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A NEW ENTRY TO THE SYNTHESIS OF PRIMIN VIA A *B*-ALKYL SUZUKI–MIYAURA CROSS-COUPLING REACTION

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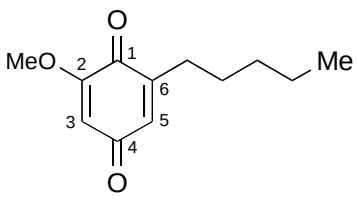
Dedicated to Professor Dr. Ei-ichi Negishi on the occasion of his 77th birthday

Abstract – Primin, a biologically active benzoquinone natural product, was efficiently synthesized in 56% overall yield in six steps starting from commercially available 5-iodovanillin. The synthetic method involves crucial steps, including a *B*-alkyl Suzuki–Miyaura cross-coupling reaction to directly install an alkyl side chain in an aromatic ring and elaboration of quinone functionality by degradative oxidation using Fremy's salt to yield the target primin.

Primin, 2-methoxy-6-pentyl-1,4-benzoquinone (**1**) (Figure 1), was first isolated as the allergenic principle of the plant *Primula obconia*.[1] Subsequently, this natural product was also isolated from the plant *Miconia* sp.[2] and the fungus *Botryosphaeria* sp.[3] In 2001, Kingston et al. reported the isolation of **1** from the plant *Miconia lepidota* collected from the Suriname rainforest.[4] This substance was found to exhibit antiproliferative activity against M109 murine lung cancer cells (IC_{50} = 10 μg/mL) and A2780 human ovarian cancer cells (IC_{50} = 2.9 μg/mL).[4] It has also been reported that primin displays antibacterial activity against *Staphylococcus aureus* (ATTC 25923) and methicillin-resistant *Staphylococcus aureus* (MRSA) with equal MIC values of 8 μg/mL.[5]

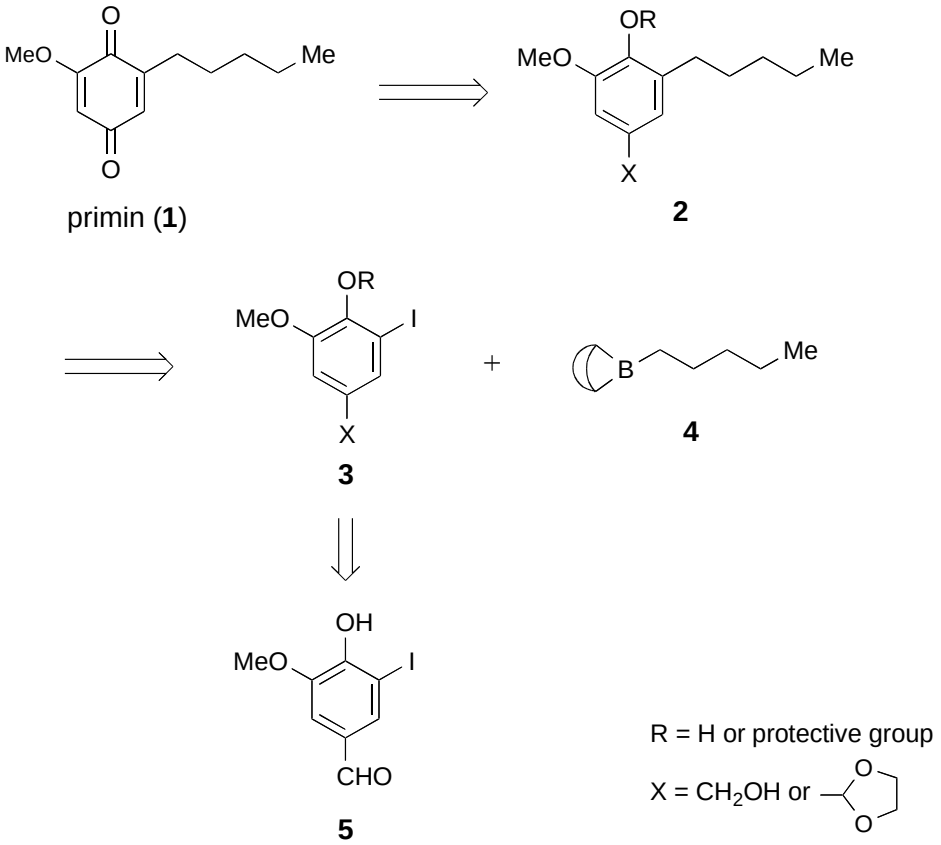


primin (**1**)

Figure 1. Structure of primin (**1**)

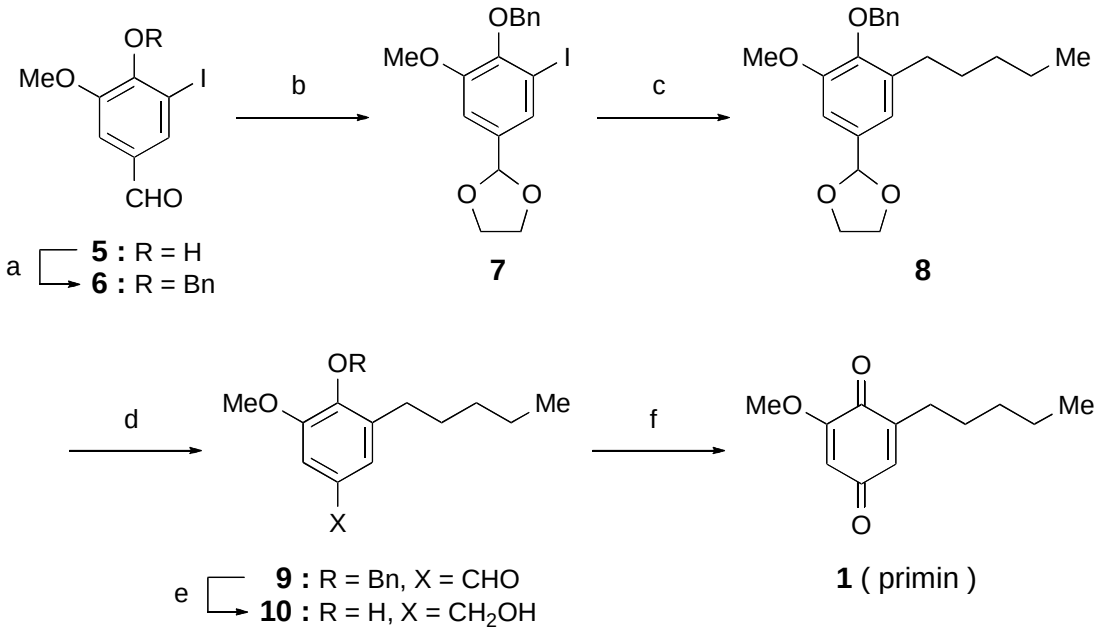
In the course of our continuing research on the synthesis of biologically active quinoid natural products,[6] we became interested in the synthesis of primin and its analogues with the aim of searching for potential anticancer agents. Several reports on the synthesis of primin have been published to date,[4,7] which involved strategic methods for the introduction of the alkyl side chain at the aromatic nucleus and the formation of the 1,4-benzoquinone moiety via oxidation of hydroquinone or phenol derivatives. However, some of these syntheses required severe and/or difficult reaction conditions, the yields were often unsatisfactory, and several of these methods are limited by the nature of the substituent in the aromatic rings. Therefore, we investigated an alternative, more flexible, and reliable method for the synthesis of primin, as well as its analogues. In this paper, we describe our results on the synthesis of primin using a *B*-alkyl Suzuki–Miyaura cross-coupling reaction[8] and degradative phenol oxidation[9] as the key steps.

Our synthetic plan for primin (**1**) is outlined in Scheme 1. We envisioned that the target molecule **1** could be derived from phenolic compound **2** by its oxidative degradation to the corresponding quinone.[9] Intermediate **2** with the requisite alkyl side chain and appropriate functional groups was to be prepared via the *B*-alkyl Suzuki–Miyaura cross-coupling reaction[8] between aryl iodide **3**, which is accessible from 5-iodovanillin (**5**), and organoborane **4**. To the best of our knowledge, the utilization of the direct alkylation method (cf. **3** + **4** → **2**) for synthesizing **1** is unknown to date, and thus, this approach posed a challenge from the viewpoint of synthesis.



Scheme 1. Synthetic plan for primin (**1**)

As shown in Scheme 2, the synthesis commenced with protection of the phenolic hydroxy group in commercially available 5-iodovanillin (**5**) to give the corresponding benzyl (Bn) ether **6** in 86% yield. Initial attempts to realize the *B*-alkyl Suzuki–Miyaura cross-coupling reaction of **6** and organoborane **4** [prepared in situ by hydroboration of 1-pentene with 9-borabicyclo[3.3.1]nonane (9-BBN)] resulted in an unsatisfactory yield of the coupling product (ca. ~50%). Therefore, we decided to conduct this cross-coupling reaction after protecting the sensitive formyl group in **6** as the ethylene acetal **7** (88%). As a result, the critical cross-coupling reaction of **7** with **4** proceeded smoothly and cleanly under the optimized conditions [$PdCl_2$(dppf) (5 mol%), Cs_2CO_3, THF, reflux, 30 min]; the desired coupling product **8**[10] was obtained in high yield (92%). Subsequent acidic hydrolysis of the ethylene acetal moiety in **8** followed by hydrogenation of the resulting aldehyde **9** (H_2, 10% Pd/C, EtOH, rt, 3 h), provided *p*-hydroxybenzyl alcohol **10** in 94% yield after the two steps. Finally, the critical quinone formation reaction was successfully achieved by oxidative degradation of **10** using Fremy's salt [$(KSO_3)_2NO$] in pH 6.0 phosphate buffer/$CHCl_3$ (4:1) at room temperature, resulting in the formation of target **1**[11] in high yield (86%).



Scheme 2. Synthesis of primin (**1**). (a) benzyl bromide, K_2CO_3, acetone, reflux, 86%; (b) ethylene glycol, *p*-TsOH·H_2O, benzene, reflux, 88%; (c) 1-pentene, 9-BBN, THF, rt; add. **7**, $PdCl_2$(dppf) (5 mol%), Cs_2CO_3, THF, reflux, 92%; (d) 1 M HCl, THF, rt, 99%; (e) H_2, 10% Pd/C, EtOH, rt, 95%; (f) Fremy's salt, pH 6.0 phosphate/$CHCl_3$ (4:1), rt, 86%. 9-BBN = 9-borabicyclo[3.3.1]nonane, dppf =1,1'-bis(diphenylphosphino)ferrocene, Fremy's salt = potassium nitrosodisulfonate.

Thus, we have accomplished the synthesis of primin (**1**) in 56% overall yield in six steps from the commercially available starting material **5**. The key steps of the synthesis involve the *B*-alkyl Suzuki–Miyaura cross-coupling reaction of aryl iodide **7** and organoborane **4** to introduce the requisite

alkyl side chain in the aromatic ring (**7** → **8**, Scheme 2) and elaboration of the quinone functionality by oxidative degradation of phenolic compound **10** to complete the projected synthesis (**10** → **1**, Scheme 2). The main advantages of the present methods are the higher yield, milder reaction conditions, and greater flexibility in producing primin analogues that with various alkyl side chains when compared to other reported methods.[4,7] On the basis of the results of this study, we are currently synthesizing additional analogues of **1** with the aim of exploring their structure–activity relationships. In addition, further investigations to identify the action mechanism of **1** by using synthetic samples are in progress.

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REFERENCES AND NOTES

1. (a) H. Schildknecht, H. Bayer, and H. Schmidt, *Z. Naturforsch*, 1967, **22b**, 36; (b) B. Bloch and P. Karrer, *Vjschr. Naturforsch. Ges.*, 1927, **72**, 1 (*Chem. Abstr.*, 1928, **22**, 2784).
2. (a) E. Bernays, A. Lupi, R. M. Bettolo, C. Mastrofrancesco, and P. Tagliatesta, *Experientia*, 1984, **40**, 1010; (b) G. B. Marini-Bettolo, F. D. Monache, O. G. da Lima, and S. B. Coelho, *Gazz. Chim. Ital.*, 1971, **101**, 41.
3. W. Pongcharoen, V. Rukachaisirikul, S. Phongpaichit, and J. Sakayaroj, *Chem. Pharm. Bull.*, 2007, **55**, 1404.
4. A. A. L. Gunatilaka, J. M. Berger, R. Evans, J. S. Miller, J. H. Wisse, K. M. Neddermann, I. Bursuker, and D. G. I. Kingston, *J. Nat. Prod.*, 2001, **64**, 2.
5. D. Tasdemir, R. Brun, V. Yardley, S. G. Franzblau, and P. Rüedi, *Chem. Biodivers.*, 2006, **3**, 1230.
6. (a) K. Narita, K. Nakamura, Y. Abe, and T. Katoh, *Eur. J. Org. Chem.*, 2011, 4985; (b) J. Sakurai, T. Oguchi, K. Watanabe, H. Abe, S. Kanno, M. Ishikawa, and T. Katoh, *Chem. Eur. J.*, 2008, **14**, 829; (c) A. Suzuki, M. Nakatani, M. Nakamura, K. Kawaguchi, M. Inoue, and T. Katoh, *Synlett*, 2003, 329; (d) M. Nakamura, A. Suzuki, M. Nakatani, T. Fuchikami, M. Inoue, and T. Katoh, *Tetrahedron Lett.*, 2002, **43**, 6929; (e) T. Katoh, M. Nakatani, S. Shikita, R. Sampe, A. Ishiwata, O. Ohmori, M. Nakatani, and S. Terashima, *Org. Lett.*, 2001, **3**, 2701.
7. (a) A. K. Bhattacharya, T. Kaur, and K. N. Ganesh, *Synthesis*, 2010, 1141; (b) L.-Q. Wu, C.-G. Yang, L.-M. Yang, and L.-J. Yang, *J. Chin. Chem. Soc.*, 2009, **56**, 47; (c) C. J. Davis, T. E. Hurst, A. M. Jacob, and C. J. Moody, *J. Org. Chem.*, 2005, **70**, 4414; (d) A. M. Jacob and C. J. Moody,

Tetrahedron Lett., 2005, **46**, 8823; (e) C. J. Davis and C. J. Moody, *Synlett*, 2002, 1874; (f) S. Mabic, L. Vaysse, C. Benezra, and J.-P. Lepoittevin, *Synthesis*, 1999, 1127; (g) S. S. Arogba, *Org. Prep. Proced. Int.*, 1991, **23**, 639; (h) L. W. Bieber, A. de Andrade Chiappeta, M. A. de Moraes e Souza, R. M. Generino, and P. R. Neto, *J. Nat. Prod.*, 1990, **53**, 706; (i) O. G. de Lima, G. B. Marini-Bettolo, F. Delle Monache, J. S. Coelho, L. I. d'Albuquerque, G. M. Maciel, A. Lacerda, and D. G. Martins, *Rev. Inst. Antibiot.*, 1970, **10**, 29 (*Chem. Abstr.*, 1970, **77**, 29622).

8. For a review on *B*-alkyl Suzuki–Miyaura cross-coupling reaction, see: S. R. Chemler, D. Trauner, and S. J. Danishefsky, *Angew. Chem. Int. Ed.*, 2001, **40**, 4544.
9. For some examples of degradative phenol oxidation, see: (a) J. M. Saá, A. Llobera, A. G. Raso, A. Costa, and P. M. Deyá, *J. Org. Chem.*, 1988, **53**, 4263; (b) P. M. Deyá, M. Dopico, A. G. Raso, J. Morey, and J. M. Saá, *Tetrahedron*, 1987, **43**, 3523; (c) J. M. Saá, J. Morey, and C. Rubido, *J. Org. Chem.*, 1986, **51**, 4471; (d) J. M. Saá, J. Morey, and A. Costa, *Tetrahedron Lett.*, 1986, **27**, 5125.
10. Data for **8**. Colorless oil; IR (neat) 1091, 1158, 1216, 1507 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.84 (3H, t, J = 6.8 Hz), 1.25–1.29 (4H, m), 1.48–1.57 (2H, m), 2.54 (2H, dt, J = 1.9, 7.8 Hz), 3.89 (3H, s), 4.02–4.07 (2H, m), 4.14–4.17 (2H, m), 4.97 (2H, s), 5.73 (1H, s), 6.89 (1H, d, J = 1.9 Hz), 6.92 (1H, d, J = 1.9 Hz), 7.82–7.39 (3H, m), 7.45 (2H, dd, J = 1.4, 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 22.4, 30.1, 30.2, 31.8, 55.7, 65.2 (2C), 74.6, 103.7, 107.7, 120.1, 127.7, 127.9, 128.1, 128.2, 128.3, 132.9, 136.9, 137.9, 146.6, 152.7; HRMS (EI) calcd for $C_{22}H_{28}O_4$ (M^+), 356.1988, found 356.1994.
11. Data for primin (**1**). Yellow crystals: mp 62–63 °C (from MeOH) {lit.,[2b] mp 64–65 °C; lit.,[7a] mp 62–63 °C; lit.,[7c] mp 64.5–65.5 °C; lit.,[7h] mp 61–62 °C}; IR (KBr) 1655, 1681 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.88 (3H, t, J = 6.8 Hz), 1.31–1.34 (4H, m), 1.47–1.55 (2H, m), 2.41 (2H, t, J = 7.3 Hz), 3.82 (3H, s), 5.87 (1H, s), 6.48 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 22.3, 27.4, 28.6, 31.3, 56.2, 107.1, 132.9, 147.6, 158.8, 182.1, 187.6; HRMS (EI) calcd for $C_{12}H_{16}O_3$ (M^+), 208.1099, found 208.1099.