Supporting Information

Synthetic Studies of Neoclerodane Diterpenes from *Salvia divinorum*: Exploration of the 1-Position

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Contents of Supporting Information

Experimental Section

Unless otherwise indicated, all reagents were purchased from commercial suppliers and were used without further purification. All melting points were determined on a Thomas – Hoover capillary melting apparatus and are uncorrected. The ^{1}H NMR and ^{13}C NMR spectra were recorded at 300 MHz on a Bruker Avance-300 spectrometer or on a Bruker AMX-600 spectrometer using $CDCl_3$ as solvent, δ values in ppm (TMS as internal standard), and *J* (Hz) assignments of ^{1}H resonance coupling. Thin-layer chromatography (TLC) was performed on 0.25 mm Analtech GHLF silica gel plates. Spots on TLC were visualized with vanillin/H_2SO_4 in EtOH. Silica Gel (32-63 μ particle size) from Bodman Industries (Atlanta, GA) was used for column chromatography. Analytical HPLC was carried out on an Agilent 1100 Series Capillary HPLC system with diode array detector at a flow rate of 3 mL/min using an Agilent Eclipse XDB-C18 column (4.6 × 150 mm, 5 μm). Peaks were detected at 209, 214 and 254 nm. Elemental analyses were performed by Atlantic Microlabs, Norcross, GA.

1α-Hydroxysalvinorin A (4a).[6,16] A mixture of **2a** (1.78 g, 4.11 mmol) and THF (40 mL) was magnetically stirred at gentle reflux for 5 min. To this was added an aqueous solution of $NaBH_4$ (760 mg, 20.09 mmol in 6 mL) in portions. After stirring at reflux for 10 min following the first addition, a second addition of aqueous $NaBH_4$ was made (152 mg, 4.02 mmol in 0.7 mL) and reflux was continued for 5 min. The reaction mixture was immediately chilled in an ice bath and progress of the reaction was checked by TLC. The reaction was mixture diluted with EtOAc (50 mL) and extracted with saturated sodium chloride (2 × 30 mL). The aqueous phases were extracted, in turn, with EtOAc (2 × 15 mL) and the combined organic phases were dried (Na_2SO_4) and evaporated to a foam. The crude product was purified by column chromatography (CH_2Cl_2 with increasing amounts of EtOAc) to give 1.34 g of **4a** (77%) as a white solid, mp 110-111° C. The ^{1}H and ^{13}C spectra of **4a** were in agreement with previously reported data.[16] HPLC (25% CH_3CN/ 75% H_2O) t_R = 10.3 min; Purity = 99.04%.

1α-Hydroxyherkinorin (4b). A mixture of **2b**[11] (100 mg, 0.20 mmol) and THF (8 mL) was magnetically stirred at gentle reflux for 5 min. To this was added an aqueous solution of $NaBH_4$ (38 mg, 1.00 mmol in 4 mL) slowly. After stirring at reflux for 10 min following the first addition, a second addition of aqueous $NaBH_4$ was made (8 mg, 0.21 mmol in 1 mL) and reflux was continued for 5 min. The reaction mixture was immediately chilled in an ice bath and progress of the reaction was checked by TLC. The reaction was mixture diluted with EtOAc (30 mL) and extracted with saturated sodium chloride (2 × 30 mL). The aqueous phases were extracted, in turn, with EtOAc (2 × 15 mL) and the combined organic phases were dried (Na_2SO_4) and evaporated to a foam. The crude product was purified by column chromatography (Hexanes/EtOAc, 6:4) to give 45 mg of **4b** (45%) as a white solid, mp 125-127 °C; ^{1}H NMR ($CDCl_3$): δ 1.36 (dd, *J* = 3.3, 13.5 Hz, 1H); 1.43 (s, 3H); 1.46 (s, 3H); 1.73 (m, 3H); 1.81 (dd, *J* = 3.0, 6.3 Hz, 1H); 1.93 (dt, *J* = 2.7, 3.6, 12.9 Hz, 1H); 2.11 (m, 3H); 2.28 (dd, *J* = 2.7, 13.2 Hz, 1H); 2.43 (dd, *J* = 5.4, 13.2 Hz, 1H); 2.50 (dd, *J* = 12.6, 25.8 Hz, 1H); 3.69 (s, 3H); 4.45 (br.s, 1H); 4.95 (ddd, *J* = 3.3, 4.5, 12.3 Hz, 1H); 5.53 (dd, *J* = 5.4, 11.4 Hz, 1H); 6.41 (dd, *J* = 0.9, 1.8 Hz, 1H); 7.41 (dd, *J* = 1.5, 1.8 Hz, 1H); 7.44 (dd, *J* = 0.9, 1.5 Hz, 1H); 7.45 (m, 2H); 7.59 (tt, *J* = 1.2, 2.1, 7.2 Hz, 1H); 8.01 (m, 2H); HRMS *m*/*z* 497.2181 (calcd for $C_{28}H_{33}O_8$, 497.2175); HPLC (40% CH_3CN/ 60% H_2O) t_R = 9.2 min; Purity = 98.78%.

1α-Mesyloxysalvinorin A (5). To a stirred solution of **4** (868 mg, 2.00 mmol) in dry acetonitrile (10 mL) under argon was added DMAP (1.10 g, 9.00 mmol) followed by methanesulfonic anhydride (696 mg, 4.00 mmol). The reaction mixture was heated at reflux for 1 h. After cooling to room temperature, the reaction mixture was diluted with ethyl acetate (40 mL) and extracted with a mixture of 1M phosphoric acid and saturated NaCl (40 mL, 1:1) followed by a mixture of saturated $NaHCO_3$ and saturated NaCl (30 mL, 1:2). The aqueous phases were extracted, in turn, with ethyl acetate (2 × 20 mL), and the combined organic phases were dried (Na_2SO_4) and evaporated to give 1.01 g (99%) of **5** as a foam. A sample was crystallized from CH_2Cl_2 /EtOH to give pure **5**, mp 190-194 °C (dec.); ^{1}H NMR ($CDCl_3$): δ 1.26 (d, *J* = 1.8 Hz, 1H); 1.32 (s, 3H); 1.43 (s, 3H); 1.58 (s, 3H); 1.69 (m, 2H); 1.89 (m, 2H);

2.08 (d, *J* = 2.7 Hz, 1H); 2.11 (s, 3H); 2.16 (m, 1H); 2.30 (m, 1H); 2.31 (s, 1H); 2.49 (dd, *J* = 5.4, 12.9 Hz, 1H); 3.23 (s, 3H); 3.71 (s, 3H); 4.80 (m, 1H); 5.36 (br s, 1H); 5.56 (dd, *J* = 5.4, 11.4 Hz, 1H); 6.42 (dd, *J* = 0.9, 1.5 Hz, 1H); 7.42 (dd, *J* = 1.5, 1.8 Hz, 1H); 7.47 (dd, *J* = 0.9, 1.8 Hz, 1H); Anal. ($C_{24}H_{32}O_{10}S$): C, H, O.

1α-Mesyloxysalvinorin B (6). A mixture of crude **5** (1.28 g, 2.50 mmol) was stirred with DCM (2 mL) under argon and a solution of 1 drop of 50% aqueous sodium hydroxide in 8 mL of methanol was added quickly in portions. Crystals of starting material that initially appeared dissolved within 1-2 min and a heavy precipitate of product began to form. The reaction mixture was chilled to -10° C and after 1 h was filtered to give 844 mg (70%) of **6** as a crystalline product. A sample was recrystallized from CH_2Cl_2/EtOH to give pure **6**, mp 160-162 °C (dec.); ^{1}H NMR ($CDCl_3$): δ 1.18 (s, 1H); 1.31 (s, 3H); 1.43 (s, 3H); 1.57 (s, 3H); 1.65 (m, 2H); 1.86 (m, 2H); 2.05 (m, 1H); 2.16 (m, 1H); 2.20 (s, 1H); 2.48 (d, *J* = 5.4 Hz, 1H); 2.57 (dd, *J* = 5.4, 13.2 Hz, 1H); 3.26 (s, 3H); 3.71 (s, 3H); 5.34 (br s, 1H); 5.55 (dd, *J* = 5.4, 11.7 Hz, 1H); 6.41 (d, *J* = 1.2 Hz, 1H); 7.42 (dd, *J* = 1.5, 1.8 Hz, 1H); 7.46 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 16.17, 18.17, 18.72, 28.79, 37.39, 37.48, 39.88, 41.04, 43.90, 51.95, 53.12, 55.04, 55.23, 71.41, 71.94, 79.89, 108.61, 125.56, 139.75, 144.03, 172.47, 173.83.

Elimination of 6. A stirred solution of DMAP (122 mg, 1.00 mmol) in DMSO (3 mL) under argon was rapidly heated to 170° C. After 3 min, **6** (240 mg, 0.51 mmol) was added and stirring was continued for 10 min. The rapidly cooled reaction mixture was poured into a mixture of saturated aqueous NaCl (40 mL) and 1M phosphoric acid (7 mL). The resulting aqueous mixture was extracted with EtOAc (20 mL) and the organic phase was washed with a mixture of saturated NaCl (20 mL) and saturated $NaHCO_3$ (7 mL). The aqueous phases were extracted, in turn, with EtOAc (10 mL). The combined organic phases were dried (Na_2SO_4) and evaporated to a residue (208 mg), which was purified by column chromatography, eluting with CH_2Cl_2 containing increasing amounts of EtOAc to afford 143 mg (76%) of **7** and 43 mg (22%) of **8**.

1-Deoxo-1,10-dehydrosalvinorin B (7). mp 121-122 °C (EtOAc/hexanes); ^{1}H NMR ($CDCl_3$): δ 1.34 (s, 3H); 1.35 (s, 3H); 1.43 (dd, *J* = 3.6, 13.5 Hz, 1H); 1.91 (m, 4H); 2.13 (m, 1H); 2.18 (m, 1H); 2.23 (dd, *J* = 3.7, 6.5 Hz, 1H); 2.42 (d, *J* = 13.5 Hz, 1H); 2.44 (dd, *J* = 6.0, 13.5 Hz, 1H); 4.35 (m, 1H); 5.50 (d, *J* = 2.1 Hz, 1H); 5.55 (dd, *J* = 5.4, 12.0 Hz, 1H); 6.43 (dd, *J* = 0.9, 1.8 Hz, 1H); 7.43 (dd, *J* = 1.5, 1.8 Hz, 1H); 7.47 (dd, *J* = 0.9, 1.5 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 18.74, 21.98, 23.26, 31.14, 37.43, 38.58, 38.96, 43.15, 50.24, 51.81, 52.88, 67.53, 72.05, 108.67, 124.24, 125.79, 139.67, 144.04, 150.15, 172.47, 173.50.

2-keto-1-deoxosalvinorin A (8). mp 227-228 °C (EtOAc/hexanes); ^{1}H NMR ($CDCl_3$): δ 1.12 (s, 3H); 1.26 (s, 3H); 1.41 (dd, *J* = 3.9, 12.9 Hz, 1H); 1.49 (dd, *J* = 6.6, 8.1Hz, 1H); 1.66 (m, 2H); 1.82 (dt, *J* = 3.0, 13.5 Hz, 1H); 2.15 (dd, *J* = 3.0, 6.0 Hz, 1H); 2.19 (dd, *J* = 3.0, 5.4 Hz, 1H); 2.23 (dd, *J* = 5.4, 13.5 Hz, 1H); 2.40 (s, 1H); 2.47 (m, 3H); 2.81 (dd, *J* = 12.6, 15.0 Hz, 1H); 3.71 (s, 3H); 5.48 (dd, *J* = 5.4, 11.4 Hz; 1H); 6.39 (dd, *J* = 1.5, 1.5 Hz, 1H); 7.42 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 14.50, 14.52, 18.45, 36.62, 37.24, 3796, 38.23, 40.57, 43.70, 51.15, 52.09, 53.97, 55.13, 71.87108.56, 125.69, 139.55, 144.14, 171.65, 172.12, 208.16.

2-Keto-1-deoxo-1,10-dehydrosalvinorin A (9). A mixture of **7** (253 mg, 0.68 mmol) and manganese dioxide (2 g) in toluene (10 mL) was heated at reflux for 20 min. This was followed by the addition of manganese dioxide (2 g), 20 min reflux, then manganese dioxide (1 g) and a further 20 min reflux. The hot mixture was filtered (filter aide) and the precipitate was washed with EtOAc. The filtrate was evaporated to give the product (198 mg, 0.53 mmol, 78%). A sample was recrystallized from EtOAc to give **9**, mp 192-194 °C; ^{1}H NMR ($CDCl_3$): δ 1.41 (s, 3H); 1.48 (s, 3H); 1.63 (dd, *J* = 0.9, 13.5 Hz, 1H); 1.90 (m, 2H); 2.02 (dd, *J* = 1.2, 10.5 Hz, 1H); 2.33 (m, 2H); 2.52 (m, 2H); 2.90 (dd, *J* = 14.4, 24 Hz, 1H); 2.93 (s, 1H); 3.73 (s, 3H); 5.58 (dd, *J* = 5.4, 11.4 Hz, 1H); 5.94 (s, 1H); 6.42 (dd, *J* = 0.9, 1.8 Hz, 1H); 7.44 (dd, *J* = 1.8, 1.8 Hz, 1H); 7.47 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 18.22, 22.05, 22.51, 36.60,

37.51, 38.16, 39.86, 41.90, 49.19, 52.19, 52.91, 71.66, 108.54, 123.95, 125.37, 139.72, 144.24, 171.02, 172.10, 172.13, 197.68; HPLC (32% CH_3CN/ 68% H_2O) t_R = 3.7 min; Purity = 98.31%.

1-Deoxosalvinorin B (10). A solution of **8** (51 mg, 0.14 mmol) in acetonitrile (1.5 mL) was treated with a solution of $NaBH_4$ (20 mg, 0.53 mmol) in water (0.3 mL). TLC indicated nearly complete reduction after 1 min. After 15 min, the reaction mixture was diluted with EtOAc (6 mL) and washed with saturated NaCl (2 × 10 mL). The aqueous phases were extracted, in turn, with EtOAc (2 × 5 mL), and the combined organic phases were dried (Na_2SO_4) and evaporated to a residue. Two recrystallizations from EtOAc/hexanes gave 21 mg (41%) of **10** as a white solid, mp 160-162° C; ^{1}H NMR ($CDCl_3$): δ 1.04 (dd, *J* = 2.4, 12.9 Hz, 1H); 1.08 (s, 3H); 1.10 (s, 3H); 1.27 (m, 2H); 1.43 (dd, *J* = 11.1, 12.6 Hz, 1H); 1.65 (m, 3H); 1.77 (m, 2H); 1.89 (m, 2H); 2.07 (dd, *J* = 3.9, 7.2 Hz, 1H); 2.11 (d, *J* = 1.2 Hz, 1H); 2.16 (d, *J* = 3.3 Hz, 1H); 2.32 (dd, *J* = 5.7, 13.2 Hz; 1H); 3.67 (s, 3H); 5.50 (dd, *J* = 5.4, 11.1 Hz, 1H); 6.40 (dd, *J* = 0.9, 1.5 Hz, 1H); 7.42 (dd, *J* = 1.5, 1.8 Hz, 1H); 7.44 (m, 1H); ^{13}C NMR ($CDCl_3$): δ 14.90, 15.30, 18.53, 30.69, 33.99, 36.46, 37.16, 38.29, 44.28, 51.50, 51.67, 53.33, 54.69, 70.33, 72.02, 108.62, 126.01, 139.51, 144.04, 144.55, 173.24.

1-Deoxo-1,10-dehydrosalvinorin A (11a). To a stirred solution of **4a** (291 mg, 0.67 mmol) and DMAP (488 mg, 3.99 mmol) in dry acetonitrile (6 mL) under argon was added methanesulfonic anhydride (313 mg, 1.80 mmol). The reaction was stirred at reflux for 1 h, when complete conversion to the mesylate was indicated by TLC. Trimethyphenylammonium chloride (257 mg, 1.50 mmoles) was added and the mixture was heated at reflux for 1. The solvent was removed under reduced pressure and the residue was distributed between CH_2Cl_2 (8 mL) and 1 M H_3PO_4 (35 mL). The organic phase was washed with saturated $NaHCO_3$ (20 mL), and the aqueous phases were extracted, in turn with CH_2Cl_2 (2 × 4 mL). The combined organic portion was dried (Na_2SO_4) and the solvent was removed under reduced pressure to afford a crude residue. The residue was purified by column chromatography (eluent: CH_2Cl_2/EtOAc, 9:1) to give 213 mg (76% overall) of **11a**. A portion of the product was recrystallized

from EtOAc/hexanes to give **11a**, mp 129-131° C; ^{1}H NMR ($CDCl_3$): δ 1.36 (s, 6H); 1.44 (m, 1H); 1.88 (m, 2H); 2.04 (m, 2H); 2.07 (s, 3H); 2.20 (m, 3H); 2.41 (dd, *J* = 5.4, 13.2 Hz, 1H); 2.48 (dd, *J* = 2.4, 13.8 Hz, 1H); 3.69 (s, 3H); 5.39 (dd *J* = 2.7, 7.2 Hz, 1H); 5.42 (dd, *J* = 1.8, 5.1 Hz, 1H); 5.54 (dd, *J* = 5.4, 11.7 Hz, 1H); 6.43 (dd, *J* = 0.9, 1.5 Hz, 1H); 7.43 (dd, *J* = 1.5, 1.8 Hz, 1H); 7.47 (dd, *J* = 0.9, 1.8 Hz, 1H); Anal. ($C_{23}H_{28}O_7$): C, H, O.

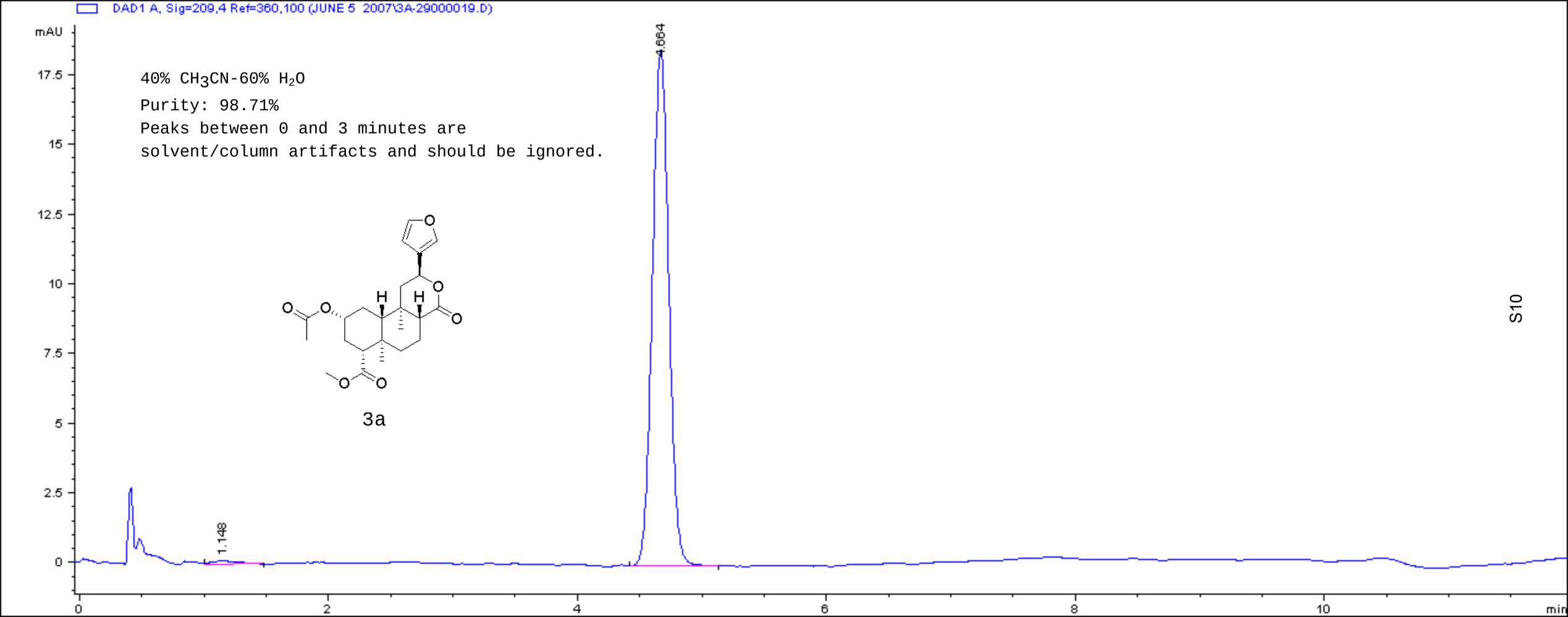
1-Deoxo-1,10-dehydroherkinorin (11b). A solution of **7** (50 mg, 0.134 mmol), benzoyl chloride (56 mg, 0.40 mmol), NEt_3 (20 mg, 0.20 mmol) and a catalytic amount of DMAP in CH_2Cl_2 (20 mL) was stirred at room temperature overnight. Absolute MeOH (15 mL) was added and the solvent was removed under reduced pressure. CH_2Cl_2 (25 mL) was added to the residue and the solution was washed with 2N HCl (3 × 30 mL), 2N NaOH (3 × 30 mL) and saturated NaCl (2 × 20 mL) and dried (Na_2SO_4). Removal of the solvent under reduced pressure to afford crude. The residue was purified by column chromatography (eluent: Hexanes/EtOAc, 7:3) to give 25 mg (40%) of **11b** as a white solid, mp 85-87 °C; ^{1}H NMR ($CDCl_3$): δ 1.38 (s, 3H); 1.41 (s, 3H); 1.49 (dd, *J* = 4.0, 13.0 Hz, 1H); 1.92 (m, 3H); 2.24 (m, 4H); 2.43 (dd, *J* = 5.4, 13.5 Hz, 1H); 2.57 (dd, *J* = 2.7, 13.2 Hz, 1H); 3.71 (s, 3H); 5.53 (dd, *J* = 5.1, 11.4 Hz, 1H); 5.57 (s, 1H); 5.66 (m, 1H); 6.43 (dd, *J* = 0.9, 1.8 Hz, 1H); 7.42 (dd, *J* = 1.5, 1.8 Hz, 1H); 7.45 (d, *J* = 0.9 Hz, 1H); 7.47 (dt *J* = 0.6, 0.9, 2.4 Hz, 2H); 7.58 (tt, *J* = 1.2, 1.5, 2.4, 7.2 Hz, 1H); 8.05 (dt, *J* = 1.5, 1.8, 6.9 Hz, 2H); HRMS (*m*/*z*): $[M+H]^+$ calcd for $C_{28}H_{30}O_7$, 478.1992; found, 478.2006; HPLC (50% CH_3CN/ 50% H_2O) t_R = 6.7 min; Purity = 98.46%.

1-Deoxoherkinorin (3b). A solution of **10** (50 mg, 0.133 mmol), benzoyl chloride (56 g, 0.40 mmol), NEt_3 (40 mg, 0.40 mmol) and a catalytic amount of DMAP in CH_2Cl_2 (20 mL) was stirred at room temperature overnight. Absolute MeOH (15 mL) was added and the solvent was removed under reduced pressure. CH_2Cl_2 (25 mL) was added to the residue and the solution was washed with 2N HCl (3 × 30 mL), 2N NaOH (3 × 30 mL) and saturated NaCl (3 × 20 mL) and dried (Na_2SO_4). Removal of the solvent under reduced pressure afforded a crude product. The residue was purified by column

chromatography (eluent: Hexanes/EtOAc, 7:3) to give 23 mg (40%) of **3b** as a white solid, mp 95-97 °C; ^{1}H NMR ($CDCl_3$): δ 1.09 (s, 3H); 1.17 (s, 3H); 1.23 (m, 1H); 1.37 (m, 1H); 1.61 (dd, *J* = 4.5, 12.6 Hz, 2H); 1.69 (m 2H); 1.78 (dt, *J* = 2.7, 2.7, 13.5 Hz, 1H); 2.04 (m, 3H); 2.16 (m, 1H); 2.27 (dd, *J* = 1.8, 12.0 Hz, 1H); 2.31 (dd, *J* = 2.7, 13.8 Hz, 1H); 3.68 (s, 3H); 5.00 (tt *J* = 5.4, 5.4, 10.8 Hz, 1H); 5.48 (dd, *J* = 5.7, 11.1 Hz, 1H); 6.41 (dd, *J* = 0.9, 1.8 Hz, 1H); 7.44 (m, 4H); 7.57 (tt, *J* = 1.2, 1.5, 2.4, 7.5 Hz, 1H); 8.04 (dt, *J* = 1.2, 2.1, 7.5 Hz, 2H); HRMS (*m*/*z*): $[M]^+$ calcd for $C_{28}H_{32}O_8$, 480.2148; found, 480.2135; HPLC (50% CH_3CN/ 50% H_2O) t_R = 6.7 min; Purity = 98.52%.

Elemental Analysis for compounds **5** and **11a**.

Cmpd	Molecular Formula	Calculated	Found
5	$C_{24}H_{32}O_{10}S$	C, 56.24; H, 6.29; O, 31.21	C, 56.04; H, 6.35; O, 30.93
11a	$C_{23}H_{28}O_{7}$	C, 66.33; H, 6.78; O, 26.89	C, 66.06; H, 6.74; O, 26.89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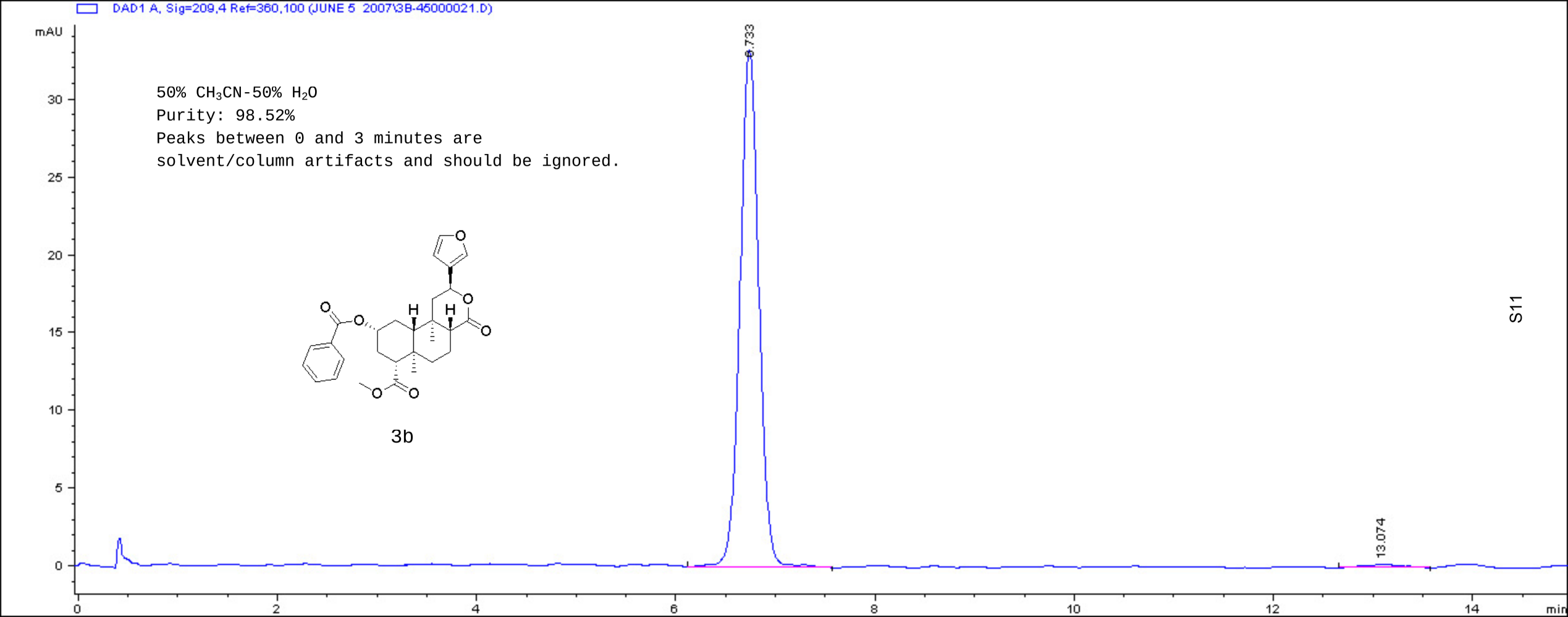
15
12.5
10
7.5
5
2.5
0
4.664
1.148
40% CH3CN-60% H2O
Purity: 98.71%
Peaks between 0 and 3 minutes are
solvent/column artifacts and should be ignored.
3a
S10
0
2
4
6
8
10
min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50% CH3CN-50% H2O
Purity: 98.52%
Peaks between 0 and 3 minutes are
solvent/column artifacts and should be ignored.
6.733
13.074
S11
min

3b

DAD1 A, Sig=209,4 Ref=360,100 (JUNE 5 2007\4A000007.D)

mAU

25% CH_3CN-75% H_2O
Purity: 99.04%
Peaks between 0 and 3 minutes are
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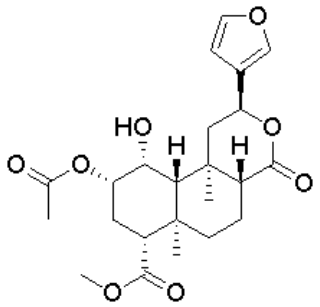

4a

8.857

10.322

S12

min

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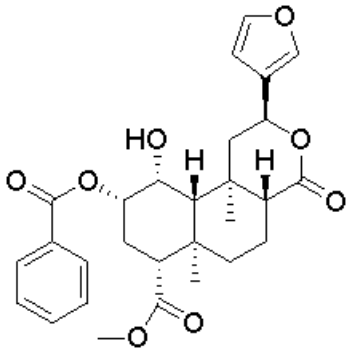
mAU

40% CH_3CN-60% H_2O
Purity: 98.78%
Peaks between 0 and 3 minutes are
solvent/column artifacts and should be ignored.

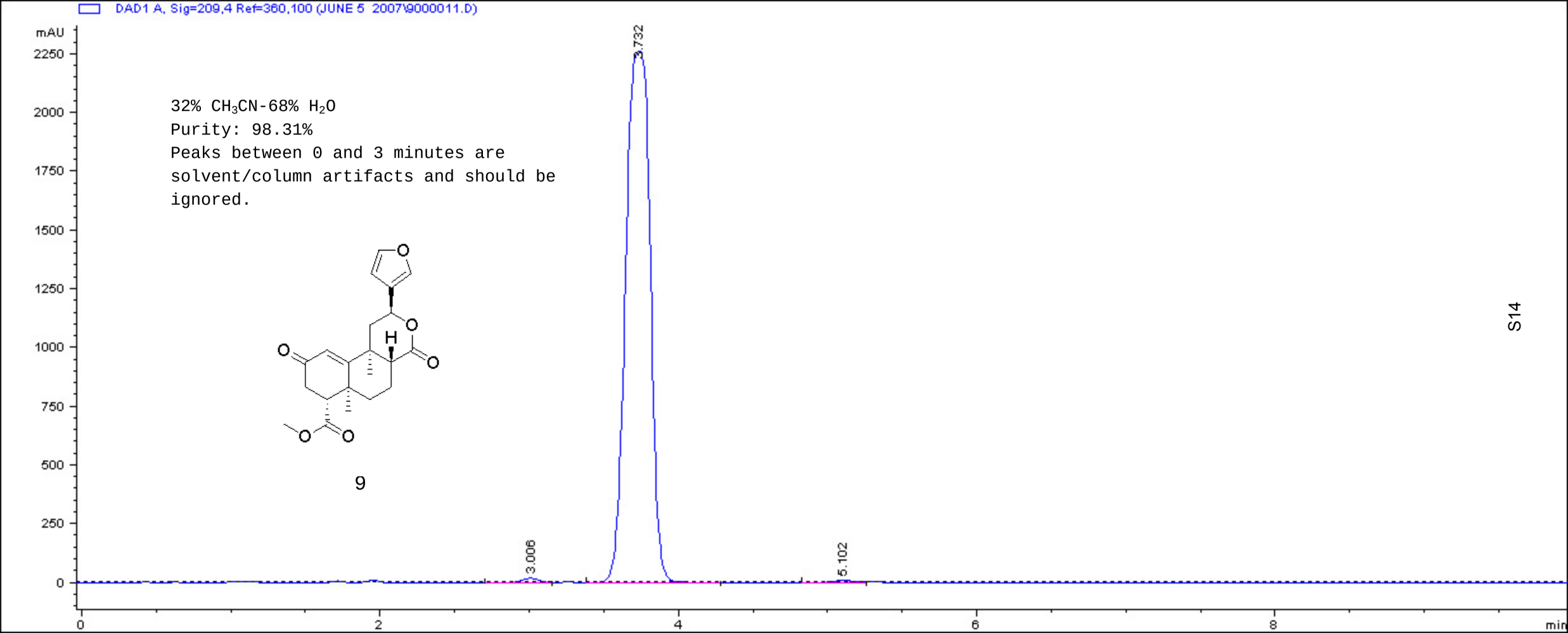


4b

3.514

9.208

min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5.102
0
2
4
6
8
min
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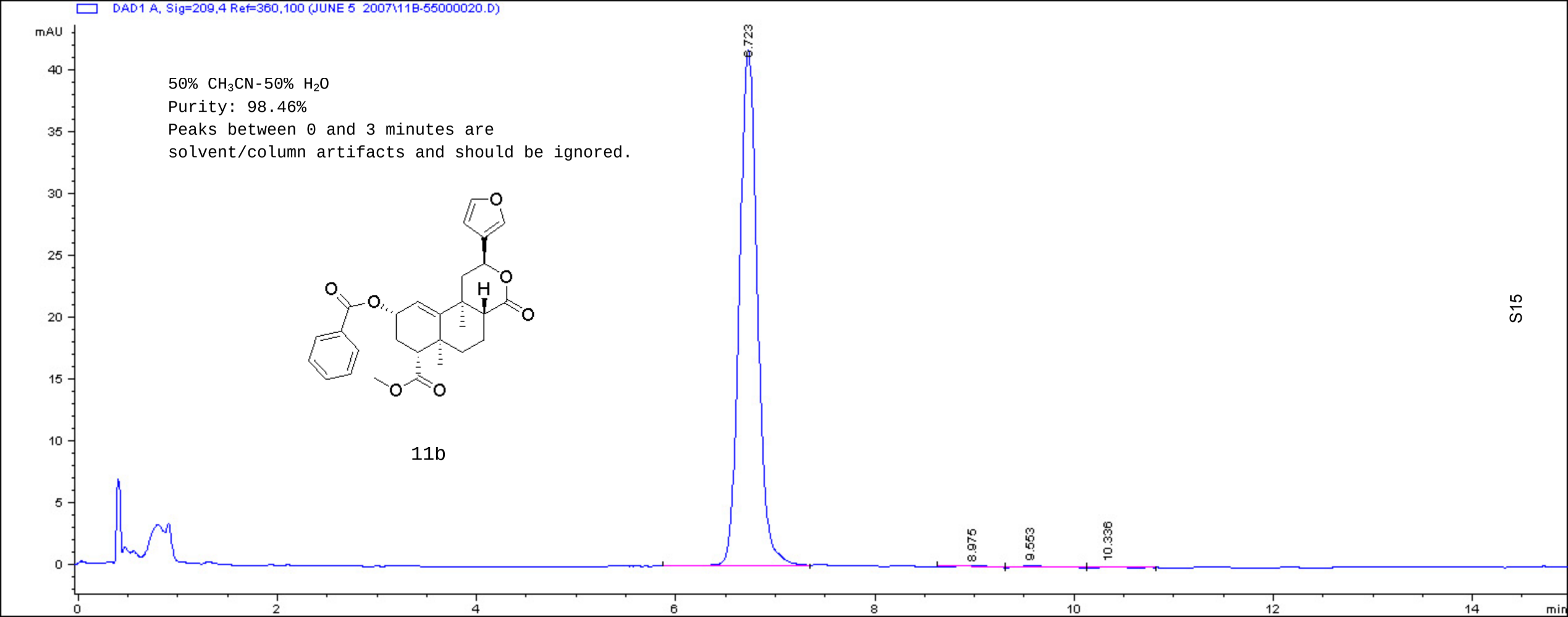
Purity: 98.31%
Peaks between 0 and 3 minutes are solvent/column artifacts and should be ignored.
9
S14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mAU
50% CH3CN-50% H2O
Purity: 98.46%
Peaks between 0 and 3 minutes are
solvent/column artifacts and should be ignored.
11b
6.723
8.975
9.553
10.336
S15
min