Supplementary Material (ESI) for Chemical Communications

Supplementary Material

Tin Triflate-Mediated Total Synthesis of Circumdatin F, Sclerotigenin, Asperlicin C, and Other Quinazolino[3,2-*a*][1,4]benzodiazepines

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General procedure for total synthesis of quinazolino[3,2-a][1,4]benzodiazepines (1a－h).

A suspension of isatoic anhydride (2.5 g, 15.3 mmol) and anthranilic acid (2.3 g, 16.8 mmol) in water (50 mL) was refluxed for 2 h and then cooled. The solid product was filtered and washed with water to obtain bis(anthranilic acid) (3.4 g, 87%) as pale yellow powder with excellent purity.

To a solution of sulfuric acid (2 mL) in methanol (40 mL) was added bis(anthranilic acid) (2 g, 7.8 mmol). The reaction mixture was heated to reflux for 4 days and then cooled. The solution was concentrated under reduced pressure to give brown oil and poured into water (20 mL). The pH was adjusted to 8 with 10% NaOH in ice bath and then extracted with CH_2Cl_2 (3×20 mL). The combined organic layers were dried (Na_2SO_4) and evaporated to afford a brown residue, and purified by flash chromatography (ethyl acetate/hexane = 1:7) to give the desired methyl ester (1.8 g, 86%) as a light yellow solid.

For tripeptide preparation, EDC (92 mg, 0.48 mmol) was added to a solution of the aforementioned methyl ester (100 mg, 0.37 mmol) and *N*-Cbz-L-Amino acid (0.37 mmol) in CH_2Cl_2 (3 mL). The reaction mixture was stirred at ambient temperature for 3－6 h. The mixture was washed with 10% citric acid (3×5 mL) and dried (Na_2SO_4), concentrated under reduced pressure to afford a solid residue, which was further purified by flash chromatography (ethyl acetate/hexane = 1:4) to give the desired Cbz-protected tripeptide

product (82－98% yield) as white solids.

The Cbz-protected tripeptide was then deprotected by catalytic hydrogenation. To a solution of tripeptide (100 mg, 0.37 mmol) in methanol (15 mL) was added catalytic amount of 20% $Pd(OH)_2/C$ and a balloon of hydrogen. This deprotection reaction by hydrogenation was allowed to proceed until the protected tripeptide was completely consumed. The reaction mixture was filtered and concentrated under reduced pressure to give the product as the colorless solid (91－100% yield).

To a microwave reaction vessel was added the tripeptide (30 mg, 0.066-0.078 mmol), $Sn(OTf)_2$ (0.066-0.078 mmol) and DMF (0.4 mL). The vessel was placed inside a CEM Discover single-mode microwave synthesizer equipped with a magnetic stirrer where it was exposed to microwaves at 140 ^oC (30 W) for 5 - 10 min. After reaction DMF was removed under reduced pressure and poured the water (5 mL). The solution was extracted with dichloromethane (3×5 mL). The combined organic layers were dried (Na_2SO_4) and evaporated to afford a brown residue and finally purified by flash column chromatography (ethyl acetate/CH_2Cl_2 = 1:6) to obtain the desired quinazolino[3,2-*a*][1,4]benzodiazepines **1a-g** (34－85 % yield) as white solids.

(7S)-6,7-Dihydro-7-methylquinazolino[3,2-a][1,4]-benzodiazepine-5,13-dione

(circumdatin F, ***1a****)* white solid; mp 256－257 ^oC; $[\alpha]^{20}_D$ = －121.5 ^{o} (*c* 1.0, $CHCl_3$);

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.71 (t, *J* = 6.8 Hz, CH_3, 3H), 4.35 (quin, *J* = 6.4 Hz, NCH, 1H), 6.80 (d, *J* = 5.6 Hz, NH, 1H), 7.50—7.77 (m, ArH, 6H), 7.97 (dd, *J* = 7.2, 1.2 Hz, ArH, 1H), 8.17 (d, *J* = 7.9 Hz, ArH, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.2, 49.9, 121.2, 127.2, 127.4, 127.6, 128.3, 128.8, 129.8, 130.6, 131.2, 133.4, 134.7, 146.0, 154.9, 161.5, 168.1; $[\alpha]_D^{20}$ = -121.5 ^{o} (*c* 1.0, $CHCl_3$); FAB-HRMS *m/z* $[M+H]^+$ calcd for $C_{17}H_{14}N_3O_2$ 292.1086, found 292.1090.

6,7-Dihydroquinazolino[3,2-a][1,4]-benzodiazepine-5,13-dione (sclerotigenin, ***1b****)* white solid; mp 310—313 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.00 (dd, *J* = 15.4, 6.6 Hz, NCH_2, 1H), 4.18 (dd, *J* = 15.4, 5.1 Hz, NCH_2, 1H), 7.58—7.65 (m, ArH, 4H), 7.71 (d, *J* = 8.0 Hz, ArH, 1H), 7.79 (d, *J* = 7.4 Hz, ArH, 1H), 7.89 (t, *J* = 7.6 Hz, ArH, 1H), 8.18 (d, *J* = 7.7 Hz, ArH, 1H), 8.89 (t, *J* = 5.3 Hz, NH, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 46.4, 127.1, 127.3, 127.8, 128.7, 129.0, 129.6, 130.8, 130.9, 133.6, 135.4, 146.3, 155.0, 161.2, 167.2; FAB-HRMS *m/z* $[M+H]^+$ calcd for $C_{16}H_{12}N_3O_2$ 278.0930, found 278.0927.

(7S)-6,7-Dihydro-7-((indol-2-yl)methyl)quinazolino[3,2-a][1,4]-benzodiazepine-5,13-dio ne (asperlicin C, ***1c****)* white solid; mp 314—315 ^{o}C; $[\alpha]^{20}_D$ = —224.3 ^{o} (*c* 1.0, DMSO); ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.36—3.44 (m, indolyl-CH_2, 1H), 3.66 (dd, *J* = 14.8, 4.8 Hz, indolyl-CH_2, 1H), 4.39—4.41 (m, NCH, 1H), 6.92 (t, *J* = 7.6 Hz, ArH, 1H), 7.02 (t, *J* = 7.6 Hz, ArH, 1H), 7.32—7.34 (m, ArH, 2H), 7.52—7.70 (m, ArH, 6H), 7.85 (d, *J*

= 8.0 Hz, ArH, 4H), 7.91 (d, *J* = 7.2 Hz, ArH, 1H), 8.20 (d, *J* = 8.0 Hz, ArH, 1H), 8.92 (d, *J* = 6.4 Hz, ArH, 1H), 10.87 (bs, NH, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 24.6, 54.8, 110.0, 111.6, 118.5, 118.6, 121.1, 121.2, 124.7, 127.1, 127.3, 127.7, 127.8, 128.9, 129.0, 130.9, 131.4, 133.2, 135.4, 136.2, 146.2, 156.2, 161.2, 167.0; FAB-HRMS *m/z* $[M+H]^+$ calcd for $C_{25}H_{19}N_4O_2$ 407.1508, found 407.1502.

(7S)-6,7-Dihydro-7-isobutylquinazolino[3,2-a][1,4]-benzodiazepine-5,13-dione ***(1d)***

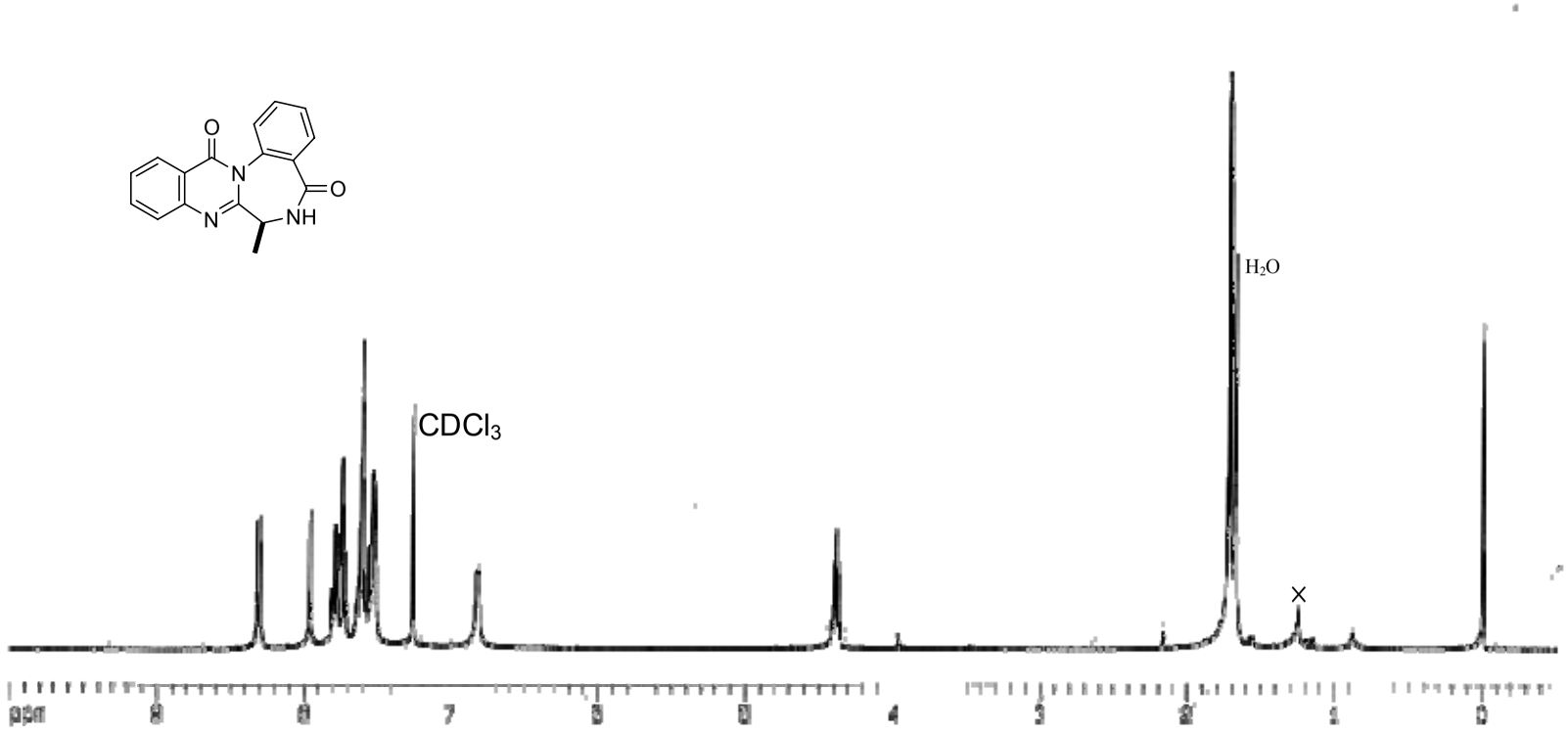
white solid; mp 226－227 °C; $[\alpha]^{20}_D$ = －171.3 ° (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (d, *J* = 6.4 Hz, CH_3, 3H), 1.00 (d, *J* = 6.8 Hz, CH_3, 3H), 1.90－2.01 (m, CH_2, 2H), 2.13－2.18 (m, CH, 1H), 4.20 (q, *J* = 2.4 Hz, NCH, 1H), 6.85 (s, NH, 1H), 7.48－7.77 (m, ArH, 6H), 7.96 (d, *J* = 7.6 Hz, ArH, 1H), 8.28 (d, *J* = 7.8 Hz, ArH, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.9, 23.0, 24.3, 37.8, 52.3, 121.3, 127.3, 127.5, 127.7, 128.3, 128.9, 129.7, 130.5, 131.3, 133.5, 134.7, 146.1, 154.6, 161.6, 168.2; FAB-HRMS *m/z* $[M+H]^+$ calcd for $C_{20}H_{20}N_3O_2$ 334.1556, found 334.1548.

(7S)-7-Benzyl-6,7-dihydroquinazolino[3,2-a][1,4]-benzodiazepine-5,13-dione ***(1e)***

white solid; mp 141－143 °C; $[\alpha]^{20}_D$ = －103.7 ° (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.30 (dd, *J* = 14.4, 8.4 Hz, $PhCH_2$, 1H), 3.69 (dd, *J* = 14.8, 5.6 Hz, $PhCH_2$, 1H), 4.40 (q, *J* = 6.0 Hz, NCH, 1H), 7.20－7.34 (m, ArH, 5H), 7.39－7.47 (m, ArH, 2H), 7.57－7.66 (m, ArH, 4H), 7.87 (d, *J* = 7.6 Hz, ArH, 1H), 8.04 (d, *J* = 6.0 Hz, NH, 1H), 8.10 (d,

J = 7.6 Hz, ArH, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 35.2, 55.6, 121.1, 126.8, 127.1, 127.4, 127.5, 128.2, 128.5, 128.8, 129.5, 129.8, 130.4, 131.1, 133.2, 134.6, 136.9, 154.1, 161.4, 168.3; FAB-HRMS *m/z* $[M+H]^+$ calcd for $C_{23}H_{18}N_3O_2$ 368.1399, found 368.1394.

(7S)-6,7-Dihydro-7-hexahydropyrrolo[1',2':1,2]quinazolino[3,2-a][1,4]-benzodiazepine-5,13-dione ***(1f)*** white solid; mp 227－230 °C; $[\alpha]^{20}_D$ = －109.4 ° (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.08－2.19 (m, CH_2, 2H), 2.28-2.35 (m, CH_2, 1H), 3.15－3.20 (m, CH_2, 1H), 3.60-3.64 (m, CH_2, 1H), 3.77－3.81 (m, CH_2, 1H), 4.55 (d, *J* = 7.6 Hz, NCH), 7.45－7.57 (m, ArH, NH, 5H), 7.70－7.80 (m, ArH, 2H), 7.99 (d, *J* = 7.7 Hz, ArH, 1H), 8.29 (d, *J* = 7.8 Hz, ArH, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.6, 26.9, 46.5, 58.8, 121.4, 127.3, 127.4, 127.5, 128.3, 128.6, 129.8, 130.7, 132.3, 133.1, 134.7, 146.0, 153.5, 161.6, 164.4 ; FAB-HRMS *m/z* $[M+H]^+$ calcd for $C_{19}H_{16}N_3O_2$ 318.1243, found 318.1240.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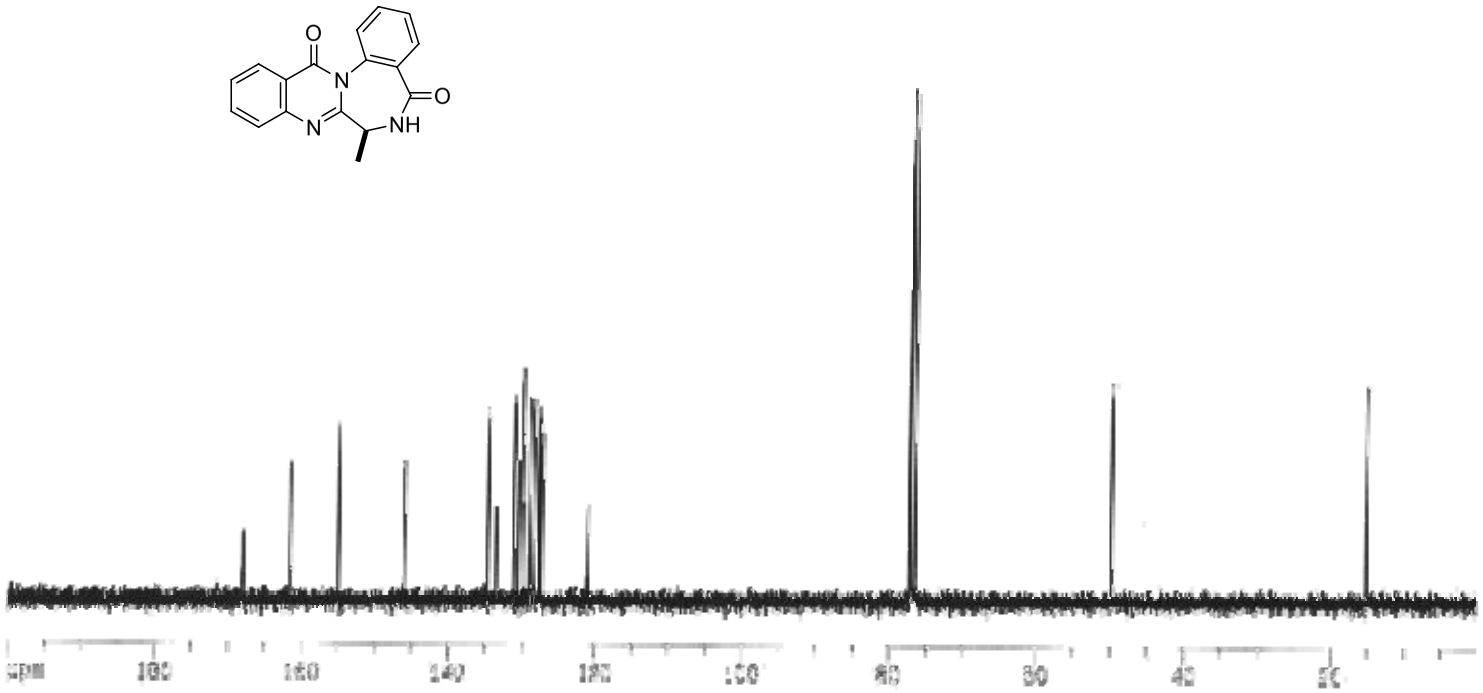
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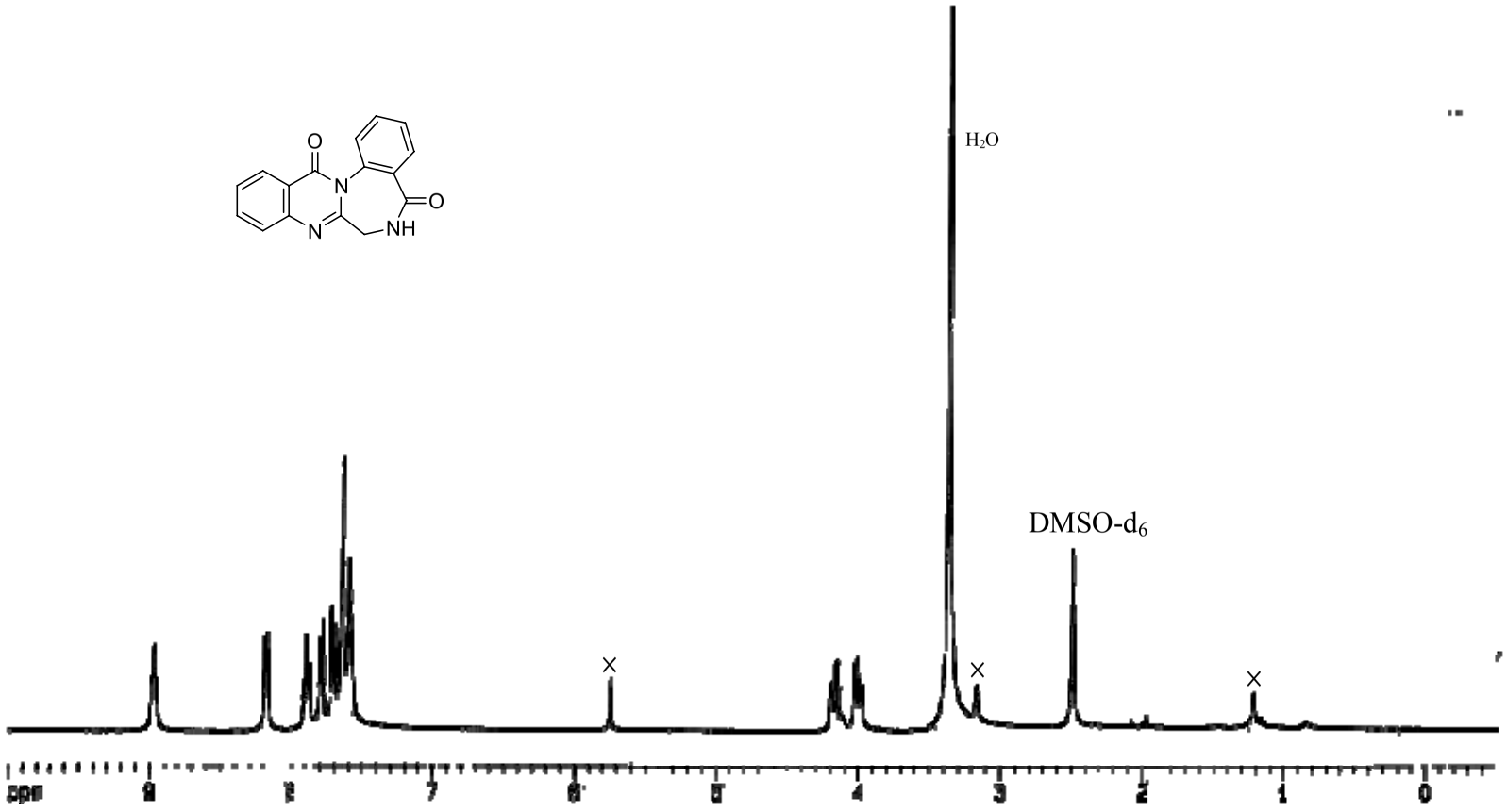
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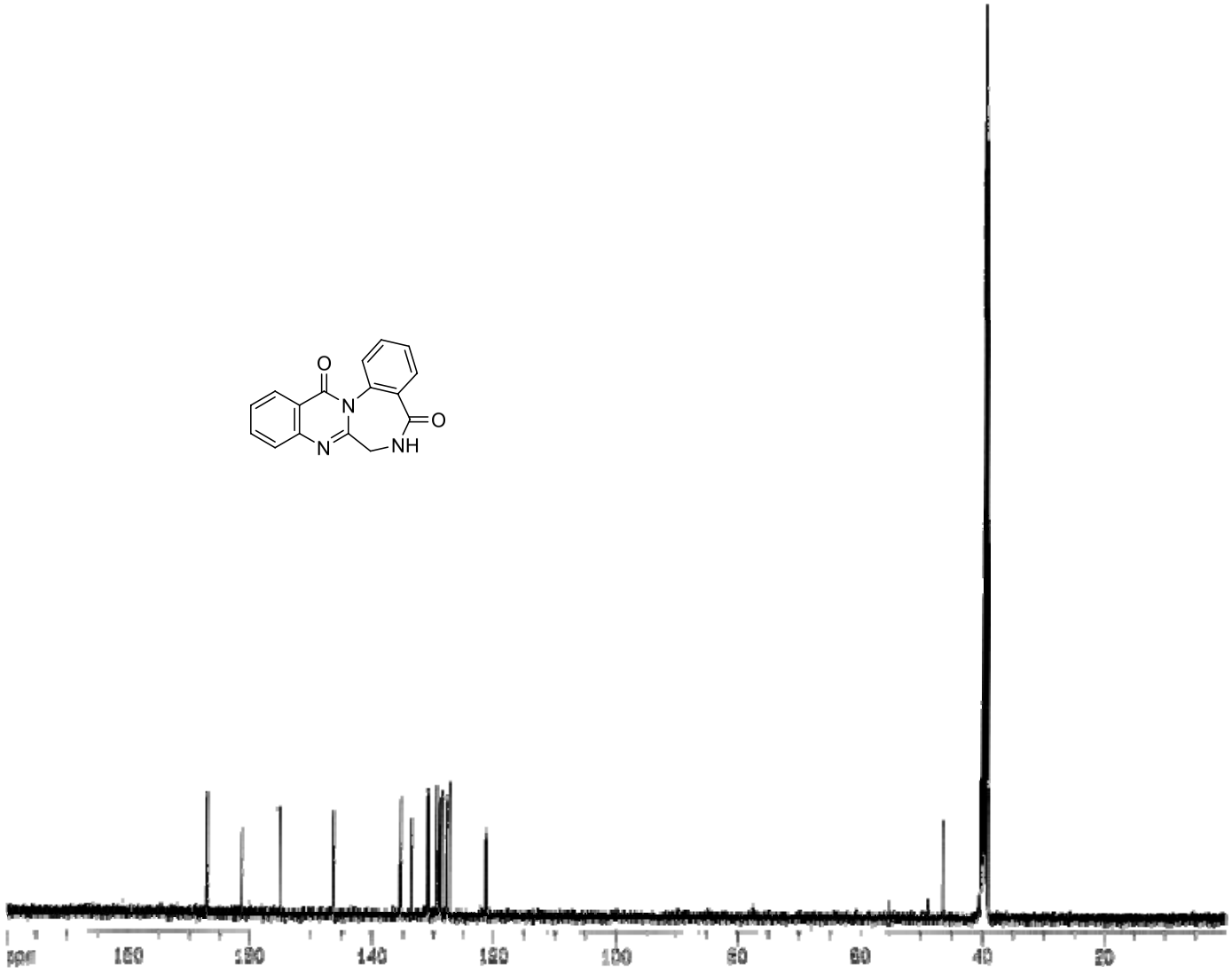
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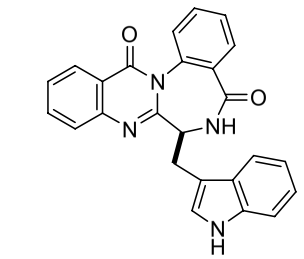
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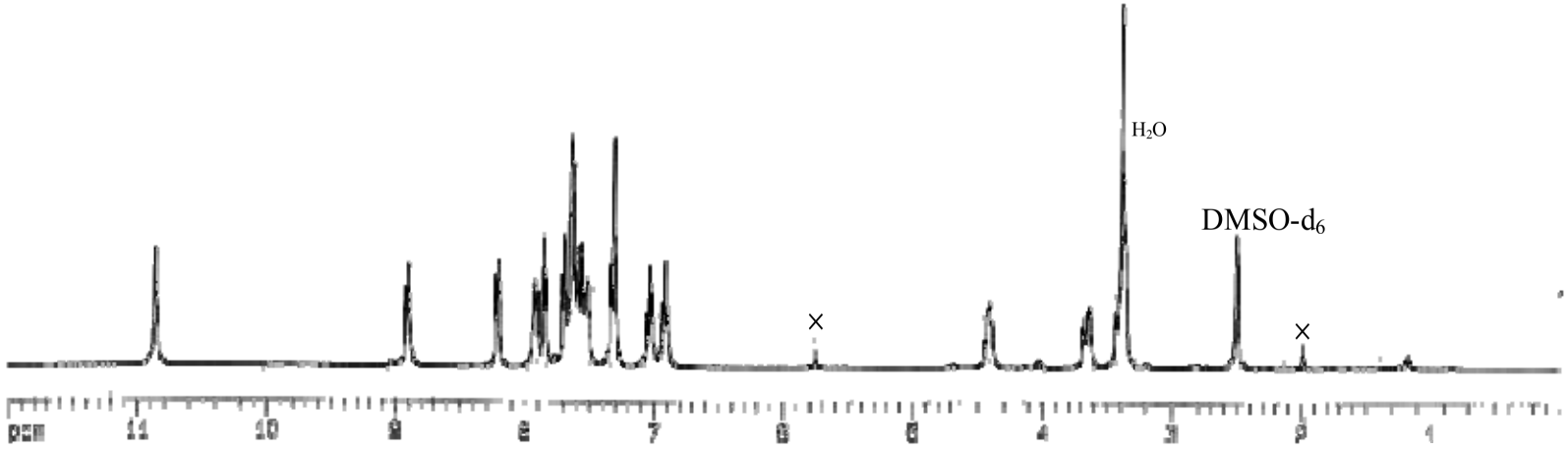
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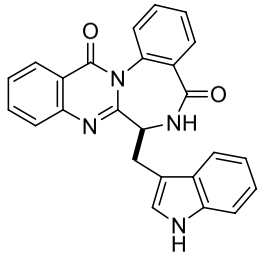
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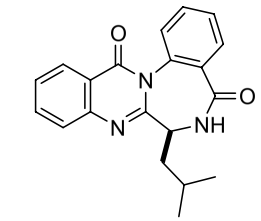
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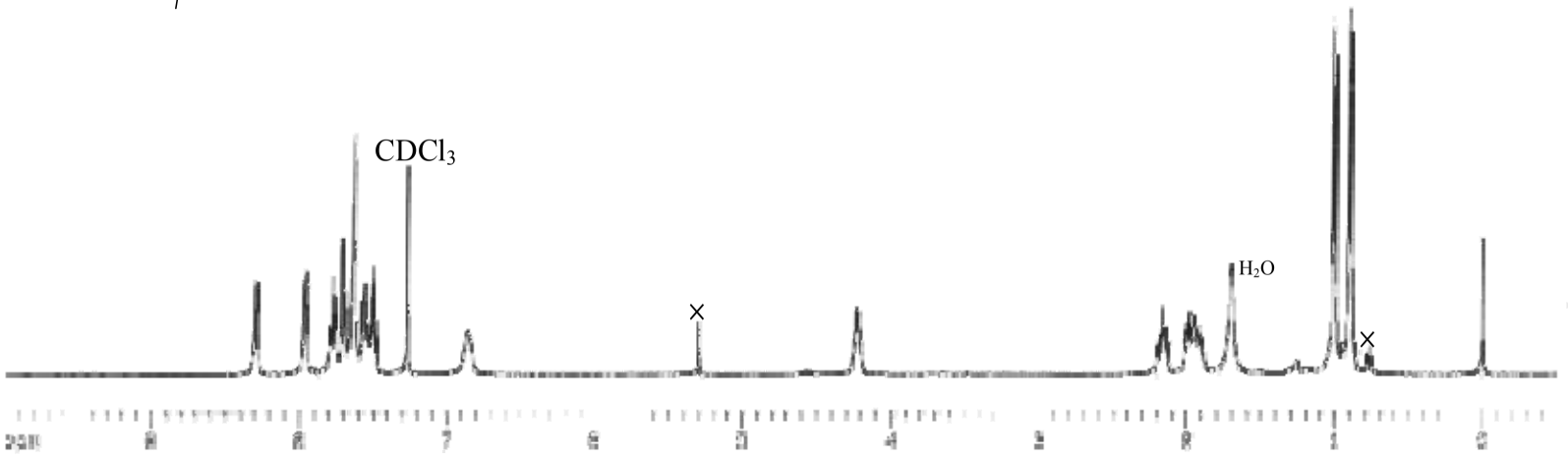
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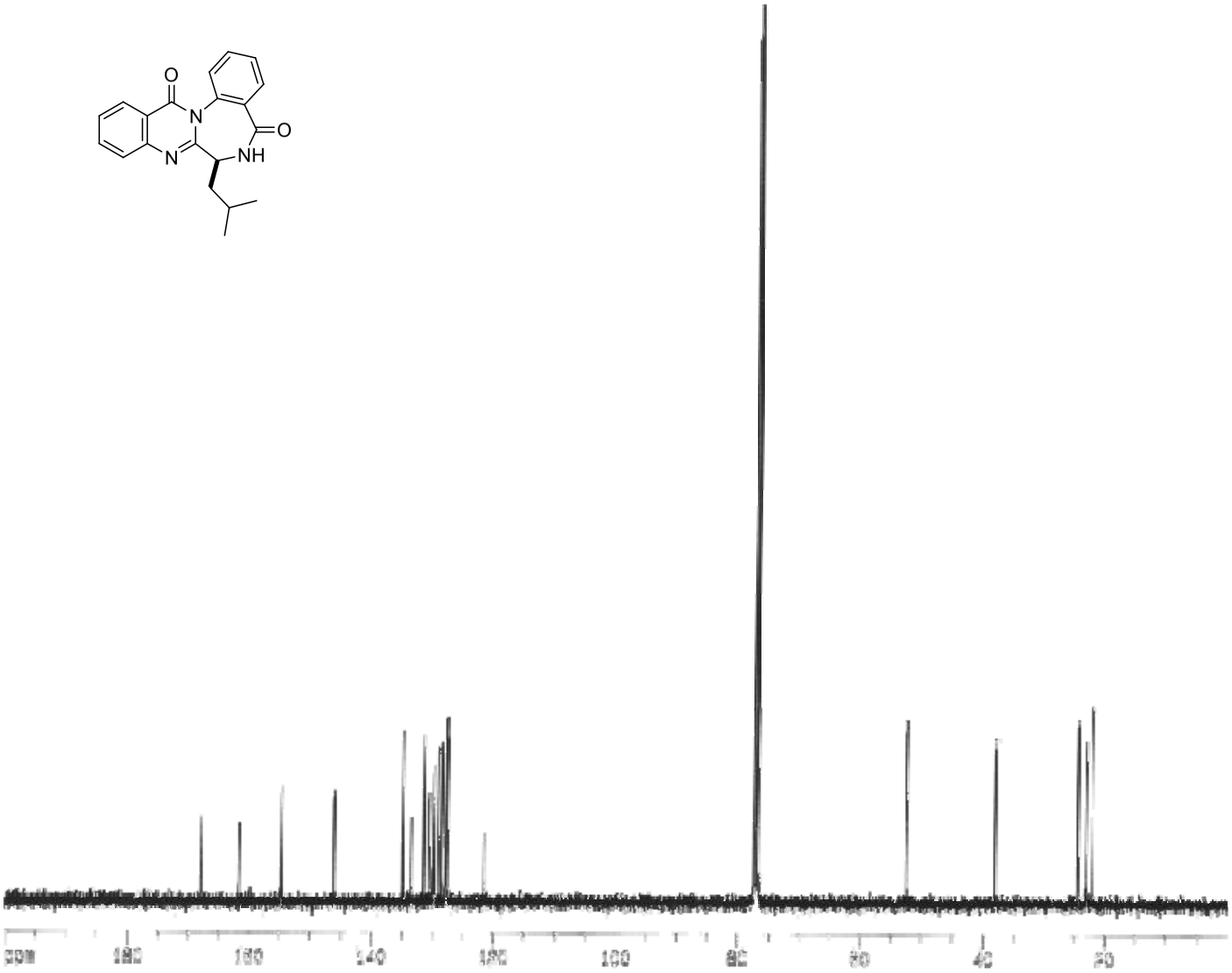
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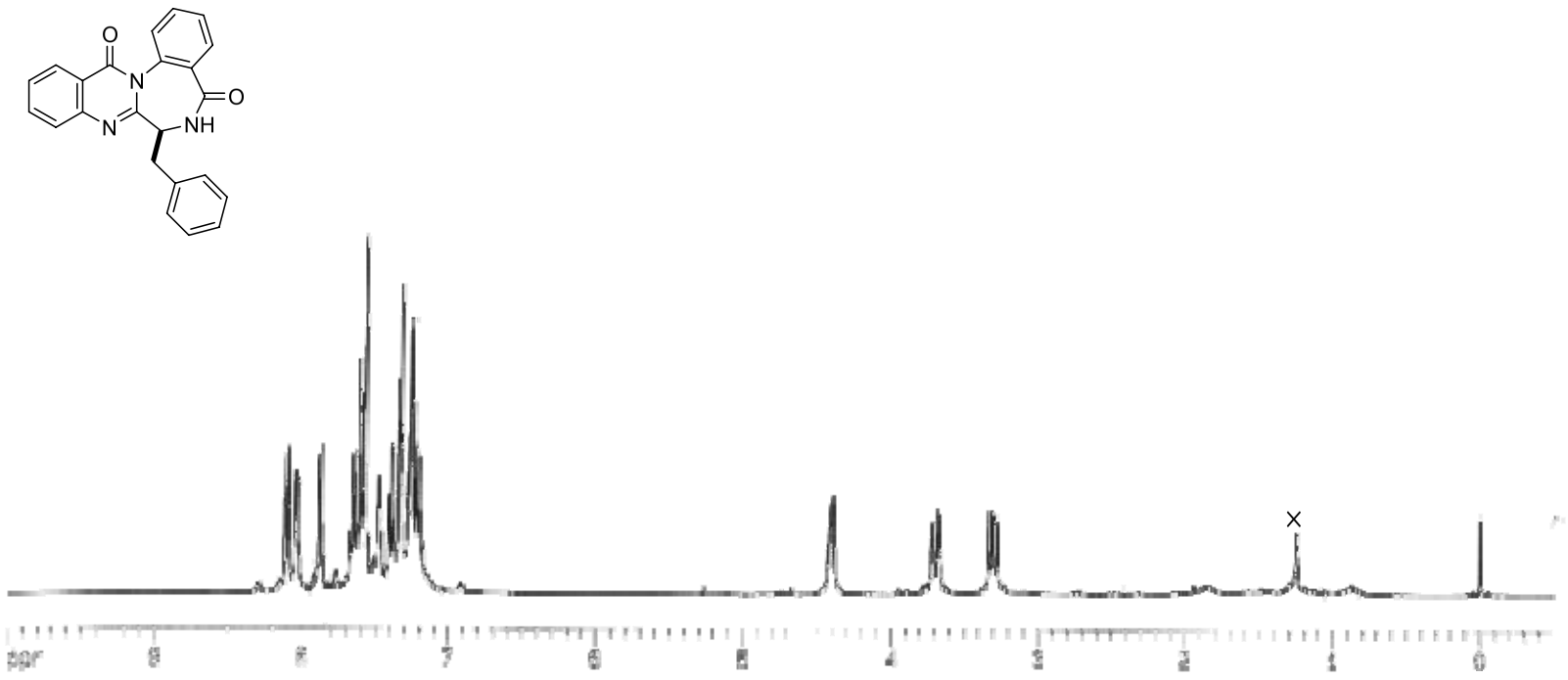
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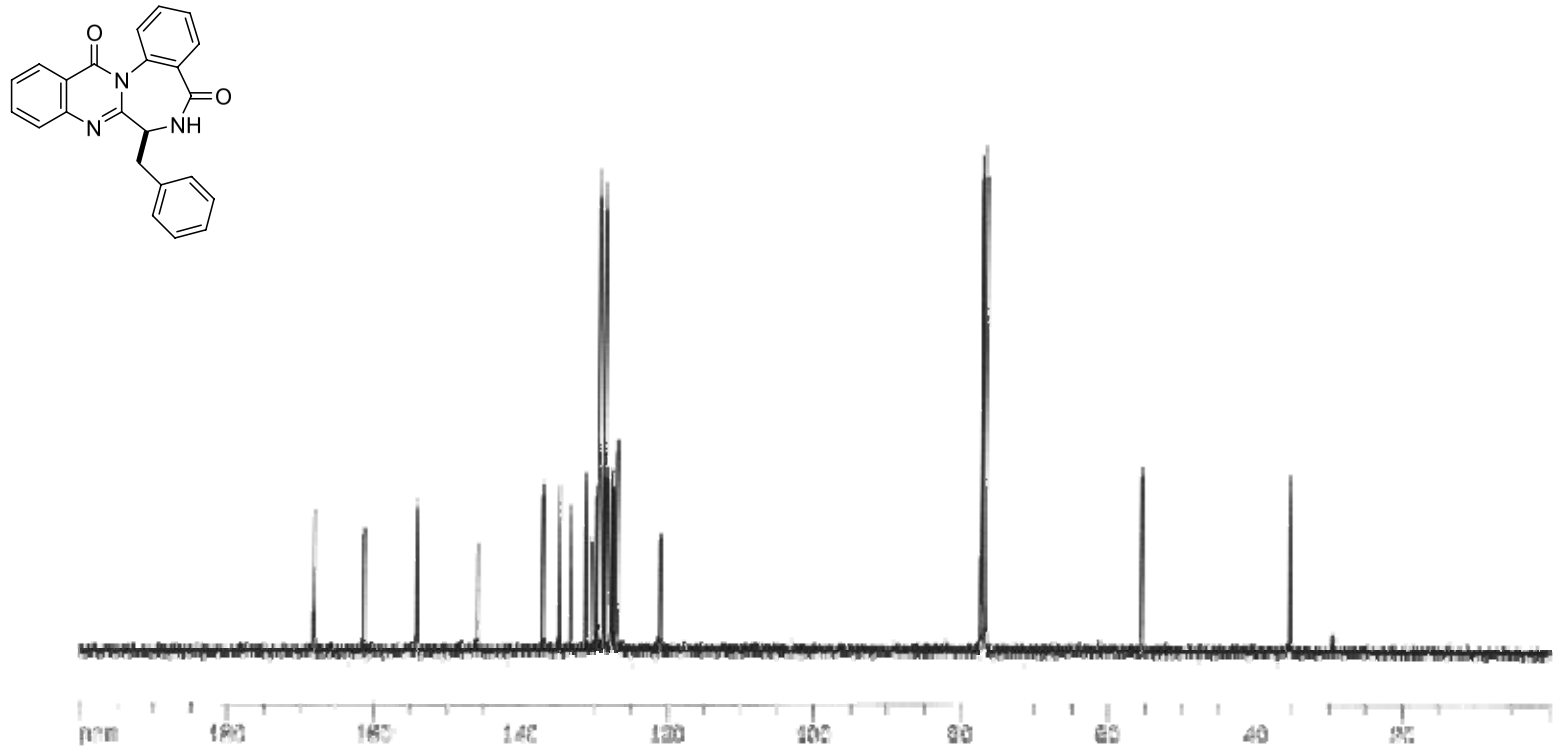
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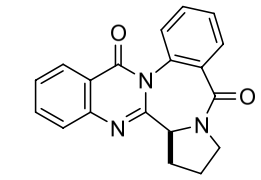
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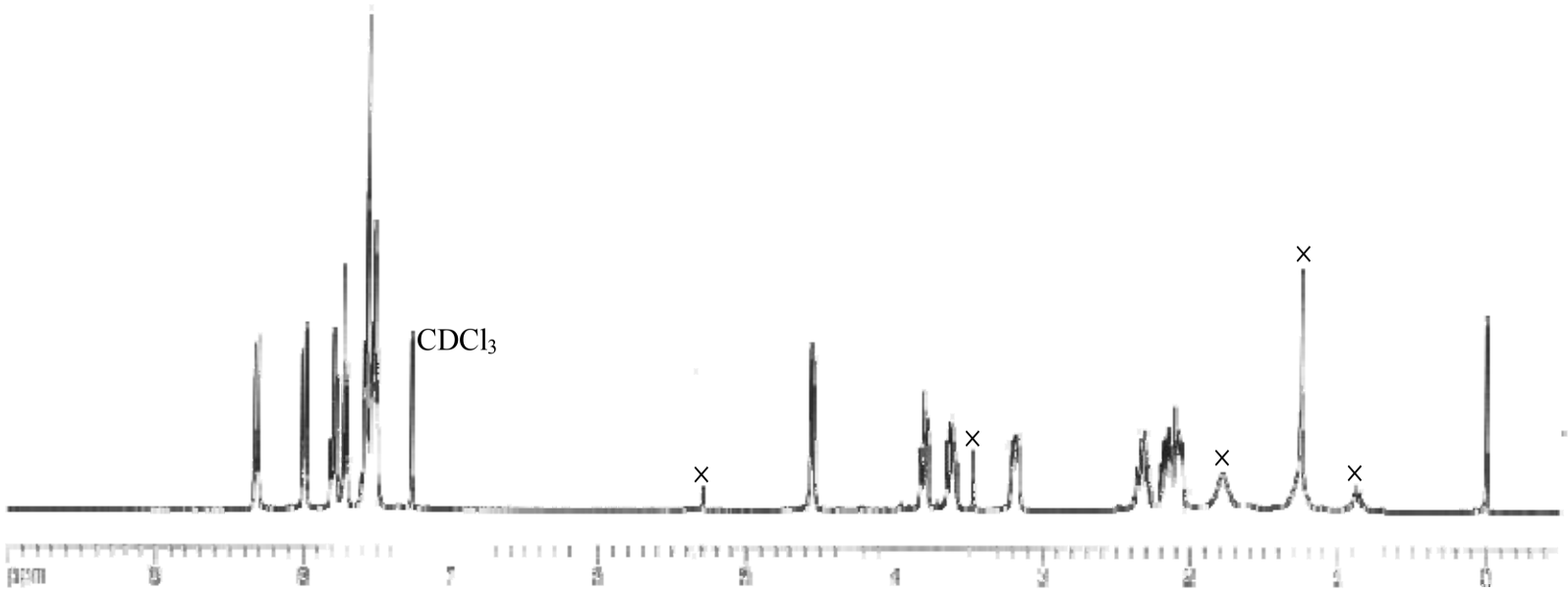
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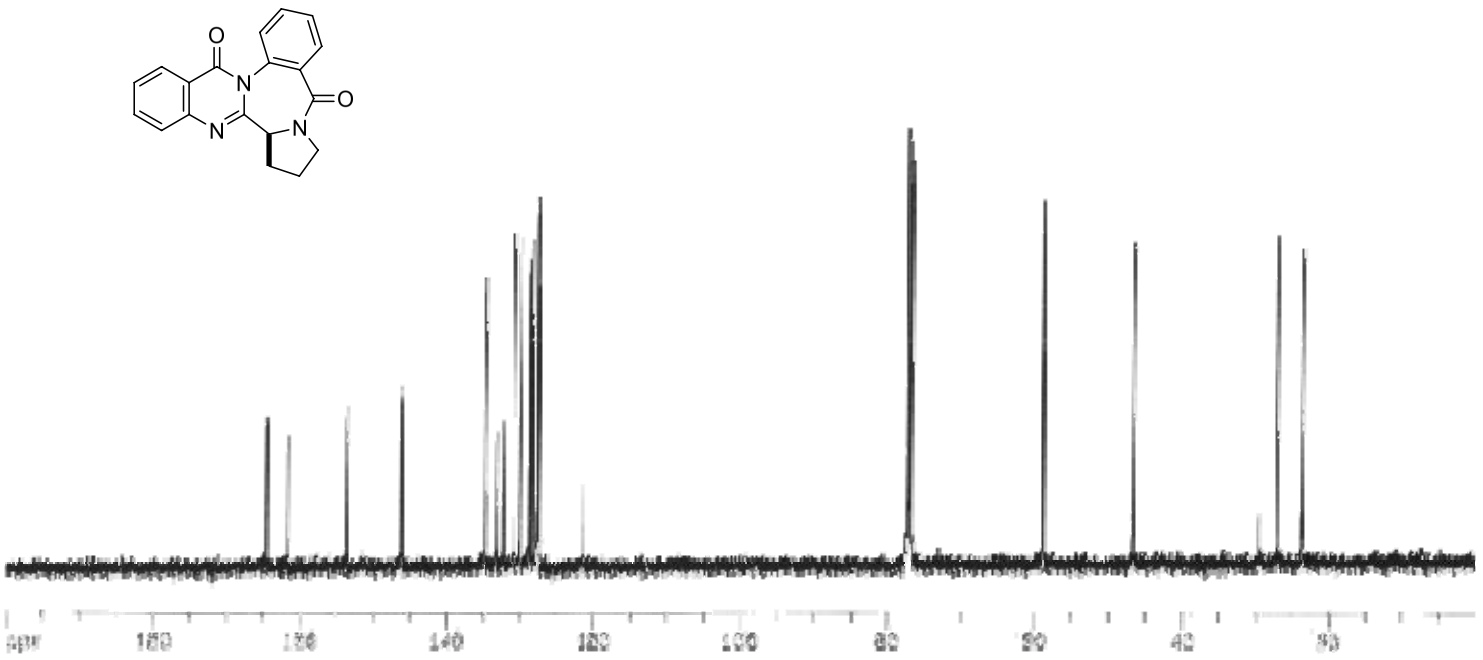
O
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Figure S1. ^{1}H NMR (400 MHz) spectrum of the methyl protons of synthetic circumdatin F, prepared from L-Ala by conventional heating at 140 ^{o}C for 3 h, in $CDCl_3$ after the addition of 0.09 equiv of the chiral shift reagent (+)-Eu(hfc)$_3$. From the spectrum, 11.6% racemization during the synthesis of circumdatin F was detected.