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Synthesis of 3-Alkyl and Arylapomorphines

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Abstract: The synthesis of 3-alkyl and arylapomorphines **18**–**20** has been accomplished by using the Suzuki–Miyaura cross-coupling reaction of vinyl- and allylhalide morphinanedienes or arylhalide apocodeines and arylboronic acids.

Keywords: 3-alkyl and arylapomorphines, arylboronic acids, palladium, Suzuki cross-coupling

Thebaine (**1**) is the only morphinanediene-type alkaloid of poppy. Because of to its easily convertable structure, it is one of the most important natural raw materials of the pharmaceutical industry. The synthesis of 7-substituted-6-demethoxythebaine derivatives has already more than 20 years of history. First, 7-bromo (**3**) and 7-chloromorphinanedienes (**2**), then the 7-thiocianato derivative (**4**) were prepared from thebaine (**1**) via mesyl esters of 7-α-substituted neopines.[1,2] The obtained morphinanedienes **2**–**4** were rearranged and O-demethylated in acidic medium to form the corresponding 3-substituted apomorphines[3–5] **8**–**10** (Fig. 1).

Dopamine receptor binding studies emphasize the importance of the presence of a hydrophobic group in the proximity of 2-position of the aporphine skeleton.[6–8] This effect correlates with the model of dopamine D_2 receptors suggested by Ramsby et al., who describe the a lipophillic cavity on the surface of the receptor near to the binding site.[9]

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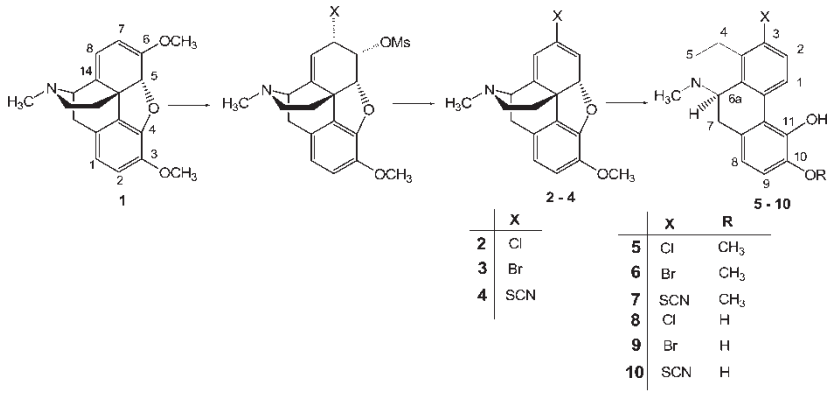


Figure 1. Synthesis and rearrangement of 7-substituted morphinanedienes.

In the recent article, we report the synthesis of some 3-alkyl and arylapomorphines with Suzuki–Miyaura cross-coupling reaction. Palladium-catalyzed transformations of codeine and morphine were first accomplished by Davies et al.[10,11] Palladium-catalyzed dehydroxylation reaction on the morphinan skeleton was recently thoroughly investigated.[6] Suzuki–Miyaura reaction on morphinans was used by Hedberg et al. for the preparation of 3-aryl-3-demethoxycodeines.[12] Søndergaard et al. applied this reaction on the aporphine skeleton for the synthesis of 2-arylaporphines from triflates.[13] In one of our previous articles, we described a synthetic route to 2-alkyl and arylapomorphines through this palladium-catalyzed cross-coupling reaction of 2-bromoapocodeine.[14] Based on our latest results, we planned to prepare the aimed apomorphines using the available arylbromide **6** and vinylbromide **3** (Fig. 2).

Synthetic route I was based on our previously published method for the synthesis of 2-arylapomorphines.[14] Acid-catalyzed rearrangement of 7-bromo-6-demetoxythebaine (**3**) into 3-bromoapocodeine (**6**) was first performed, then the Suzuki–Miyaura reaction was accomplished from the obtained haloapocodeine to yield 3-alkyl and arylapocodeines **15**–**17** (Fig. 3).

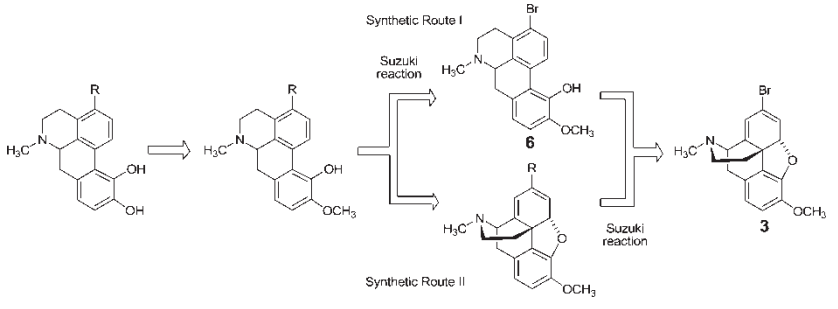


Figure 2. Retrosynthetic strategies.

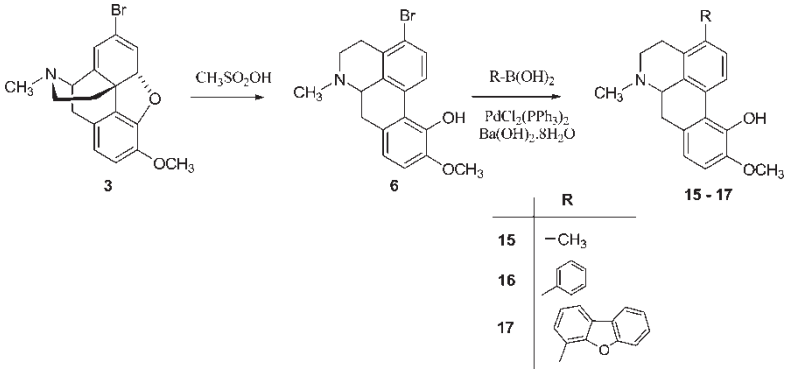


Figure 3. Synthetic route I.

The cross-coupling was catalyzed by $PdCl_2(PPh_3)_2$ or $Pd(PPh_3)_4$; no significant difference was observed in the corresponding yields. Classic Suzuki cross-coupling partners, boronic acids, were applied. Barium hydroxide was found to be an appropriately strong base to accomplish the reductive elimination step of the reaction in the solvent mixture of 1,4-dioxane and water (ratio 4:1).

We revealed a potential second reaction route (synthetic route II) to the products; the cross-coupling step was directly performed on 7-bromo-6-demethoxythebaine (**3**, Fig. 4).

The same reaction conditions were applied in both reaction routes for the Suzuki reactions and the rearrangement steps. Almost the same yields were observed irrespective of the type of the basic molecule of the palladium-catalyzed cross-coupling reaction (i.e., vinyl- and allyl-type bromo derivative or aryl-type bromo derivative). The yields of the Suzuki–Miyaura cross-coupling steps of the two synthetic routes are summarized in Table 1.

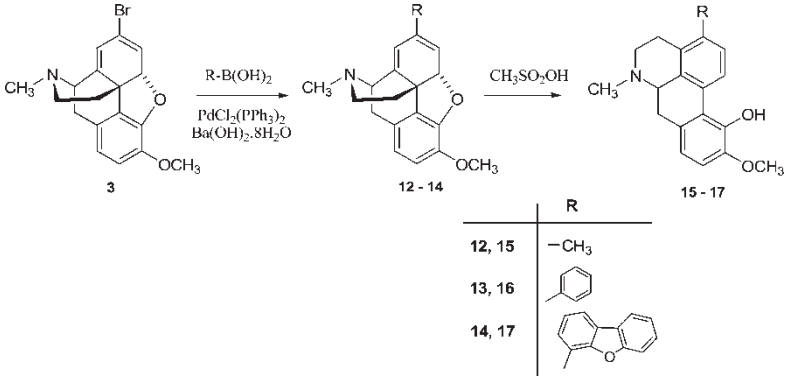
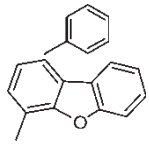


Figure 4. Synthetic route II.

Table 1. Comparison of yields of synthetic routes I and II

Compound	R	Yield (%), synthetic route I	Yield (%), synthetic route II
15	-CH_3	55	62
16		84	88
17		86	86

The conversion of apocodeines **15**–**17** into apomorphines **18**–**20** was carried out by means of the methanesulfonic acid/methionine reagent combination, which was successfully used earlier by our laboratory[15] (Fig. 5).

The receptor binding test for the presented apomorphine derivatives **18**–**20** is in progress; the results and the structure–activity relationships will be published in due course.

The Diels–Alder reactions of 7-alkyl and 7-aryl-6-demethoxythebaines **12**–**14** are being examined to explore the stereochemistry and the opiate receptor affinity of the products.

EXPERIMENTAL

Melting points were determined with a Kofler hot-stage apparatus and are uncorrected. Thin-layer chromatography (TLC) was performed on precoated Merck 5554 Kieselgel 60 F_{254} foils using chloroform–methanol (4:1) mobile phase. The spots were visualized with Draggendorf's reagent. ^{1}H NMR spectra were recorded on a Bruker WP 200 SY spectrometer; chemical shifts are reported in parts per million (ppm) (δ) from internal TMS, and coupling constants (J) are measured in Hertz. ^{13}C NMR spectra were recorded on a Bruker AM 360 instrument; chemical shifts are also reported in ppm (δ) and are presented for **13**, **16**, and **19** (R = Ph). Mass spectral measurements were performed with an Automass Multi

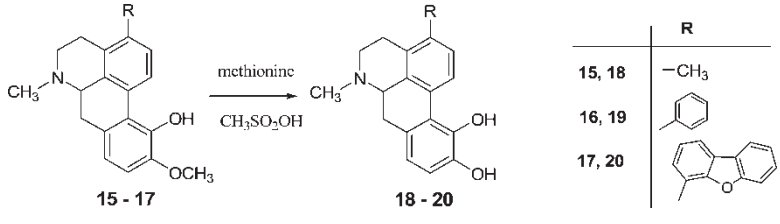


Figure 5. O-demethylation of 3-substituted apocodeines.

(ThermoQuest) instrument in the EI mode (direct inlet). The source temperature was 140°C; ionization was 70 eV. Optical rotation was determined with a Perkin-Elmer model 241 polarimeter. Elemental analyses (C, H, N, S) were obtained on a Carlo Erba 1106 analyzer.

Acid-Catalyzed Rearrangement of Morphinanediens (General Procedure A)

A mixture of the dien (1.48 mmol) and methanesulfonic acid (5 ml) was stirred for 20 min at 0°C. Then the reaction mixture was added dropwise, with stirring and external ice cooling, to a solution of potassium hydrogen carbonate (10 g) in water (50 ml). After extraction with chloroform (3 × 15 ml), the combined extracts were washed with saturated brine, dried ($MgSO_4$), and concentrated in vacuum. The residue was submitted to purification by means of column chromatography (Kieselgel 40, chloroform–methanol 1:1) to yield appropriate apocodeines.

Cross-coupling of Halo Derivatives with Aryl- and Methylboronic Acids (General Procedure B)

A mixture of the halo-derivative (3 mmol), the aryl- or methylboronic acid (3 mmol), $Pd(PPh_3)_2Cl_2$ (0.15 mmol), and $Ba(OH)_2 \cdot 8H_2O$ (3 mmol) was boiled in 1,4-dioxane–H_2O = (4:1) under reflux for 30 min. After evaporation at reduced pressure, the residue was dissolved in chloroform (20 ml) and filtered. The filtrate was evaporated, and the residue was purified by flash chromatography (silica, chloroform–methanol 1:1) to yield aryl- and alkyl-derivatives.

Synthetic Route I

3-Bromoapocodeine (***6***)

Compound **6** was prepared from 1000 mg (2.79 mmol) of 7-bromo-6-demethoxythebaine (**1**) in agreement with general procedure A. White crystalline solid; mp. 88–90°C, Yield: 950 mg (95%), Spectral data were in agreement with previously published results.[3]

3-Methylapocodeine (***15***)

Compound **15** was prepared from 3-bromoapocodeine (**6**) in agreement with general procedure B. Off-white crystalline solid; mp 210°C (decomposition). Yield: 430 mg (55%), Anal. calc. for $C_{19}H_{21}NO_2$ (%): C, 77.26; H, 7.17; N,

4.74; O, 10.83. Found (%): C, 77.30; H, 7.15; N, 4.75; O, 10.80, $[\alpha]_D^{25}$ −82 (c 0.1, chloroform); MS m/z (%) 295 (M^+, 52%); ^{1}H NMR (200 MHz, $CDCl_3$) $\delta = 8.09$ (d, 1H, H1, $J_{1,2} = 9.3$ Hz), 7.06 (d, 1H, H2, $J_{1,2} = 9.3$ Hz), 6.75 (dd, 2H, H8, H9), 6.35 (s, 1H, OH), 3.89 (s, 3H, OCH_3), 3.31–2.84 (m, 4H, $H4_a$, $H5_a$, $H5_b$, $H6_a$), 2.81–2.32 (m, 6H, $H4_b$, $H7_a$, $H7_b$, NCH_3), 2.21 (s, 3H, Ar-CH_3).

3-Phenylapocodeine (***16***)

Compound **16** was prepared from 3-bromoapocodeine (**6**) in agreement with general procedure B. White crystalline solid; mp 107–110°C. Yield: 795 mg (84%). $C_{24}H_{23}NO_2$ (%): C, 80.64; H, 6,49; N, 3.92; O, 8.95. Found (%): C, 80.67; H, 6.46; N, 3.94; O, 8.93, $[\alpha]_D^{25}$ −62 (c 1.52, chloroform); MS m/z (%) 357 (M^+, 49); ^{1}H NMR (200 MHz, $CDCl_3$) $\delta = 8.26$ (d, 1H, H1, $J_{1,2} = 8.1$ Hz), 7.42–7.23 (m, 5H, −3Ph), 7.21 (d, 1H, H2, $J_{1,2} = 8.1$ Hz), 6.73 (dd, 2H, H8, H9), 6.40 (s, 1H, OH), 3.88 (s, 3H, OCH_3), 3.28–2.82 (m, 5H, $H4_a$, $H5_a$, $H5_b$, $H6_a$, $H7_b$), 2.76–2.26 (m, 5H, $H4_b$, $H7_a$, NCH_3); ^{13}C NMR (90 MHz, $CDCl_3$) $\delta =$ 145.97, 143.19, 141.57, 140.51, 134.86, 130.80, 130.30, 130.01, 129.20, 128.05, 127.65, 126.78, 126.01, 120.37, 118.45, 109.17 (Ar), 63.28 ($C6_a$), 59.30 (OCH_3), 53.20 (C5), 44.04 (=NCH_3), 34.57 (C7), 28.53 (C4)

3-(4-Dibenzofuranyl)-apocodeine (***17***)

Compound **17** was prepared from 3-bromoapocodeine (**6**) in agreement with general procedure B. Brown crystalline solid; mp 114–120°C. Yield: 1019 mg (86%). Anal. calc. for $C_{30}H_{25}NO_3$ (%): C, 80.51; H, 5.63; N, 3.13; O, 10.73. Found (%): C, 80.48; H, 5.65; N, 3.18; O, 10.69. $[\alpha]_D^{25}$ +51 (c 0.30, chloroform); MS m/z (%) 447 (M^+, 51); ^{1}H NMR (200 MHz, $CDCl_3$) $\delta = 8.44$ (s, 1H, H1, $J_{1,2} = 8.1$ Hz), 8.11-7.29 (m, 7H, 3-Ar), 6.85 (m, 3H, H3, H8, H9), 6.41 (s, 1H, OH), 3.94 (s, 3H, OCH_3), 3.42–2.29 (m, 10H, $H4_a$, $H4_b$ $H5_a$, $H5_b$, $H6_a$, $H7_a$, $H7_b$, NCH_3)

Synthetic Route II

7-Methyl-6-demethoxythebaine (***12***)

Compound **12** was prepared from 7-bromo-6-demethoxythebaine (**3**) in agreement with general procedure B. Brown crystalline solid; mp 177–179°C. Yield: 758 mg (92%). Anal. calc. for $C_{19}H_{21}NO_2$ (%): C,77.26; H, 7.17; N, 4.74; O,10.83, Found (%): C, 77.29; H, 7.14; N, 4.76 O, 10.81. $[\alpha]_D^{25}$ −123 (c 0.15, chloroform); MS m/z (%) 295 (M^+, 56%); ^{1}H NMR (200 MHz, $CDCl_3$) $\delta = 6.68$ (dd, 2H, H1, H2), 5.55–4.90 (m, 2H, H6, H8),

3.89 (s, 3H, OCH_3), 3.82–2.59 (m, 5H, H5, $H10_a$, $H10_b$, $H16_a$, $H16_b$), 2.52 (s, 3H, NCH_3), 2.38–1.21 (m, 6H, 7-CH_3, $H9_a$, $H15_a$, $H15_b$)

7-Phenyl-6-demethoxythebaine (***13***)

Compound **13** was prepared from 7-bromo-6-demethoxythebaine (**3**) in agreement with general procedure B. White crystalline solid; mp 92–95°C. Yield: 678 mg (68%). Anal. calc. for $C_{24}H_{23}NO_2$ (%): C, 80.64; H, 6.49; N, 3.92; O, 8.95, Found (%): C, 80.68; H, 6.45; N, 3.95; O, 8,92. $[\alpha]_D^{25}$ −312 (c 2.12 chloroform); MS m/z (%) 357 (M^+, 72%); ^{1}H NMR (200 MHz, $CDCl_3$) $\delta = 7.39–7.09$ (m, 5H, 7-Ph), 6.58 (dd, 2H, H1, H2), 5.95 (s, 1H, H8), 5.84 (d, 1H, H6, $J_{5\text{-}6} = 3.0$ Hz), 5.58 (s, 1H, H5, $J_{5\text{-}6} = 3.0$ Hz), 3.81 (s, 3H, OCH_3), 3.71–3.20 (m, 2H, $H10_a$, $H10_b$), 2.91–2.54 (m, 3H, $H9_a$, $H16_a$, $H16_b$), 2.43 (s, 3H, NCH_3), 2.30–1.68 (m, 2H, $H15_a$, $H15_b$); ^{13}C NMR (90 MHz, $CDCl_3$) $\delta = 145.00$ (C4), 142.99 (C3), 141.28 (C7), 133.39 (C14), 132.27 (C12), 130.85 (C11), 128.35, 128.21, 127.68, 127.28, 126.79, 126.07 (7-Ar), 118.87 (C1), 118.32 (C8), 113.88 (C6), 112.80 (C2), 90.00 (C5), 61.52 (C9), 56.41 (OCH_3), 46.24 (C16), 43.50 (C13), 42.48 (=NCH_3), 37.55 (C15), 29.29 (C10).

7-(4-Dibenzofuranyl)-6-demethoxythebaine (***14***)

Compound **14** was prepared from 7-bromo-6-demethoxythebaine (**3**) in agreement with general procedure B. Yellow crystalline solid; mp 81–85°C. Yield: 986 mg (79%). Anal. calc. for $C_{30}H_{25}NO_3$ (%): C, 80.51; H, 5.63; N, 3.13; O, 10.73. Found (%): C, 80.55; H, 5.67; N, 3.10; O, 10.68; $[\alpha]_D^{25}$ −202 (c 0.44, chloroform); MS m/z (%) 447 (M^+, 80%); ^{1}H NMR (200 MHz, $CDCl_3$) $\delta = 8.08–7.12$ (m, 7H, 7-Ar), 6.68 (dd, 2H, H1, H2,), 6.39 (d, 1H, H6, $J_{5\text{-}6} = 2.2$ Hz), 6.31 (s, 1H, H8), 5.76 (d, 1H, H5, $J_{5\text{-}6} = 2.2$ Hz), 3.91 (s, 3H, OCH_3), 3.55–2.65 (m, 4H, $H10_a$, $H10_b$, $H16_a$, $H16_b$), 2.55 (s, 3H, NCH_3), 2.52–1.81 (m, 3H, $H9_a$, $H15_a$, $H15_b$).

3-Methylapocodeine (***15***)

Compound **15** was prepared from 7-methyl-6-demethoxythebaine (**12**) according to general procedure A. Yield: 470 mg (62%); all the physical and spectral data are in agreement with the details presented in synthetic route I.

3-Phenylapocodeine (***16***)

Compound **16** was prepared from 7-phenyl-6-demethoxythebaine (**13**) according to general procedure A. Yield: 597 mg (88%); all the physical and spectral data are in agreement with the details presented in synthetic route I.

3-(4-Dibenzofuranyl)-apocodeine (*17*)

Compound **17** was prepared from 7-(4-dibenzofuranyl)-6-demethoxythebaine (**14**) according to general procedure A. Yield: 848 mg (86%); all the physical and spectral data are in agreement with the details presented in synthetic route I.

O-Demethylation of 3-Substituted Apocodeines to Yield Corresponding 2-Substituted Apomorphines (General Procedure C)

A mixture of 3-substituted apocodeine (4.562 mmol), methionine (1 g, 6.702 mmol), and methanesulfonic acid (4 ml) was boiled at 90°C for 4 h. After cooling, the pH of the mixture was set to 10 by concentrated NH_3 solution and extracted with chloroform (3 × 15 ml). The organic layers were collected, washed with saturated NaCl solution, dried over anhydrous $MgSO_4$, and evaporated. The residue was subjected to silica-gel column chromatography. Elution with chloroform–methanol (1:1) gave the corresponding apomorphines.

3-Methylapomorphine Hydrochloride (*18*)

Compound **18** was prepared from 3-methylapocodeine (**15**) according to general procedure C. White crystalline solid; mp 200–205°C (HCl salt, decomposition). Yield: 283 mg (56%). Anal. calc. for $C_{19}H_{22}ClNO_2$ (%): C, 68.77; H; 6.68; Cl, 10.68; N, 4.22; O, 9.64. Found (%): C, 68.75; H, 6.70; N, 4.25; Cl, 10.70; O, 9.60, $[\alpha]_D^{25}$ −52 (c 0.10, DMSO); MS m/z (%) 331 (M^+, 63); ^{1}H NMR (200 MHz, DMSO-d6) $\delta = 9.05$ (s, 1H, OH), 8.20 (d, 1H, H1, $J_{1\text{-}2} = 7.8$ Hz), 7.16 (d, 1H, H2, $J_{1\text{-}2} = 7.8$ Hz), 3.25–1.95 (m, 13H, $H4_a$, $H4_b$, $H5_a$, N-CH_3, Ar-CH_3 $H5_b$, $H6_a$, $H7_a$, $H7_b$).

3-Phenylapomorphine Hydrochloride (*19*)

Compound **19** was prepared from 3-phenylapocodeine (**16**) according to general procedure C. Green crystalline solid; mp 205–210°C (HCl salt). Yield: 381 mg (60%). Anal. calc. for $C_{24}H_{24}ClNO_2$ (%): C, 73.18; H, 6.14; Cl, 9.00; N, 3.56; O, 8.12. Found (%): C, 73.21; H, 6.10; N, 3.53; Cl, 9.04; O, 8.12. $[\alpha]_D^{25}$ −64 (c 0.20, ethanol); MS m/z (%) 3.93 (M^+, 64); ^{1}H NMR (200 MHz, DMSO-d6) $\delta = 11.24$ (s, 1H, OH), 9.82 (s, 1H, OH), 8.44 (d, 1H, H1, $J_{1\text{-}2} = 7.8$ Hz), 7.58–7.12 (m, 6H, H2, 3-Ph), 6.78 (dd, 2H, H8, H9), 4.34 (dd, 1H, $H6_a$), 3.46–2.48 (m, 9H, $H4_a$, $H4_b$, $H5_a$, N-CH_3, $H5_b$, $H7_a$, $H7_b$); ^{13}C NMR (90 MHz, DMSO-d6) $\delta = 145.07$, 143.44, 140.09, 139.46, 131.73, 129.26, 128.97, 128.69, 128.60, 127.56, 127.46, 127.01, 124.77, 119.65, 118.60, 114.57 (Ar), 61.78 ($C6_a$), 51.17 (C5), 41.05 (=NCH_3), 30.64 (C7), 25.04 (C4).

3-(4-Dibenzofuranyl)-apomorphine Hydrochloride (***20***)

Compound **20** was prepared from 3-(4-dibenzofuranyl)-apocodeine (**17**) according to general procedure C. Green crystalline solid; mp $>240^{\circ}C$ (HCl salt). Yield: 392 mg (44%). Anal. calc. for $C_{30}H_{26}ClNO_3$ (%): C, 74.45; H, 5.41; Cl, 7.33; N, 2.89; O, 9.92. Found (%): C, 74.48; H, 5.39; Cl, 7.30; N, 2.91; O, 9.92. $[\alpha]_D^{25}$ +48 (c 0.20, methanol); MS m/z (%) 483 (M^+, 32); ^{1}H NMR (200 MHz, DMSO-d6) $\delta = 9.95$ (s, 1H, OH), 9.08 (s, 1H, OH), 8.55 (d, 1H, H1, $J_{1\text{-}2} = 9.5$ Hz), 8.31 (d, 1H, H2, $J_{1\text{-}2} =$ 9.5 Hz), 7.84–7.41 (m, 7H, 3-Ar), 6.87 (dd, 2H, H8, H9), 4.45 (dd, 1H, $H6_a$), 4.20–2.41 (m, 9H, $H4_a$, $H4_b$, $H5_a$, $H5_b$, $H7_a$, $H7_b$, NCH_3).

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