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Carbohydrate-based synthesis of crocacin: stereoselective Heck reaction of carbohydrate 5,6-ene- and 5,6-yne-derivatives with aromatic halides

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Abstract—The Heck reaction between a carbohydrate 5,6-ene derivative **9** and an aromatic halide exclusively gave rise to the β-carbohydrate-substituted *trans*-styrene derivative **8**; while the corresponding Wittig reaction produced a *cis*/*trans* mixture in which the *cis*-isomer predominated. The application of the Heck reaction is described to synthesize the intermediate **5**, commonly used in the synthesis of members of the crocacin family. © 2003 Elsevier Science Ltd. All rights reserved.

The crocacin group of natural products have attracted unprecedented interest, primarily because of their significant biological activities coupled with characteristic structural features.[1] The structures of crocacins (Fig. 1) offer ample opportunities for synthetic chemists to develop unique approaches.[2] However, carbohydrate based protocols seem to be missing from the artillery in spite of the fact that chiral centers in D-glucose can be seemingly transformed to produce the crocacin skeleton, enantioselectively. Crocacins A–D (**1**–**4**) possess antifungal and cytotoxic activities and are regularly found in the extracts of *Chondromyces crocactus* and *Chondromyces pediculatus*. Synthetic efforts[2] towards crocacins A–D have been significantly influenced by the synthesis of the advanced intermediate **5** (Fig. 1) which is then elaborated to install variable side chains. The Evans aldol reaction based synthetic protocols seem to be the most commonly used approaches for crocacin synthesis.[2] We have investigated for the first time a carbohydrate-based synthesis of **5**.

While planning the strategy, we were confronted with a need to produce the β-carbohydrate-substituted styrene derivative **8**. The most logical approach would be the Wittig reaction between 5-sugar-carboxylaldehyde **6**[3] and benzylidenetriphenylphosphorane (prepared from $BnPPh_3Br$ and *n*-BuLi). The reaction conducted at room temperature gave a product whose ^1H NMR spectrum revealed the formation of *cis*/*trans*-isomers **7** and **8** (84:16), with the unwanted *cis* isomer being formed predominantly (Scheme 1).

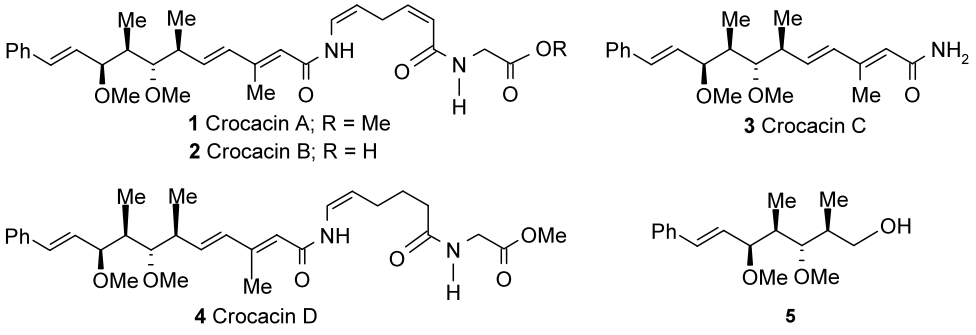

Figure 1.

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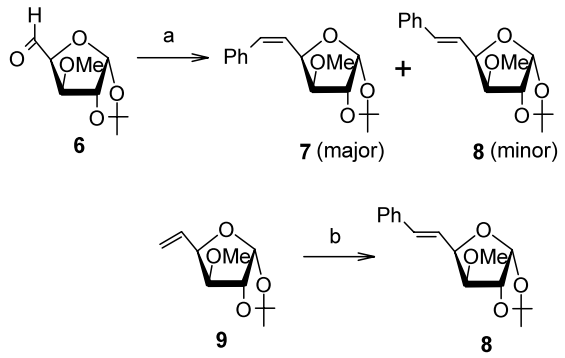
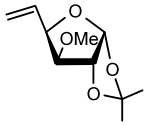
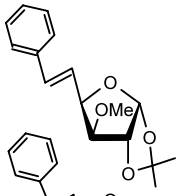
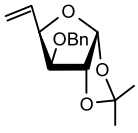
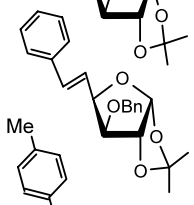
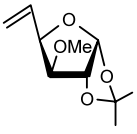
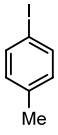
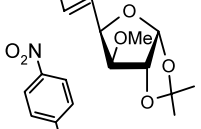
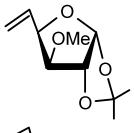
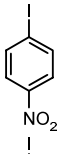
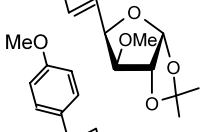
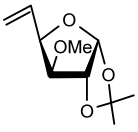
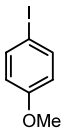
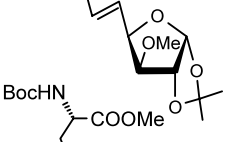
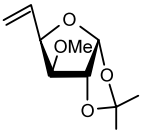
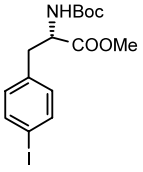
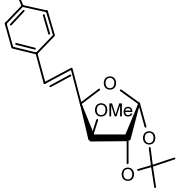


Scheme 1. *Reagents and conditions*: (a) $PhCH_2PPh_3Br$, *n*-BuLi, THF; (b) iodobenzene, $Pd(OAc)_2$, PPh_3, Et_3N, Bu_4NI, DMF, 110°C.

When the reaction was performed at 0°C, the *cis* isomer **7** was formed in 95% yield with 5% of the *trans*-isomer. Furthermore in refluxing THF, a *trans*:*cis* mixture (**8**/**7**) in a 25:75 ratio was observed. All our attempts to prepare the *trans*-isomer with acceptable selectivity and yield via the Wittig reaction were unsuccessful.

The Heck reaction[4] between an olefin and an aromatic halide favors the *trans*-olefin derivative. However, the application of this reaction to 5,6-ene derivatives of sugar substrates, to our knowledge, has not been reported so far. We attempted a reaction between 1,2-*O*-isopropylidine-3-*O*-methyl-α-D-*xylo*-hex-5-enofuranose **9**[5] with iodo-benzene in the presence of $Pd(OAc)_2$, PPh_3, Et_3N and Bu_4NI in DMF at 110°C. In our first attempt, the requisite *trans*-isomer **8** was formed almost exclusively in 54% yield. The starting material **9** was also recovered in 15% yield. The structure of **8** was confirmed by the ^1H NMR spectrum in which the olefinic protons appeared at δ 6.29 and δ 6.73 with a characteristic-coupling constant ($J=16.0$ Hz). With a view to investigating the versatility of this reaction, but more importantly, to understand the effect of substituents on the benzene ring, a number of Heck reac-

Table 1.

Entry	Substrate[a]	Halide	Product[b]	Time (h)	Yield[c] (%)
1				6	54
2				7	55
3				7.5	56
4				30	40
5				6	62
6				8	52

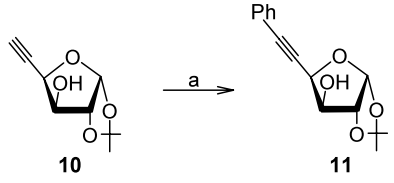
a) Prepared *via* a literature procedure (ref 5); b) confirmed by analytical and spectroscopic data; c) isolated yields.

tions were examined as shown in Table 1. In all the cases studied, exclusive formation of the *trans*-isomer was observed. The reaction (entry **6**) involving the coupling of the sugar with a L-phenylalanine residue is indeed interesting from a synthetic point of view. In general, electron-donating substituents on benzene rings favor the Heck reaction with good yields (Table 1).

We also investigated the Heck reaction with 5,6-yne derivative **10**[6] and were gratified to observe that it worked efficiently. The structure of **11** was confirmed by spectroscopic and elemental analysis. Table 2 shows reactions of sugar 5,6-yne derivative **10** with aryl halides. It is pertinent to mention that compounds of type **11** are difficult to synthesize other than by the Heck reaction (Scheme 2).

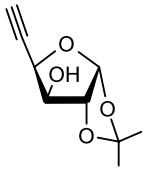
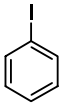
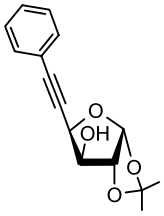
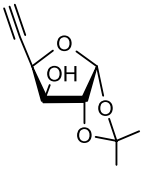
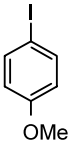
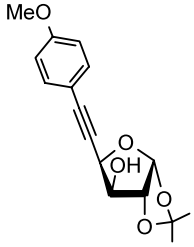
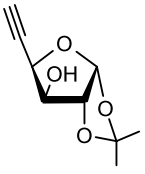
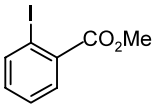
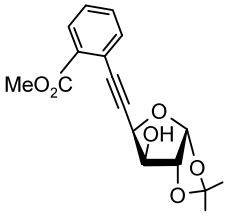
Having successfully developed a new protocol to prepare β-carbohydrate-substituted *trans*-styrene derivatives, we directed our efforts to apply this method to prepare the common intermediate **5** for crocacin (Scheme 3). 1,2:5,6-Di-*O*-cyclohexylidene-D-glucofuranose **12** was successively[7] subjected to (i) oxidation (PDC, MS, Ac_2O, DCM) to 3-ulose **13**; (ii) Wittig reaction with $Ph_3P{=}CH_2$ to the *exo*-methylene derivative **14** and (iii) catalytic reduction to 3-*C*-methyl-3-deoxy derivative **15**. The conversion of **15** into 5,6-ene **17** by standard reaction pathways, was accomplished in three steps.[8] The Heck reaction of **17** with iodobenzene under the conditions reported above furnished the *trans*-styrene derivative **18**. In the ^1H NMR spectrum of **18**, the characteristic olefinic protons were located at 6.07 and 6.63 ppm ($J = 16.2$ Hz). Treatment of **18** with methanol and Amberlyst IR120 gave the methyl furanoside **19** and simultaneously exposed the 2-OH group which was blocked as methyl ether **20**. The methyl glycosidic bond was hydrolyzed to give **21** with 20% AcOH in H_2O and then treated with MeMgCl in THF to afford the diol **22**. The sterically hindered OH group at C-5 was exploited to selectively protect the C-2-OH group using TBSOTf to give **23**. The Mitsunobu reaction of **23** with *p*-nitrobenzoic acid, PPh_3-DEAD followed by hydrolysis with LiOH in MeOH gave **24**. A comparison of the ^1H NMR spectra of **23** and **24** clearly indicated that inversion had indeed occurred. Next the free OH group was methylated to afford di-*O*-methyl derivative **25**.

The next critical reaction was the introduction of the methyl group at C-2 (cf. **5**) for which a route involving

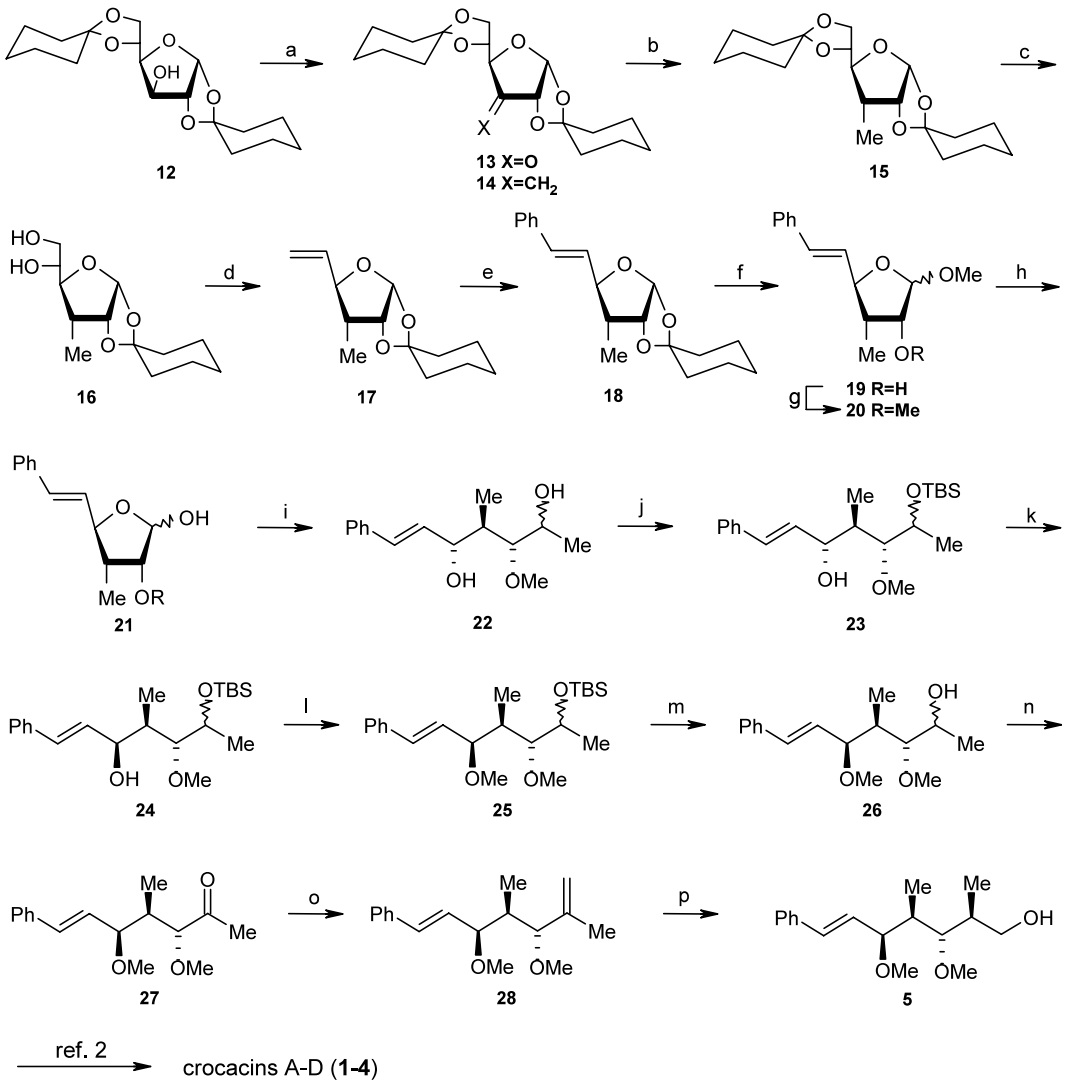


Scheme 2. *Reagents and conditions*: iodobenzene, $Pd(PPh_3)_4$, piperidine, rt.

Table 2.

Entry	Substrate[a]	Halide	Product[b]	Time (h)	Yield[c] (%)
1				6	85
2				6	81
3				18	65

a) Prepared *via* a literature procedure (ref 6); b) confirmed by analytical and spectroscopic data; c) isolated yields.



Scheme 3. *Reagents and conditions*: (a) (i) PDC, 4 Å MS, Ac_2O, DCM, rt, 12 h, 78%; (ii) $PPh_3{=}CH_2$, THF, −10°C, 0.5 h, 67%; (b) 10% Pd–C, H_2, 50 psi., 3 h, 97%; (c) 0.8% H_2SO_4, MeOH, 24 h, 83%; (d) (i) MsCl, NEt_3, DCM, 0°C–rt, 2 h, 95%; (ii) EtCOMe, NaI, reflux, 6 h, 74%; (e) Ph–I, $Pd(OAc)_2$, PPh_3, NEt_3, TBAI, DMF, 110°C, 6 h, 63%; (f) Amberlyst IR-120 (H^+) resin, MeOH, reflux, 8 h, 82%; (g) NaH, MeI, THF, rt, 3 h, 95%; (h) 20% aq. CH_3CO_2H, cat. H_2SO_4, 80°C, 6 h, 79%; (i) MeMgCl, THF, rt, 2.5 h, 75%; (j) TBSOTf, 2,6-lutidine, DCM, −78°C, 1.5 h, 86%; (k) (i) DEAD, TPP, 4-nitrobenzoic acid, THF, rt, 5 h, 66%; (ii) LiOH, MeOH, rt, 2 h, 62%; (l) KH, MeI, THF, rt, 3.5 h, 96%; (m) TBAF, THF, rt, 36 h, 93%; (n) Dess–Martin-Periodinane, DCM, rt, 2 h, 91%; (o) $Ph_3P{=}CH_2$, THF, −10°C, 8 h, 85%; (p) 9-BBN, THF, rt, 2 h, CH_3COONa, H_2O_2, 0°C–rt, 7 h, 64%.

stereoselective hydroboration–oxidation of the 2-isopropene functionality was planned. Thus compound **25** was first desilylated with TBAF in THF, oxidized to ketone **27** and then subjected to a Wittig reaction to give **28**. The stereochemical outcome of the hydroboration–oxidation of a terminal 2-isopropylene with an adjacent chiral hydroxyl substituent giving rise to the *syn* product has been reported in the presence of Wilkinson's catalyst,[9] whilst the uncatalysed hydroboration–oxidation provides the *anti*-product. Indeed, the reaction of compound **28** with 9-BBN followed by oxidation with H_2O_2 in the presence of sodium acetate gave exclusively the required product **5**. The structure of **5** was confirmed by spectroscopic and analytical data[10] which were identical with reported values.[2]

In conclusion, we have shown that Heck reaction of carbohydrate based olefins and acetylene derivatives occurs smoothly. This reaction has been utilized to prepare a common intermediate for crocacin synthesis.

Acknowledgements

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References

1. (a) Kunze, B.; Jansen, R.; Hofle, G.; Reichenbach, H. *J. Antibiot*. **1994**, *47*, 881–886; (b) Jansen, R.; Washausen, P.; Kunze, B.; Reichenbach, H.; Hofle, G. *Eur. J. Org. Chem*. **1999**, *5*, 1085–1089.
2. (a) Feutrill, J. T.; Lilly, M. J.; Rizzacasa, M. A. *Org. Lett*. **2000**, *2*, 3365–3367; (b) Chakraborty, T. K.; Jayaprakash, S. *Tetrahedron Lett*. **2001**, *42*, 497–499; (c) Chakraborty, T. K.; Jayaprakash, S.; Laxman, P. *Tetrahedron* **2001**, *57*, 9461–9467; (d) Dias, L. C.; de Oliveira, L. G. *Org. Lett*. **2001**, *3*, 3951–3954; (e) Feutrill, J. T.; Lilly, M. J.; Rizzacasa, M. A. *Org. Lett*. **2002**, *4*, 525–527.
3. Sueda, N.; Ohrui, H.; Kuzuhara, H. *Tetrahedron Lett*. **1979**, *20*, 2039–2042.
4. (a) Whitcombe, N. J.; Hii, K. K.; Gibson, S. E. *Tetrahedron* **2001**, *57*, 7449–7476; (b) Crisp, G. T. *Chem. Soc. Rev*. **1998**, *27*, 427–436; (c) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev*. **2000**, *100*, 3009–3066.
5. Josan, J. S.; Eastwood, F. W. *Carbohydr. Res*. **1968**, *7*, 161–166.
6. Yadav, J. S.; Chander, M. C.; Rao, C. S. *Tetrahedron Lett*. **1989**, *30*, 5455–5458.
7. Rosenthal, A.; Sprinzl, M. *Can. J. Chem*. **1969**, *47*, 3941–3945.
8. Jones, J. K. N.; Thompson, J. L. *Can. J. Chem*. **1957**, *35*, 955–959.
9. (a) Still, W. C.; Barrish, J. C. *J. Am. Chem. Soc*. **1983**, *105*, 2487–2489; (b) Burgess, K.; Cassidy, J.; Ohlmeyer, M. J. *J. Org. Chem*. **1991**, *56*, 1020–1027; (c) Burgess, K.; Ohlmeyer, M. J. *Tetrahedron Lett*. **1989**, *30*, 5861–5864; (d) Evans, D. A.; Fu, G. C.; Hoveyda, A. H. *J. Am. Chem. Soc*. **1988**, *110*, 6917–6918; (e) Burgess, K.; Ohlmeyer, M. J. *Chem. Rev*. **1991**, *91*, 1179–1191.
10. **Spectroscopic data of 8**: ^{1}H NMR ($CDCl_3$, 200 MHz)—δ 1.34 (s, 3H), 1.54 (s, 3H), 3.42 (s, 3H), 3.68 (d, 1H, $J=3.5$ Hz), 4.62 (d, 1H, $J=3.5$ Hz), 4.75 (m, 1H), 5.94 (d, 1H, $J=3.5$ Hz), 6.29 (dd, 1H, $J=8.0$, 16.0 Hz), 6.73 (d, 1H, $J=16.0$ Hz), 7.3 (m, 5H); ^{13}C NMR ($CDCl_3$, 50 MHz)—δ 26.1, 26.7, 58.1, 81.2, 82.2, 86.1, 104.7, 111.4, 123.1, 126.6, 127.3, 128.4, 133.8, 136.5. Anal. calcd for $C_{16}H_{20}O_4$: C, 69.56; H, 7.24. Found: C, 70.30; H, 7.10. **Spectroscopic data of 11**: ^{1}H NMR ($CDCl_3$, 200 MHz)—δ 1.33 (s, 3H), 1.52 (s, 3H), 2.28 (brs, 1H), 4.25 (d, 1H, $J=4.0$ Hz), 4.64 (d, 1H, $J=4.0$ Hz), 5.11 (d, 1H, $J=4.0$ Hz), 6.01 (d, 1H, $J=4.0$ Hz), 7.2–7.6 (m, 5H); ^{13}C NMR ($CDCl_3$, 50 MHz)—δ 26.0, 26.7, 72.8, 76.1, 81.6, 84.0, 104.8, 111.8, 121.5, 128.2, 128.9, 131.9, 159.7. Anal. calcd for $C_{15}H_{16}O_4$: C, 69.23; H, 6.15. Found: C, 68.80; H, 6.80. **Spectroscopic data of 18**: ^{1}H NMR (500 MHz, $CDCl_3$)—δ 1.07 (d, 3H, $J=6.5$ Hz), 1.2–1.85 (m, 11H), 4.26 (t, 1H, $J=8.1$ Hz), 4.57 (t, 1H, $J=3.2$ Hz), 5.85 (d, 1H, $J=3.2$ Hz), 6.07 (dd, 1H, $J=16.2$, 8.1 Hz), 6.63 (d, 1H, $J=16.2$ Hz), 7.2–7.4 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$)—δ 9.0, 23.7, 24.0, 25.1, 36.1, 36.4, 44.7, 82.1, 83.6, 104.6, 111.9, 126.6, 127.0, 127.8, 128.5, 133.1, 136.6. Anal. calcd for $C_{19}H_{24}O_3$: C, 76.00; H, 8.00. Found: C, 76.44; H, 8.30. **Spectroscopic data of 28**: ^{1}H NMR (500 MHz, $CDCl_3$)—δ 0.75 (d, 3H, $J=7.1$ Hz), 1.60 (s, 3H), 1.69 (m, 1H), 3.22 (s, 3H), 3.34 (s, 3H), 3.49 (d, 1H, $J=10.1$ Hz), 4.20 (dd, 1H, $J=6.7$, 3.3 Hz), 4.92 (s, 1H), 4.99 (s, 1H), 6.17 (dd, 1H, $J=16.1$, 6.7 Hz), 6.57 (d, 1H, $J=16.1$ Hz), 7.2–7.4 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$)—δ 9.7, 15.9, 41.0, 55.9, 57.3, 80.7, 87.0, 115.8, 126.5, 127.4, 128.6, 130.0, 131.3, 137.2, 143.1. Anal. calcd for $C_{17}H_{24}O_2$: C, 78.46; H, 9.23. Found: C, 78.03; H, 9.52. **Spectroscopic data of 5**: ^{1}H NMR (500 MHz, $CDCl_3$)—δ 0.90 (d, 3H, $J=7.0$ Hz), 1.20 (d, 3H, $J=7.0$ Hz), 1.86 (m, 2H), 2.77 (brs, 1H), 3.27 (dd, 1H, $J=9.5$, 2.7 Hz), 3.31 (s, 3H), 3.51 (dd, 1H, $J=11.2$, 4.3 Hz), 3.54 (s, 3H), 3.82 (dd, 1H, $J=11.2$, 3.4), 4.05 (dd, 1H, $J=7.2$, 2.0 Hz), 6.16 (dd, 1H, $J=16.3$, 7.2 Hz), 6.56 (d, 1H, $J=16.3$ Hz), 7.2–7.4 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$)—δ 10.5, 16.4, 36.1, 42.5, 56.4, 61.6, 64.6, 81.2, 88.6, 126.5, 127.7, 128.6, 129.4, 132.3, 136.9. Anal. calcd for $C_{17}H_{26}O_3$: C, 73.38; H, 9.35. Found: C, 73.92; H, 8.97.