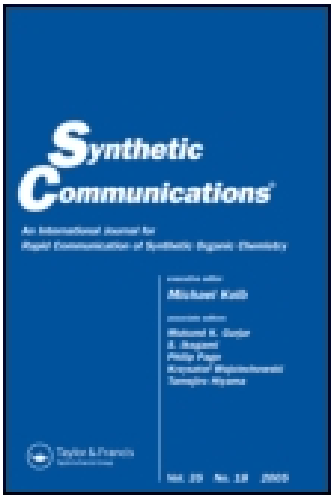

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Synthesis of Dihydrobenzo[*h*]coumarins and Their 4-Methyl Analogs

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Abstract: Dihydrobenzo[*h*]coumarins (**5a**–**7a**) and their 4-methyl analogs (**5b**–**7b**) were synthesized from 1-naphthol via two different synthetic routes. One pathway is the direct condensation of 5,8-dihydro-1-naphthol (**9**) with malic acid or ethyl acetoacetate, affording 7,10-dihydrobenzo[*h*]coumarins **7a** and **7b**, respectively. The other is through the oxidation of 7,8,9,10-tetrahydrobenzo[*h*] coumarins (**15a**–**b**), followed by the reduction of the carbonyl group and dehydration of hydroxyl group, giving 7,8-dihydrobenzo[*h*]coumarins (**5a**, **b**) and 9,10-dihydrobenzo[*h*]coumarins (**6a**, **b**). The regio selectivities for the oxidation reactions of **15a, b** were rationalized on the basis of quantum chemical calculations and further confirmed by the X-ray crystallographic analysis of the derivatives of oxidation products.

Keywords: Dihydrobenzo[*h*]coumarins, 4-methyl-dihydrobenzo[*h*]coumarins, 7,8,9,10-tetrahydrobenzo[*h*]coumarins, oxidation, regioselectivity

INTRODUCTION

3′,4′-Di-*O*-(−)-camphanoyl-(+)-*cis*-khellactone (DCK, **1**) and numerous DCK analogs have been demonstrated to have an extremely potent inhibitory activity against HIV-1 replication in H9 lymphocytic cells in previous research.[1–6] Selected modifications to the DCK skeleton are very desirable to clarify the mechanism of action and identify the pharmacophores in this class of potent anti-HIV agents. To this end, a new series of DCK analogs,

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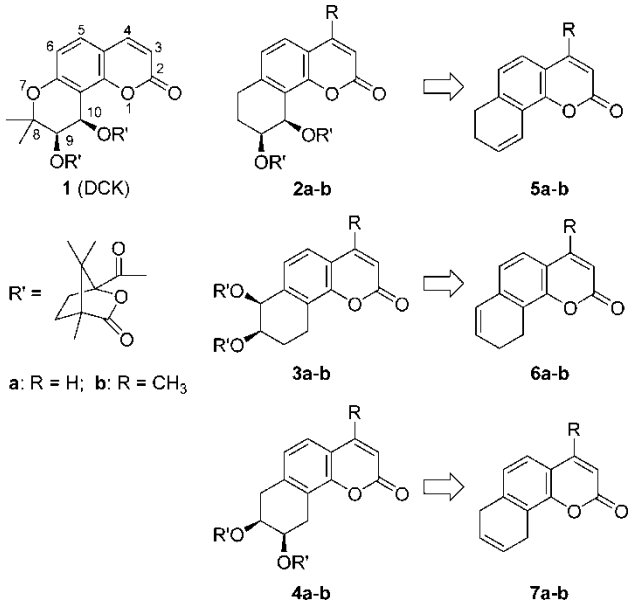
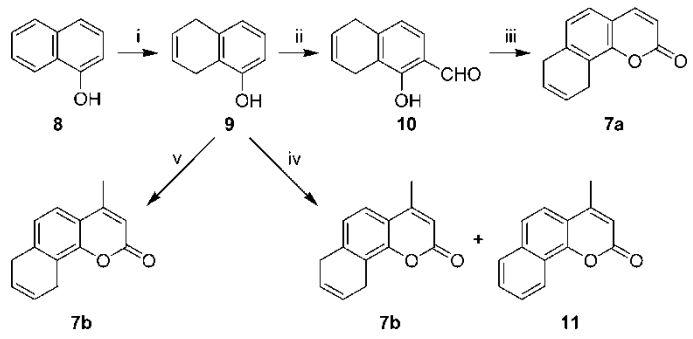


Figure 1. Structures of DCK (**1**), 7-carbo-DCK analogs (**2**) and their regioisomers (**3**, **4**), and dihydrobenzo[*h*]coumarins **5**–**7**.

namely 7-carbo-DCK derivatives (**2a**, **b**) and their corresponding regioisomers (**3**, **4**) (Fig. 1) were designed. Compounds **2a**, **b** can be considered the bioisosteres of DCK analogs, which might provide valuable insight into the effect of 7-oxygen atoms and 8,8-dimethyl groups on the anti-HIV activity. Moreover, the regioisomers (**3**, **4**) might shed some light on the positional effect of two camphanoyl ester groups on the activity. According to retrosynthetic analysis, dihydrobenzo[*h*]coumarins (**5a**–**7a**) and their 4-methyl analogs (**5b**–**7b**) are the key intermediates for the synthesis of **2**–**4**. More important, the coumarin derivatives themselves also represent one type of fundamental heterocyclic compounds with several bioactivities, and excellent results have been shown in a decade of extensive research.[7–9] Herein, we report the synthesis and characterization of a variety of dihydrobenzo[*h*]coumarins **5**–**7** (Fig. 1).

RESULTS AND DISCUSSION

As shown in Scheme 1, the key intermediate to synthesize **7a**, **b** is 5,8-dihydro-l-naphthol (**9**), which was prepared in a 71% yield by Birch reduction from 1-naphthol (**8**) with Li/NH_3(liq.)[10] We previously reported that the condensation reaction of **9** with ethyl acetoacetate gave 4-methyl-7,10-dihydrobenzo[*h*]coumarin (**7b**) together with an aromatized by-product

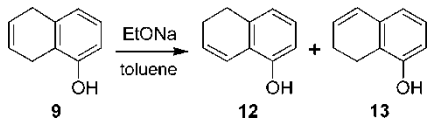


Scheme 1. Synthetic route of **7a**, **b**: (i) Li/NH_3 (liq.), $-78^{\circ}C$; (ii) paraformaldehyde, 2,6-lutidine, $SnCl_4$, toluene, 95–100°C, 10 h; (iii) Ac_2O, NaOAc, 160°C, 8 h; (iv) $CH_3COCH_2COOC_2H_5$, CH_3SO_3H, Na_2SO_3, 120°C, 5 h; and (v) $CH_3COCH_2COOC_2H_5$, $POCl_3$, benzene, reflux, 1 h.

4-methylbenzo[*h*]coumarin **(11)**.[11] It was found that the reaction conditions, particularly the absolutel absence of oxygen, is critical for this acid-catalyzed condensation of **9** to **7b**, which otherwise almost completely converts to the aromatized product **11**. Under the optimized conditions, that is, under Ar atmosphere with CH_3SO_3H as a catalyst in the presence of antioxidant Na_2SO_3 at 100–120°C, **7b** and **11** could be obtained in the ratio of 70:30 with moderate yield (49%). The better yield (60–71%) of **7b** was obtained by using $POCl_3$ instead of CH_3SO_3H or *p*-toluenesulfonic acid as the catalyst in refluxing benzene.[12,13] No aromatized product **11** was observed under these reaction conditions, which is probably due to the low reaction temperature. A trial of the synthesis of **7a** through the condensation of **9** with malic acid in HOAc in the presence of H_2SO_4 demonstrated that only benzo[*h*]coumarin was obtained. Alternatively, the synthesis of **7a** was accomplished under Ar by the condensation of 5,8-dihydro-l-hydroxynaphthalene-2-carbaldehyde **(10)** with acetic anhydride in the presence of sodium acetate. Compound **10** was obtained in 60% yield by treatment of phenol **(9)** with paraformaldehyde in toluene in the presence of $SnCl_4$ coupled with 2,6-lutidine.[14]

According to retrosynthetic analysis, 5,6-dihydro-1-naphthol **(12)** and 7,8-dihydro-1-naphthol **(13)** may act as the key synthetic precursors for **5** and **6**, respectively. However the attempts to prepare **12** and **13** by regioisomerization of **9** under basic condition[15] always resulted in an inseparable mixture (Scheme 2). Thus, we switched our attention to the synthesis of **5** and **6** through an alternative route.

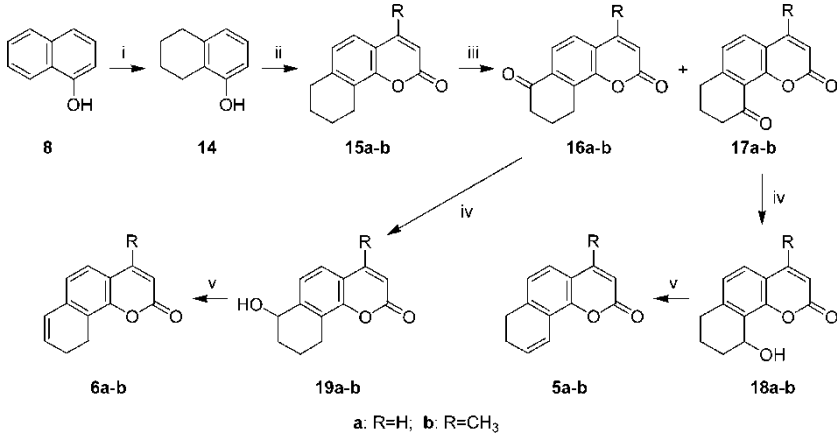
As illustrated in Scheme 3, the synthesis of **5**, **6** was accomplished via a five-step reaction sequence. 5,6,7,8-Tetrahydro-l-naphthol **(14)** was prepared in 74% yield by reducing cheap and readily available 1-naphthol **(8)** with Raney Ni-A1 alloy in an alkaline aqueous solution.[16] The condensation of **14** with malic acid in HOAc in the presence of H_2SO_4 gave



Scheme 2. Regioisomerization of **9**.

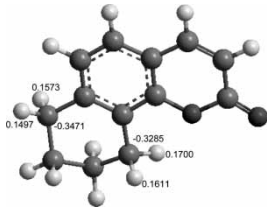
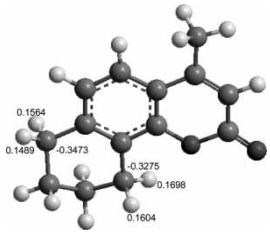
7,8,9,10-tetrahydrobenzo[*h*]coumarin **(15a)** in a yield of 60%. The yield was greatly enhanced in comparison with the literature method (16% yield).[17] The condensation of **14** with ethyl acetoacetate in the presence of $POCl_3$ furnished the expected 4-methyl-7,8,9,10-tetrahydrobenzo[*h*]coumarin **(15b)** in a yield of 70%.

The oxidation of both **15a** and **15b** with CrO_3 in HOAc[18] afforded two products with different polarities ($R_f = 0.3$ and 0.05, on silica-gel plate, eluent: hexane–EtOAc3:1), respectively. The compounds with larger R_f values are the major products (42% or 51% yields), and the others having smaller R_f values are the minors (22% or 9%). From their ^1H NMR, ^{13}C NMR, and MS spectra, it is clear that the benzylic 7- or 10-positions CH_2 of **15a** and **15b** have been oxidized to a carbonyl group, affording two regioisomers **16a**, **b** and **17a**, **b**, respectively. However, we were unable to distinguish **16** and **17** from each other simply on the basis of these data. After many trials for growing single crystals of these ketone products failed, we calculated the electronic density distribution at 7- and 10-carbons of compounds **15a**, **b** using DFT (B3LYP) implemented in the Gaussian98 suite of programs. The results indicated that the 7-carbons of **15a**, **b** possess higher electronic densities than those of 10-carbons (Table 1), suggesting that 7-position



Scheme 3. Synthetic route of **5**, **6**: (i) Raney Ni-Al alloy, 1% aq. KOH/water, 90°C, 2 h; (ii) **15a**: malic acid, H_2SO_4, HOAc, 130°C, 6 h; **15b**: $CH_3COCH_2COOC_2H_5$, $POCl_3$, 100°C, 18 h; (iii) CrO_3, HOAc, rt, 3 days; (iv) $NaBH_4$, CH_3OH, 1–4 h; (v) 2% H_2SO_4, reflux, 6–16 h.

Table 1. Electronic distribution of C7 and C10 in compounds **15a**, **b**[a]

Compound	Diagram	Atomic charges	Atomic charges with hydrogens sumed into heavy atoms
15a		C7: −0.3471, H: 0.1573, H: 0.1497 C10: −0.3285, H: 0.1700, H: 0.1611	C7: −0.0400 C10: +0.0026
15b		C7: −0.3473, H: 0.1564, H: 0.1489 C10: −0.3275, H: 0.1698, H: 0.1604	C7: −0.0420 C10: +0.0027

[a]All the calculations were performed at the DFT level using the hybrid functional B3LYP with the Gaussian98 suite of programs. All atoms were treated with an all-electron 6-31* basis set.

carbons should be easier to be oxidized than 10-position carbons. Therefore, the major oxidation products of **15a**, **b** were tentatively assigned to be **16a** (42% yield) and **16b** (51% yield) with larger R_f value, and the minors **17a** (22% yield) and **17b** (9% yield) with smaller R_f values, respectively. In comparison with the oxidation of **15a**, the higher regioselectivity for the reaction of **15b** might be attributed to its bigger difference of the electronic distribution at 7-carbon (−0.0420) and 10-carbon (+0.0027).

In addition, the calculation on the dipole moments of compounds **16a**, **b** and **17a**, **b** demonstrated that the former have smaller μ values and thus are less polar components with bigger R_f values (Table 2). Accordingly, these results are consistent with speculation based on the calculation of electronic distribution mentioned previously, which was further confirmed by the X-ray crystallographic analysis of the reduction product of **16a** and the reduction −dehydration product of **16b** (Figs. 2 and 3).

Other oxidants such as CANL[19] and $KMnO_4/CuSO_4 \cdot 5H_2O$[20]were also examined and resulted in low yield or no reaction.

Reduction of **16a**, **b** and **17a**, **b** with $NaBH_4$ in methanol gave 7-hydroxy or 10-hydroxy-7,8,9,10-tetrahydrobenzo[*h*]coumarin (**19a**, **18a**) and their 4-methyl analogs (**19b**, **18b**) in the yields of 79% and 66%, and 74% and

Table 2. Calculated dipole moments of compounds **16a**, **b** and **17a**, **b**

Dipole moments (Debye)	Compounds
1.6215	**16a**
7.4681	**17a**
2.2173	**16b**
7.7861	**17b**

94%, respectively. The X-ray single-crystal diffraction of 7-hydroxy-7,8,9, 10-tetrahydrobenzo[*h*]coumarin (**19a**) is shown in Fig. 2.

7,8-Dihydrobenzo[*h*]coumarin **(5a)** and its 4-methyl analog **5b** were obtained by the dehydration of **18a** and **18b** in refluxing acidic aqueous solution (2% H_2SO_4) in the yields of 76% and 90%, respectively. 9,10-Dihydrobenzo[*h*]coumarin (**6a**) and its 4-methyl analog **6b** were obtained similarly from **19a** and **19b** in the yields of 99% and 66%, respectively. The X-ray single-crystal diffraction of **6b** is shown in Fig. 3. According to the bond lengths illustrated in Table 3, the location of double bonds formed from dehydration could be confirmed; namely, the dehydration product of **19b** is 4-methyl-9,10-dihydrobenzo[*h*]coumarin **(6b)**.

In summary, a series of new important heterocycles dihydrobenzo[*h*] coumarins (**5**–**7**) were successfully synthesized from 1-naphthol via two different synthetic routes. The regioselectivities for the oxidation reactions of 7,8,9,10-tetrahydrobenzo[*h*]coumarins **(15)** were rationalized with quantum chemical calculations and further confirmed by the X-ray crystallographic analysis of the derivatives of the oxidation products.

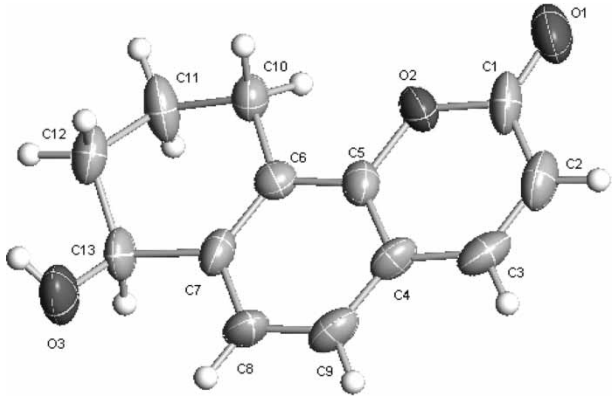


Figure 2. Molecular structure of compound **19a**.

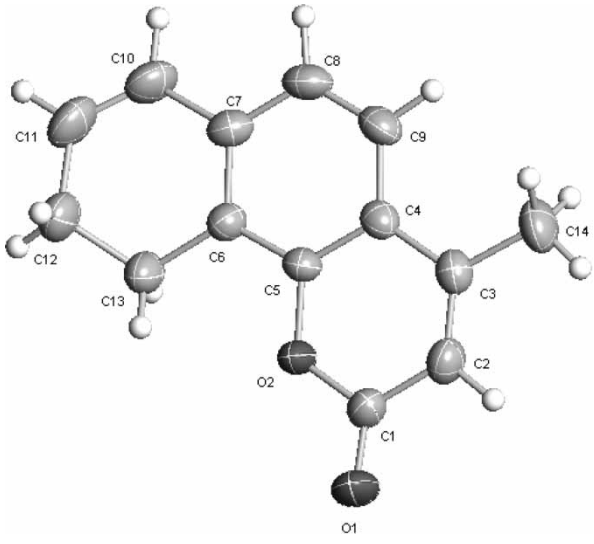


Figure 3. Molecular structure of compound **6b**.

EXPERIMENTAL

Melting points are uncorrected. Reactions were monitored by TLC on 0.2- mm silica-gel plates, and the spots were visualized by ultraviolet light. Flash-column chromatography was performed on silica gel (300–400 mesh). ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Mercury 300 spectrometer at 300.13 and 75.47 MHz, respectively, and the solvent used was $CDCl_3$ unless indicated. All chemical shifts were reported in δ units with reference to TMS (^{1}H) or the signals of the solvent (^{13}C). Elemental analysis was performed on an Elemental Vario EL apparatus. Mass spectra (EI) were taken on a Agilent 5973 N MSD spectrometer. HRMS data were determined on a Kratos Concept 1H spectrometer, Bruker ApexIII 7.0 Tesla FTMS or IonSpec 4.7 Tesla FTMS instrument.

5,8-Dihydro-l-naphthol (9). Following the procedure described in literature,[10] compound **9** was obtained from **8** as a white solid (yield, 71%): mp 69–71°C (lit.[10] 72–73.5°C). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.26–3.30 (m, 2H, 5-H), 3.39–3.42 (m, 2H, 8-H), 4.77 (bs, 1H, O-H), 5.86–5.92 (m, 2H, 6-H, 7-H), 6.60 (d, $J = 7.9$ Hz, 1H, 4-H), 6.72 (d, $J = 7.6$ Hz, 1H, 2-H), 7.04 (t, $J = 7.9$ Hz, 1H, 3-H).

4-Methyl-7,10-dihydrobenzo[*h*]coumarin (7b). The compound was synthesized following the modified procedure described in literature.[12,13] A mixture of 5,8-dihydro-l-naphthol **(9)** (0.15 g, 1.0 mmol), ethyl acetoacetate (2 g, 15.4 mmol), and phosphoryl chloride (1.5 g, 10 mmol) was refluxed in benzene (4 mL) for 1 h. The solvent was removed under vacuum, and the residue was neutralized with saturated aqueous $NaHCO_3$ to pH7 and

Table 3. Selected bond lengths [nm] for compound **6b**

Compound	Bond length
O(1)-C(1)	0.1210(2)
O(2)-C(1)	0.1369(2)
O(2)-C(5)	0.1386(2)
C(1)-C(2)	0.1436(3)
C(2)-C(3)	0.1338(3)
C(2)-H(1)	0.096(2)
C(8)-C(9)	0.1361(3)
C(8)-H(2)	0.098(2)
C(9)-H(3)	0.097(2)
C(10)-C(11)	**0.1321(3)**
C(10)-H(4)	0.099(3)
C(11)-C(12)	**0.1492(3)**
C(3)-C(4)	0.1446(3)
C(4)-C(14)	0.1497(3)
C(4)-C(5)	0.1392(2)
C(4)-C(9)	0.1406(3)
C(5)-C(6)	0.1382(3)
C(6)-C(7)	0.1405(3)
C(6)-C(13)	0.1510(3)
C(7)-C(8)	0.1398(3)
C(7)-C(10)	0.1461(3)
C(11)-H(5)	0.191(3)
C(12)-C(13)	**0.1521(3)**
C(12)-H(6)	0.102(2)
C(12)-H(7)	0.091(3)
C(13)-H(8)	0.103(2)
C(13)-H(9)	0.092(2)
C(14)-H(10)	0.098(3)
C(14)-H(11)	0.098(3)
C(14)-H(12)	0.094(4)

extracted with CH_2Cl_2 (3 × 10 mL). The combined extracts were washed with water and brine and dried ($MgSO_4$). After removal of the solvent under vacuum, the residue was chromatographed over silica gel using a mixture of petroleum–EtOAc (4:1) as eluent to afford compound **7b** (0.15 g, 71%) as colorless crystals: mp 154–155°C (lit,[12]: 150–152°C). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.43 (s, 3H, 4-CH_3), 3.47–3.56 (m, 4H, 7-CH_2, 10-CH_2), 5.88–6.00 (m, 2H, 8-H, 9-H), 6.25 (s, lH, 3-H), 7.06 (d, $J = 8.4$ Hz, lH, 5-H), 7.41 (d, $J = 8.1$ Hz, 1H, 6-H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 161.17, 152.84, 151.12, 138.89, 124.21, 123.78, 123.18, 122.76, 121.62, 117.44, 113.78, 29.63, 23.75, 18.76. MS (El) m/z (%): 212 (M^+, 100), 184 (23), 169 (15), 155 (14), 141 (9), 115 (9).

5,8-Dihydro-l-hydroxynaphthalene-2-carbaldehyde (10). A 50-mL flask containing 5,8-dihydro-l-naphthol **(9)** (3 g, 20.5 mmol), $SnCl_4$ (0.72 mL, 1.634 g, 2.05 × 3 mmol), 2,6-lutidine (2.79 mL, 20.5 × 1.16 mmol), and toluene (12 mL) was purged with argon. After the reaction mixture was stirred for 30 min, well-ground paraformaldehyde (1.5 g, 20.5 × 2.5 mmol) was added. The mixture was stirred for 10 h at 95–100°C, and then it was allowed to cool to room temperature. The solution was acidified to pH < 2 with 2.0 M aqueous HCl and extracted with ether (3 × 30 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, and the solvent was removed under the reduced pressure. The residue was purified by flash column chromatography (silica gel, hexane–ethyl acetate, 10:1) to give **10** as a yellow solid (2.14 g, 60%): mp 43–45°C. IR (neat): 3033, 2861, 1635, 1497, 1426, 1310, 1221, 1085, 983, 740 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 3.28–3.32 (m, 2H, 8-H), 3.39–3.45 (m, 2H, 5-H), 5.82–5.88 (m, 1H, 7-H), 5.91–5.98 (m, 1H, 6-H), 6.76 (d, $J = 8.1$ Hz, 1H, 4-H), 7.32 (d, $J = 8.1$ Hz, 1H, 3-H), 9.81 (s, 1H, 1-OH), 11.44 (s, 1H, 2-CHO). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 196.08, 159.55, 144.29, 130.49, 124.11, 123.21, 122.96, 119.97, 117.96, 30.27, 23.27. MS (EI) m/z (%): 174 (M^+, 1.69), 169 (65.54), 147 (17.02), 119 (18.17), 97 (44.44), 69 (100.00), 59 (16.87), 45 (18.81). Anal. calcd. for $C_{11}H_{10}O_2$: C, 75.84; H, 5.79, found: C, 75.54 H, 5.96.

7,10-Dihydrobenzo[*h*]coumarin (7a). A drop concentrated H_2SO_4 was added to a flask containing **10** (0.31 g, 1.78 mmol), acetic anhydride (0.53 g, 0.5 mL, 5.2 mmol), and NaOAc (0.21 g, 2.56 mmol). The mixture was heated at 160°C for 8 h. After cooling to room temperature, the solution was poured into water (20 mL), extracted with ether (3 × 20 mL), and dried over anhydrous Na_2SO_4. Product **7a** was obtained as a yellow solid after purification by chromatography on a silica-gel column (hexane–acetate, 6:1) (0.117 g, 33%): mp 162–164°C. ^1H NMR (300 MHz, $CDCl_3$)δ 3.46–3.55 (m, 4H, 7-H, 10-H), 5.90–6.01 (m, 2H, 8-H, 9-H), 6.38 (d, $J = 9.6$ Hz, 1H, 3-H), 7.05 (d, $J = 7.8$ Hz, 1H, 6-H), 7.29 (d, $J = 7.8$ Hz, 1H, 5-H), 7.69 (d, $J = 9.6$ Hz, 1H, 4-H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 161.20, 151.64, 143.81, 139.08, 124.95, 124.51, 123.57, 123.24, 122.66, 116.31, 115.10, 29.68, 23.50. MS (El) m/z (%): 198 (M^+, 100.00), 197 (25.26), 170 (33.09), 169 (28.41), 141 (62.12), 115 (39.71). HRMS calcd. mass for $C_{13}H_{10}O_2$:198.0681, found 198.0662.

5,6,7,8-Tetrahydro-1-naphthol (14). Compound **14** was prepared from **8** following the literature procedure[16] as white needles (yield, 74%): mp 66–68°C (lit.[21]: 67–69°C). ^1H NMR (300 MHz, $CDCl_3$) δ 1.75–1.87 (m, 4H, 6-H, 7-H), 2.64 (t, $J = 6.0$ Hz, 2H, 8-H), 2.75 (t, $J = 6.5$ Hz, 2H, 5-H), 4.71 (s, 1H, 1-OH), 6.60 (d, $J = 7.8$ Hz, 1H, 2-H), 6.68 (d, J = 7.8 Hz, 1H, 4-H), 6.99 (t, $J = 7.8$ Hz, 1H, 3-H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 153.34, 142.21, 138.90, 125.93, 123.29, 121.52, 111.72, 29.53, 22.72, 22.70, 22.69.

7,8,9,10-tetrahydrobenzo[*h*]coumarin (15a). Compound **15a** was synthesized from **14** following a modified literature procedure.[17] A well-ground mixture of 5,6,7,8-tetrahydro-l-naphthol **(14)** (3 g, 20.2 mmol) and malic acid (4.2 g, 31.3 mmol) was added to a hot solution of concentrated sulfuric acid (10 mL) in acetic acid (5 mL). The mixture was stirred and kept at 130°C for 6 h, and then it was allowed to cool to room temperature and poured carefully onto ice water (50 mL) while it was stirred vigorously for 30 min. The aqueous solution was extracted with ethyl acetate (3×30 mL), and the combined organic fractions were washed with H_2O, saturated $NaHCO_3$ (aq.), and brine and dried over anhydrous $MgSO_4$. After the removal of the solvent, the residue was submitted to flash-column chromatography (silica gel, petroleum-ethyl acetate, 5:1) to afford **15a** as white needles (2.42 g, 60%): mp 150–152°C (lit.[17]: 147–148°C). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.83–1.85 (m, 4H, 8-H, 9-H), 2.84–2.93 (m, 4H, 7-H, 10-H), 6.35 (d, $J = 9.3$ Hz, 1H, 3-H), 7.01 (d, $J = 8.1$ Hz, 1H, 6-H), 7.21 (d, $J = 8.1$ Hz, 1H, 5-H), 7.66 (d, $J = 9.3$ Hz, 1H, 4-H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 161.40, 152.17, 143.92, 142.46, 125.52, 125.25, 124.33, 116.09, 114.92, 29.92, 22.48, 22.43, 22.04. MS (El) m/z (%): 200 (M^+, 100.00), 172 (62.91), 144 (43.73), 128 (17.97), 115 (24.28). HRMS calcd. mass for $C_{13}H_{12}O_2$:200.0837, found 200.0838.

9,10-Dihydro-8*H*-benzo[*h*]coumarin-7-one (16a) and 8,9-dihydro-7*H*-benzo[*h*]coumarin-10-one (17a). CrO_3 (1.05 g, 9 mmol) in H_2O (0.4 mL) and HOAc (2.5 mL) were dropwise added to a flask containing 7,8,9,10-tetrahydrobenzo[*h*]coumarin **(15a)** (0.6 g, 3 mmol) in 4.5 mL of acetic acid while stirring in an ice bath. After addition, the cooling bath was removed and the solution was stirred for 72 h. The mixture was neutralized with 2.0 M aqueous NaOH and extracted with CH_2Cl_2 (3×30 mL). The combined organic layers were washed with H_2O (3×10 mL) and brine and dried over anhydrous Na_2SO_4. After removal of the solvent under the reduced pressure, the residue was purified by column chromatography on silica gel (hexane–ethyl acetate, 5:1) to give the major product **16a** as a white solid (0.27 g, 42%) and the minor product **17a** as a yellow solid (0.14 g, 22%). **16a**: mp 236–238°C. IR (KBr): 3081, 2951, 2878, 1727, 1681, 1482, 1282, 1106, 968, 906, 865, 853 cm^{-1}. H NMR (300 MHz, $CDCl_3$) δ 2.18–2.26 (m, 2H, 9-H), 2.73 (t, $J = 6.8$ Hz, 2H, 8-H), 3.18 (t, $J = 6.2$ Hz, 2H, 10-H), 6.54 (d, $J = 9.5$ Hz, 1H, 3-H), 7.44 (d, $J = 8.1$ Hz, 1H, 5-H), 7.74 (d, $J = 9.5$ Hz, 1H, 4-H), 7.97 (d, $J = 8.1$ Hz, 1H, 6-H). MS (EI) m/z (%): 214 (M^+, 100.00), 186 (98.17), 158 (65.13), 130 (47.62), 102 (37.78). HRMS calcd. mass for $C_{13}H_{10}O_3$:214.0630; found 214.0625. **17a**: mp 169–171°C. IR (KBr): 3059, 2919, 1728, 1697, 1621, 1594, 1550, 1426, 1305, 1287, 1189, 1175, 1133, 934, 879, 841, 779 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.11–2.20 (m, 2H, 8-H), 2.73 (t, $J = 6.6$ Hz, 2H, 9-H), 3.06 (t, $J = 6.0$ Hz, 2H, 7-H), 6.44 (d, $J = 9.6$ Hz, 1H, 3-H), 7.19 (d, $J = 8.1$ Hz, 1H, 6-H), 7.56 (d, $J = 7.8$ Hz, 1H, 5-H), 7.68 (d, $J = 9.3$ Hz, 1H, 4-H). MS (EI) m/z (%): 214 (M^+, 66.23), 186 (100.00), 158 (22.16),

130 (44.43), 102 (30.00). HRMS (MALDI-DHB) calcd. mass for $C_{13}H_{10}O_3$ $[M^+ + Na]$: 237.0522; found 237.0496.

10-Hydroxy-7,8,9,10-tetrahydrobenzo[*h*]coumarin (18a). $NaBH_4$ (24 mg, 0.63 mmol) was added to a flask containing **17a** (119 mg, 0.56 mmol) and methanol (4 mL). After stirring at rt for 1 h, the solvent was removed under vacuum, and the residue was purified on a silica-gel column (hexane–ethyl acetate, 1:1) to give **18a** as a white solid (80 mg, 66%): mp 123–125°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.79–1.94 (m, 2H, 8-H), 1.99–2.07 (m, 1H, 9-H), 2.11–2.18 (m, 1H, 9-H), 2.77–2.83 (m, 1H, 10-OH), 2.88–2.91 (m, 1H, 7-H), 2.96–2.97 (m, 1H, 7-H), 5.34 (br, 1H, 10-H), 6.37 (d, $J = 9.3$ Hz, 1H, 3-H), 7.06 (d, $J = 8.1$ Hz, 1H, 6-H), 7.32 (d, $J = 7.8$ Hz, 1H, 5-H), 7.69 (d, $J = 9.6$ Hz, 1H, 4-H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 160.67, 152.95, 143.97, 142.88, 126.62, 126.52, 125.46, 116.58, 115.05, 61.24, 30.61, 29.99, 17.61. MS (EI) m/z (%): 216 (M^+, 46.27), 198 (69.67), 188 (22.53), 160 (100.00), 131 (41.77), 115 (33.12), 77 (26.49). HRMS calcd. mass for $C_{13}H_{12}O_3$:216.0786;found 216.0781.

7,8-Dihydrobenzo[*h*]coumarin (5a). A suspension of **18a** (490 mg, 2.27 mmol) in aqueous H_2SO_4 (2%, 13 mL) was refluxed for 6 h under stirring. After cooling to room temperature, the mixture was extracted with ethyl acetate (3 × 20 mL), and the combined organic fractions were washed with H_2O, saturated $NaHCO_3$ (aq.), and brine and dried over anhydrous Na_2SO_4. After removal of the solvent under the reduced pressure, the residue was purified by column chromatography on silica gel (petroleum–ethyl acetate, 1:1) to provide product **5a** as a white solid (340 mg, 76%): mp 99–101°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.32–2.41 (m, 2H, 8-H), 2.87 (t, $J = 8.4$ Hz, 2H, 7-H), 6.17–6.23 (m, 2H, 9-H), 6.34 (d, $J = 9.3$ Hz, 1H, 3-H), 7.01–7.07 (m, 2H, 6-H, 10-H), 7.22 (d, $J = 7.8$ Hz, 1H, 5-H), 7.65 (d, $J = 9.6$ Hz, 1H, 4-H). MS (EI) m/z (%): 198 (M^+, 100.00), 197 (29.06), 170 (31.83), 169 (28.43), 141 (56.68) 139 (20.34), 115 (35.71). HRMS (MALDI-DHB) calcd. mass for $C_{13}H_{10}O_2$ $[M^+ + Na]$: 221.0573; found 221.0574.

7-Hydroxy-7,8,9,10-tetrahydrobenzo[*h*]coumarin (19a). Following the same procedure for the preparation of **18a**, **19a** was obtained from **16a** as a white solid (yield, 79%): mp 160–162°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.80–1.95 (m, 3H, 9-H, 7-OH), 2.00–2.10 (m, 2H, 8-H), 2.80–2.91 (m, 1H, 10-H), 2.96–3.06 (m, 1H, 10-H), 4.84–4.86 (m, 1H, 7-H), 6.41 (d, $J = 9.6$ Hz, 1H, 3-H), 7.35 (d, $J = 7.8$ Hz, 1H, 6-H), 7.43 (d, $J = 7.5$ Hz, 1H, 5-H), 7.69 (d, $J = 10.2$ Hz, 1H, 4-H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 161.14, 151.55, 143.68, 143.29, 125.60, 125.07, 124.28, 117.28, 115.90, 67.90, 31.74, 22.47, 17.92. MS (EI) m/z (%): 216 (M^+, 88.56), 198 (100.00), 188 (90.90), 159 (65.85), 131 (39.89), 115 (34.58), 77 (31.15). HRMS calcd. mass for $C_{13}H_{12}O_3$:216.0786; found 216.0787.

Single crystal X-ray diffraction data of 19a. Crystal with dimensions of 0.511 mm × 0.267 mm × 0.083 mm for compound **19a** was selected and

mounted on a Bruker Smart CCD diffractometer with graphite monochromatized Mo $K\alpha$ radiation ($\lambda = 0.071073$ nm). Diffraction data were collected using ω-2θ scans at room temperature (293 K). A perspective view of the structure is depicted in Fig. 2. Empirical formula: $C_{13}H_{12}O_3$. Formula weight: 216.23. Crystal system: monoclinic. Space group: Cc. Unit cell dimensions: $a = 2.5765$ (3) nm, $b = 0.72986$ (8) nm, $c = 2.2733$ (3) nm, $\beta = 107.486(4)^\circ$. $V = 4.0773$ (8) nm^3. Theta range for data collection is from 1.66 to 28.43°. $Z = 16$. $Dc = 1.409\ g/cm^3$. $F(000) = 1824$. Refinement method: full-matrix least-squares on F^2. Goodness of fit on F^2: 0.906. Final R indices [$I > 2\sigma(I)$]: 0.0691, 0.1549. R indices (all data): 0.0957, 0.1718. Largest did peak and hole: 0.295 and $-338\ e/nm^3$.

9,10-Dihydrobenzo[*h*]coumarin (6a). Following the same procedure for the preparation of **5a**, **6a** was obtained from **19a** as a white solid (yield, 99%): mp 122–124°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.35–2.43 (m, 2H, 9-H), 3.04 (t, $J = 8.7$Hz, 2H, 10-H), 6.18–6.24 (m, 1H, 8-H), 6.34 (d, $J = 9.3$ Hz, 1H, 3-H), 6.51 (d, $J = 13.2$ Hz, 1H, 7-H), 6.96 (d, $J = 8.1$ Hz, 1H, 6-H), 7.26 (d, $J = 7.5$ Hz, 1H, 5-H), 7.65 (d, $J = 9.3$ Hz, 1H, 4-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.20, 150.92, 143.76, 137.77, 132.00, 126.94, 125.65, 122.29, 117.82, 115.05, 22.15, 19.01. MS (EI) m/z (%): 198 (M^+, 100.00), 170 (31.27), 155 (12.43), 141 (63.31), 128 (5.61), 115 (49.31). HRMS (MALDI-DHB) calcd. mass for $C_{13}H_{11}O_2$ [$M^{+1} + H$]: 199.0754; found 199.0731.

4-Methyl-7,8,9,10-tetrahydrobenzo[*h*]coumarin (15b). $POCl_3$ (1.9 mL) was added to a flask containing **14** (3.0 g, 23 mmol) and ethyl acetoacetate (3.0 g, 23 mmol). The mixture was heated at 100°C for 18 h. After cooling to room temperature, the solution was neutralized with saturated Na_2CO_3 (aq.) and extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed with water (20 mL) and brine (20 mL), and dried over anhydrous $MgSO_4$. After the removal of the solvent under the reduced pressure, the residue was submitted to silica-gel chromatography separation (petroleum–ethyl acetate, 5:1) to afford product **15b** as a white solid (3.0 g, 70%). Recrystallization from petroleum–ethyl acetate yielded white needles: mp 114–116°C (lit.[17]: 119–120°C). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.79–1.85 (m, 4H, 8-H, 9-H), 2.40 (s, 3H, 4-CH_3), 2.82–2.91 (m, 4H, 7-H, 10-H), 6.20 (s, 1H, 3-H), 7.01 (d, $J = 8.1$ Hz, 1H, 6-H), 7.32 (d, $J = 8.1$ Hz, 1H, 5-H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 161.22, 152.84, 151.48, 142.12, 125.43, 124.85, 120.89, 117.05, 113.46, 29.74, 22.61, 22.33, 22.06, 18.68. MS (EI) m/z (%): 214 (M^+, 100.00), 186 (100.00), 171 (39.81), 158 (100.00), 128 (43.27), 115 (45.05). Anal. calcd. for $C_{14}H_{14}O_2$: C, 78.48; H, 6.59. found: C, 78.32; H, 6.91.

4-Methyl-9,10-dihydro-8*H*-benzo[*h*]coumarin-7-one (16b) and 4-methyl-8,9-dihydro-7*H*-benzo[*h*]coumarin-10-one (17b). Following the same procedure for the preparation of **16a** and **17a**, **16b** and **17b** were obtained from **15b** as a white solid (yield, 51%) and a yellow solid (yield, 9%), respectively. **16b**: mp 226–228°C. ^{1}H NMR (300 MHz, $CDCl_3$)

δ 2.17–2.25 (m, 2H, 9-H), 2.49 (s, 3H, 4-CH_3), 2.72 (t, $J = 6.3$ Hz, 2H, 8-H), 3.18 (t, $J = 6.3$ Hz, 2H, 10-H), 6.40 (s, 1H, 3-H), 7.56 (d, $J = 8.4$ Hz, 1H, 5-H), 7.98 (d, $J = 8.4$ Hz, 1H, 6-H). ^{13}C NMR ($CDC1_3$, 75 MHz) δ 197.30, 160.16, 152.09, 150.77, 134.44, 132.66, 122.84, 122.15, 122.00, 116.62, 38.51, 22.53, 22.11, 18.80. MS (EI) m/z (%): 228 (M^+, 100.00), 213 (27.49), 200 (100.00), 172 (84.19), 144 (44.86), 115 (59.67). HRMS calcd. mass for $C_{14}H_{12}O_3$ 228.0786; found 228.0778. **17b**: mp 147–149°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.11–2.19 (m, 2H, 8-H), 2.44 (s, 3H, 4-CH3), 2.73 (t, $J = 6.6$ Hz, 2H, 9-H), 3.05 (t, $J = 6.0$ Hz, 2H, 7-H), 6.31 (s, 1H, 3-H), 7.20 (d, $J = 8.4$ Hz, 1H, 6-H), 7.68 (d, $J = 8.4$ Hz, 1H, 5-H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 195.27, 159.81, 152.65, 151.59, 149.39, 128.53, 124.32, 121.36, 118.96, 114.72, 40.47, 30.70, 22.57, 19.00. MS (EI) m/z (%): 228 (M^+, 74.22), 200 (100.00), 172 (29.95), 144 (52.17), 115 (69.67). HRMS (MALDI-DHB) calcd. mass for $C_{14}H_{12}O_3$ [$M^{+I} + Na$] 251.0679; found 251.0675.

10-Hydroxy-4-methyl-7,8,9,10-tetrahydrobenzo[*h*]coumarin (18b). Following the same procedure for the preparation of **18a**, **18b** was obtained from **17b** as a white solid (yield, 94%): mp 158–160°C. ^{1}H NMR (300 MHz, $CDC1_3$) δ 1.83–2.20 (m, 4H, 8-H, 9-H), 2.43 (s, 3H, 4-CH3), 2.77–2.95 (m, 3H, 7-H, 10-OH), 5.33–5.35 (m, 1H, 10-H), 6.25 (s, 1H, 3-H), 7.08 (d, $J = 8.4$ Hz, 1H, 6-H), 7.45 (d, $J = 8.4$ Hz, 1H, 5-H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 160.57, 153.04, 152.30, 142.60, 126.63, 125.11, 123.16, 117.63, 113.58, 61.26, 30.59, 29.85, 18.78, 17.52. MS (EI) m/z (%): 230 (M^+, 49.37), 212 (73.32), 202 (21.45), 174 (100.00), 146 (47.31), 145 (44.92), 128 (31.54), 115 (72.79), 91 (28.31), 77 (33.10), 39 (40.58). HRMS (MALDI-DHB) calcd. mass for $C_{14}H_{14}O_3$ [$M^{+1} + Na$]: 253.0835; found 253.0848.

4-Methyl-7,8-dihydrobenzo[*h*]coumarin (5b). Following the same procedure for the preparation of **5a**, **5b** was obtained from **18b** as a white solid (yield, 90%): mp 76–78°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.33–2.43 (m, 5H, 4-CH3, 8-H), 2.88 (t, $J = 8.1$ Hz, 2H, 7-H), 6.17–6.24 (m, 2H, 3-H, 9-H), 7.05–7.12 (m, 2H, 6-H, 10-H), 7.36 (d, $J = 7.5$ Hz, 1H, 5-H). MS (EI) m/z (%): 212 (M^+, 57.14), 182 (31.19), 169 (15.08), 149 (81.28), 85 (55.12), 71 (72.46), 57 (100.00), 43 (76.56), 41 (44.84). HRMS calcd. mass for $C_{14}H_{12}O_2$:212.0832; found 212.0854.

7-hydroxy-4-methyl-7,8,9,10-tetrahydrobenzo[*h*]coumarin (19b). Following the same procedure for the preparation of **18a**, **19b** was obtained from **16b** as a white solid (yield, 74%): mp 195–197°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 81.84–1.95 (m, 3H, 9-H, 7-OH), 2.00–2.09 (m, 2H, 8-H), 2.43 (s, 3H, 4-CH3), 2.86–2.91 (m, 1H, 10-H), 2.96–3.04 (m, 1H, 10-H), 4.84–4.86 (m, 1H, 7-H), 6.27 (s, 1H, 3-H), 7.44 (d, $J = 8.4$ Hz, 1H, 6-H), 7.48 (d, $J = 8.4$ Hz, 1H, 5-H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 161.09, 152.68, 151.00, 143.14, 125.68, 123.94, 121.70, 118.38, 114.42, 67.90, 31.73, 22.69, 18.75, 18.01. MS (EI) m/z (%): 230 (M^+, 91.53), 212 (98.91), 202 (78.65), 173 (93.53), 145 (49.32), 128 (42.05), 115 (100.00), 91

(45.74), 77 (45.35). HRMS calcd. mass for $C_{14}H_{14}O_3$: 230.0943; found 230.0929.

4-Methyl-9,10-dihydrobenzo[h]coumarin (6b). Following the same procedure for the preparation of **5a**, **6b** was obtained from **19b** as a white solid (yield, 66%): mp 150–152°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.39–2.43 (m, 5H, 4-CH_3, 9-H), 3.05 (t, $J = 8.4$ Hz, 2H, 10-H), 6.20–6.24 (m, 2H, 3-H, 8-H), 6.49–6.53 (m, 1H, 7-H), 6.99 (d, $J = 8.4$ Hz, 1H, 6-H), 7.40 (d, $J = 7.5$ Hz, I H, 5-H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 161.14, 152.63, 150.41, 137.61, 131.84, 126.85, 122.33, 122.23, 121.96, 118.87, 113.81, 22.24, 19.20, 18.72. MS (EI) m/z (%): 212 (M^+, 100.00), 184 (41.62), 169 (28.59), 155 (34.19), 128 (32.10), 115 (46.35). HRMS calcd. mass for $C_{14}H_{12}O_2$: 212.0832; found 212.0833.

Single crystal X-ray diffraction data of 6b. A crystal with dimensions of 0.566 mm × 0.248 mm × 0.087 mm for compound **6b** was selected and mounted on a Bruker Smart CCD diffractometer with graphite monochromatized Mo $K\alpha$ radiation ($\lambda = 0.071073$ nm). Diffraction data were collected using ω-2θ scans at room temperature (293 K). A perspective view of the structure is depicted in Fig. 3 and the selected bond lengths are listed in Table 3. Empirical formula: $C_{14}H_{12}O_2$. Formula weight: 212.24. Crystal system: monoclinic. Space group: $P2(1)/c$. Unit cell dimensions: $a = 0.73063$ (11) nm, $b = 2.0333$ (3) nm, $c = 0.73063$ (11) nm, $(3 = 96.507(3)^\circ$. $V = 1.0784$ (3) nm^3. Theta range for data collection is from 2.98 to 25.99°. $Z = 4$. $Dc = 1.307$ g/cm^3. $F(000) = 448$. Refinement method: full-matrix least-squares on F^2. Goodness of fit on F^2: 0.975. Final R indices [$I > 2\sigma(I)$]: 0.0596, 0.1431. R indices (all data): 0.0839, 0.1556. Largest diff. peak and hole: 0.231 and −237 e/nm^3.

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