 5

A nucleophile **4a**–**g** (1.0 mmol) was added to a stirred solution of compound **3** or **3a** (0.3 mmol) in the mixture of solvents of acetone/water (10 mL, v/v = 9/1; NaN_3 **4a**; NaSCN **4c**), 1,4-dioxane/water (10 mL, v/v = 4/1; $NaSO_2Tol$ **4b**; NaSPh **4d**) or THF/HOAc (10 mL, v/v = 9/1; NaOAc **4e**) at rt. The reaction mixture was stirred at reflux for 6–10 h. The reaction solvent was evaporated. The residue was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with brine, dried, filtered, and evaporated under reduced pressure to afford the crude product. Purification on silica gel (hexanes/EtOAc = 6/1–1/1) afforded compounds

5a–**f**. All of the new compounds were characterized by infrared (IR), ^{1}H NMR, ^{13}C NMR, and high-resdution mass spectrometry (HRMS). Representative data of 2-[1-(toluene-4-sulfonyl)ethyl]anthraquinone (**5b**) are as follows: Yellowish solid; yield: 60% (70 mg); mp = 184–185 °C (recrystallized from hexanes and EtOAc); R_f = 0.3 (hexanes/EtOAc, 3/1); IR ($CHCl_3$): ν_{max} 3278, 3022, 1732, 1660, 1601, 1450 cm^{-1}. HRMS (ESI, $M^+ + 1$) calcd. for $C_{23}H_{19}O_4S$: 391.1004 found: 391.1012, ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.31–8.26 (m, 2H), 8.22 (d, J = 8.0 Hz, 1H), 8.01 (d, J = 2.0 Hz, 1H), 7.83–7.78 (m, 2H), 7.70 (dd, J = 2.0, 8.0 Hz, 1H), 7.49 (d, J = 8.0 Hz, 2H), 7.22 (d, J = 8.0 Hz, 2H), 4.41 (q, J = 7.2 Hz, 1H), 2.38 (s, 3H), 1.82 (d, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 182.65, 182.44, 145.15 (2×), 140.64, 134.88, 134.25 (2×), 133.47, 133.38, 133.34, 133.35, 129.62 (2×), 129.14 (2×), 128.16, 127.39, 127.27, 127.25, 65.79, 21.59, 14.17. Anal. calcd. for $C_{23}H_{18}O_4S$: C, 70.75; H, 4.65. Found: C, 70.98; H, 4.82.

Synthesis of Skeleton 1

CuI (190 mg, 1.0 mmol), Et_3N (200 mg, 2.0 mmol), and different alkynes **6a**–**h** (1.0 mmol) were added to a solution of compound **5a** (110 mg, 0.4 mmol) in anhydrous dimethylformamide (DMF, 4 mL) at rt. The reaction mixture was stirred at 80 °C for 2 h, then cooled to rt. Saturated $NaHCO_{3(aq)}$ (5 mL) was added to the reaction mixture, and the solvent was evaporated under reduced pressure. The residue was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with brine, dried, filtered, and evaporated under reduced pressure to afford the crude product. Purification on silica gel (hexanes/EtOAc = 2/1–1/2) afforded compounds **1a**–**h**. Representative data of 2-[1-(4-phenyl[1,2,3]triazol-1-yl)ethyl]anthraquinone **(1a)** are as follows: Yellowish solid; yield: 52% (79 mg); mp = 188–189 °C (recrystallized from hexanes and EtOAc); R_f = 0.4 (hexanes/EtOAc, 3/1). HRMS (ESI, $M^+ + 1$) calcd; for $C_{24}H_{18}N_3O_2$: 380.1399; found: 380.1343. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.31–8.27 (m, 4H), 7.83–7.78 (m, 5H), 7.67 (dd, J = 2.0, 8.0 Hz, 1H), 7.42–7.38 (m, 2H), 7.33–7.29 (m, 1H), 6.03 (q, J = 6.8 Hz, 1H), 2.13 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 182.62, 182.38, 148.16, 146.36 (2×), 134.36, 134.27, 133.96, 133.34 (2×), 132.10, 130.32, 128.81 (2×), 128.34, 128.28, 127.30 (2×), 125.72 (2×), 124.89, 118.32, 59.83, 21.12. Anal. calcd. for $C_{24}H_{17}N_3O_2$: C, 75.97; H, 4.52; N, 11.08. Found: C, 76.22; H, 4.84; N, 11.31.

Synthesis of Skeleton 8

NaH (60% in oil, 40 mg, 1.0 mmol) and NaI (142 mg, 1.0 mmol) were added to a solution of compound **5b** (117 mg, 0.3 mmol) in anhydrous THF (10 mL) at rt. After 10 min, alkyl halide **7a**–**e** (1.0 mmol) was added the reaction mixture at rt. The reaction mixture was stirred at reflux for 5 h, then cooled to rt. Saturated $NaHCO_{3(aq)}$ (5 mL) was added to the reaction mixture, and the solvent was evaporated under reduced pressure. The residue was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with brine, dried, filtered, and evaporated under reduced pressure to afford crude product. Purification on silica gel (hexanes/EtOAc = 4/1–2/1) afforded compounds **8a**–**e**. Representative data of 2-[1-methyl-1-(toluene-4-sulfonyl)but-3-enyl]anthraquinone **(8a)** are as follows: Yellowish solid;

yield: 88% (113 mg); mp = 164–165 °C (recrystallized from hexanes and EtOAc); $R_f = 0.3$ (hexanes/EtOAc, 3/1); IR ($CHCl_3$): ν_{max} 3374, 3152, 1726, 1662, 1578 cm^{-1}; HRMS (ESI, $M^+ + 1$) calcd for $C_{26}H_{23}O_4S$ 431.1317; found 431.1322. ^1H NMR (400 MHz, $CDCl_3$): δ 8.34–8.27 (m, 2H), 8.25 (d, $J = 8.4$ Hz, 1H), 8.11 (d, $J = 2.0$ Hz, 1H), 7.93 (dd, $J = 2.0$, 8.4 Hz, 1H), 7.85–7.79 (m, 2H), 7.29 (d, $J = 8.0$ Hz, 2H), 7.14 (d, $J = 8.0$ Hz, 2H), 5.42–5.31 (m, 1H), 5.17 (dd, $J = 1.2$, 15.6 Hz, 1H), 5.05 (dd, $J = 1.2$, 10.8 Hz, 1H), 3.48 (dd, $J = 6.4$, 14.4 Hz, 1H), 2.90 (dd, $J = 8.4$, 14.4 Hz, 1H), 2.36 (s, 3H), 1.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 182.75, 182.56, 145.12, 142.09, 135.00, 134.50, 134.35, 134.27, 133.43, 132.87, 132.78, 131.54, 130.62, 130.39 (2×), 129.23 (2×), 127.87, 127.30, 127.24, 126.92, 120.73, 68.78, 38.26, 21.57, 19.36. Anal. calcd. for $C_{26}H_{22}O_4S$: C, 72.54; H, 5.15. Found: C, 72.78; H, 5.43.

Synthesis of Skeleton 9

A freshly prepared Na(Hg) (100 mg) was added to a solution of compounds **8a**–**e** (0.1 mmol) in anhydrous MeOH (10 mL) at rt. After 5 min, the reaction mixture was stirred at reflux for 2 h, and then cooled to rt. Saturated $NaHCO_{3(aq)}$ (5 mL) was added to the reaction mixture, and the solvent was evaporated under reduced pressure. The residue was extracted with DCM (3 × 30 mL). The combined organic layers were washed with brine, dried, filtered, and evaporated under reduced pressure to afford crude product. Purification on silica gel (hexanes/EtOAc = 4/1–2/1) afforded compounds **9a**–**e**. Representative data of 2-(1-methylbut-3-enyl)anthraquinone **(9a)**. are as follows: Yellowish gum; yield: 90% (25 mg); $R_f = 0.4$ (hexanes/EtOAc, 8/1); IR ($CHCl_3$): ν_{max} 3332, 3167, 1727, 1668, 1595 cm^{-1}. HRMS (ESI, $M^+ + 1$) calcd, for $C_{19}H_{17}O_2$: 277.1228; found: 277.1234. ^1H NMR (400 MHz, $CDCl_3$): δ 8.31–8.28 (m, 3H), 8.24 (d, $J = 8.0$ Hz, 1H), 7.81–7.76 (m, 2H), 7.62 (dd, $J = 2.0$, 8.0 Hz, 1H), 5.75–5.65 (m, 1H), 5.03–4.97 (m, 2H), 3.03–2.98 (m, 1H), 2.47–2.37 (m, 2H), 1.35 (d, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 182.41, 182.94, 154.11, 135.99 (2×), 134.00, 133.89, 133.56, 133.53, 133.06, 131.72, 127.52, 127.14, 127.09, 125.60, 116.82, 42.09, 40.09, 21.07.

SUPPORTING INFORMATION

Experimental data and scanned photocopies of ^1H and ^{13}C NMR spectral data are provided. This material can be found via the Supplementary Content section of this article's Web page.

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