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SYNTHESIS OF 8-AMINO-(DIHYDROFURAN-FUSED PERHYDROPHENANTHRENE) VIA COPPER-MEDIATED AMINATION REACTION

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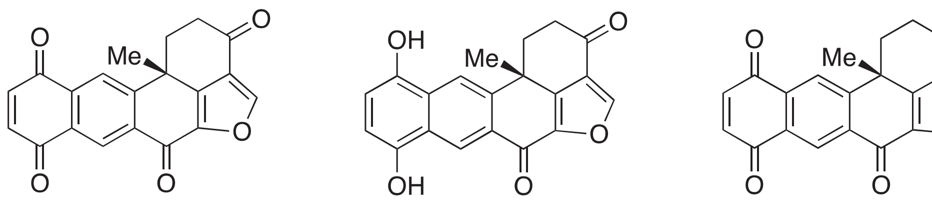
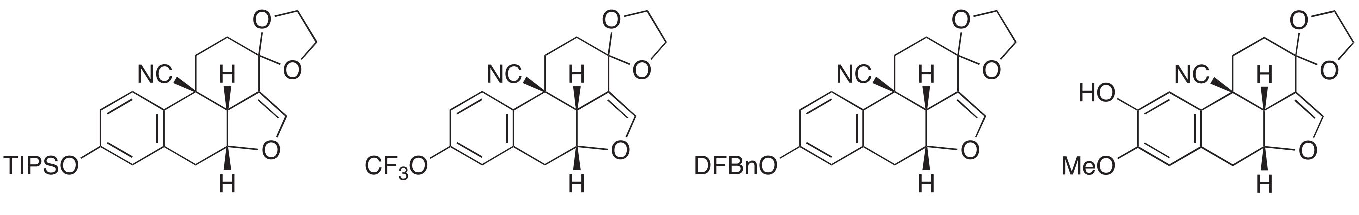
This paper is dedicated to Professor Victor Snieckus on the occasion of his 77th birthday.

Abstract – Introduction of nitrogen substituents on a highly functionalized dihydrofuran-fused perhydrophenanthrene (DF) core was examined. Acetamide functionality could be introduced on the DF by copper-mediated Buchwald-type coupling. On the other hand, installation of free amino group on a DF was established via an aryl azide under the copper-mediated condition reported by Helquist and co-workers.

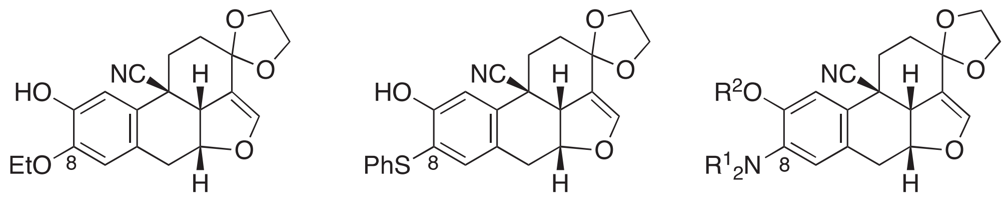
Naturally occurring biologically active pentacyclic polyketides such as halenaquinone, halenaquinol, and xestoquinone were known to possess furan-fused highly oxygenated structure.[1] Their structural and biological feature attracted synthetic organic chemists[2] and we also developed an effective preparation of similar tetracyclic dihydrofurans (DFs) using originally elaborated *o*-quinodimethane chemistry.[3] The biological evaluations on our DFs revealed that they show several fascinating biological activities. Firstly, dihydrofuran **1** was proved to exhibit anti-virus activity against HVJ.[4] This dihydrofuran **1** also showed dose-dependent enhancement of a heat-induced apoptosis in human lymphoma U937 cells.[5] Further structure-activity-relationship studies afforded potent anti-influenza agents, trifluoromethyl ether **2** and 3,5-difluorobenzyl ether **3**.[6] Additionally, **4** has been expected as novel anti-Alzheimer's disease agent for its axonal and dendritic extension activities in Aβ-damaged neurons.[7] Recently, extensive SAR studies on **4** suggested the efficiency of the introduction of hetero atom on the C8 position and finally proved that EtO- (**5**) or PhS- (**6**) substituent markedly enhance the dendritic extension effect.[8] However, we could never have estimated the dendritic extension activities of nitrogen-introduced analogues for its difficulty in installing nitrogen functionalities on the common precursor in our previous report.[8] Thus, the importance of the hetero atoms on the C8 position of DFs prompted us to develop a reaction which enable the late-stage introduction of amino group on DFs. We describe herein the synthesis of 8-amino-DFs **7**, which could be a pivotal intermediate for further SAR studies, via copper-mediated amination reaction.



halenaquinone halenaquinol xestoquinone



1 (antiviral and apoptosis inducing agent) **2** (anti-influenza) **3** (anti-influenza) DFBn = 3,5-difluorobenzyl **4** (anti-Alzheimer's agent)

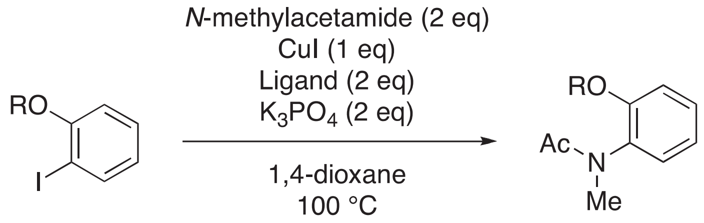


5 (anti-Alzheimer's agent) **6** (anti-Alzheimer's agent) **7**

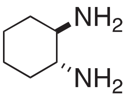
Figure 1. Natural and designed, biologically active fused furans

Prior to the synthetic studies, we examined a Cu-mediated introduction of *N*-methylacetamide on a simple model substrate, *o*-iodophenols under the conditions reported by Buchwald and co-workers (Table 1).[9,10] The coupling reaction of *o*-(TBSO)-iodobenzene (**8a**) with *N*-methylacetamide (2 eq) was conducted in the presence of CuI (1 eq), DMEDA (2 eq) and K_3PO_4 (2 eq), at 100 °C in DMSO to give a complex mixture including *o*-iodophenol (**8b**) as a detectable product (entry 1). Dehalogenation reaction dominantly proceeded with *o*-iodophenol (**8b**) as a substrate (entry 2). On the other hand, *o*-(*p*-methoxybenzyloxy)-iodobenzene (**8c**) afforded corresponding acylanilide **9c** in 7% yield (entry 3). The addition of (±)-*trans*-1,2-cyclohexanediamine as a ligand slightly improve the yield of **9c** to 20% (entry 4).

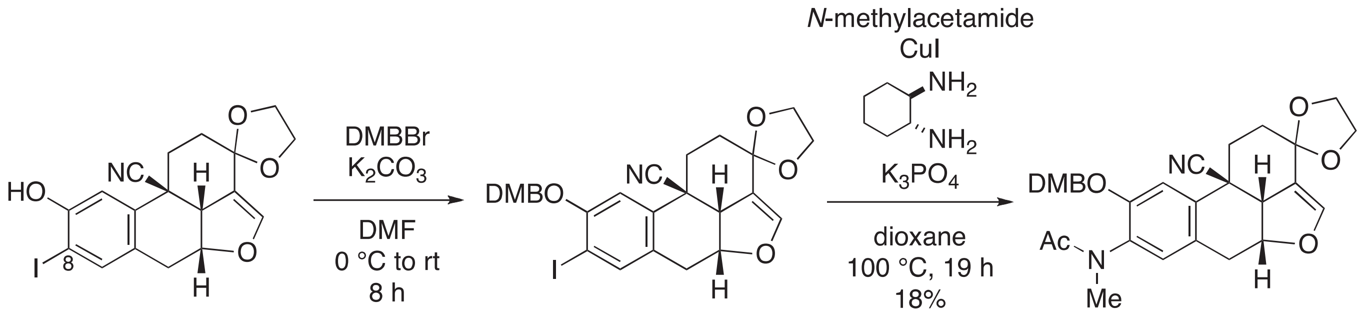
Table 1. Cu-mediated amidation of DF with *N*-methylacetamide



8a, **8b** or **8c** **9a**, **9b** or **9b**

entry		R	Ligand	time (h)	yield (%)	
1	**8a**	TBS	DMEDA	2.5	**9a**	0
2	**8b**	H	DMEDA	2.5	**9b**	0
3	**8c**	PMB	DMEDA	13	**9c**	7
4	**8c**	PMB		24	**9c**	20

With these results, we examined an installation of *N*-acetyl-*N*-methyl amino group on our dihydrofuran-fused perhydrophenanthrene **10**[8] as depicted in Scheme 1. Phenolic hydroxyl group was uneventfully protected as DMB ether **11**, which could be cleaved under a milder condition than that for PMB ether. Cu-mediated coupling between **11** and *N*-methylacetamide took place to afford the corresponding anilide **12** in 18% yield accompanied with inevitable decomposition of the substrate including dehalogenation reaction.

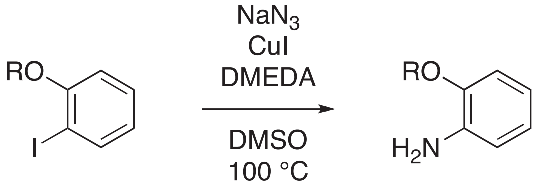


10 **11** **12**

Scheme 1. Introduction of *N*-Ac-*N*-Me amino group on DF

Aiming at the synthesis and biological evaluation of broad nitrogen-substituted DFs, next we examined a preparation of the pivotal free aniline derivative. As indicated in Table 2, Cu-mediated amination reaction with NaN_3, which was reported by Helquist and co-workers,[11] was employed on *o*-iodophenols. Although, similar to the amidation reaction, unprotected phenolic hydroxyl group would prevent the desired amination reaction (entry 1), *o*-(*p*-methoxybenzyloxy)-iodobenzene worked well to provide the aniline **13c** in 40% yield (entry 2). Finally, it was found that **8c** was effectively transformed into the desired **13c** with 52% in the presence of the excess amount of NaN_3 (entry 4).

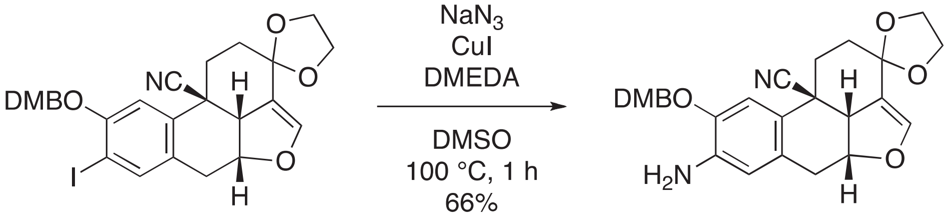
Table 2. Cu-mediated amination reaction with NaN_3



8b or **8c** **13b** or **13c**

entry		R	NaN_3 (eq)	time (h)	yield (%)	
1	**8b**	H	2	16	**13a**	0
2	**8c**	PMB	2	2.5	**13c**	40
3	**8c**	PMB	5	1.5	**13c**	45
4	**8c**	PMB	10	0.5	**13c**	52

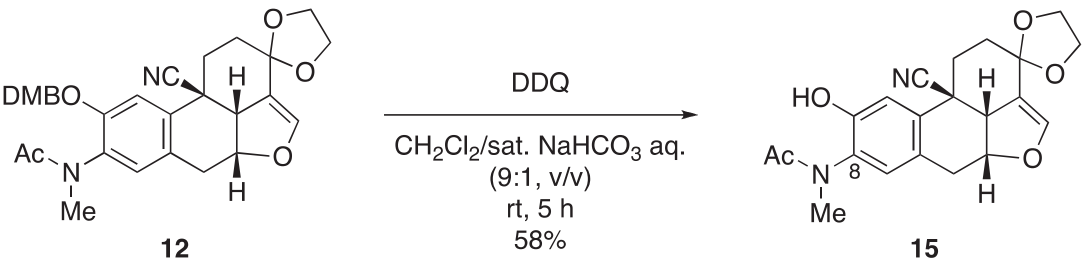
Under the optimal condition, DF **11** could be converted into desired aniline **14**, pivotal aniline congener for further derivatization, in good yield (66%) as denoted in Scheme 2.



11 **14**

Scheme 2. Cu-mediated amination of DF

Finally, cleavage of the DMB group on the anilide **12** was performed as Scheme 3. Under quite mild condition such as DDQ in basic media, DF **15** was successfully obtained in 58% remaining the acid labile, acetal and dihydrofuran functional groups untouched.



Scheme 3. Successful oxidative cleavage of DMB ether

In summary, we investigated the late-stage introduction of amino group into biologically potent DF core and could fortunately establish the key aniline derivatives in good yield based on Cu-mediated amination strategy. Further derivatization from the common aniline **14** and biological evaluation of the nitrogen-substituents on DFs are now in progress in our laboratory.

EXPERIMENTAL

Materials were obtained from commercial suppliers and used without further purification. Column chromatography was performed on Cica Silica Gel 60 N (spherical, neutral, 40–50 μm or 63–210 μm). Reaction and chromatographical fractions were monitored by employing precorted silica gel 60 F_{254} plates (Merck). All melting points were determined on Yanaco micro melting point apparatus and uncorrected. NMR spectra were recorded on JEOL ECX 400 spectrometer with $CHCl_3$ (7.26 ppm for ^1H) or $CDCl_3$ (77.0 ppm for ^{13}C) as an internal standard. Chemical shifts are expressed in δ (ppm) values, and coupling constants are expressed in hertz (Hz). The following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br s = broad singlet, dd = double-doublet, dt = double-triplet, td = triple-doublet, tt = triple-triplet, ddd = double-double-doublet, dddd = double-double-double-doublet. IR spectra were measured on JASCO FT/IR-660. MS spectra were recorded on JEOL D-200, JEOL JMS-GCmateII or JEOL AX 505 spectrometer.

General Procedure for Cu-mediated Amidation Reaction of Aryl Iodide (Table 1).

Under an Ar atmosphere, to a solution of the aryl iodide **8c** (100 μmol) in dioxane (0.2 M) were added *N*-methylacetamide (2 eq), CuI (1 eq), ligand (2 eq), and K_3PO_4 (2 eq) at rt, and the mixture was stirred at 100 °C until the starting material was completely consumed (monitored by TLC). The reaction mixture was then cooled to rt, diluted with saturated aqueous NH_4Cl and AcOEt, and stirred for 40 min at rt. After filtration through Celite, the aqueous phase was extracted with AcOEt. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting oil was purified by column chromatography on silica gel (AcOEt/hexane, 3:1, v/v) to afford the amide **9c**.

8-Iodo-9-(3,4-dimethoxy-benzyloxy)-3-[1.3]dioxolan-2,3,5a,10c-tetrahydro-1*H*,6*H*-5-oxaacephenanthrylene-10b-carbonitrile (11): Under an Ar atmosphere, to a solution of 3,4-dimethoxy-benzyl alcohol

(272 mg, 1.62 mmol) in CH_2Cl_2 (8.1 mL) was added dropwise PBr_3 (305 μL, 3.24 mmol) at 0 °C, and the mixture was stirred for 8 h. The reaction was quenched with H_2O, and the aqueous phase was extracted with $CHCl_3$. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting bromide was used without purification. Under an Ar atmosphere, to a solution of the phenol **10**[8] (341 mg, 780 μmol) and the above bromide in DMF (3.9 mL) was added K_2CO_3 (216 mg, 1.62 μmol) at 0 °C, and the mixture was stirred for 8 h at rt. The reaction was quenched with H_2O, and the aqueous phase was extracted with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting oil was purified by column chromatography on silica gel (AcOEt/CH_2Cl_2, 1:100, v/v) to afford the benzyl ether **11** (416 mg, 708 μmol, 91%) as a colorless solid (mp 192–193 °C); ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.66 (1H, ddd, J = 3.7, 13.7, 14.2 Hz), 1.77 (1H, ddd, J = 3.7, 3.7, 13.7 Hz), 2.52 (1H, ddd, J = 3.7, 14.2, 14.7 Hz), 2.74 (1H, td, J = 3.7, 14.7 Hz), 3.07 (1H, dd, J = 2.3, 15.8 Hz), 3.18 (1H, dd, J = 3.2, 15.8 Hz), 3.84–4.01 (11H, m), 5.02 (1H, d, J = 11.4 Hz), 5.10 (1H, d, J = 11.4 Hz), 5.26 (1H, ddd, J = 2.3, 3.2, 10.5 Hz), 6.01 (1H, d, J = 1.8 Hz), 6.77 (1H, s), 6.86 (1H, d, J = 8.0 Hz), 6.96 (1H, dd, J = 1.8, 8.0 Hz), 7.07 (1H, d, J = 1.8 Hz), 7.72 (1H, s); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 29.2, 29.7, 31.3, 32.6, 35.8, 50.9, 55.9, 55.9, 63.7, 65.3, 71.6, 79.6, 87.6, 104.4, 110.1, 110.5, 111.1, 119.5, 121.4, 128.6, 129.8, 132.3, 140.9, 143.3, 148.9, 149.2, 156.8; IR (KBr): 2240 cm^{-1}; MS (EI): m/z 587 (M^+); HRMS (EI): calcd for $C_{27}H_{26}INO_6$: 587.0805, found: 587.0800.

***N*-[10b-Cyano-9-(3,4-dimethoxy-benzyloxy)-3-[1.3]dioxolan-2,3,5a,10c-tetrahydro-1*H*,6*H*-5-oxaace-phenanthrylene-8-yl]-*N*-methyl-acetamide (12):** Under an Ar atmosphere, to a solution of the iodide **11** (32.3 mg, 55.0 μmol) in dioxane (275 μL) were added *N*-methylacetamide (8.40 μL, 110 μmol), CuI (10.5 mg, 55.0 μmol), (±)-*trans*-1,2-cyclohexanediamine (13.2 μL, 110 μmol), and K_3PO_4 (29.3 mg, 110 μmol) at rt, and the mixture was stirred for 4 h at 100 °C. Then to the reaction mixture were further added *N*-methylacetamide (8.40 μL, 110 μmol), CuI (10.5 mg, 55.0 μmol), (±)-*trans*-1,2-cyclohexanediamine (13.2 μL, 110 μmol), and K_3PO_4 (29.3 mg, 110 μmol), and the mixture was stirred for 15 h at 100 °C. The reaction mixture was then cooled to rt, diluted with saturated aqueous NH_4Cl and AcOEt, and stirred for 40 min at rt. After filtration through Celite, the aqueous phase was extracted with AcOEt. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting oil was purified by column chromatography on silica gel (AcOEt/hexane, 3:1, v/v) to afford the amide **12** (5.3 mg, 9.95 μmol, 18%) as a colorless oil; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.62–1.93 (5H, m), 2.53–2.62 (1H, m), 2.78 (1H, dd, J = 2.7, 14.7 Hz), 3.09 (1H, d, J = 16.0 Hz), 3.17 (3H, s), 3.21 (1H, dd, J = 3.2, 16.0 Hz), 3.83–4.05 (11H, m), 4.99 (1H, d, J = 11.4 Hz), 5.05 (1H, d, J = 11.4 Hz), 5.30 (1H, ddd, J = 3.2, 5.5, 10.1 Hz), 6.03 (1H, d, J = 1.8 Hz), 6.84–6.88 (3H, m), 6.95 (1H, s), 7.10 (1H, s); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 21.9, 25.9, 29.6, 31.9, 32.9, 35.7, 36.1, 51.0, 53.8, 55.9, 63.8, 65.3, 70.7, 79.5, 104.4, 110.1, 110.2, 111.2, 111.8, 119.4, 125.1, 128.6, 130.6, 131.7, 133.6, 143.4, 149.3, 153.3, 171.1; IR (neat): 1660, 2223 cm^{-1}; MS (EI): *m/z* 532 (M$^+$); HRMS (EI): calcd for $C_{30}H_{32}N_2O_7$: 532.2210, found: 532.2210.

General Procedure for Cu-mediated Amination Reaction of Aryl Iodide (Table 2).

Under an Ar atmosphere, to a solution of the iodide **8c** (100 μmol) in DMSO (0.3 M) were added NaN_3 (2~10 eq), CuI (1 eq), and DMEDA (1.3 eq) at rt, and the mixture was stirred for 1 h at 100 °C. The reaction mixture was then cooled to rt, diluted with saturated aqueous NH_4Cl and AcOEt, and stirred for 1 h at rt. The mixture was filtered through Celite, and the aqueous phase was extracted with AcOEt. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting oil was purified by column chromatography on silica gel (AcOEt/hexane, 1:1, v/v) to afford the amine **13c**.

8-Amino-9-(3,4-dimethoxy-benzyloxy)-3-[1.3]dioxolan-2,3,5a,10c-tetrahydro-1*H*,6*H*-5-oxaacephenanthrylene-10b-carbonitrile (14): Under an Ar atmosphere, to a solution of the iodide **11** (25.7 mg, 43.8 μmol) in DMSO (146 μL) were added NaN_3 (28.5 mg, 438 μmol), CuI (8.3 mg, 43.8 μmol), and DMEDA (6.12 μL, 56.9 μmol) at rt, and the mixture was stirred for 1 h at 100 °C. The reaction mixture was then cooled to rt, diluted with saturated aqueous NH_4Cl and AcOEt, and stirred for 1 h at rt. The mixture was filtered through Celite, and the aqueous phase was extracted with AcOEt. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting oil was purified by column chromatography on silica gel (AcOEt/hexane, 1:1, v/v) to afford the amine **14** (13.7 mg, 28.8 μmol, 66%) as a colorless oil; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.75–1.84 (2H, m), 2.44–2.52 (1H, m), 2.74 (1H, ddd, *J* = 3.2, 3.2, 14.7 Hz), 2.98 (1H, dd, *J* = 2.3, 16.0 Hz), 3.15 (1H, dd, *J* = 3.7, 16.0 Hz), 3.84–4.01 (11H, m), 4.93 (1H, d, *J* = 10.7 Hz), 4.99 (1H, d, *J* = 10.7 Hz), 5.25 (1H, ddd, *J* = 2.3, 3.7, 10.5 Hz), 6.03 (1H, d, *J* = 1.8 Hz), 6.63 (1H, s), 6.75 (1H, s), 6.87 (1H, d, *J* = 8.2 Hz), 6.95–6.96 (2H, m); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 29.2, 29.8, 31.3, 33.1, 35.3, 51.0, 55.9, 55.9, 63.6, 65.3, 71.2, 79.9, 104.7, 110.4, 110.9, 111.1, 116.7, 119.6, 120.4, 122.5, 128.4, 129.3, 137.0, 143.2, 145.5, 149.0, 149.1; IR (neat): 2226, 3374 cm^{-1}; MS (EI): *m/z* 476 (M$^+$); HRMS (EI): calcd for $C_{27}H_{28}N_2O_6$: 476.1947, found:476.1970.

***N*-[10b-Cyano-9-hydroxy-3-[1.3]dioxolan-2,3,5a,10c-tetrahydro-1*H*,6*H*-5-oxaacephenanthrylene-8-yl]-*N*-methyl-acetamide (15):** To a solution of benzyl ether **12** (7.9 mg, 14.8 μmol) in CH_2Cl_2/sat. $NaHCO_3$ aq. (150 μL, 9:1, v/v) was added DDQ (13.4 mg, 59.2 μmol), and the mixture was stirred for 5 h at rt. The reaction mixture was diluted with saturated aqueous $NaHCO_3$, and the aqueous phase was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting oil was purified by column chromatography on silica gel (MeOH/CH_2Cl_2, 1:50, v/v) to afford the phenol **15** (3.3 mg, 8.63 μmol, 58%) as a colorless oil; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.82–2.04 (5H, m), 2.56 (1H, ddd, *J* = 4.1, 14.7, 14.7 Hz), 2.84 (1H, d, *J* = 14.7 Hz), 3.07 (1H, d, *J* = 16.0

Hz), 3.20–3.25 (4H, m), 3.88–4.04 (5H, m), 5.30 (1H, ddd, J = 2.7, 5.5, 10.5 Hz), 6.06 (1H, d, J = 1.4 Hz), 7.01 (1H, s), 7.04 (1H, s); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 22.3, 29.7, 31.3, 32.8, 35.6, 36.2, 40.5, 50.9, 63.8, 65.4, 79.5, 104.6, 110.4, 115.9, 127.7, 129.4, 130.3, 132.7, 143.2, 151.6, 172.5; IR (neat): 1636, 2231, 3223 cm^{-1}; MS (EI): m/z 382 (M^+); HRMS (EI): calcd for $C_{21}H_{22}N_2O_5$: 382.1529, found: 382.1508.

ACKNOWLEDGEMENT

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