Total synthesis of siphonazole, a structurally unusual bis-oxazole natural product

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ELECTRONIC SUPPLEMENTARY INFORMATION

(*E*)-Methyl 2-[(3-*tert*-butyldimethylsiloxy-4-methoxyphenyl)propenoylamino]-3-oxobutanoate 4

A solution of cinnamamide **3** (2.00 g, 6.40 mmol) and dirhodium tetraacetate (71 mg, 0.20 mmol, 2.50 mol%) in dry dichloromethane (30 mL) was heated to reflux. A solution of methyl 2-diazo-3-oxobutanoate (1.50 g, 10.3 mmol) in dichloromethane (5 mL) was added *via* syringe pump over a 16 h period. After the addition was complete the reaction mixture was heated under reflux for a further 4 h. After removal of the solvent under reduced pressure, the crude product was purified by chromatography (eluting ethyl acetate/light petroleum, 3:2) to give the *title compound* as a light green oil (2.40 g, 90%); (Found: MNa^{+}, 444.1832. $C_{21}H_{31}NNaO_6Si$ requires 444.1813); ν_{max} ($CHCl_3$)/cm^{-1} 3416, 2939, 1756, 1729, 1668, 1626, 1491, 1361, 1275, 1137, 1031; δ_H (400 MHz; $CDCl_3$) 7.53 (1 H, d, *J* 15.6, C<u>H</u>=CHCONH), 7.08 (1H, dd, *J* 8.3, 2.0, ArH), 7.04 (1H, d, *J* 2.0, ArH), 6.83 (1H, d, *J* 8.3, ArH), 6.72 (1H, d, *J* 6.4, N<u>H</u>), 6.33 (1H, d, *J* 15.6, CH=C<u>H</u>CONH), 5.40 (1H, d, *J* 6.4, NHC<u>H</u>), 3.84 (3H, s, OMe), 3.83 (3H, s, OMe), 2.43 (3H, s, Me), 1.01 (9H, s, CMe_3), 0.17 (6H, s, $SiMe_2$); δ_C (100 MHz; $CDCl_3$) 198.7 (C), 166.7 (C), 165.7 (C), 152.9 (C), 145.1 (CH), 142.4 (C), 127.4 (C), 123.0 (CH), 119.6 (CH), 116.6 (CH), 111.7 (CH), 63.1 (C), 55.4 (Me), 53.4 (Me), 28.1 (Me), 25.7 (Me), 18.4 (C), -4.6 (Me); *m/z* (ESI) 444 ($M+Na^{+}$, 99%), 422 (MH^{+}, 31), 291 (100).

Methyl 2-(3-*tert*-butyldimethylsiloxy-4-methoxystyryl)-5-methyloxazole-4-carboxylate 5

A solution of β-ketoamide **4** (2.40 g, 5.70 mmol) and triethylamine (3.10 mL, 22.8 mmol) in dry dichloromethane (10 mL) was added dropwise over a period of 1 h to a solution of triphenylphosphine (3.00 g, 11.4 mmol) and iodine (2.90 g, 11.4 mmol) in dry dichloromethane (20.0 mL) at room temperature. After the addition was complete the reaction mixture was stirred for a further 1 h at which point no starting material could be observed by TLC analysis of the reaction mixture. The mixture was quenched with water (25 mL). The organic layer was washed with water (25 ml) and brine (25 mL), then dried ($MgSO_4$). After removal of the solvent under reduced pressure, the crude material was purified by chromatography to give the *title compound* (eluting with ethyl acetate/light petroleum, 1:1 + 0.5% triethylamine) as a light yellow solid (1.86 g, 81%); mp 97-99 °C; (Found: C, 62.3; H, 7.2; N, 3.5. $C_{21}H_{29}NO_5Si$ requires C, 62.5; H, 7.2; N, 3.5%); (Found: MH^+, 404.1907. $C_{21}H_{30}NO_5Si$ requires 404.1888); ν_{max} ($CHCl_3$)/cm^{-1} 2951, 2858, 1719, 1616, 1443, 1352, 1305, 1140, 1103, 957; δ_H (400 MHz; $CDCl_3$) 7.40 (1 H, d, *J* 16.4, C<u>H</u>=CH), 7.06 (1H, dd, *J* 8.3, 2.1, ArH), 7.03 (1H, d, *J* 2.1, ArH), 6.83 (1H, d, *J* 8.3, ArH), 6.70 (1H, d, *J* 16.4, CH=C<u>H</u>), 3.91 (3H, s, OMe), 3.82 (3H, s, OMe), 2.65 (3H, s, Me), 1.00 (9H, s, CMe_3), 0.16 (6H, s, $SiMe_2$); δ_C (100 MHz; $CDCl_3$) 162.7 (C), 159.6 (C), 155.7 (C), 152.4 (C), 145.2 (C), 136.7 (CH), 128.2 (C), 121.9 (CH), 118.8 (CH), 111.8 (CH), 110.8 (CH), 55.4 (Me), 51.8 (C), 25.6 (Me), 18.4 (C), 12.0 (Me), -4.7 (Me); one C unobserved; *m/z* (ESI) 404 (MH^+, 100%).

Methyl 2-iodomethyl-5-methyloxazole-4-carboxylate 7

To a solution of iodoacetonitrile (5.00 g, 30.0 mmol) and dirhodium tetraacetate (177 mg, 0.40 mmol, 2.50 mol%) in dichloromethane (5 mL) heated to reflux was added dropwise a solution of methyl 2-diazo-3-oxobutanoate (2.10 g, 15.0 mmol) in dichloromethane (3 mL) over a period of 16 h. After the addition was complete the reaction mixture was heated to reflux for a further 2 h. After removal of the solvent under reduced pressure, purification by chromatography (eluting with ethyl acetate/light petroleum, 1:4) gave *title compound* as a light red solid (2.03 g, 48%); mp 81 °C; (Found: MNa^+, 303.9435. $C_7H_8INNaO_3$ requires 303.9447); ν_{max} ($CHCl_3$)/cm^{-1} 2954, 1727, 1618, 1424, 1353, 1103; δ_H (400 MHz; $CDCl_3$) 4.31 (2H, s, ICH_2), 3.88 (3H, s, OMe), 2.59 (3H, s, Me); δ_C (100 MHz; $CDCl_3$) 162.2 (C), 158.4 (C), 157.2 (C), 128.2 (C), 52.0 (Me), 12.0 (Me), -11.9 (CH_2); *m/z* (ESI) 304 ($M+Na^+$, 100%), 282 (MH^+, 23).

Methyl 2-[2-(2-(3-tert-butyldimethylsiloxy-4-methoxystyryl)-5-methyloxazol-4-yl)]-(2-oxoethyl)-5-methyloxazole-4-carboxylate 8

(a) Zinc dust (164 mg, 2.50 mmol) was placed in a Schlenk tube under an argon atmosphere and suspended in dry THF (2 mL), 1,2-dibromoethane (21.3 μL, 0.25 mmol) added and the mixture heated up to 60 °C for 5 min. After cooling to room temperature, trimethylsilyl chloride (6.40 μL, 0.05 mmol) was added and stirring continued for further 15 min. At 0 °C were aldehyde **6** (190 mg, 0.51 mmol) and boron trifluoride-etherate (127 mL, 1.00 mmol) added. Iodide **7** (226 mg, 0.81 mmol) in THF (1.5 mL) was added dropwise over a period of 3 h after which the reaction was complete. The inorganic residue was filtered off, the solvent removed under reduced pressure and the residue purified by chromatography (eluting with first ethyl acetate/light petroleum, 1:2 + 0.5% triethylamine, then ethyl acetate/light petroleum, 2:1) to give *methyl 2-[(2-(2-(3-tert-butyldimethylsiloxy-4imethoxystyryl)-5-methyloxazol-4-yl)]-(2-hydroxyethyl)-5-methyloxazole-4-carboxylate* as a light yellow solid (152 mg, 53%); mp 142 °C; (Found: MH^+, 529.2361. $C_{27}H_{37}N_2O_7Si$ requires 529.2214); ν_{max} ($CHCl_3$)/cm^{-1} 3416, 2930, 2858, 1722, 1625, 1462, 1354, 1101, 986; δ_H (400 MHz; $CDCl_3$) 7.30 (1 H, d, *J* 16.3, C<u>H</u>=CH), 7.06 (1H, dd, *J* 8.3, 2.0, ArH), 7.04 (1H, d, *J* 2.0, ArH), 6.83 (1H, d, *J* 8.3, ArH), 6.67 (1H, d, *J* 16.3, CH=C<u>H</u>), 5.18 (1H, m, C<u>H</u>OH), 3.90 (3H, s, OMe), 3.83 (3H, s, OMe), 3.39 (1H, dd, *J* 15.8, 8.8, C<u>H</u>HCHOH), 3.19 (1H, dd, *J* 15.8, 4.5, CH<u>H</u>CHOH), 2.60 (3H, s, Me), 2.35 (3H, s, Me), 1.01 (9H, s, CMe_3), 0.17 (6H, s, $SiMe_2$); OH unobserved; δ_C (100 MHz; $CDCl_3$) 162.6 (C), 160.2 (C), 160.1 (C), 156.3 (C), 152.1 (C), 145.2 (C), 144.2 (C), 136.1 (C), 135.2 (CH), 128.6 (CH), 127.2 (CH), 121.7 (CH), 118.7 (CH), 111.8 (CH), 111.5 (CH), 64.3 (Me), 55.4 (Me), 51.8 (Me), 35.4 (CH_2), 25.7 (Me), 18.4 (C), 11.9 (Me), 10.4 (Me), -4.2 (Me); *m/z* (ESI) 551 ($M+Na^+$, 100%), 529 (MH^+, 79).

(b) Dess-Martin periodinane (52 mg, 0.12 mmol) was added to a solution of the above alcohol (60 mg, 0.11 mmol) dissolved in dichloromethane (3 mL) and the mixture stirred at room temperature for 20 min. The mixture was diluted with ether (12 mL), aqueous saturated sodium hydrogen carbonate (3 mL) and aqueous sodium metabisulfite (10%; 3 mL) added, and the mixture stirred until two clear layers were formed. The organic layer was washed with water (10 mL) and brine (10 mL), dried ($MgSO_4$), the solvent removed under reduced pressure and the residue purified by chromatography (eluting with ethyl acetate/light petroleum, 1:3 + 0.5 % triethylamine) to give the *title compound* as a light red solid (44 mg, 76%); mp 116-120 °C (from light petroleum); (Found: MH^+, 527.2226. $C_{27}H_{35}N_2O_7Si$ requires 527.2214); ν_{max} ($CHCl_3$)/cm^{-1} 2931, 2857, 1624, 1593, 1354, 1274, 1102, 968; δ_H

(400 MHz; $CDCl_3$) 7.37 (1 H, d, *J* 16.3, C<u>H</u>=CH), 7.07 (1H, dd, *J* 8.3, 1.8, ArH), 7.05 (1H, d, *J* 1.8, ArH), 6.84 (1H, d, *J* 8.3, ArH), 6.67 (1H, d, *J* 16.3, CH=C<u>H</u>), 4.47 (2H, s, CH_2), 3.88 (3H, s, OMe), 3.83 (3H, s, OMe), 2.64 (3H, s, Me), 2.62 (3H, s, Me), 1.00 (9H, s, CMe_3), 0.16 (6H, s, $SiMe_2$); δ_C (100 MHz; $CDCl_3$) 189.3 (C), 162.6 (C), 159.2 (C), 157.0 (C), 156.5 (C), 155.4 (C), 152.5 (C), 145.2 (C), 137.1 (CH), 134.3 (C), 128.1 (C), 127.6 (C), 122.1 (CH), 118.9 (CH), 111.8 (CH), 110.6 (CH), 55.4 (Me), 51.8 (Me), 39.5 (CH_2), 25.6 (Me), 18.4 (C), 12.3 (Me), 11.9 (Me), -4.7 (Me); *m/z* (ESI) 527 (MH^+, 100%).

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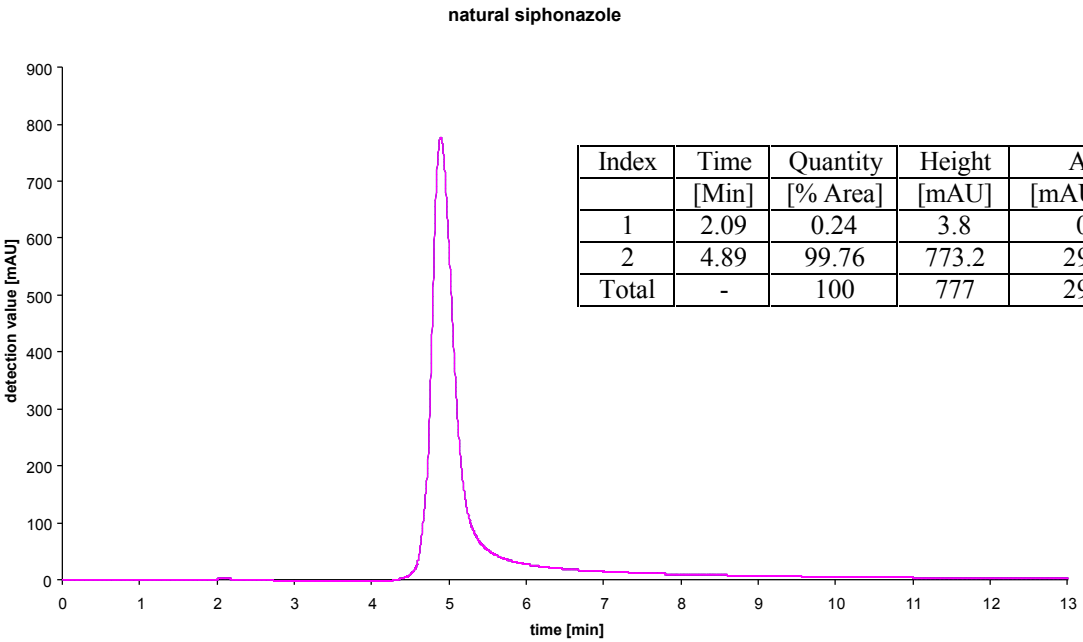
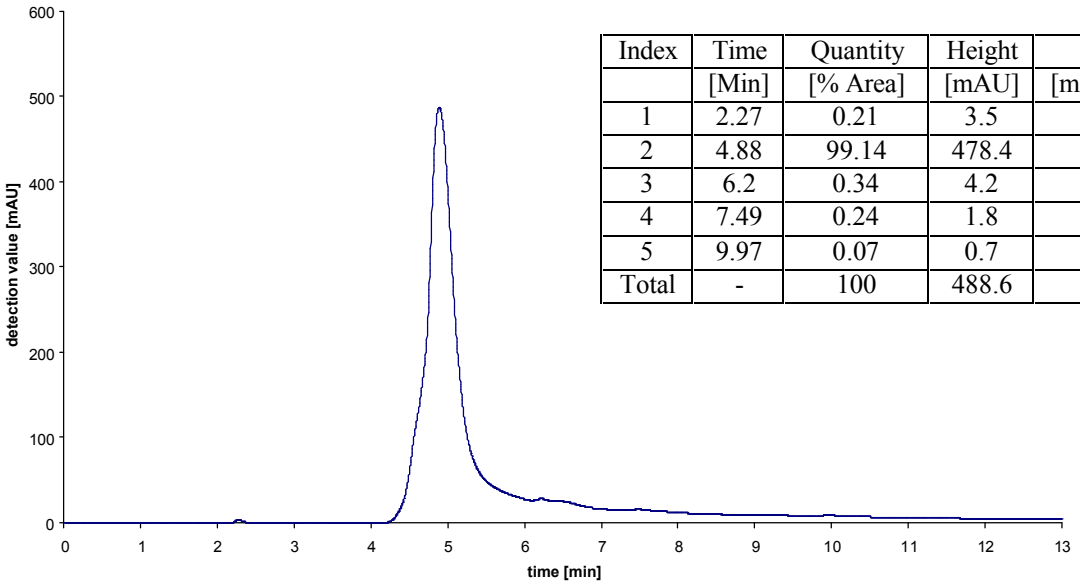
Comparison of HPLC-retention times of natural, synthetic and a mixture of natural and synthetic siphonazole

Column: Varian Polaris C_{18}, 5 mm, 250 x 4.6 mm, eluent: acetonitrile/water 75:25; flow rate: 1 $mLmin^{-1}$



Index	Time	Quantity	Height	Area	Area %
	[Min]	[% Area]	[mAU]	[mAU.Min]	[%]
1	2.09	0.24	3.8	0.7	0.242
2	4.89	99.76	773.2	291.1	99.758
Total	-	100	777	291.8	100



Index	Time	Quantity	Height	Area	Area %
	[Min]	[% Area]	[mAU]	[mAU.Min]	[%]
1	2.27	0.21	3.5	0.5	0.205
2	4.88	99.14	478.4	217.6	99.144
3	6.2	0.34	4.2	0.8	0.344
4	7.49	0.24	1.8	0.5	0.237
5	9.97	0.07	0.7	0.2	0.069
Total	-	100	488.6	219.5	100

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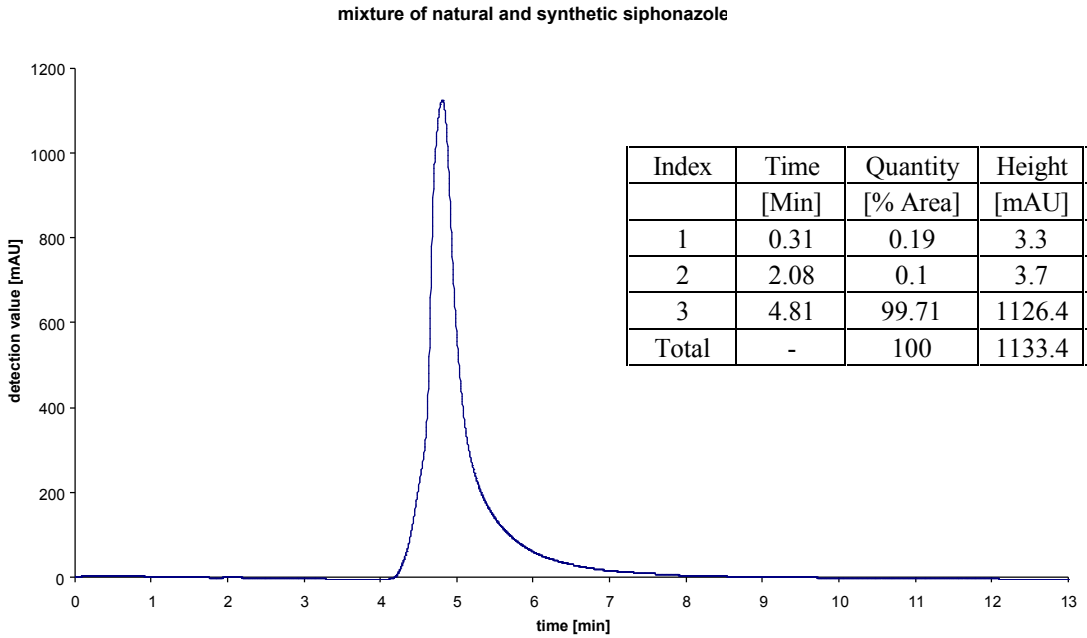

Index	Time	Quantity	Height	Area	Area %
	[Min]	[% Area]	[mAU]	[mAU.Min]	[%]
1	0.31	0.19	3.3	1.2	0.188
2	2.08	0.1	3.7	0.6	0.104
3	4.81	99.71	1126.4	618.7	99.708
Total	-	100	1133.4	620.5	100

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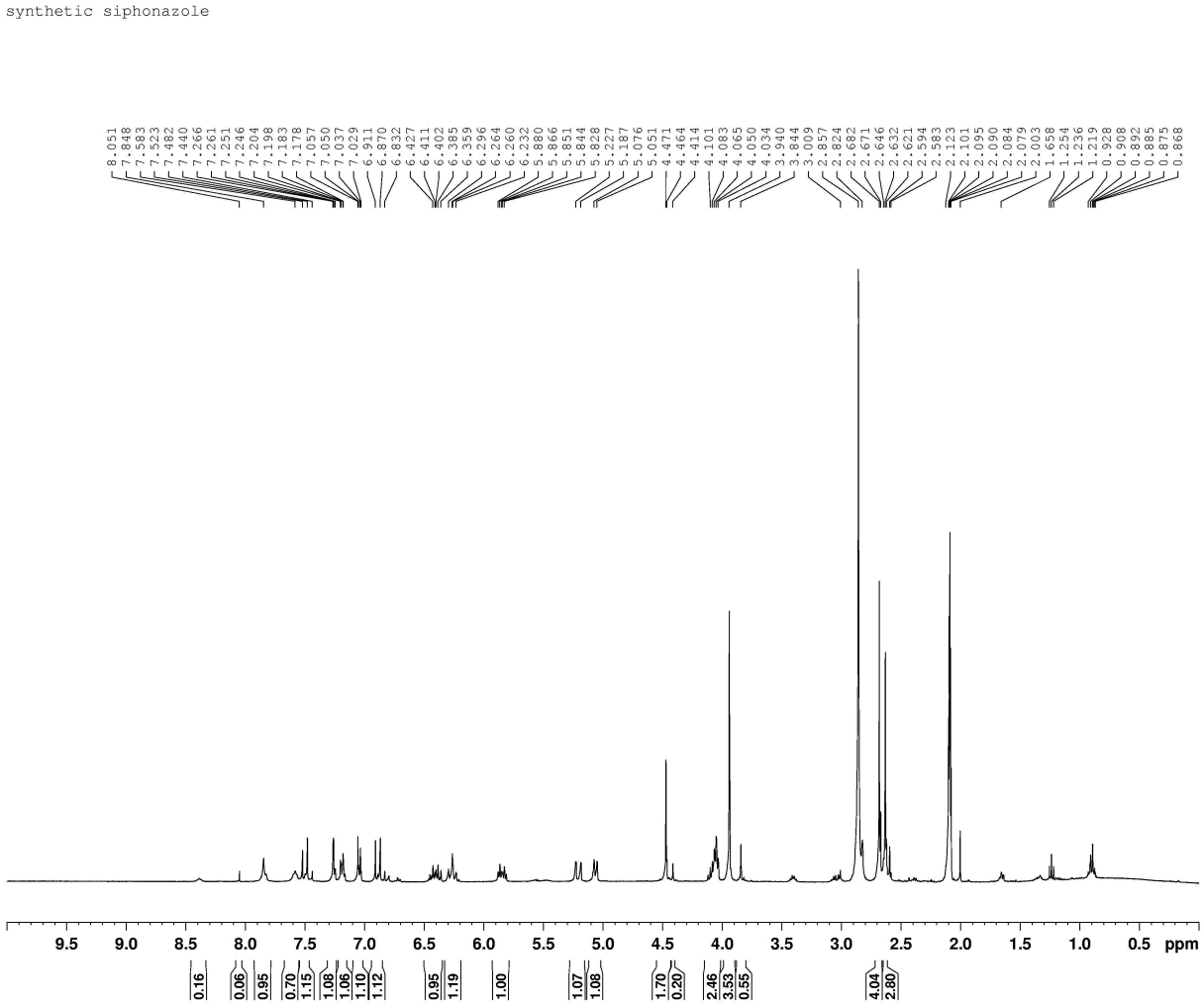
Siphonazole

Final purification by reversed phase preparative HPLC (Varian Polaris, C_{18} 250 × 21.2 mm; eluent: acetonitrile/water 65:35, flow rate 18 mL/min; retention time 6.0 min); obtained as a white solid; mp 62-65 °C (from dichloromethane) (lit.,[11] mp not given); (Found: M^+, 463.1763. $C_{25}H_{25}N_3O_6$ requires 463.1743.); ν_{max} ($CHCl_3$)/cm^{-1} 2958, 2928, 1731, 1658, 1593, 1461, 1374, 1281, 1130, 1046, 967; δ_H (400 MHz; $CDCl_3$) 7.81 (1H, s, NH), 7.47 (1 H, d, *J* 16.4, CH=C<u>H</u>), 7.23 (1H, d, *J* 2.1, ArH), 7.15 (1H, dd, *J* 8.3; 2.1, ArH), 7.01 (1H, d, *J* 8.3, ArH), 6.86 (1H, d, *J* 16.4, C<u>H</u>=CH), 6.42-6.33 (1H, m, H_2C=C<u>H</u>CH=CHCH_2NH) 6.23-6.20 (1H, m, H_2C=CHC<u>H</u>=CHCH_2NH), 5.81 (1H, dt, *J* 14.9, 5.9, H_2C=CHCH=C<u>H</u>CH_2NH), 5.20-5.15 (1H, m, <u>H_2</u>C=CHCH=CHCH_2NH), 5.04-5.02 (1H, m, <u>H_2</u>C=CHCH=CHCH_2NH), 4.44 (2H, s, C<u>H_2</u>CO), 4.02-4.00 (2H, m, CH_2CHCHCHC<u>H_2</u>NH), 3.91 (3H, s, OMe), 2.65 (3H, s, Me), 2.60 (3H, s, Me); δ_C (125 MHz; $CDCl_3$) 190.1 (C), 161.9 (C), 160.0 (C), 156.8 (C), 155.9 (C), 153.8 (C), 150.1 (C), 147.9 (C), 138.2 (CH), 137.6 (CH), 135.3 (C), 132.7 (CH), 131.9 (CH), 130.5 (C), 129.5 (C), 121.4 (CH), 117.0 (CH_2), 113.9 (CH), 112.4 (CH), 111.5 (CH), 56.3 (Me), 40.7 (CH_2), 40.0 (CH_2), 12.2 (Me), 11.5 (Me); *m/z* (EI) 463 (M^+, 100%), 410 (36), 381 (53), 277 (57), 168 (83), 127 (34).

Synthetic siphonazole. ^{1}H-NMR (acetone-d_6): Bruker AV400: 400 MHz



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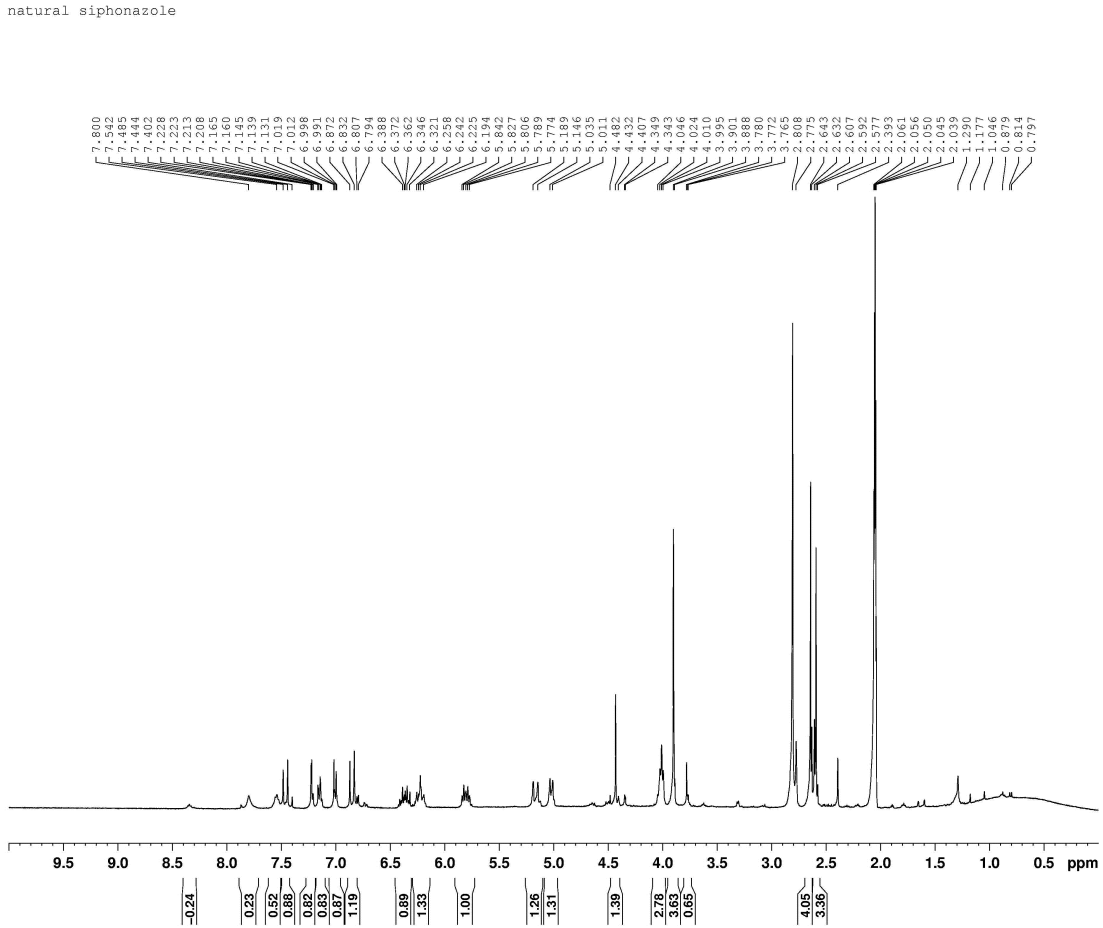
Natural siphonazole. ^{1}H-NMR (acetone-d_6): Bruker AV400: 400 MHz



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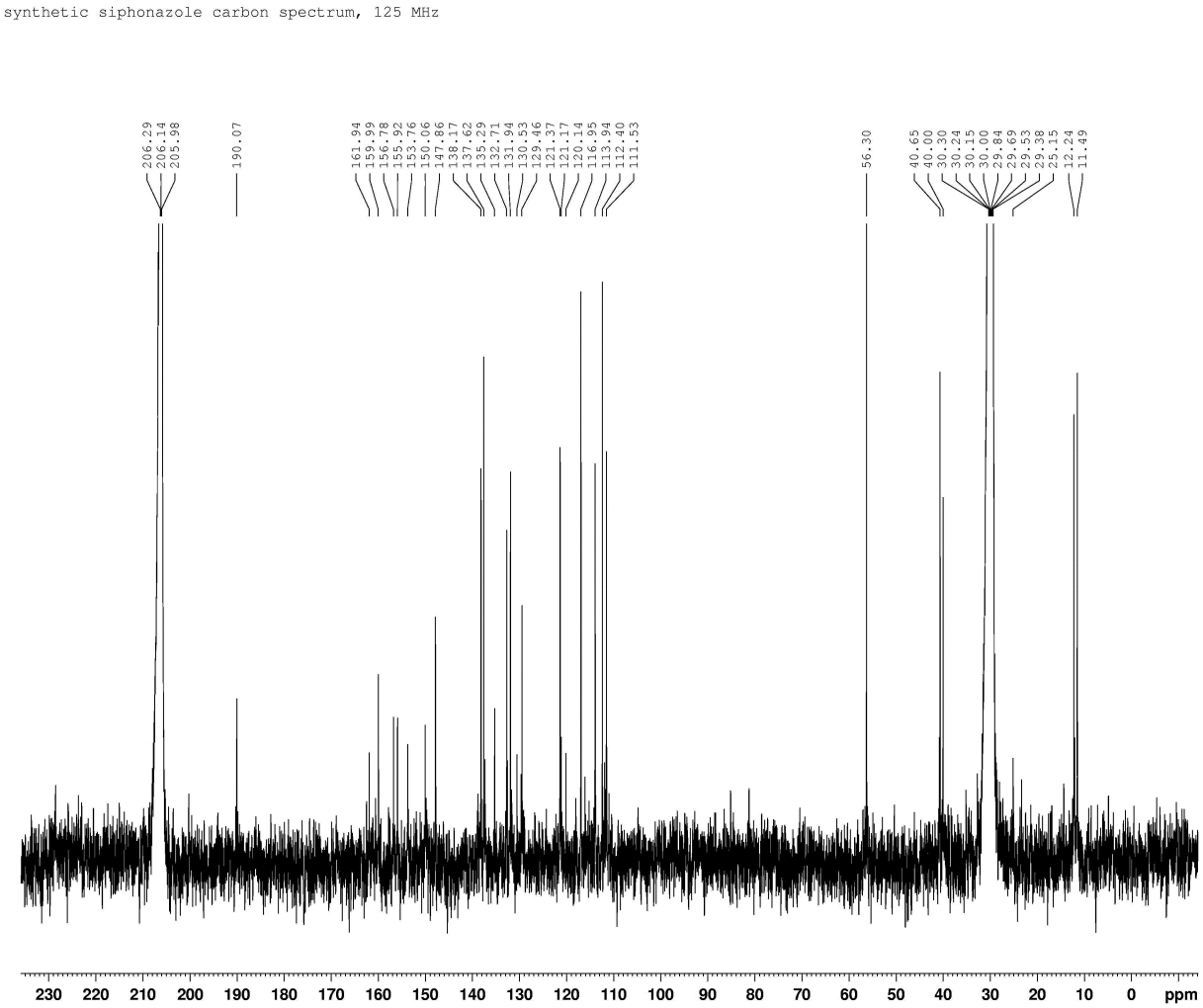
Synthetic siphonazole. ^{13}C-NMR (acetone-d_6): Bruker DRX 500: 125 MHz



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