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Process Research and Structural Studies on Nabumetone§

C. Prabhakar,† G. Bakki Reddy,† Ch. Maheedhara Reddy,† D. Nageshwar,† A. Sivalakshmi Devi,‡ J. Moses Babu,‡ K. Vyas,‡ M. R. Sarma,† and G. Om Reddy*,†,‡

Process Research and Development Division and Structural Chemistry Division, Dr. Reddy's Research Foundation, Bollaram Road, Miyapur, Hyderabad - 500 050, India

Abstract:

A short, simple and economical process for large-scale preparation of nabumetone has been developed. The single-crystal structures of nabumetone and one of its key intermediates have been determined by X-ray diffraction studies. Two impurities have been isolated and characterised.

Introduction

Nabumetone [4-(6-methoxy-2-naphthalenyl)-2-butanone] is a novel nonacidic broad-spectrum antiinflammatory, analgesic, and antipyretic agent, discovered by the Smith-Kline Beecham group[1] and launched in 1985. This drug was later licensed to Bencard, Fujisawa, Uriach, and Zambelette. Its activity is greater than that of aspirin and comparable to naproxen and indomethacin. The compound does not exhibit serious signs of toxicity even at reasonably high doses.[2] With the growing popularity in the field of nonsteroidal antiinflammatory drugs (NSAID),[3] several synthetic strategies have appeared in the literature for the preparation of nabumetone.[4] All the reported routes either use hazardous chemicals or employ tedious workup procedures. Hence, we attempted to develop a short, simple, and economical process for the preparation of nabumetone, as part of our interest in the area of NSAID.

Results and Discussion

Of all the synthetic routes available in the literature, we selected two for our development work, on the basis of their seemingly straightforward and commercially viable possibility. Scheme 1[5] deals with the bromination of β-naphthol (**1**), using molecular bromine and resulting in the formation of 2,5-dibromo-6-naphthol (**2**), which on monodebromination with tin metal afforded the 6-bromo-2-naphthol (**3**) in ~97% yield. However, the preparation of bromonaphthol **3** appeared to be cumbersome. Moreover, this step was by no means cost-effective considering that the dibromination/monodebromination sequence[6] involved a major cost factor. The bromonaphthol **3** thus obtained was O-methylated using dimethyl sulphate[7] to afford 2-bromonaroline[6] (**4**) in quantitative yield, which in turn was converted to 6-methoxy-2-naphthaldehyde[8] (**5**) via 6-methoxynaphthylmagnesium bromide using a Mg/DMF/THF recipe[9] in ~63% yield. The aldol condensation of aldehyde **5** with acetone resulted in the formation of enone[10] **6** in ~45−50% yield.

The major side products here were found to be the self-condensation products of acetone and the aldehyde. This step turned out to be the bottleneck in the process, hampering the scale-up trials. The final reduction of enone **6**, using either Pd/C or Ra·Ni, proceeded smoothly to produce nabumetone (**7**). However, after preliminary bench work on Scheme 1, it was felt that the route was not only lengthy and tedious but also low yielding. The alternative route starting from 2-acetylnaroline[11] (**8**), as shown in Scheme 2,[12] was taken up to carry out the feasibility study. Though Scheme 2 was relatively short and simple, use of sodium hydride for the preparation of the enol ketone **9** and its purification, as reported[12] in the literature, using cupric acetate chelation to yield the chelate **10** could cause problems on scale-up. To avoid the expensive and sensitive sodium hydride, several other bases were tried. We were successful in performing the reaction in ethyl acetate employing a relatively inexpensive and safe base, potassium *sec*-butoxide, with yield and purity comparable to that reported in the literature with sodium hydride. Interestingly, even the purification involving the cupric acetate complex **10**, also was not necessary. This compound **9** appealed to us as an interesting example to study various other aspects as well, concerning structural and reactivity details.[13] Compound **9** can exist in two tautomeric

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* Corresponding author: (tel) 91 40 304 5439; (fax) 91 40 304 5438; (e-mail) drf@hd1.vsnl.net.in.

† Process Research and Development Division.

‡ Structural Chemistry Division.

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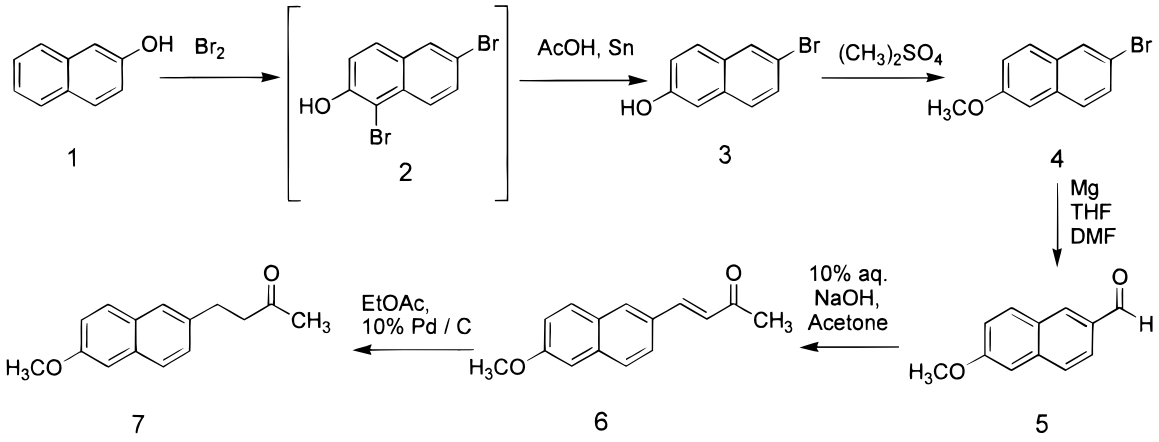
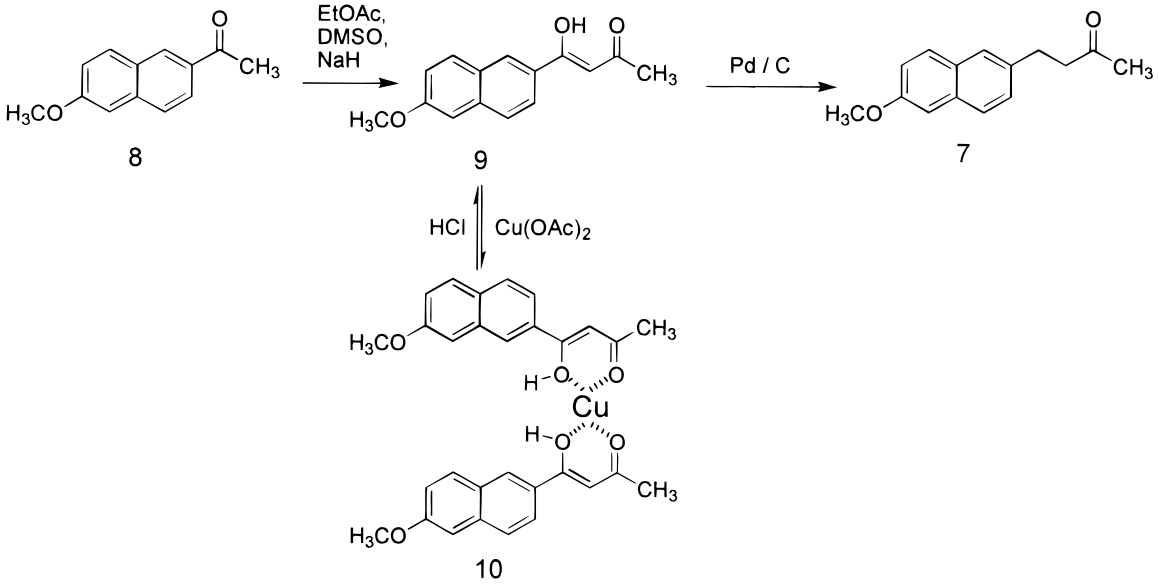
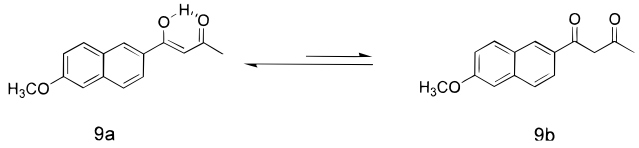
Scheme 1



Scheme 2



forms **9a** and **9b** and it was of interest for us to know in



which form it predominantly existed, both in solution and solid states.

^{1}H and ^{13}C NMR spectra were critically examined to gain insight regarding the tautomeric form in solution. DEPT proved useful in showing that the compound indeed exists in the enol ketone form **9a** in solution. The absence of a CH_2 signal and the presence of one CH signal in the aliphatic region strongly supported the structure **9a**. The single-crystal X-ray diffraction studies[14] revealed that the molecule exists in the enol form **9a** and not in the diketo form **9b**. The O(2)−C(12) bond length was found to be 1.312(5) Å, which is typical for an enolic bond.[15]

The atoms of the side chain at C(2) are approximately in the same plane of the aromatic ring. The plausible reason for this could be the additional stability the compound attains due to the intramolecular hydrogen-bonded six-membered ring as shown above. The hydrogen bond parameters are O(2)···O(3) = 2.495(5) Å, O(2)−H(14) = 1.09 Å, H(14)···O(3) = 1.55 Å, and O(2)−H(14)···O(3) = 141.2°. The molecule is stabilised by van der Waals interactions in the lattice. The ORTEP picture of **9a** is shown in Figure 1.

The next step, viz., the hydrogenation of **9** to give the drug nabumetone appeared to be simple, but in reality, this was found to be a bit complicated involving two intermediate stages. The expected sequence of events is shown in the Scheme 3.

(14) X-ray data of **9a**: $C_{15}H_{14}O_3$, monoclinic, space group $P2_1/a$, a = 8.107 (1) Å, b = 5.849 (1) Å, c = 25.878 (3) Å, β = 90.28 (1)°, V = 1227.2 (0.2) Å^3, Z = 4, D_c = 1.31 gm cm^{-3}. Cu Kα (λ = 1.5418 Å), μ = 7.41 cm^{-1}, $F(000)$ = 512. Intensity data were collected on a Rigaku AFC7S diffractometer in the $\omega/2\theta$ scan mode. A total of 2720 reflections were measured of which 2538 were "unique" and 1823 were "observed" with $I \geq 3\sigma(I)$. The intensity was corrected for Lorentz polarisation and absorption (ψ scan). The structure was solved by direct methods (SIR 92) and full matrix refinement on $|F_0|$ with non-H atoms anisotropic and H atoms isotropic converged at an R factor of 0.089, R_w = 0.106. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC).

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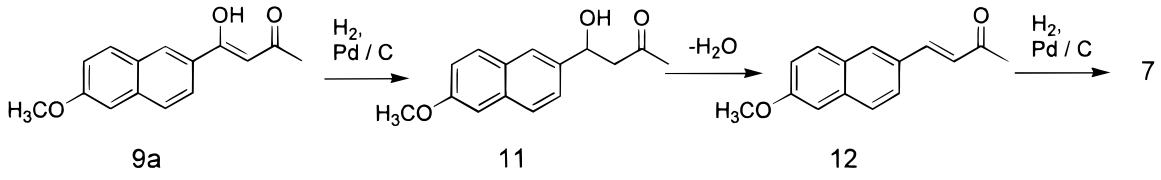
Scheme 3



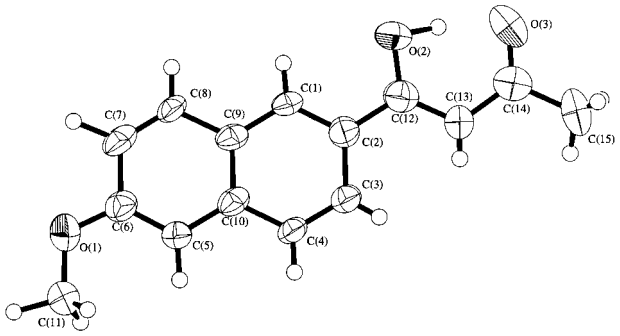


Figure 1. **Molecular structure of 9a.**

According to the literature reports,[4b,12] hydrogenation of **9a** in glacial acetic acid or ethyl acetate should give nabumetone **7** directly in 2 h at atmospheric pressure of hydrogen and room temperature. However, our several attempts to repeat the same turned out to be futile. Even after several hours of hydrogenation in glacial acetic acid, the reaction, in our hands, yielded only the hydroxy ketone **11**. The in situ dehydration of **11** to give **12** occurred only after adding a catalytic amount of concentrated sulfuric acid. With this clue, we could carry out the reaction in ethyl acetate using a catalytic amount of concentrated sulfuric acid. The reaction was completed in ~8−10 h at atmospheric pressure of hydrogen and at 60 °C. Unreacted starting material was present to the extent of 1% while the required product **7** was ~90% in the crude reaction mass. The isolated yield of nabumetone **7** was ~65% with a HPLC purity of ~99.5%. Surprisingly, the single-crystal X-ray analysis of nabumetone has not been reported in the literature to our knowledge, and hence, this study was also carried out by us.[16] Two independent molecules were found to be present in the unit cell, with marginal difference in the orientation of the side chain with respect to the aromatic ring. The molecules are held in the lattice by van der Waals contacts. The ORTEP pictures of **7** are shown in Figure 2.

The two major impurities were found to be **11** and **13**, to the extent of ~4−5% each, which were isolated and characterized.

Scale-Up Trials. With the procedures fully optimised, the scale-up trials were performed at a 5−10-kg scale. This route was operated routinely and reliably affording the expected yields and purities in all stages of the synthesis and demonstrating the robustness and viability of the process.

(16) X-ray data of **7**: $C_{15}H_{16}O_2$, monoclinic, space group $P2_1/c$, $a = 22.054$ (6) Å, $b = 5.327$ (3) Å, $c = 22.483$ (6) Å, $\beta = 110.83$ (2)°, $V = 2468.9$ (1.5) Å^3, $Z = 8$, $D_c = 1.23$ gm cm^{-3}. Cu Kα ($\lambda = 1.5418$ Å), $\mu = 6.39$ cm^{-1}, F(000) = 976. Intensity data were collected on a Rigaku AFC7S diffractometer in the $\omega/2\theta$ scan mode. A total of 5252 reflections were measured of which 5115 were "unique" and 2799 were "observed" with $I \geq 3\sigma(I)$. The intensity was corrected for Lorentz polarisation and absorption (ψ Scan). The structure was solved by direct methods (SIR 92) and full matrix refinement on $|F_0|$ with non-H atoms anisotropic and H atoms isotropic converged at an R factor of 0.048, $R_w = 0.059$. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC).

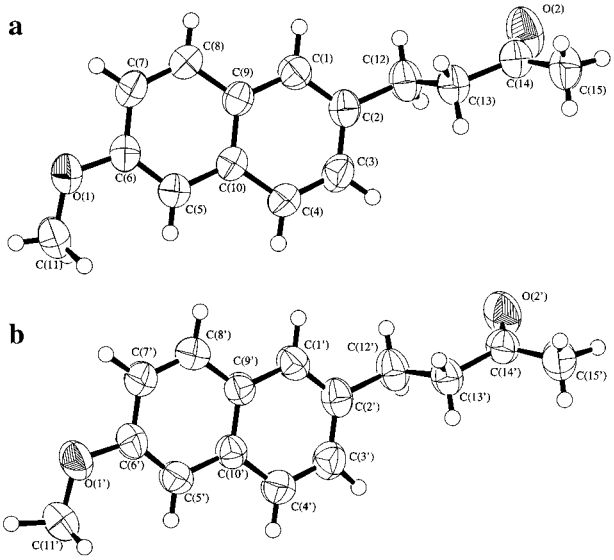
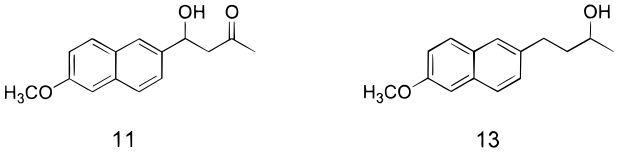


Figure 2. **(a, b) Molecular structure of 7.**



Conclusions

Process Simplicity. The simplicity of the present process is evident by the two-step sequence (Scheme 4) and by the use of a safe base and also in avoiding the cumbersome purification process by chelating with cupric acetate. Carrying out the hydrogenation in ethyl acetate with a catalytic amount of sulfuric acid makes the process simpler compared to hydrogenation in glacial acetic acid where the work up is more tedious.

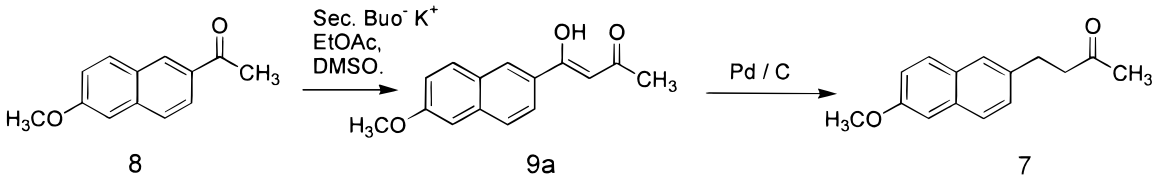
Cost-Effectiveness. Use of potassium *sec*-butoxide in place of sodium hydride and removal of copper chelation for the purification of **9a** brings cost-effectiveness to the process.

Robustness. The route has been operated routinely and reliably in 5−10-kg batches, affording the expected yields and purities in all stages of the synthesis and demonstrating the robustness and viability of the process.

Safety. With the hazardous sodium hydride replaced with the safe base, potassium *sec*-butoxide, the process becomes much safer for larger scale manufacture.

X-ray Diffraction Studies. The single-crystal X-ray diffraction studies have been carried out on the intermediate **9a** and nabumetone **7**.

Scheme 4



Impurity Profile. The two impurities **11** and **13** have been isolated and characterised.

Experimental Section

Solvents and reagents were obtained from commercial sources and were used as such without any further purification, unless specified. Acetyl naroline and 2-naphthol were procured from commercial sources and were used as such without any further purification. The melting points were recorded on a Buchi 535 and are uncorrected. The ^{1}H NMR spectra were obtained using a 200-MHz Varian Gemini spectrometer with tetramethylsilane as an internal standard. Infrared (IR) spectra were recorded using a Perkin-Elmer model 1640 apparatus. Mass spectra were recorded on MS Engine Hewlett-Packard model 5989 apparatus at DIP 20 eV. HPLC equipment consisted of a Waters 510 pump, Waters 486 UV−visible detector, Waters 746 data module, and Novapak/Hypersil C^{18} columns.

Preparation of 6-Bromo-2-Naphthol (3). To a stirred solution of 144 g of 2-naphthol (**1**) and 400 mL of acetic acid was added 320 g of bromine dissolved in 100 mL of acetic acid over a period of ∼30 min between 30 and 35 °C. A 100-mL aliquot of water was added after the complete addition of bromine/acetic acid, when a solid separated from the reaction mass. The reaction mixture was heated at 100−120 °C to dissolve the separated solid. Tin metal (2 × 25 g) was added slowly over a period of 30−45 min followed by a third lot of 100 g. The reaction mixture was heated at the same temperature for further 3 h, the reaction mass was cooled to 50 °C and filtered, and the cake was washed with 2 × 100 mL of acetic acid. The filtrate was diluted with 2 L of ice cold water, and the solid thus obtained was filtered and dried at 90−100 °C to afford 215 g (yield, 96%; purity, 97%; mp, 120−124 °C) of the title compound as a light pink powder.

Preparation of 6-Bromo-2-methoxynaphthalene (4). To a stirred mixture of 159 g of potassium carbonate, 165 mL of water, and 525 mL of acetone was added 178 g of **3**. The reaction mass was cooled to 10−15 °C, and 196 g of dimethyl sulphate was added dropwise over a period of 1 h at 10−15 °C, followed by stirring the reaction mixture at 40−50 °C for a further 3 h. The reaction mixture was dumped into 1 L of ice cold water and extracted with methylene chloride. The organic extracts were washed with water and concentrated to afford 159 g (yield, 85%; purity, 99%; mp, 103−105 °C) of the title compound.

Preparation of 6-Methoxy-2-Naphthaldehyde (5). A mixture of 30 mL of tetrahydrofuran, 15 g of dry magnesium turnings, and a speck of iodine was refluxed to initiate the reaction, to which was added 140 g of the bromo compound **4** dissolved in 350 mL of tetrahydrofuran over a period of 3 h. The reaction mixture was refluxed for a further 2 h. The reaction mixture was cooled to 10−15 °C, and a mixture of 45 mL of tetrahydrofuran and 45 mL of dimethylformamide was added slowly over a period of 45 min, followed by heating the reaction mixture at 80−90 °C for 1 h. Tetrahydrofuran was completely distilled from the reaction mass under vacuum; 1.4 L of 10% acetic acid was added and stirred at room temperature for 1 h. The reaction mixture was extracted with 4 × 300 mL of methylene chloride followed by washing the combined organic extracts with water. The solvent was concentrated under reduced pressure to afford 104 g of the crude aldehyde which was recrystallised from methanol to give 70 g (yield, 64%; purity, 95%; mp, 80−82 °C) of the title compound as a pale yellow solid.

Preparation of 4-(6-Methoxy-2-naphthalenyl)but-3-en-2-one (6). A 200-g sample of the aldehyde **5** was stirred in 3.3 L of acetone containing 70 mL of 10% sodium hydroxide for 4 h. The solution was acidified to pH 2−3 and extracted with ether. The solvent was evaporated, and the crude compound thus obtained was purified over a column to afford 135 g (yield, 50%; purity, 85%; mp, 112−114 °C) of the title compound as a pale yellow solid.

Reduction of 4-(6-Methoxy-2-naphthalenyl)-but-3-en-2-one (6) to Nabumetone (7). A 100-g sample of the unsaturated compound **6** was dissolved in 2 L of ethyl acetate, 10 mL of Ra·Ni was added, and the resultant mixture was hydrogenated at atmospheric pressure at room temperature for 4 h. The catalyst was filtered, and the solvent was distilled off to obtain the crude compound which was recrystallised in 2-propanol to afford 72 g (yield, 72%; purity, 99+%; mp, 82−84 °C) of pure **7** as a white crystalline material.

Preparation of 4-(6-Methoxy-2-naphthalenyl)-4-hydroxybut-3-en-2-one (9a). A 303-g sample of potassium *sec*-butoxide was dissolved in 800 mL of dimethyl sulfoxide in a reaction flask fitted with a mechanical stirrer, reflux condenser, thermopocket, and nitrogen inlet. A 200-g sample of acetyl naroline **8** dissolved in a mixture of 2 L dimethyl sulfoxide and 800 mL of ethyl acetate was added to the reaction flask containing potassium *sec*-butoxide at 50−60 °C. The reaction mixture was stirred at the same temperature for 1 h while monitoring the reaction by TLC. After the completion of the reaction, the reaction mass was poured into 2 L of water and acidified to pH 2 using 50% aqueous hydrochloric acid. A 2-L sample of dichloroethane was added, the mixture stirred for 15 min, and the organic layer was separated. The organic layer was washed with water untill the washings were at neutral pH, and the solvent was distilled off to afford 213 g of **9a** (yield, 88%; purity, 99.2%; mp, 118−122 °C).

Preparation of 4-(6-Methoxy-2-naphthalenyl)-2-butanone (7). A 100-g sample of **9a** was dissolved in 1.5 L of ethyl acetate at 45 °C and to this was added 0.5 mL of sulfuric acid followed by 14 g of 10% Pd/C. The reaction mixture was subjected to hydrogenation by passing hydrogen gas through the solution under efficient stirring for 8−10 h, while monitoring the reaction by TLC. After completion of the reaction, the catalyst was filtered off and the filtrate was washed with 5% sodium bicarbonate solution. The solvent was distilled under reduced pressure to afford 95 g of the crude **7**, which was recrystallised from methanol to give 61 g of pure **7** with a HPLC purity of 99.5% (yield, 65%; mp, 82−84 °C) IR 3053, 2955, 1705, 1607, 1361, 1263, 1227, 1156, 1027, 846, 815 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.14 (s, 3H), 2.82 (t, J = 7.2 Hz, 2H), 3.02 (t, J = 7.2 Hz, 2H), 3.90 (s, 3H), 6.30 (s, 1H), 7.10 (s, 1H), 7.12 (d, J = 8.6 Hz, 1H), 7.28 (d, J = 9.3 Hz, 1H), 7.54 (s, 1H), 7.66 (d, J = 9.3 Hz, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 29.30, 29.53, 44.59, 54.78, 105.35, 118.41, 125.86, 126.60, 127.19, 128.58, 132.80, 135.83, 156.97, 207.33; *m*/*z* 228 (M^+) corresponding to $C_{15}H_{16}O_2$. The mother liquor was used to isolate and characterise the two major impurities **11** and **13**. **11** (mp, 106−108 °C): IR 3474, 1703, 1609, 1386, 1267, 1230, 1159, 1074, 1028, 854, 816 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.20 (s, 3H), 2.95 (m, 2H), 3.50 (br s, −OH), 3.91 (s, 3H), 5.28 (dd, J_1 = 8 Hz, J_2 = 4 Hz, 1H), 7.12 (s, 1H), 7.14 (d, J = 8 Hz, 1H), 7.44 (d, J = 8 Hz, 1H), 7.72 (d, J = 8 Hz, 2H), 7.74 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 30.59, 51.81, 55.11, 69.81, 105.57, 118.81, 124.20, 127.00, 128.56, 129.29, 133.93, 137.94, 157.55, 208.80; *m*/*z* 244 (M^+) corresponding to $C_{15}H_{16}O_3$. **13** (mp, 95−98 °C): IR 3345, 2932, 1635, 1606, 1462, 1266, 1230, 1029, 850, 816 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.25 (d, J = 6.2 Hz, 3H), 1.86 (m, 2H), 2.62 (br s, OH), 2.85 (dd, J_1 = 8 Hz, J_2 = 6.6 Hz, 2H), 3.85 (m, 1H), 3.90 (s, 3H), 7.10 (s, 1H), 7.14 (d, J = 8.8 Hz, 1H), 7.30 (d, J = 8.4 Hz, 1H), 7.56 (s, 1H), 7.67 (d, J = 8.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 23.53, 31.96, 40.69, 55.16, 67.35, 105.62, 118.59, 126.12, 126.73, 127.69, 128.79, 129.04, 132.90, 137.16, 157.07; *m*/*z* 230 (M^+) corresponding to $C_{15}H_{18}O_2$.

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