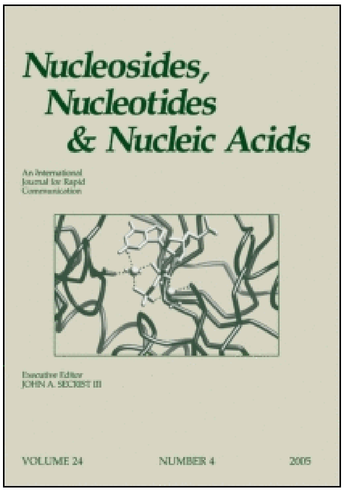

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Efficient Synthesis of Carbocyclic Nucleoside, (±)-Homocarbovir Via π-Allylpalladium Complex Formation from the Allyl N,N-Ditosylimide Substrate

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EFFICIENT SYNTHESIS OF CARBOCYCLIC NUCLEOSIDE, (±)-HOMOCARBOVIR *VIA* π–ALLYLPALLADIUM COMPLEX FORMATION FROM THE ALLYL *N,N*-DITOSYLIMIDE SUBSTRATE

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ABSTRACT: The synthesis of a carbovir analogue, (±)-homocarbovir (**3**) was achieved from norbornadiene (**4**) in seven steps and 27% overall yield. This route involves a Meinwald-type rearrangement, an acid-hydrolysis of *N*-tosyl bicyclic enamine **5**, and a Pd(0)-catalyzed coupling reaction.

INTRODUCTION

Carbocyclic nucleosides, *i.e.*, carbocyclic analogues of normal purine or pyrimidine nucleosides, are of great interest as potential antiviral and antitumor agents.[2] The recently discovered carbocyclic nucleoside, (-)-carbovir (**1a**) was reported to be an *in vitro* selective inhibitor of HIV-1 and exhibited less toxicity than other agents. The analogue of (-)-carbovir, abacavir (**1b**), which has higher oral bioavailability than carbovir,[3] is currently commercialized for the treatment of HIV infection. A recently discovered potent antiherpes agent, 4',1' α-methanocarbocyclic thymidine (**2**) showed better *in vitro* activity against HSV-1 and HSV-2 than acyclovir.[4] Because of the important biological activity of these carbocyclic nucleosides, our research has focused on the synthesis of carbovir analogues. We have chosen (±)-homocarbovir (**3**) as a target compound. The synthesis of homocarbovir (**3**) has been reported by several research groups.[5]

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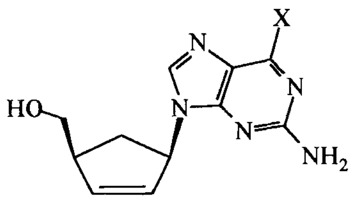
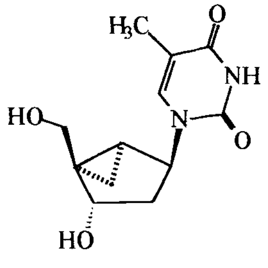
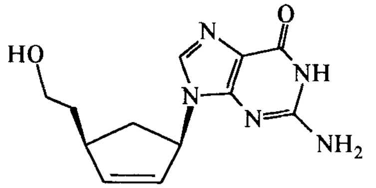


X = OH (Carbovir, **1a**)
X = NH–◁ (Abacavir, **1b**)



4',1'α-Methanocarbocyclic thymidine, **2**

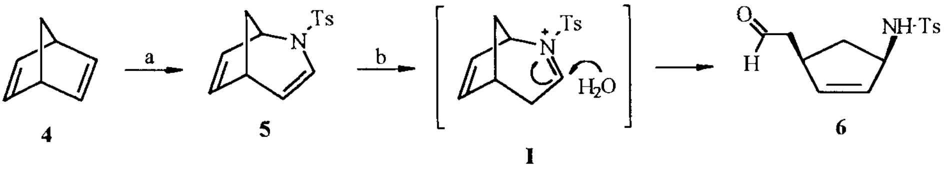


(±)-Homocarbovir, **3**

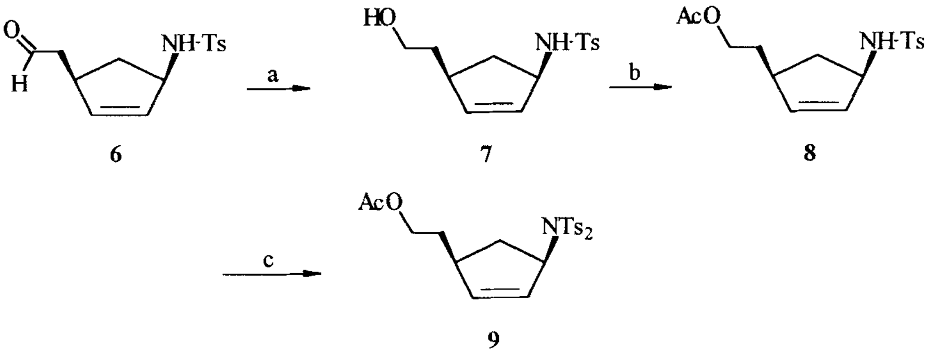
The addition of nucleophiles to π–allylpalladium complexes has been investigated by many research groups, foremost among them those of Trost[6a] and Tsuji.[6b] Trost and his co-workers have initially studied the synthesis of carbocyclic nucleosides by the direct introduction of purine moieties to cyclopentene derivatives *via* π–allylpalladium complex formation.[7] Several other groups have also applied this method to the synthesis of carbocyclic nucleosides.[8] The substrates in these reactions are allylic acetate, carbonates, and epoxides.[7] Recently, we and other group have utilized 3-(*N*,*N*-ditosylimido)cyclopentene derivatives with Pd(0) for the synthesis of (±)-carbovir.[9] We have also demonstrated the utility of Pd(0)-catalyzed coupling reactions of allyl *N*,*N*-ditosylimide with C, N, O nucleophiles.[10] In this paper, we wish to report an efficient synthesis of the carbocyclic nucleoside, (±)-homocarbovir (**3**), *via* nucleophilic attack on a π–allylpalladium complex formed from a 3-(*N*,*N*-ditosylimido) cyclopentene derivative.

RESULTS AND DISCUSSION

The *N*-tosyl bicyclic enamine **5** (Scheme 1) was prepared *via* Meinwald-type rearrangement[11] from the reaction of norbornadiene (**4**) with *p*-toluenesulfonyl azide in 76% yield. Hydrolysis of tosyl



Scheme 1. a. TsN$_3$, benzene, rt, 3d, 76%. b. 2.0 *M* HCl, THF, reflux, 2 h, 99%.



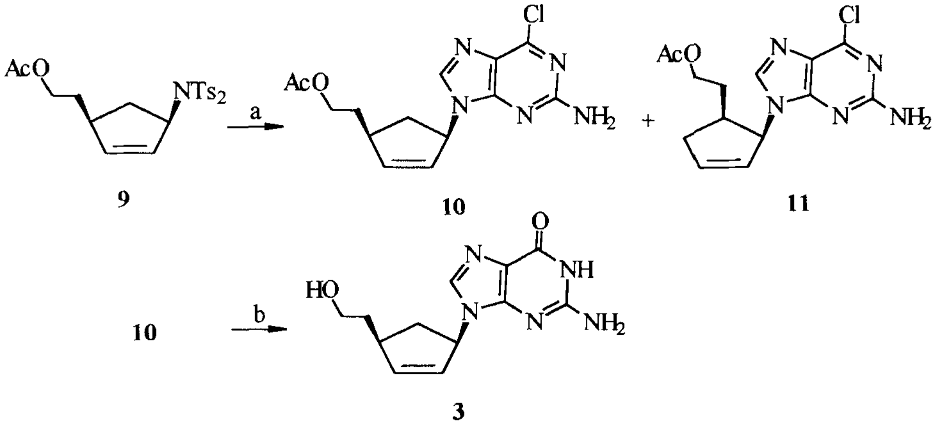
Scheme 2. a. NaBH$_4$, THF, rt, 90%. b. Ac$_2$O, pyr, rt, 99%. c. i) NaH, THF ii) TsCl, THF, HMPA, 0 °C to rt, 64% (with 29% recovery of **8**).

enamine **5** afforded quantitatively a ring opening product, *N*-tosylamido aldehyde **6**. We believe that this reaction proceeds presumably *via* the formation of iminium intermediate **I** and subsequent rapid attack of water on the iminium ion.

The *N*-tosyl amido alcohol 7 was obtained by the reduction of the aldehyde **6** with NaBH$_4$ in excellent yield. Selective acetylation of the alcohol afforded quantitatively the acetate **8**, which was then *N*-tosylated by treatment with sodium hydride and tosyl chloride to give **9** (Scheme 2).

The key coupling was then effected by treatment of **9** with the sodium salt of 2-amino-6-chloropurine in 1:1 THF:DMSO in the presence of 5 % Pd[P(OPr^i)$_3$]$_4$ which furnished the desired coupling adduct **10** and its isomer **11** as a 10:1 mixture in 71% isolated yield (Scheme 3).[12]

The 3-(*N*,*N*-ditosylimido)cyclopentene **9** served as a much better substrate than others for the formation of π-allylpalladium complex and the reaction was complete within 10 min, as we have



Scheme 3. a. i) Pd(OAc)$_2$, (i-PrO)$_3$P, THF, rt ii) n-BuLi, rt iii) 9 in THF, 2-amino-6-chloropurine, NaH, DMSO, rt, 10 min (**10**:**11** = 10:1, 71%) b. 1.0N NaOH, reflux, 2h (89%)

seen previously.[10] The attack of the anion of the purine base on the π-allylpalladium complex proceeds *via* 1,4-addition rather than 1,2-addition presumably because of steric hindrance to 1,2-addition due to the non-bonded interaction from the substituent in the cyclopentene ring. Hydrolysis of this mixture with aqueous sodium hydroxide gave (±)-homocarbovir (**3**) in 89% yield. In summary, the synthesis of a carbovir analogue, (±)-homocarbovir (**3**), was achieved from norbornadiene (**4**) in seven steps and 27 % overall yield.

(±)-Homocarbovir (**3**) was evaluated for cytotoxicity against Vero (african green monkey kidney cell) and MT-4 (HTLV-1-infected human T lymphocyte) and for antiviral activity with herpes simplex virus (HSV) and human immunodefficiency virus (HIV). Unfortunately, antiviral screening revealed that (±)-homocarbovir (**3**) did not exhibit any anti-HSV and anti-HIV activity. We are currently investigating the synthesis of phosphorylated homocarbovir and other carbocyclic nucleosides.

EXPERIMENTAL

Proton (^{1}H) NMR spectra were obtained using a Bruker ARX-360 spectrometer (360 MHz) instrument operating in Fourier transform mode. Carbon-13 (^{13}C) NMR spectra were recorded using a

Bruker ARX-360 spectrometer (90.5 MHz) instrument. Infrared spectra were recorded on Bio-Rad FTS 6000 FT-IR or Perkin-Elmer 1750 FT-IR spectrometer. Mass spectra were obtained by VG70-VSEQ with electron impact techniques. Uncorrected melting points were determined with a capillary Büchi 530 melting point apparatus. Analytical thin layer chromatography (TLC) was conducted on E. Merck 60 F254 aluminum backed silica gel plates (0.2 mm) with a fluorescent indicator. Developed plates were visualized under UV light, with iodine staining, or by dipping in 2.0 % phosphomolybdic acid solution and then heating. Flash column chromatography was performed using Merck silica gel 60 (230-400 mesh) under positive pressure of air according to the procedure of Still.[13] Reagents and solvents were of reagent grade, and solvents were purified by the known procedure[14] before use.

2-(4'-Methylphenylsulfonyl)-2-azabicyclo[3.2.1]octa-3,6-diene (5). Compound **5** was prepared by a known similar procedure.[11] To a solution of tosyl azide (2.55 g, 12.7 mmol) in anhydrous benzene (26 mL) was added norbornadiene, **4** (4.15 mL, 38.0 mmol). After being stirred for 3 days at ambient temperature, the reaction mixture was concentrated by rotary-evaporation. The residue was purified by silica gel column chromatography (diethyl ether/hexane = 1/4, v/v, $R_f = 0.22$) to give a white solid **5** (2.52 g, 76 %): mp 76-79 °C; IR (thin film) 3100, 2984, 1617, 1339, 1310, 1174, 1109, 1095, 1003, 957, 864, 754, 716, 698, 659 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.68 (d, $J = 8.3$ Hz, 2H), 7.28 (d, $J = 8.1$ Hz, 2H), 6.26 (dd, $J = 7.9$, 1.1 Hz, 1H), 6.11 (dd, $J = 5.5$, 2.8 Hz, 1H), 5.23 (ddd, $J = 7.7$, 6.5, 1.2 Hz, 1H), 5.19 (dd, $J = 5.5$, 2.5 Hz, 1H), 4.70 (s, 1H), 2.63 (quintet, $J = 3.1$ Hz, 1H), 2.4 (s, 3H), 1.7 (m, 1H), 4.26 (d, $J = 10.3$ Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 143.51, 139.10, 136.83, 129.64, 126.56, 121.68, 121.08, 110.59, 59.41, 35.79, 34.39, 21.43; MS (EI) 261 (M^+), 155, 106, 91, 79, 65.

***cis*-*N*-[4'-(Formylmethyl)cyclopent-2'-enyl]-4-methylphenylsulfonamide (6).** To a solution of tosyl enamine **5** (1.71 g, 6.53 mmol) in THF (10 mL) was added 2 *N* HCl (32.6 mL, 16.3 mmol). After being stirred for 2 h at reflux temperature, the reaction solution was adjusted to pH 7 with a saturated $NaHCO_3$, then extracted with diethyl ether (5 mL x 5). The extracts were dried with anhydrous $MgSO_4$ and concentrated to dryness *in vacuo*. The residue was purified by silica gel column chromatography (diethyl ether/hexane = 6/1, v/v, $R_f = 0.38$) to afford a white gummy solid **6** (0.808 g, 99%): IR (thin film) 3274, 3060, 2926, 2872, 2732, 1718, 1437, 1329, 1159, 1091, 1040, 909, 816, 750, 705, 666 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 9.67 (t, J = 1.0 Hz, 1H), 7.74 (d, J = 8.3 Hz, 2H), 7.74 (d, J = 0.7 Hz, 1H), 7.28 (d, J = 8.1 Hz, 2H), 5.71 (dt, J = 5.6, 1.9 Hz, 1H), 5.43 (dt, J = 5.6, 2.2 Hz, 1H), 5.28 (d, J = 8.9 Hz, 1H), 4.31 (m, 1H), 2.92 (m, 1H), 2.47 (m, 3H), 2.40 (s, 3H), 1.28 (dt, J = 13.7, 6.2 Hz, 1H); ^{13}C NMR (CDCl$_3$) δ 201.27, 143.37, 137.72, 136.79, 131.28, 129.67, 125.95, 59.12, 49.60, 38.06, 37.92, 21.43; MS (EI) 279 (M$^+$), 278 (M$^+$-1), 235, 172, 155, 124, 106, 91, 80, 65.

***cis-N*-[4'-(Hydroxyethyl)cyclopent-2'-enyl]-4-methylphenylsulfonamide (7)**. To a solution of the aldehyde **6** (1.13 g, 4.03 mmol) in THF (15 mL) was added sodium borohydride (0.187 g, 4.84 mmol). After being stirred for 1 h at ambient temperature, the reaction solution was treated with a saturated NH$_4$Cl, then extracted with diethyl ether (5 mL x 10). The extracts were dried with anhydrous MgSO$_4$ and concentrated to dryness *in vacuo*. The residue was purified by silica gel column chromatography (diethyl ether/hexane = 2/1, v/v, R$_f$ = 0.10) to afford a white solid **7** (1.02 g, 90%): mp 62-64 °C; IR (thin film) 3502, 3275, 3060, 2929, 2876, 1438, 1325, 1159, 1091, 1059, 912, 816, 743, 705, 666 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 7.76 (d, J = 8.3 Hz, 2H), 7.29 (d, J = 8.1 Hz, 2H), 5.76 (m, 1H), 5.41 (m, 1H), 5.18 (d, J = 9.1 Hz, 1H), 4.3 (m, 1H), 3.62 (m, 2H), 2.61 (m, 1H), 2.42 (s, 3H), 2.34 (dt, J = 13.6, 8.2 Hz, 1H), 1.88 (s, 1H), 1.68 (m, 1H), 1.51 (m, 1H), 1.19 (dt, J = 13.6, 5.8 Hz, 1H); ^{13}C NMR (CDCl$_3$) δ 143.31, 138.21, 137.93, 130.49, 129.68, 127.03, 60.96, 59.26, 40.97, 38.31, 38.09, 21.50; MS (EI) 281 (M$^+$), 280 (M$^+$-1), 236, 172, 155, 126, 110, 91, 80, 65.

***cis-N*-[4'-(Acetyloxyethyl)cyclopent-2'-enyl]-4-methylphenylsulfonamide (8)**. To a solution of the alcohol **7** (0.820 g, 2.92 mmol) in pyridine (6 mL) was added acetic anhydride (1.48 g, 14.6 mmol). After being stirred for 10 h at ambient temperature, the reaction solution was diluted with diethyl ether, then washed with 1 *N* HCl. The organic phase was dried with anhydrous MgSO$_4$ and concentrated to dryness *in vacuo*. The residue was purified by silica gel column chromatography (diethyl ether/hexane = 2/1, v/v, R$_f$ = 0.10) to afford a gummy solid **8** (0.939 g, 99%): IR (thin film) 3237, 2957, 2932, 2863, 1738, 1437, 1367, 1331, 1246, 1161, 1094, 1042, 909, 816, 666 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 7.74 (d, J = 8.2 Hz, 2H), 7.27 (d, J = 7.3 Hz, 2H), 5.71 (m, 1H), 5.39 (m, 1H), 5.16 (d, J = 9.0 Hz, 1H), 4.29 (m, 1H), 3.99 (m, 2H), 2.51 (m, 1H), 2.40 (s, 3H), 2.33 (dt, J = 13.5, 7.8 Hz, 1H), 1.97 (s, 3H), 1.69 (dq, J = 13.7, 6.5 Hz, 1H), 1.53 (dq, J = 15.0, 6.6 Hz, 1H), 1.11 (dt, J = 13.4, 6.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 171.02, 143.21, 137.86, 137.48, 130.73, 129.58, 126.94, 62.72, 5912, 40.99, 38.23, 34.51, 21.38, 20.84; MS (EI) 322 (M^+-1), 280, 236, 168, 155, 108, 92, 91, 80, 65.

***cis*-*N*-[4'-(Acetyloxyethyl)cyclopent-2'-enyl], *N*-(4-methylphenylsulfonyl)-4-methylphenyl sulfonamide (9).** To a solution of compound **8** (0.128 g, 0.390 mmol) in anhydrous THF (5 mL) and HMPA (5 mL) was added sodium hydride (80% dispersion in mineral oil, 0.013 g, 0.43 mmol) under argon at 0 °C. Then, a solution of *p*-toluenesulfonyl chloride (0.083 g, 0.43 mmol) in anhydrous THF (2 mL) was added to the solution. After being stirred for 1 h at ambient temperature, the reaction solution was diluted with diethyl ether (5 mL), then washed with saturated brine solution. The organic phase was dried with anhydrous $MgSO_4$ and concentrated to dryness *in vacuo*. The residue was purified by silica gel column chromatography (diethyl ether/hexane = 2/1, v/v) to afford a white solid **9** (R_f = 0.40; 0.0864 g, 64%) with starting material **8** (R_f = 0.35; 0.0364 g, 29%): IR(thin film) 2955, 1738, 1597, 1367, 1242, 1167, 1086, 1041, 870, 814, 663 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.91 (d, J = 8.4 Hz, 4H), 7.33 (d, J = 8.2 Hz, 4H), 5.77 (dt, J = 5.5, 2.4 Hz, 1H), 5.54 (dt, J = 9.1, 2.2 Hz, 1H), 5.33 (m, 1H), 4.08 (dt, J = 9.1, 6.0 Hz, 1H), 4.03 (dt, J = 11.6, 6.1 Hz, 1H), 2.63 (m, 1H), 2.44 (s, 6H), 2.35 (dt, J = 13.0, 8.7 Hz, 1H), 2.01 (s, 3H), 1.84 (m, 2H), 1.70 (dq, J = 14.2, 6.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 171.04, 144.65, 137.80, 135.86, 129.53, 128.73, 128.16, 67.52, 63.00, 41.23, 35.73, 33.90, 21.59, 20.90; MS (EI) 322 (M^+-Ts), 310, 261, 182, 171, 155, 139, 108, 92, 91, 77, 65, 64.

***cis*-2-Amino-6-chloro-9-[4'-(acetyloxyethyl)cyclopent-2'-enyl]purine (10).** Triisopropyl phosphite (95%, 0.0601 mL, 0.239 mmol) was added at 25 °C to a solution of $Pd(OAc)_2$ (98%, 0.0068 g, 0.033 mmol) in dry THF (1.0 mL) under argon. After being stirred for 15 min, *n*-BuLi (2.0 *M* in hexane, 0.03 mL, 0.06 mmol) was added at 25 °C. The resulting mixture was stirred for 15 min to obtain tetrakis(triisopropylphosphite)palladium(0) catalyst. The *in situ* prepared Pd(0) catalyst was added to a solution of 2-amino-6-chloropurine (0.136 g, 0.794 mmol) and sodium hydride (60% dispersion in mineral oil, 0.0318 g, 0.794 mmol) in anhydrous DMSO (5 mL) *via* cannula at 25 °C. Then, a solution of the ditosylimide **9** (0.316 g, 0.662 mmol) in dry THF (4.0 mL) was added to the reaction mixture. After being stirred for 10 min, the reaction mixture was diluted with ethyl acetate (5.0 mL) and washed with saturated brine solution (10 mL). The aqueous phase was extracted with ethyl acetate (5.0 mL x 5). The organic phase was dried with anhydrous $MgSO_4$ and concentrated to dryness *in vacuo*. The residue was purified by silica gel column chromatography (diethyl ether only) to afford a yellow gummy solid mixture, **10** and **11** (R_f = 0.29; **10/11** = 10/1, 0.152 g, 71%): Compound **10**; IR (thin film) 3323, 3206, 1735, 1611, 1561, 1510, 1463, 1403, 1244, 1140, 1043, 1001, 905, 785, 643 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.76 (s, 1H), 6.15 (m, 1H), 5.81 (m, 1H), 5.49 (m, 1H), 5.39 (s, 2H), 4.13 (m, 2H), 2.89 (m, 1H), 2.83 (dt, J = 12.9, 8.1 Hz, 1H), 2.02 (s, 3H), 1.90 (dq, J = 13.7, 6.6 Hz, 1H), 1.73 (dq, J = 13.8, 6.9 Hz, 1H), 1.58 (dt, J = 12.9, 6.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 171.07, 158.97, 153.45, 151.11, 140.48, 140.43 128.31, 125.513 62.70, 59.75, 41.88, 38.10, 34.14, 20.91; MS (EI) 321 (M^+), 262, 235, 170, 169, 134, 93, 77, 66, 65.

***cis*-9-[4'-(Hydroxyethyl)cyclopent-2'-enyl]guanine, (±)-homocarbovir (3)**. To a mixture **10/11** (0.199 g, 0.619 mmol) was added 1 *N* NaOH (18.5 mL, 18.5 mmol). The reaction mixture was heated at reflux temperature. After being stirred for 2 h, the reaction mixture was neutralized to *p*H 7-8 with 4.0 *N* HCl. After removal of water by evaporation, the residue was diluted with methanol (40 mL). To this solution, silica gel (~1.5 g) was added, and then the resulting suspension was dried under the reduced pressure. By the pre-loaded silica gel column chromatography with $CHCl_3$/MeOH (5/1, v/v, R_f = 0.29), a white solid **3** was obtained (0.145 g, 89%): mp 216 °C (decomp.), mp (lit.)[5a] 220 °C (decomp.); IR (thin film) 3284, 1650, 1325, 1159, 1093, 1065, 993, 924, 815 cm^{-1}; ^1H NMR ($CDCl_3$) δ 10.7 (s, 1H), 7.56 (s, 1H), 6.44 (s, 2H), 6.16 (m, 1H), 5.85 (m, 1H), 5.31 (m, 1H), 4.44 (t, J = 4.9 Hz, 1H), 3.47 (m, 2H), 2.82 (m, 1H), 2.67 (dt, J = 13.2, 8.2 Hz, 1H), 1.69 (dq, J = 13.3, 6.6 Hz, 1H), 1.48 (m, 2H); ^{13}C NMR (DMSO-d_6) δ 157.22, 153.82, 151.22, 140.75, 135.16, 128.76, 117,21, 59.66, 59.00, 41.76, 38.92, 38.59; MS (EI) 261 (M^+), 151, 110, 91, 79, 77, 66.

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