Total Synthesis of (±)-Cylindricines A and B

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SUPPORTING INFORMATION

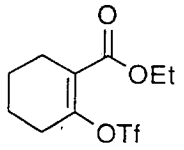
Experimental Section

General. Unless otherwise noted, materials were obtained from commercial suppliers and were used without further purification. Diethyl ether (Et_2O) and tetrahydrofuran (THF) were distilled from Na/benzophenone immediately prior to use. Triethylamine (Et_3N), diisopropylamine (*i*-Pr_2NH), diisopropylethylamine (DIEA), dichloromethane (CH_2Cl_2), toluene, and benzene were distilled from calcium hydride immediately prior to use. Organolithium reagents were titrated periodically with diphenylacetic acid and Grignard reagents were titrated with 1,10-phenanthroline and 1.0 M *s*-butanol in xylene. Unless otherwise noted, organic layers were dried over anhydrous $MgSO_4$, filtered through a funnel equipped with a glass frit and concentrated *in vacuo* with a rotary evaporator at aspirator pressure (approximately 30 mm Hg.) Compounds containing amines were dried over anhydrous K_2CO_3. All non-aqueous reactions were conducted under a dry nitrogen atmosphere. Glassware was flame-dried and cooled under positive nitrogen pressure prior to use.

For analytical thin layer chromatography, Merck kieselgel 60 F_{254} (250 micron thickness) plates were used. Chromatography, as described by the procedure of Still,[1] was performed with EM silica gel 60 (230-400 mesh). IR spectra were determined as thin films on NaCl plates unless otherwise noted. NMR spectra were measured as solutions in $CDCl_3$ and chemical shifts are expressed in ppm of the δ scale relative to chloroform at 7.26 ppm (^1H) or 77.0 ppm (^{13}C) unless otherwise specified. The chemical shifts for ^1H NMR spectra obtained in C_6D_6 are expressed in

ppm of the δ scale relative to benzene at 7.16 ppm. Significant ^{1}H NMR data are tabulated in order: chemical shift (multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad), number of protons, coupling constant(s) in Hertz). HPLC was performed with a Rainin Dynamax 60A silica gel column. Elemental analyses were performed by the Microanalytical Laboratory, operated by the College of Chemistry, University of California, Berkeley and by MHW Laboratories of Phoenix, Arizona.

Trifluoromethanesulfonic anhydride (Tf_2O). The procedure of Stang[2] was modified. Phosphorus pentoxide (7.50 g, 26.4 mmol) and trifluoromethanesulfonic acid (10.0 g, 66.6 mmol) were combined in a flask. The flask was capped with a glass stopper, the mixture was shaken gently to mix, and the slurry was allowed to sit at rt for 1.5 h. A nitrogen-flushed, cotton-wrapped shortpath distillation apparatus was attached and the flask was immersed in a preheated 125 °C oil bath. Distillation under a nitrogen atmosphere afforded 6.92 g (74%) of Tf_2O as a colorless liquid.



16

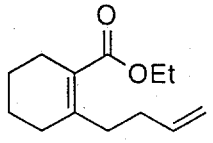
Ethyl 2-trifluoromethanesulfonyloxy-1-cyclohexene-1-carboxylate (16). A solution of DIEA (3.76 mL, 21.6 mmol) in CH_2Cl_2 (115 mL) was stirred at -78 °C. Ethyl 2-cyclohexanonecarboxylate (2.30 mL, 14.4 mmol) was added via syringe and the solution was stirred for 1 h. Tf_2O (3.40 mL, 20.2 mmol) was added slowly via syringe and the solution was stirred for an additional 10 min at -78 °C. The rapidly darkening solution was then warmed to rt and allowed to stir for 6 days. The dark brown reaction mixture was poured into a separatory funnel containing CH_2Cl_2 (90 mL). The solution was washed with water (2 x 70 mL) and the aqueous layer was then extracted with CH_2Cl_2 (20 mL). The combined organic layers were washed with brine (70 mL) then dried, filtered, and concentrated to an oil containing dark resinous

solids. Column chromatography (5%, 10% EtOAc/hexanes) afforded 4.26 g of a yellow oil containing the desired product along with recovered starting material. This oil was dissolved in MeOH (30 mL) and the solution was cooled to 0 °C. Sodium borohydride (545 mg, approximately one equivalent) was added and the bubbling mixture was stirred for 5 min at 0 °C. The solution was then warmed to rt and stirred for 30 min. The solution was poured into a separatory funnel containing Et_2O (45 mL) and saturated aqueous NH_4Cl (45 mL) and the layers were shaken and separated. The organic layer was washed sequentially with 30 mL each of saturated aqueous $NaHCO_3$, water, and brine. The organic layer was dried, filtered and concentrated to yield 4.05 g of a yellow oil. Column chromatography (1%, 3% EtOAc/hexanes) yielded 3.55 g (82%) of **16** as a colorless oil. ^1H NMR data matched the literature values.[3]

4-Iodo-1-butene. Triphenylphosphine (6.85 g, 26.1 mmol), 3-buten-1-ol (1.50 mL, 17.4 mmol), and imidazole (2.37 g, 34.8 mmol) were combined in a flask, followed by the addition of CH_3CN (8 mL) and THF (25 mL). The solution was cooled to 0 °C and I_2 (7.51 g, 29.6 mmol) was added in three portions over 5 min. The dark solution was warmed to rt and stirred for 25 min, then poured into a separatory funnel containing 0.5 M aqueous $Na_2S_2O_3$ (50 mL) and pentane (50 mL). The layers were shaken and separated. The pentane layer was washed with 0.5 M aqueous $Na_2S_2O_3$ (25 mL) and then the combined aqueous layers were extracted with pentane (4 x 30 mL). The combined pentane layers were washed with brine (50 mL). The solution was dried and filtered through a plug of silica gel which was eluted with pentane (100 mL). The filtrate was then concentrated to afford 2.28 g (72%) of 4-iodo-1-butene as a colorless liquid. ^1H NMR data matched the literature values.[4]

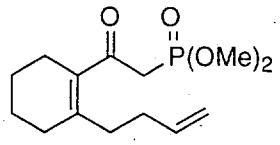
4-Lithio-1-butene. The alkyllithium reagent was synthesized according to the procedure of Negishi.[5] A solution of 4-iodo-1-butene (422 mg, 2.32 mmol) in Et_2O (5 mL) was cooled to -78 °C. *Tert*-butyllithium (3.25 mL, 4.87 mmol, 1.5 M in pentane) was added via syringe and the solution was stirred for 1 h at -78 °C. The solution was then warmed to rt and

used directly in the cuprate reaction with a presumed yield of 90% (the value determined by Negishi).



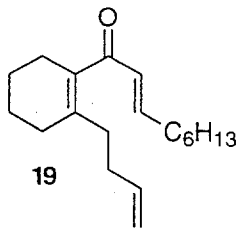
17

Ethyl 2-(3-butenyl)-1-cyclohexene-1-carboxylate (17). A flask containing CuCN (186 mg, 2.08 mmol) was flame-dried and cooled under a stream of dry nitrogen. Et_2O (13 mL) was added and the flask was cooled to -45 °C. Via cannula, a solution of 4-lithio-1-butene (2.09 mmol) in Et_2O (5 mL) was added slowly with a rinse of Et_2O (3 mL). The reddish-brown solution was stirred for 30 min, followed by the addition via cannula of **16** (450 mg, 1.49 mmol) in Et_2O (3 mL). The mixture was stirred for 1.5 h at -45 °C, then quenched by the addition of a 9:1 solution of saturated aqueous NH_4Cl/concentrated NH_4OH (10 mL) and warmed to rt. The mixture was poured into a separatory funnel containing Et_2O (30 mL) and the layers were shaken and separated. The aqueous layer was extracted with Et_2O (15 mL), then the combined organic layers were washed with 0.5 M aqueous HCl (2 x 30 mL), saturated aqueous $NaHCO_3$ (30 mL), and finally brine (30 mL). The solution was dried, filtered and concentrated to 437 mg of a yellow oil. Column chromatography (3% EtOAc/hexanes) afforded 306 mg (99%) of **17** as a colorless oil. The compound appears once in the literature in impure form, and no analytical data is provided.[6] ^{1}H NMR (300 MHz): δ 5.90 - 5.76 (m, 1); 5.01 (dm, 1, J = 17.1)[7]; 4.94 (dm, 1, J = 10.2)[7]; 4.17 (q, 2, J = 7.1); 2.43 - 2.38 (m, 2); 2.27 - 2.11 (m, 6); 1.61 - 1.55 (m, 4); 1.28 (t, 3, J = 7.1). ^{13}C NMR (125 MHz): δ 169.2, 148.0, 138.5, 125.1, 114.4, 59.9, 34.8, 32.8, 31.3, 26.5, 22.3 (2 peaks), 14.3. IR: 1711, 1227 cm^{-1}. Anal. Calcd. for $C_{13}H_{20}O_2$: C, 74.96; H, 9.67. Found: C, 75.28; H, 9.96.



18

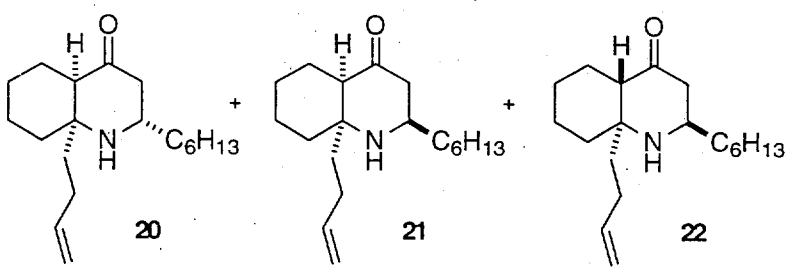
Dimethyl (2-(2-(3-butenyl)-1-cyclohexenyl)-2-oxo-ethyl)-phosphonate (18). A solution of dimethyl methylphosphonate (0.305 mL, 2.81 mmol) in THF (2 mL) was stirred at -78 °C. To this solution was added *n*-butyllithium (1.08 mL, 2.75 mmol, 2.55 M in hexanes) and the solution was stirred for 30 min. A solution of **17** (272 mg, 1.31 mmol) in THF (0.5 mL) was added via cannula with two rinses of THF (0.5 mL each). The solution was stirred for 1.5 h at -78 °C, then warmed to rt and stirred overnight. The reaction was quenched by the addition of saturated aqueous NH_4Cl (15 mL) and the mixture was poured into a separatory funnel containing CH_2Cl_2 (15 mL). The layers were shaken and separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 8 mL) and the combined organic layers were dried, filtered and concentrated to afford 560 mg of a yellow oil. Column chromatography (5%, 20%, 40%, 60%, 70% EtOAc/hexanes) yielded 358 mg (96%) of **18** as a colorless, viscous oil. ^1H NMR (500 MHz): δ 5.84 - 5.76 (m, 1); 5.00 (dm, 1, J = 17.1)[7]; 4.92 (dm, 1, J = 10.2)[7]; 3.76 (d, 6, J = 11.2); 3.20 (d, 2, J = 22.1); 2.29 - 2.26 (m, 4); 2.19 - 2.12 (m, 4); 1.64 - 1.56 (m, 4). ^{13}C NMR (125 MHz): δ 196.5 (d, J = 6.5), 147.0, 138.3, 132.9 (d, J = 2.9), 114.6, 52.9 (d, J = 6.4), 39.5 (d, J = 131), 34.6, 32.7, 30.9, 27.0, 22.3, 22.0. IR: 1678, 1253, 1039 cm^{-1}. Anal. Calcd. for $C_{14}H_{23}O_4P$: C, 58.73; H, 8.10. Found: C, 58.47; H, 8.22.



19

1-(2-(3-Butenyl)-1-cyclohexenyl)-2(*E*)-nonen-1-one (19). To a slurry of LiCl (80.0 mg, 1.89 mmol) in CH_3CN (14 mL) was added **18** (458 mg, 1.60 mmol), followed by CH_3CN rinses (3 x 0.5 mL). Via syringe, DIEA (0.397 mL, 1.76 mmol) was then added,

followed by the addition of heptanal (0.223 mL, 1.60 mmol). The cloudy white reaction mixture was stirred for 45 h at rt. The mixture was diluted with Et_2O (12 mL) and poured into a separatory funnel containing brine (30 mL). The layers were shaken and separated and the aqueous layer was extracted with Et_2O (3 x 5 mL). The combined organic layers were dried, filtered and concentrated to an oil. Column chromatography (3%, 25%, 60%, 80%, 100% EtOAc/hexanes) afforded 388 mg (88%) of **19** as a pale yellow oil. ^1H NMR data matched the literature values.[8]



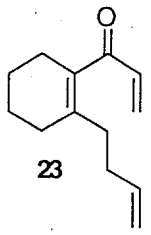
(2α,4aα,8aα)-, (2β,4aα,8aα)-, and (2β,4aβ,8aα)-8a-(3-Butenyl)-2-hexyloctahydro-4-quinolinone (20-22). In a resealable thick-walled pyrex tube **19** (96.8 mg, 0.353 mmol) was stirred in ammonia-saturated EtOH (2.0 mL). Concentrated NH_4OH (1.0 mL) was added and the tube was sealed tightly. The cloudy mixture was heated in a 100 °C oil bath for 16 h, during which time the solution became clear yellow. The tube was allowed to cool to rt and the solution was transferred via pipet to a separatory funnel. Following the addition of 6 M aqueous NaOH (5 mL) the mixture was shaken, then extracted with CH_2Cl_2 (6 x 4 mL). The combined organic layers were washed with brine then dried, filtered and concentrated to an oil. Column chromatography (5%, 10%, 15%, 20% EtOAc/hexanes) afforded 80.5 mg (78% total; 50% + 9% + 19%) of amine isomers **20-22** as pale yellow oils. ^1H NMR data matched the literature values.[8]

(2α,4aα,8aα)-8a-(3-Butenyl)-2-hexyloctahydro-4-quinolinone (20): from 28c. To a solution of **28c** (7.2 mg, 0.0165 mmol) in THF (0.8 mL) was added 49.5 μL (0.0495 mmol, 1.0 M in THF) of TBAF. The solution was stirred at rt for 1 h, then water

(1 mL) was added and the mixture was transferred to a separatory funnel containing 6 M aqueous NaOH (3 mL) and Et_2O (3 mL). The mixture was shaken and the layers were separated. The aqueous layer was extracted with Et_2O (2 x 5 mL) and the combined organic layers were dried, filtered and concentrated to yield 4.3 mg of a pale yellow oil, which consisted of the *cis* and *trans* isomers of **20**. The oil was taken up in MeOH (0.3 mL) and 6 M aqueous NaOH (0.15 mL) was added. The solution was stirred at rt for 7 h, then transferred to a separatory funnel containing 6 M aqueous NaOH (3 mL) and CH_2Cl_2 (3 mL). The mixture was shaken and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 2 mL) and the combined organic layers were dried, filtered and concentrated to yield an oil. Column chromatography (10% EtOAc/hexanes) afforded 4.0 mg (83%) of **20**. ^{1}H NMR data matched the literature values.[8]

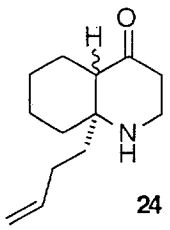
(2α,4aα,8aα)-8a-(3-Butenyl)-2-hexyloctahydro-4-quinolinone (20): from 29c. To a solution of **29c** (22.3 mg, 0.0512 mmol) in THF (2.6 mL) was added 0.154 mL (0.154 mmol, 1.0 M in THF) of TBAF. The solution was stirred at rt for 50 min, then water (3 mL) was added and the mixture was transferred to a separatory funnel containing 6 M aqueous NaOH (5 mL) and Et_2O (5 mL). The mixture was shaken and the layers were separated. The aqueous layer was extracted with Et_2O (3 x 5 mL) and the combined organic layers were dried, filtered and concentrated to yield an oil. Column chromatography (10% EtOAc/hexanes) afforded 13.2 mg (89%) of **20**. ^{1}H NMR data matched the literature values.[8]

(2α,4aα,8aα)-8a-(3-Butenyl)-2-hexyloctahydro-4-quinolinone (20): from 31. A solution of **31** (4.9 mg, 0.0150 mmol) and $AgNO_3$ (4.7 mg, 0.0277 mmol) in MeOH (0.2 mL) was heated to reflux for 15 h. The mixture was cooled to rt, then concentrated to a residue. Column chromatography (5%, 10% EtOAc/hexanes) afforded 4.1 mg (94%) of **20**. ^{1}H NMR data matched the literature values.[8]



23

1-(2-(3-Butenyl)-1-cyclohexenyl)-2-propen-1-one (23). To a solution of **18** (423 mg, 1.48 mmol) in benzene (28 mL) was added NaH (72.0 mg, 1.80 mmol, 60% dispersion in mineral oil). The reaction was stirred for 30 min at rt, then paraformaldehyde (133 mg, 4.44 mmol) was added and the cloudy white reaction was stirred a further 1.5 h. Following the addition of 1M aqueous HCl (8 mL) the mixture was poured into a separatory funnel containing brine (20 mL) and CH_2Cl_2 (25 mL). The mixture was shaken and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (4 x 10 mL). The combined organic layers were washed with brine then dried, filtered and concentrated to an oil. Column chromatography (5% EtOAc/hexanes) afforded 243 mg (86%) of **23** as a pale yellow oil. ^{1}H NMR (400 MHz): δ 6.43 (dd, 1, J = 10.3, 17.5); 6.20 (dd, 1, J = 1.5, 17.5); 5.91 (dd, 1, J = 1.5, 10.4); 5.79 - 5.69 (m, 1); 4.98 (dd, 1, J = 1.7, 17.1)[7]; 4.92 (dd, 1, J = 1.8, 10.2)[7]; 2.16 - 2.08 (m, 8); 1.67 - 1.61 (m, 4). ^{13}C NMR (100 MHz): δ 200.4, 139.5, 138.1, 136.5, 132.9, 130.0, 114.7, 34.3, 32.4, 28.9, 27.1, 22.4, 22.2. IR: 1659 cm^{-1}. Anal. Calcd. for $C_{13}H_{18}O$: C, 82.06; H, 9.54. Found: C, 81.93; H, 9.77.



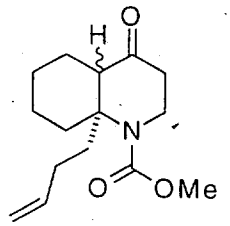
24

***Cis* and *trans* 8a-(3-butenyl)octahydro-4(1*H*)-quinolinone (24).** In a resealable thick-walled pyrex tube **23** (438 mg, 2.30 mmol) was stirred in ammonia-saturated EtOH (7.0 mL). Concentrated NH_4OH (3.5 mL) was added and the tube was sealed tightly. The cloudy mixture was heated in a 105 °C oil bath for 18.5 h, during which time the solution became

clear yellow. The tube was allowed to cool to rt and the solution was transferred via pipet to a separatory funnel. Following the addition of 6 M aqueous NaOH (10 mL) the mixture was shaken, then extracted with CH_2Cl_2 (5 x 15 mL). The combined organic layers were washed with brine then dried, filtered and concentrated to afford 463 mg (97%) of crude amine isomers **24** (pale yellow oil) in sufficient purity for subsequent reactions. Anal. Calcd. for $C_{13}H_{21}NO$: C, 75.32; H, 10.21; N, 6.76. Found: C, 75.63; H, 10.56; N, 6.50. For the purpose of individual analysis the isomers could be separated via column chromatography (70%, 80%, 90% EtOAc/hexanes).

less polar isomer: ^{1}H NMR (400 MHz): δ 5.84 - 5.74 (m, 1); 5.00 (dd, 1, J = 1.6, 17.1)[7]; 4.92 (d, 1, J = 10.1)[7]; 3.23 - 3.17 (m, 1); 3.09 - 3.02 (m, 1); 2.55 - 2.47 (m, 1); 2.19 - 2.13 (m, 2); 2.09 - 1.89 (m, 3); 1.74 - 1.49 (m, 6); 1.43 - 1.18 (m, 4). ^{13}C NMR (125 MHz): δ 212.9, 138.5, 114.6, 57.5, 56.7, 40.3, 39.2, 37.3, 34.0, 26.6, 25.2, 24.0, 21.4. IR: 1706, 1640 cm^{-1}.

more polar isomer: ^{1}H NMR (400 MHz): δ 5.82 - 5.72 (m, 1); 4.99 (dd, 1, J = 1.7, 17.1)[7]; 4.91 (dd, 1, J = 1.7, 10.1)[7]; 3.25 - 3.19 (m, 1); 3.09 - 3.02 (m, 1); 2.51 - 2.42 (m, 1); 2.32 - 2.25 (m, 2); 2.01 - 1.76 (m, 4); 1.68 - 1.56 (m, 3); 1.47 (br s, 1); 1.43 - 1.29 (m, 2); 1.26 - 1.15 (m, 3). ^{13}C NMR (125 MHz): δ 210.4, 138.4, 114.6, 61.4, 59.8, 42.6, 41.3, 36.0, 26.0, 25.3, 25.0, 21.6, 20.4. IR: 1708, 1639 cm^{-1}.



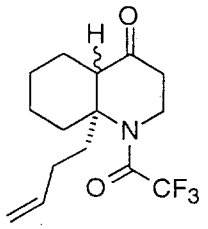
25a

***Cis* and *trans* methyl 8a-(3-butenyl)octahydro-4-quinolinone-1-carboxylate (25a).** A solution of **24** (208 mg, 1.00 mmol) in CH_3CN (4.1 mL) was stirred at rt. Solid K_2CO_3 (240 mg, 1.74 mmol) was added, followed by methyl chloroformate (0.116 mL, 1.50 mmol). The slurry was stirred for 50 h at rt, then saturated aqueous NH_4Cl (8 mL) was

added. The solution was poured into a separatory funnel and extracted with CH_2Cl_2 (5 x 8 mL). The organic layer was washed with brine (20 mL) then dried, filtered and concentrated to yield an oil. Column chromatography (5%, 10%, 15%, 20% EtOAc/hexanes) afforded 215 mg (81%) of **25a** (colorless oil) as a mixture of *cis* and *trans* isomers. Anal. Calcd. for $C_{15}H_{23}NO_3$: C, 67.90; H, 8.74; N, 5.28. Found: C, 67.60; H, 9.03; N, 5.43. For the purpose of individual analysis the isomers could be separated via column chromatography (5%, 10%, 15%, 20% EtOAc/hexanes). The identities of the *cis* and *trans* isomers were determined using DEPT and HMQC NMR experiments.

***cis* isomer (less polar):** ^{1}H NMR (500 MHz): δ 5.85 - 5.77 (m, 1); 5.04 (dd, 1, J = 1.6, 17.1)[7]; 4.96 (dd, 1, J = 1.6, 10.2)[7]; 4.39 (ddd, 1, J = 2.7, 5.3, 14.0); 3.69 (s, 3); 3.48 (ddd, 1, J = 4.2, 11.7, 14.0); 2.90 (br s, 1); 2.59 (br m, 1); 2.53 - 2.40 (m, 2); 2.35 (m, 1); 2.17 - 2.15 (m, 1); 2.10 - 2.04 (m, 2); 2.03 - 1.97 (m, 1); 1.56 - 1.40 (m, 6). ^{13}C NMR (125 MHz): δ 210.5, 155.6, 138.1, 114.9, 61.3, 52.3, 49.7, 40.6, 39.5, 35.5, 32.8, 27.9, 22.0, 21.9, 21.1. IR: 1719, 1697 cm^{-1}.

***trans* isomer (more polar):** ^{1}H NMR (500 MHz): δ 5.74 - 5.66 (m, 1); 4.95 (dd, 1, J = 1.6, 17.1)[7]; 4.90 (br d, 1, J = 9.5)[7]; 4.22 (ddd, 1, J = 3.3, 5.6, 14.2); 3.76 (ddd, 1, J = 4.4, 11.2, 14.2); 3.69 (s, 3); 2.79 (br d, 1, J = 12.8); 2.70 (dd, 1, J = 3.1, 11.9); 2.58 - 2.51 (m, 1); 2.48 - 2.43 (m, 1); 2.19 - 2.13 (m, 1); 1.95 - 1.86 (m, 2); 1.83 - 1.80 (m, 1); 1.77 - 1.64 (m, 3); 1.59 - 1.38 (m, 3); 1.28 - 1.18 (m, 1). ^{13}C NMR (125 MHz): δ 210.1, 155.8, 138.0, 114.6, 62.8, 55.2, 52.2, 39.7, 39.6, 37.1, 30.7, 28.3, 24.5, 22.1, 20.7. IR: 1721, 1699 cm^{-1}.

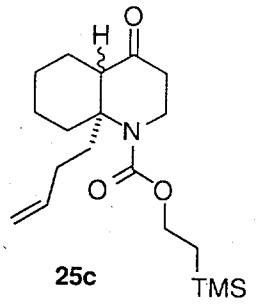


25b

***Cis* and *trans* 8a-(3-butenyl)octahydro-4-quinolinone-1-((trifluoromethyl)carbonyl) (25b).** A solution of **24** (150 mg, 0.723 mmol) in CH_2Cl_2 (3.6 mL) was stirred at rt. Triethylamine (0.302 mL, 2.17 mmol) was then added, followed by trifluoroacetic anhydride (0.205 mL, 1.45 mmol). The mixture was stirred for 6 h, then poured into a separatory funnel containing saturated aqueous $NaHCO_3$ (10 mL). The layers were shaken and separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 3 mL). The combined organic layers were dried, filtered and concentrated to yield a dark oil. Column chromatography (5%, 10%, 15% EtOAc/hexanes) afforded 209 mg (96%) of **25b** (colorless oil) as a mixture of *cis* and *trans* isomers. Anal. Calcd. for $C_{15}H_{20}F_3NO_2$: C, 59.40; H, 6.65; N, 4.62. Found: C, 59.38; H, 7.00; N, 4.55. For the purpose of individual analysis the isomers could be separated via column chromatography (5%, 10%, 15% EtOAc/hexanes).

***cis* isomer (less polar):** ^{1}H NMR (500 MHz): δ 5.85 - 5.77 (m, 1); 5.07 (dd, 1, J = 1.5, 17.1)[7]; 5.00 (dd, 1, J = 1.1, 10.1)[7]; 4.07 (br d, 1, J = 14.5); 3.77 - 3.70 (m, 1); 3.06 - 3.05 (m, 1); 2.91 (br d, 1, J = 13.7); 2.71 - 2.65 (m, 1); 2.56 - 2.53 (m, 2); 2.25 - 2.22 (m, 1); 2.18 - 2.02 (m, 3); 1.60 - 1.44 (m, 5); 1.31 - 1.25 (m, 1). ^{13}C NMR (125 MHz):[9] δ 207.9, 156.2, 137.4, 115.5, 65.1, 48.8, 41.4, 39.1, 33.4, 30.5, 27.9, 21.8, 21.4, 20.6. IR: 1726, 1688, 1189, 1139 cm^{-1}.

***trans* isomer (more polar):** ^{1}H NMR (500 MHz): δ 5.71 - 5.63 (m, 1); 4.96 (dd, 1, J = 1.3, 17.1)[7]; 4.92 (dd, 1, J = 1.3, 10.5)[7]; 4.04 - 4.00 (m, 1); 3.93 (ddd, 1, J = 4.2, 11.8, 14.7); 3.02 - 2.99 (m, 1); 2.80 (dd, 1, J = 3.1, 11.8); 2.66 - 2.59 (m, 1); 2.57 - 2.51 (m, 1); 2.46 - 2.37 (m, 1); 2.00 - 1.96 (m, 1); 1.86 - 1.68 (m, 5); 1.62 - 1.42 (m, 3); 1.30 - 1.21 (m, 1). ^{13}C NMR (125 MHz): δ 207.7, 156.1 (m, J = 34.7), 137.3, 116.3 (q, J = 289), 115.3, 66.4, 54.6, 40.1 (q, J = 4.7), 39.3, 35.7, 29.4, 28.5, 24.4, 22.0, 20.6. IR: 1726, 1690 cm^{-1}.



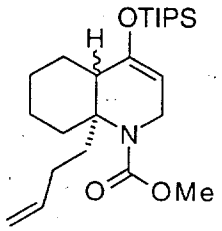
25c

***Cis* and *trans* (2-trimethylsilyl)ethyl 8a-(3-butenyl)octahydro-4-quinolinone-1-carboxylate (25c).** A solution of **24** (29.0 mg, 0.140 mmol) in CH_3CN (0.7 mL) was stirred at rt. Solid K_2CO_3 (48.4 mg, 0.350 mmol) was added, followed by TEOC-OSu[10] (72.6 mg, 0.280 mmol). The slurry was stirred at rt for 24 h, then poured into a separatory funnel containing CH_2Cl_2 (3 mL) and saturated aqueous $NaHCO_3$ (3 mL). The layers were shaken and separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 3 mL) and the organic layer was dried, filtered and concentrated to yield an oil which solidified upon standing. Column chromatography (5%, 10%, 15% EtOAc/hexanes with 3% Et_3N added) afforded 41.9 mg (85%) of **25c** (colorless oil) and 1.6 mg (6%) of recovered **24**. Anal. Calcd. for $C_{19}H_{33}NO_3Si$: C, 64.89; H, 9.47; N, 3.99. Found: C, 64.70; H, 9.78; N, 4.22. For the purpose of individual analysis the isomers could be separated via column chromatography (5%, 10%, 15% EtOAc/hexanes).

***cis* isomer (less polar):** ^{1}H NMR (400 MHz): δ 5.85 - 5.75 (m, 1); 5.02 (dd, 1, J = 1.0, 17.1)[7]; 4.94 (d, 1, J = 10.1)[7]; 4.39 (ddd, 1, J = 2.7, 4.9, 14.1); 4.16 (t, 2, J = 8.2); 3.45 (ddd, 1, J = 4.7, 11.4, 13.8); 2.89 (br s, 1); 2.61 (br m, 1); 2.52 - 2.34 (m, 3); 2.16 - 1.94 (m, 4); 1.55 - 1.38 (m, 6); 1.00 (t, 1, J = 8.7); 0.03 (s, 9). ^{13}C NMR (125 MHz): δ 210.5, 155.3, 138.1, 114.8, 63.3, 61.2, 49.7, 40.4, 39.5, 35.6, 32.9, 27.9, 22.0, 21.8, 21.1, 17.8, -1.3, -1.5, -1.7. IR: 1721, 1692, 838 cm^{-1}.

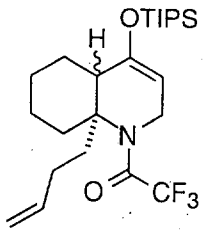
***trans* isomer (more polar):** ^{1}H NMR (500 MHz): δ 5.75 - 5.66 (m, 1); 4.95 (ddd, 1, J = 1.5, 3.1, 17.2)[7]; 4.90 (d, 1, J = 10.2)[7]; 4.25 (ddd, 1, J = 3.2, 5.7, 14.2); 4.22 - 4.13 (m, 2); 3.74 (ddd, 1, J = 4.3, 11.3, 14.4); 2.83 (br d, 1, J = 12.7); 2.71 (dd, 1, J = 3.1, 11.9); 2.58 - 2.51 (m, 1); 2.45 (ddd, 1, J = 3.4, 4.2, 18.7); 2.22 - 2.16 (m, 1); 1.94 - 1.88 (m, 2);

1.83 - 1.80 (m, 1); 1.77 - 1.69 (m, 2); 1.66 - 1.64 (m, 1); 1.59 - 1.38 (m, 3); 1.28 - 1.18 (m, 1); 1.05 - 0.99 (m, 2); 0.04 (s, 9). ^{13}C NMR (125 MHz): δ 210.4, 155.6, 138.2, 114.7, 63.4, 62.8, 55.3, 39.8, 39.5, 37.3, 30.8, 28.5, 24.6, 22.2, 20.8, 17.9, -1.5 (three peaks). IR: 1722, 1693, 838 cm^{-1}.



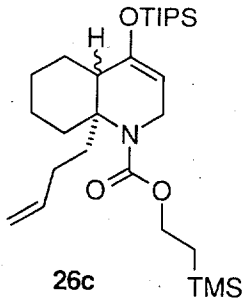
26a

***Cis* and *trans* methyl 8a-(3-butenyl)-4-triisopropylsilyloxy-2,4a,5,6,7,8-hexahydroquinoline-1-carboxylate (26a).** A solution of *i*-Pr$_2$NH (93.0 μL, 0.664 mmol) in THF (1.3 mL) was stirred at 0 °C. Via syringe, *n*-butyllithium (0.245 mL, 0.611 mmol, 2.50 M in hexanes) was added and the solution was stirred for 10 min. The vessel was cooled to -78 °C and a solution of **25a** (135 mg, 0.509 mmol) in THF (0.9 mL) was added via cannula with a rinse of THF (0.4 mL). The solution was stirred for 30 min and triisopropylsilyl trifluoromethanesulfonate (0.165 mL, 0.614 mmol) was then added dropwise via syringe. The solution was stirred for 15 min at -78 °C and then warmed to 0 °C over 15 min. The reaction was quenched with the addition of saturated aqueous $NaHCO_3$ (4 mL) and the mixture was poured into a separatory funnel containing Et_2O (6 mL) and saturated aqueous $NaHCO_3$ (6 mL). The layers were shaken and separated and the aqueous layer was extracted with Et_2O (4 mL). The combined organic layers were washed with water (7 mL) and then with brine (7 mL). The solution was dried, filtered and concentrated to yield an oil. Rapid column chromatography (5%, 10% EtOAc/hexanes) afforded 197 mg (92%) of **26a** (colorless oil) as a mixture of *cis* and *trans* isomers. The mixture of isomers was used immediately in the ensuing CAN oxidation procedure; however, a copy of the ^{1}H NMR spectrum is included in the supplementary information for the reader's reference.



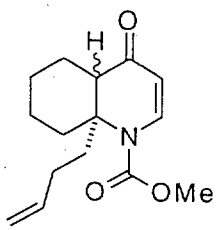
26b

***Cis* and *trans* 8a-(3-butenyl)-4-triisopropylsilyloxy-2,4a,5,6,7,8-hexahydroquinoline-1-((trifluoromethyl)carbonyl) (26b).** Following the procedure for **26a**, 190 mg (0.626 mmol) of **25b** was converted to 255 mg (89%) of **26b** (colorless oil). The mixture of isomers was used immediately in the ensuing CAN oxidation procedure; however, a copy of the ^{1}H NMR spectrum is included in the supplementary information for the reader's reference.



26c

***Cis* and *trans* (2-trimethylsilyl)ethyl 8a-(3-butenyl)-4-triisopropylsilyloxy-2,4a,5,6,7,8-hexahydroquinoline-1-carboxylate (26c).** Following the procedure for **26a**, 93.0 mg (0.264 mmol) of **25c** was converted to 130 mg (97%) of **26c** (colorless oil). The mixture of isomers was used immediately in the ensuing CAN oxidation procedure; however, a copy of the ^{1}H NMR spectrum is included in the supplementary information for the reader's reference.

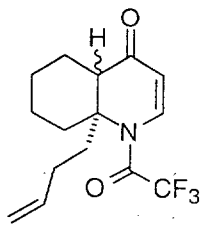


27a

***Cis* and *trans* methyl 8a-(3-butenyl)-4a,5,6,7,8-pentahydro-4-quinolinone-1-carboxylate (27a).** A solution of **26a** (197 mg, 0.467 mmol) in anhydrous DMF (4.7 mL) was stirred at 0 °C. Ceric ammonium nitrate (1.28 g, 2.34 mmol) was added in 5 portions over 20 min. The orange solution was stirred for 1.5 h, then poured into a separatory funnel containing water (10 mL). The aqueous solution was extracted with Et_2O (5 x 10 mL) and the combined organic layers were washed with saturated aqueous $NaHCO_3$ (2 x 20 mL) and brine (20 mL). The solution was dried, filtered and concentrated to yield a yellow oil. Column chromatography (10%, 15%, 20% EtOAc/hexanes) afforded 111 mg (90%) of **27a** as a colorless oil. Anal. Calcd. for $C_{15}H_{21}NO_3$: C, 68.42; H, 8.04; N, 5.32. Found: C, 68.34; H, 8.08; N, 5.39. The mixture of *cis* and *trans* isomers could easily be separated via HPLC using 15% EtOAc/hexanes as the solvent system.

***trans* isomer (less polar):** ^{1}H NMR (400 MHz): δ 7.72 (d, 1, J = 8.5); 5.75 - 5.65 (m, 1); 5.30 (d, 1, J = 8.5); 4.96 (ddd, 1, J = 1.7, 3.3, 17.2)[7]; 4.91 (ddd, 1, J = 1.3, 2.9, 10.2)[7]; 3.79 (s, 3); 3.22 - 3.17 (m, 1); 2.62 (dd, 1, J = 3.8, 11.8); 2.22 - 2.14 (m, 2); 1.96 - 1.88 (m, 2); 1.82 - 1.69 (m, 3); 1.56 (tdd, 1, J = 1.1, 3.9, 13.4); 1.43 - 1.16 (m, 3). ^{13}C NMR (125 MHz): δ 195.0, 153.8, 143.3, 137.9, 114.8, 106.7, 67.2, 53.9, 53.6, 34.2, 28.0, 26.6, 24.5, 22.5, 21.1. IR: 1739, 1675, 1609 cm^{-1}.

***cis* isomer (more polar):** ^{1}H NMR (400 MHz): δ 7.69 (d, 1, J = 8.5); 5.72 - 5.62 (m, 1); 5.22 (dd, 1, J = 1.4, 8.5); 4.95 (dd, 1, J = 3.2, 17.2)[7]; 4.89 (dd, 1, J = 2.8, 10.2)[7]; 3.80 (s, 3); 3.12 - 3.09 (m, 1); 2.17 - 2.06 (m, 2); 1.98 - 1.88 (m, 2); 1.74 - 1.56 (m, 4); 1.47 - 1.38 (m, 1); 1.31 - 1.20 (m, 3). ^{13}C NMR (125 MHz): δ 197.6, 153.7, 143.4, 137.6, 114.9, 105.1, 64.6, 53.7, 53.4, 34.7, 32.2, 27.7, 27.6, 24.5, 21.7. IR: 1739, 1673, 1604 cm^{-1}.

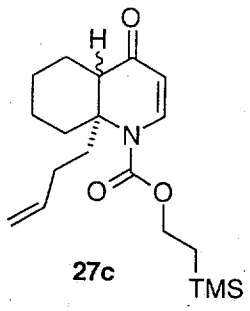


27b

***Cis* and *trans* 8a-(3-butenyl)-4a,5,6,7,8-pentahydro-4-quinolinone-1-((trifluoromethyl)carbonyl) (27b).** A solution of **26b** (217 mg, 0.472 mmol) in anhydrous DMF (4.7 mL) was stirred at 0 °C. Ceric ammonium nitrate (1.30 g, 2.37 mmol) was added in 7 portions over 20 min. The orange solution was then stirred for 7 h and poured into a separatory funnel containing water (15 mL). The aqueous solution was extracted with Et_2O (3 x 10 mL) and the combined organic layers were washed with saturated aqueous $NaHCO_3$ (2 x 10 mL), water (10 mL) and brine (10 mL). The solution was dried, filtered and concentrated to yield a yellow oil. Column chromatography (10%, 15% EtOAc/hexanes) afforded 135 mg (95%) of **27b** as a colorless oil. Anal. Calcd. for $C_{15}H_{18}F_3NO_2$: C, 59.79; H, 6.02; N, 4.65. Found: C, 59.70; H, 5.93; N, 4.73 . The mixture of *cis* and *trans* isomers could easily be separated via HPLC using 15% EtOAc/hexanes as the solvent system.

***trans* isomer (less polar):** ^{1}H NMR (400 MHz): δ 7.36 (ddd, 1, J = 1.9, 3.8, 8.4); 5.74 - 5.64 (m, 1); 5.54 (d, 1, J = 8.5); 4.98 (ddd, 1, J = 1.6, 3.1, 17.1)[7]; 4.93 (ddd, 1, J = 1.2, 2.7, 10.1)[7]; 3.33 - 3.28 (m, 1); 2.73 (dd, 1, J = 3.9, 12.0); 2.27 - 2.13 (m, 2); 1.98 - 1.75 (m, 5); 1.52 (tdd, 1, J = 1.1, 3.7, 13.3); 1.45 - 1.19 (m, 3). ^{13}C NMR (100 MHz): δ 193.7, 156.9 (q, 1, J = 36.6), 138.6 (q, 1, J = 4.7), 137.1, 115.7 (q, 1, J = 291), 115.2, 110.5, 71.4, 54.6, 33.3, 27.9, 26.4, 24.1, 22.4, 21.2. IR: 1732, 1684, 1619, 1192, 1148 cm^{-1}.

***cis* isomer (more polar):** ^{1}H NMR (400 MHz): δ 7.35 (ddd, 1, J = 1.7, 3.3, 8.5); 5.73 - 5.63 (m, 1); 5.48 (dd, 1, J = 1.4, 8.4); 4.98 (ddd, 1, J = 1.5, 3.1, 17.1)[7]; 4.94 (ddd, 1, J = 1.4, 2.8, 10.2)[7]; 3.22 - 3.18 (m, 1); 2.29 (ddd, 1, J = 1.2, 3.8, 12.0); 2.21 - 2.11 (m, 1); 2.05 - 1.93 (m, 2); 1.81 - 1.63 (m, 4); 1.52 - 1.41 (m, 1); 1.39 - 1.22 (m, 2); 1.13 - 1.01 (m, 1). ^{13}C NMR (100 MHz): δ 196.0, 157.1 (q, 1, J = 36.8), 138.5 (q, 1, J = 4.8), 137.0, 115.7 (q, 1, J = 291), 115.4, 108.9, 68.3, 53.7, 34.6, 31.1, 27.5, 24.2, 21.6. IR: 1733, 1682, 1614, 1208, 1150 cm^{-1}.

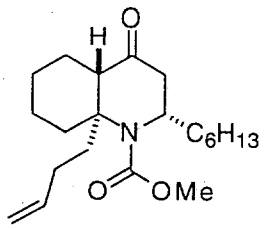


27c

***Cis* and *trans* (2-trimethylsilyl)ethyl 8a-(3-butenyl)-4a,5,6,7,8-pentahydro-4-quinolinone-1-carboxylate (27c).** Following the procedure for **27a**, 163 mg (0.321 mmol) of **26c** was converted to 102 mg (91%) of **27c** (colorless oil). Anal. Calcd. for $C_{19}H_{31}NO_3Si$: C, 65.29; H, 8.94; N, 4.01. Found: C, 64.92; H, 8.97; N, 4.05. The mixture of *cis* and *trans* isomers could easily be separated via HPLC using 15% EtOAc/hexanes as the solvent system.

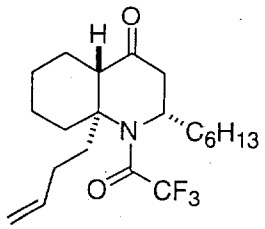
***trans* isomer (less polar):** ^{1}H NMR (400 MHz): δ 7.74 (d, 1, J = 8.5); 5.77 - 5.67 (m, 1); 5.30 (d, 1, J = 8.5); 4.98 (dm, 1, J = 17.1)[7]; 4.92 (dm, 1, J = 10.3)[7]; 4.29 - 4.23 (m, 2); 3.23 (dm, 1, J = 13.1); 2.63 (dd, 1, J = 3.6, 11.9); 2.27 - 2.14 (m, 2); 2.01 - 1.88 (m, 2); 1.83 - 1.70 (m, 3); 1.61 - 1.53 (m, 1); 1.43 - 1.21 (m, 3); 1.10 - 1.05 (m, 2); 0.06 (s, 9). ^{13}C NMR (100 MHz): δ 195.1, 153.4, 143.5, 138.0, 114.7, 106.4, 67.1, 65.5, 53.9, 34.3, 28.1, 26.7, 24.5, 22.5, 21.2, 17.6, -1.6 (3 peaks). IR: 1734, 1676, 1609 cm^{-1}.

***cis* isomer (more polar):** ^{1}H NMR (400 MHz): δ 7.73 (d, 1, J = 8.5); 5.76 - 5.66 (m, 1); 5.23 (dd, 1, J = 1.3, 8.5); 4.98 (dm, 1, J = 17.1)[7]; 4.92 (dm, 1, J = 10.2)[7]; 4.32 - 4.27 (m, 2); 3.15 (dd, 1, J = 4.2, 11.7); 2.19 - 2.10 (m, 2); 2.04 - 1.92 (m, 2); 1.78 - 1.59 (m, 4); 1.50 - 1.39 (m, 1); 1.33 - 1.19 (m, 3); 1.11 - 1.06 (m, 2); 0.07 (s, 9). ^{13}C NMR (100 MHz): δ 197.7, 153.5, 143.6, 137.7, 114.9, 104.8, 65.7, 64.6, 53.5, 34.8, 32.3, 27.9, 27.7, 24.7, 221.9, 17.7, -1.5 (3 peaks). IR: 1733, 1674, 1605 cm^{-1}.



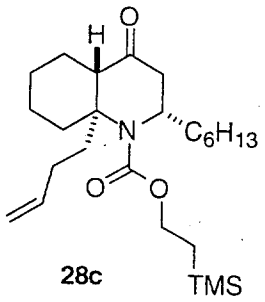
28a

Methyl (2α,4aβ,8aα)-8a-(3-butenyl)-2-hexyloctahydro-4-quinolinone-1-carboxylate (28a). A mixture of **27a** (*trans* isomer) (40.9 mg, 0.155 mmol) and $CuBr•Me_2S$ (128 mg, 0.620 mmol) in THF (1.5 mL) was stirred for 1 h at rt. The slurry was then cooled to -78 °C and $BF_3•Et_2O$ (78.2 μL, 0.636 mmol) was added dropwise. The mixture was stirred a further 1 h at -78 °C and then hexylmagnesium bromide (0.233 mL, 0.465 mmol, 2.0 M in Et_2O) was added dropwise at a rate of one drop per minute. The opaque, creamy brown reaction mixture turned golden yellow upon addition of the Grignard reagent. The mixture was stirred a further 2 h at -78 °C, then quenched with a 9:1 solution of saturated aqueous NH_4Cl/concentrated NH_4OH (3 mL) and warmed to rt. The mixture was transferred into a separatory funnel containing Et_2O (4 mL). The layers were shaken and separated and the aqueous layer was extracted with Et_2O (5 x 4 mL). The combined organic layers were washed with water (2 x 10 mL) and brine (10 mL). The solution was dried, filtered and concentrated to yield an oil. Column chromatography (5%, 10% EtOAc/hexanes) afforded 46.0 mg (85%) of **28a** as a colorless oil. ^1H NMR (500 MHz): δ 5.73 - 5.65 (m, 1); 4.94 (dd, 1, J = 1.4, 17.0)[7]; 4.89 (dd, 1, J = 1.0, 10.2)[7]; 4.46 - 4.42 (m, 1); 3.70 (s, 3); 3.04 (br d, 1, J = 10.8); 2.78 (dd, 1, J = 2.9, 11.6); 2.70 (dd, 1, J = 7.5, 19.6); 2.46 (d, 1, J = 19.6); 2.23 - 2.18 (m, 1); 2.07 - 2.04 (m, 1); 1.94 - 1.80 (m, 3); 1.77 - 1.62 (m, 4); 1.50 - 1.18 (m, 12); 0.88 (t, 3, J = 6.8). ^{13}C NMR (125 MHz): δ 209.1, 156.0, 138.2, 114.7, 63.0, 54.5, 52.2, 52.0, 41.2, 39.4, 38.9, 31.7, 31.3, 29.0, 28.9, 27.6, 24.8, 22.6, 22.4, 20.7, 14.0. IR: 1718, 1702 cm^{-1}. Anal. Calcd. for $C_{21}H_{35}NO_3$: C, 72.17; H, 10.09; N, 4.01. Found: C, 72.38; H, 10.35; N, 3.96.



28b

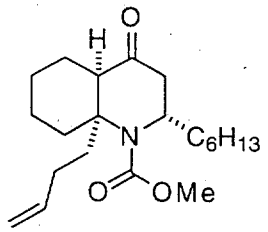
(2α,4aβ,8aα)-8a-(3-Butenyl)-2-hexyloctahydro-4-quinolinone-1-((trifluoromethyl)carbonyl) (28b). Following the procedure for **28a**, 23.0 mg (0.0763 mmol) of **27b** (*trans* isomer) was converted to 26.5 mg (90%) of **28b** (colorless oil). ^{1}H NMR (400 MHz): δ 5.71 - 5.61 (m, 1); 4.97 - 4.91 (m, 2); 4.14 (dd, 1, *J* = 6.8, 13.7); 3.20 - 3.18 (m, 1); 2.96 (dd, 1, *J* = 2.9, 11.5); 2.72 (dd, 1, *J* = 6.8, 19.7); 2.57 (dd, 1, *J* = 1.3, 19.7); 2.54 - 2.47 (m, 1); 2.12 - 2.08 (m, 1); 1.92 - 1.81 (m, 4); 1.77 - 1.41 (m, 6); 1.39 - 1.21 (m, 9); 0.89 (t, 3, *J* = 6.7). ^{13}C NMR (100 MHz): δ 206.6, 156.3 (q, *J* = 34.3), 137.3, 116.5 (q, *J* = 290), 115.3, 67.0, 54.1, 53.1 (q, *J* = 3.8), 40.6, 39.7, 37.9, 31.5, 29.0, 28.8, 27.6, 24.7, 22.5, 22.1, 20.5, 14.0. IR: 1723, 1686 cm^{-1}. Anal. Calcd. for $C_{21}H_{32}F_3NO_2$: C, 65.09; H, 8.32; N, 3.61. Found: C, 64.95; H, 8.28; N, 3.56.



28c

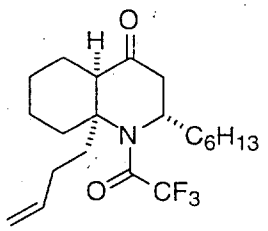
(2-Trimethylsilyl)ethyl (2α,4aβ,8aα)-8a-(3-butenyl)octahydro-4-quinolinone-1-carboxylate (28c). Following the procedure for **28a**, 13.3 mg (0.038 mmol) of **27c** (*trans* isomer) was converted to 14.4 mg (87%) of **28c** (colorless oil). ^{1}H NMR (500 MHz): δ 5.74 - 5.66 (m, 1); 4.94 (d, 1, *J* = 17.1)[7]; 4.90 (d, 1, *J* = 9.6)[7]; 4.47 (br s, 1); 4.23 - 4.12 (m, 2); 3.08 (br d, 1, *J* = 9.8); 2.78 (dd, 1, *J* = 2.8, 11.6); 2.70 (dd, 1, *J* = 7.6, 19.7); 2.46 (d, 1, *J* = 19.6); 2.26 - 2.21 (m, 1); 2.06 - 2.04 (m, 1); 1.95 - 1.80 (m, 3); 1.76 - 1.61 (m, 4); 1.54 - 1.22 (m, 12); 1.06 - 0.99 (m, 2); 0.89 (t, 3, *J* = 6.8); 0.05 (s, 9). ^{13}C

NMR (125 MHz): δ 209.3, 155.8, 138.3, 114.6, 63.3, 62.9, 54.5, 51.8, 41.3, 39.5, 39.0, 31.7, 31.4, 29.0, 29.0, 27.6, 24.9, 22.6, 22.4, 20.7, 17.9, 14.0, -1.5 (3 peaks). IR: 1720, 1694, 838 cm^{-1}. Anal. Calcd. for $C_{25}H_{45}NO_3Si$: C, 68.91; H, 10.41; N, 3.21. Found: C, 69.01; H, 10.40; N, 3.19.



29a

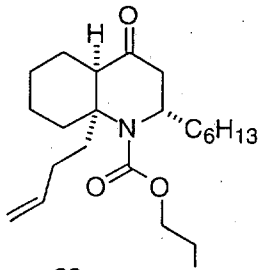
Methyl (2α,4aα,8aα)-8a-(3-butenyl)-2-hexyloctahydro-4-quinolinone-1-carboxylate (29a). Following the procedure for **28a**, 41.1 mg (0.156 mmol) of **27a** (*cis* isomer) was converted to 42.2 mg (77%) of **29a** (colorless oil). ^1H NMR (500 MHz): δ 5.87 - 5.79 (m, 1); 5.04 (d, 1, J = 17.1)[7]; 4.97 (d, 1, J = 10.2)[7]; 4.42 (br s, 1); 3.70 (s, 3); 2.76 - 2.55 (m, 5); 2.43 - 2.40 (m, 1); 1.96 - 1.87 (m, 3); 1.74 - 1.70 (m, 1); 1.60 - 1.12 (m, 15); 0.87 (t, 3, J = 6.7). ^{13}C NMR (125 MHz): δ 209.4, 154.0, 138.3, 114.7, 61.6, 52.2, 51.4, 48.7, 41.4, 37.4, 35.7, 31.7, 31.9, 28.9, 28.5, 27.0, 22.5, 22.0, 21.9, 21.2, 14.0. IR: 1716, 1700 cm^{-1}. Anal. Calcd. for $C_{21}H_{35}NO_3$: C, 72.17; H, 10.09; N, 4.01. Found: C, 72.14; H, 10.20; N, 3.93.



29b

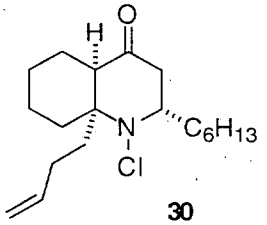
(2α,4aα,8aα)-8a-(3-Butenyl)-2-hexyloctahydro-4-quinolinone-1-((trifluoromethyl)carbonyl) (29b). Following the procedure for **28a**, 64.4 mg (0.214 mmol) of **27b** (*cis* isomer) was converted to 65.1 mg (79%) of **29b** (colorless oil). ^1H NMR (400 MHz): δ 5.87 - 5.77 (m, 1); 5.07 (dd, 1, J = 1.5, 17.1)[7]; 5.00 (dd, 1, J = 1.0,

10.1)[7]; 4.11 - 4.07 (m, 1); 2.97 - 2.91 (m, 2); 2.88 - 2.80 (m, 1); 2.69 (d, 2, J = 3.6); 2.48 - 2.44 (m, 1); 2.00 - 1.92 (m, 3); 1.80 (br m, 1); 1.62 - 1.42 (m, 5); 1.25 - 1.16 (m, 10); 0.87 (t, 3, J = 7.1). ^{13}C NMR (125 MHz):[9] δ 207.1, 156.0 (m, 1, J = 34.1), 137.5, 115.4, 65.8, 52.4, 48.7, 40.4, 38.3, 33.5, 31.6, 30.3, 28.9, 28.8, 27.1, 22.4, 21.8, 21.8, 21.0, 14.0. IR: 1721, 1687 cm^{-1}. Anal. Calcd. for $C_{21}H_{32}F_3NO_2$: C, 65.09; H, 8.32; N, 3.61. Found: C, 65.19; H, 8.51; N, 3.75.



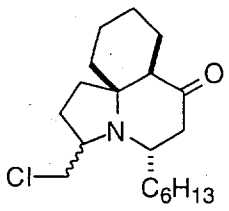
29c

(2-Trimethylsilyl)ethyl (2α,4aα,8aα)-8a-(3-butenyl)octahydro-4-quinolinone-1-carboxylate (29c). Following the procedure for **28a**, 48.4 mg (0.138 mmol) of **27c** (*cis* isomer) was converted to 48.8 mg (81%) of **29c** (colorless oil). ^{1}H NMR (400 MHz): δ 5.87 - 5.77 (m, 1); 5.03 (d, 1, J = 17.0)[7]; 4.96 (d, 1, J = 10.1)[7]; 4.43 (br s, 1); 4.16 (t, 2, J = 8.8); 2.74 - 2.53 (m, 5); 2.40 (br d, 1, J = 13.6); 1.95 - 1.86 (m, 3); 1.74 - 1.67 (m, 1); 1.60 - 1.11 (m, 15); 1.04 - 0.99 (m, 1); 0.86 (t, 2, J = 7.0); 0.04 (s, 9). ^{13}C NMR (125 MHz): δ 209.6, 155.4, 138.4, 114.7, 63.3, 61.5, 51.2, 48.7, 41.5, 37.4, 35.8, 31.7, 29.0, 28.6, 27.1, 22.5, 22.4, 22.0, 21.9, 21.2, 17.9, 14.0, -1.4, -1.6, -1.8. IR: 1717, 1694, 838 cm^{-1}. Anal. Calcd. for $C_{25}H_{45}NO_3Si$: C, 68.91; H, 10.41; N, 3.21. Found: C, 68.54; H, 10.19; N, 3.33.



30

(2α,4aα,8aα)-8a-(3-Butenyl)-1-chloro-2-hexyloctahydro-4-quinolinone (30). A solution of **20** (102 mg, 0.350 mmol) in CH_2Cl_2 (7 mL) was stirred at rt. N-chlorosuccinimide (140 mg, 1.05 mmol) was added and the mixture was stirred for 21 h, then concentrated to a residue. Column chromatography (2%, 4% EtOAc/hexanes) afforded 110 mg (97%) of **30** as a colorless oil. ^1H NMR data matched the literature values.[8]



31

Cylindricine A and *epi*-cylindricine A (31). The THF, glacial AcOH, and distilled deionized water used in this procedure were purged well with argon to remove any dissolved oxygen. A solution of **30** (26.0 mg, 0.0798 mmol) in THF (1.1 mL) was stirred at -5 °C. A bright green solution of glacial AcOH (0.35 mL), water (0.35 mL), and THF (0.70 mL) containing CuCl (7.4 mg, 0.0748 mmol) and $CuCl_2$ (53.3 mg, 0.396 mmol) was prepared. This green copper salt solution was added to the reaction mixture dropwise via syringe over 8 min. The green reaction mixture was then stirred at -5 °C for 50 min. In order to neutralize the acid, 6 M aqueous NaOH (3.0 mL) was added slowly dropwise and the reaction turned from bright green to a darker blue-green. The mixture was transferred to a separatory funnel containing water (10 mL), brine (10 mL) and CH_2Cl_2 (10 mL). The layers were shaken and separated and the aqueous layer was extracted with CH_2Cl_2 (5 x 5 mL). The combined organic layers were dried, filtered and concentrated to yield an oil. Rapid column chromatography (3% EtOAc/hexanes) afforded 22.1 mg (85%) of **31** (pale yellow oil) as a 1.14:1.00 (45%:40%) mixture of cylindricine A and *epi*-cylindricine A. The isomers were separated by HPLC (3% EtOAc/hexanes); each compound's ^1H NMR data matched the literature values.[8,11]

(1) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

(2) Stang, P. J.; Dueber, T. E. *Org. Synth.* **1988**, *Coll. Vol. 6*, 757.

(3) Lin, H.-S.; Rampersaud, A. A.; Zimmerman, K.; Steinberg, M. I.; Boyd, D. B. *J. Chin. Chem. Soc.* **1993**, *40*, 273.

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(5) Negishi, E.; Swanson, D. R.; Rousset, C. J. *J. Org. Chem.* **1990**, *55*, 5406.

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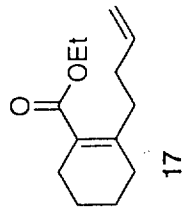
(7) These peaks do not show first-order coupling; however, it is possible to distinguish the major *J* values.

(8) Snider, B. B.; Liu, T. *J. Org. Chem.* **1997**, *62*, 5630.

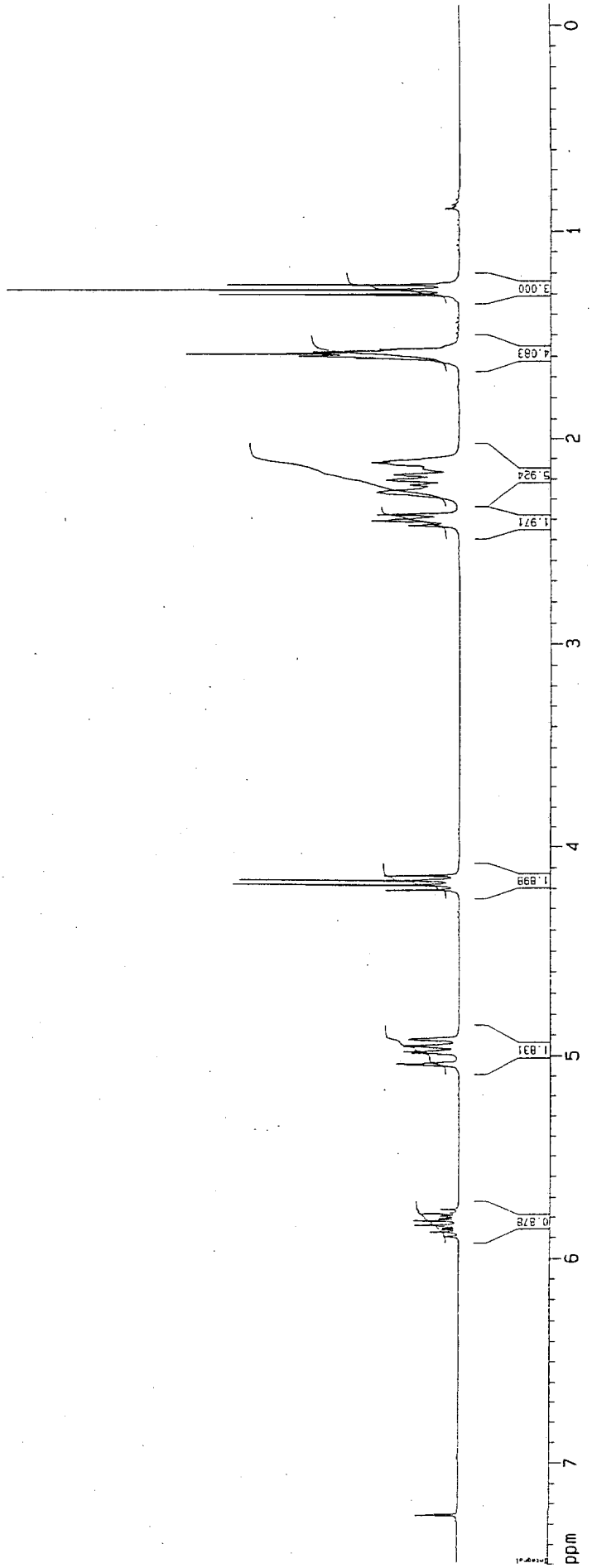
(9) The CF_3 multiplet was not visible in the ^{13}C NMR spectrum of this compound, even using an extended d1 delay period. However, the amide carbonyl stretch is clearly visible in the IR spectrum.

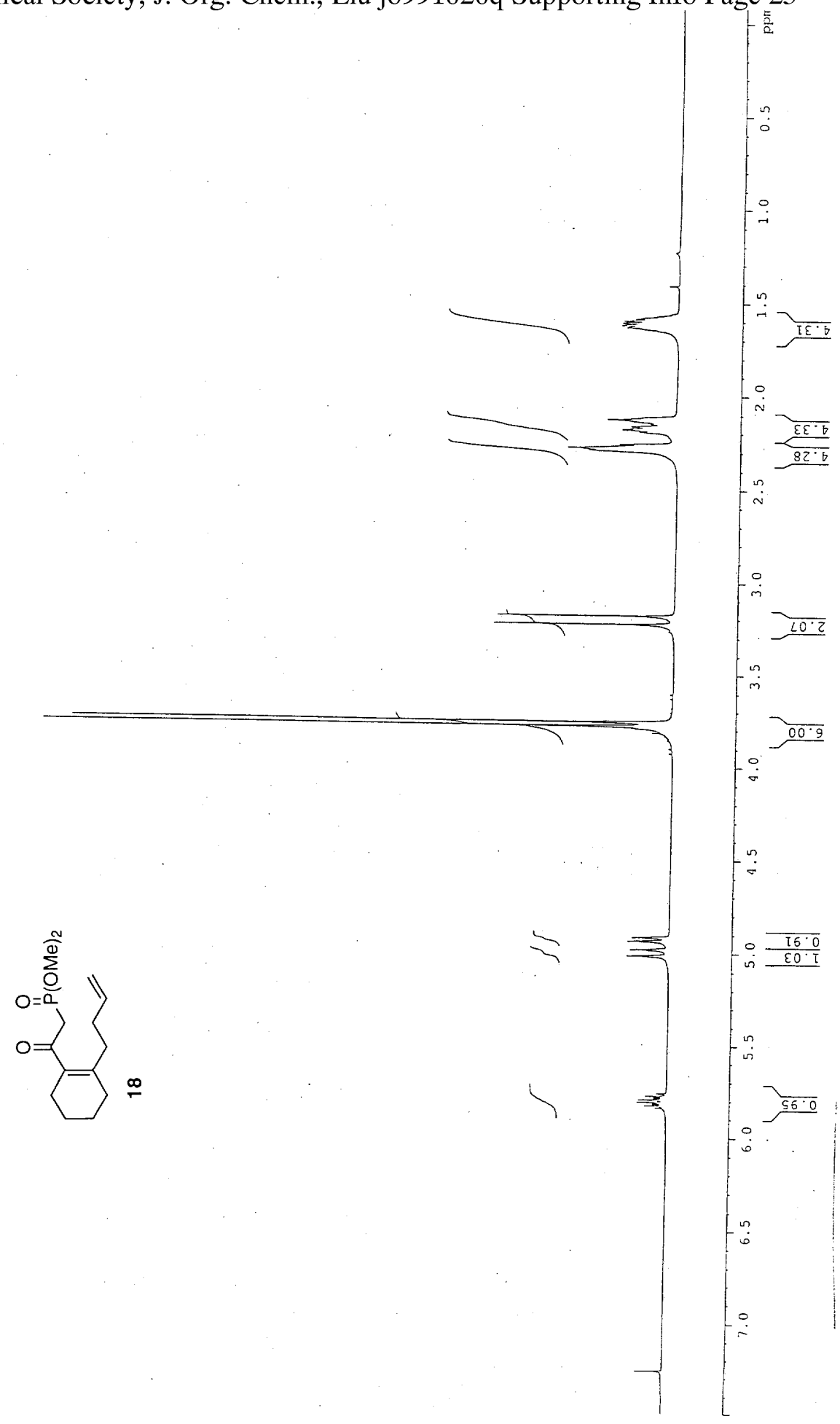
(10) Shute, R. E.; Rich, D. H. *Synthesis* **1987**, *4*, 346.

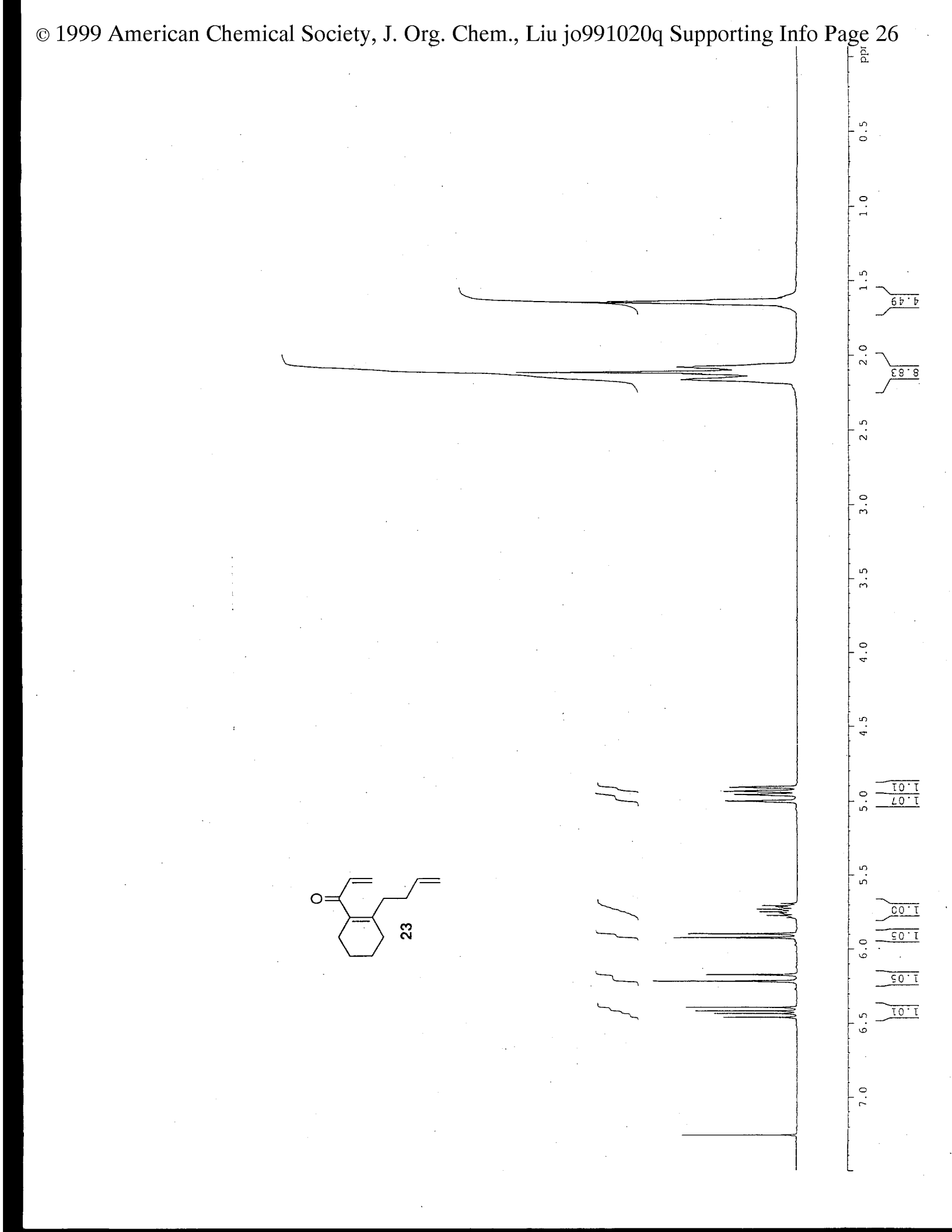
(11) The ^1H NMR spectra of synthetic cylindricine A and of the mixture of synthetic cylindricines A and B were compared to ^1H NMR spectra kindly provided by Professor Adrian J. Blackman of the University of Tasmania, Hobart. The spectra of the natural compounds were plotted with reference to the solvent peak of C_6D_6 at 7.40 ppm; the spectra of the synthetic compounds were plotted with reference to the solvent peak of C_6D_6 at 7.16 ppm. With allowance made for this difference, the data were identical.

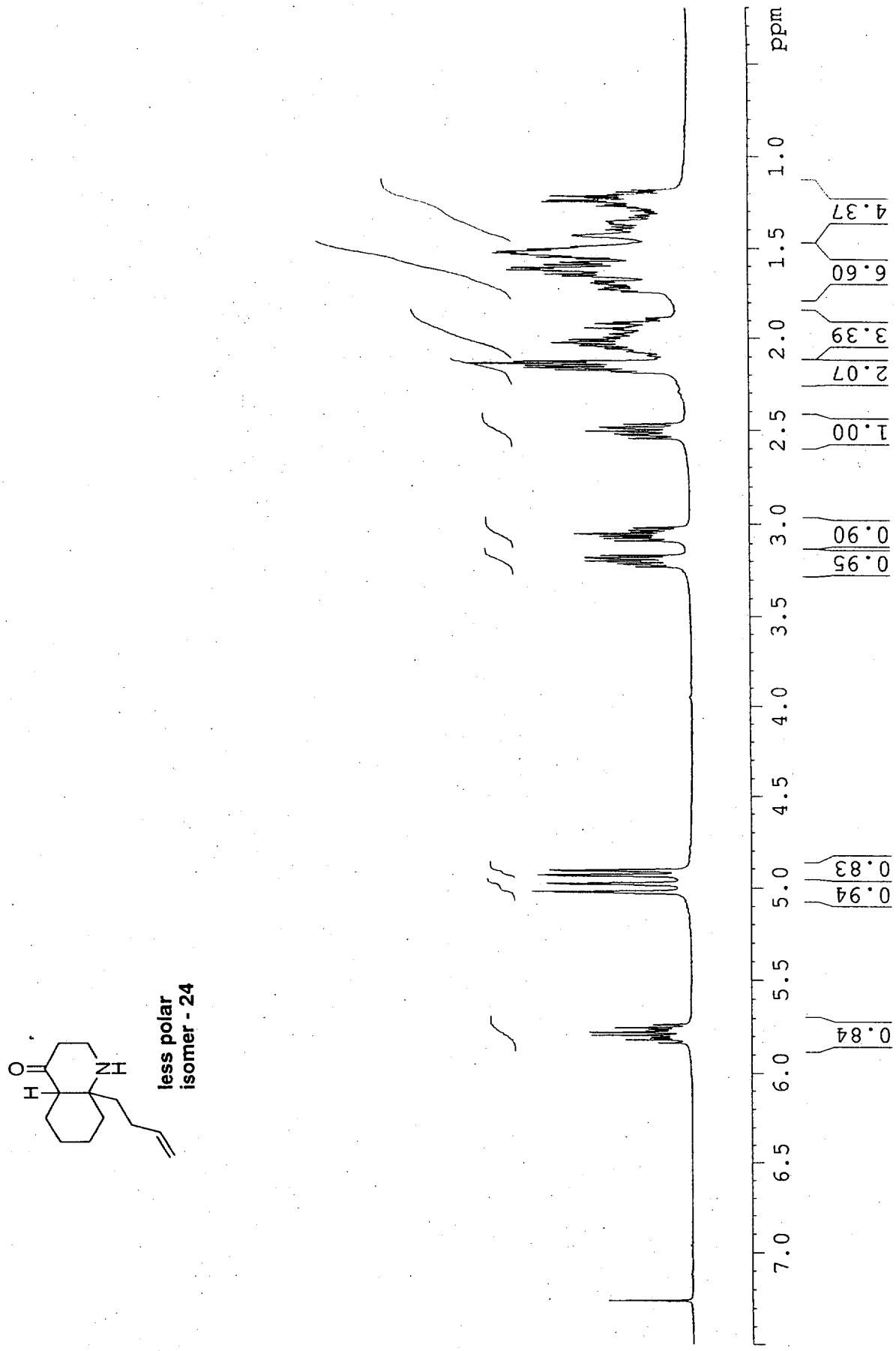


17





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6.0
6.5
7.0
4.37
6.60
3.39
2.07
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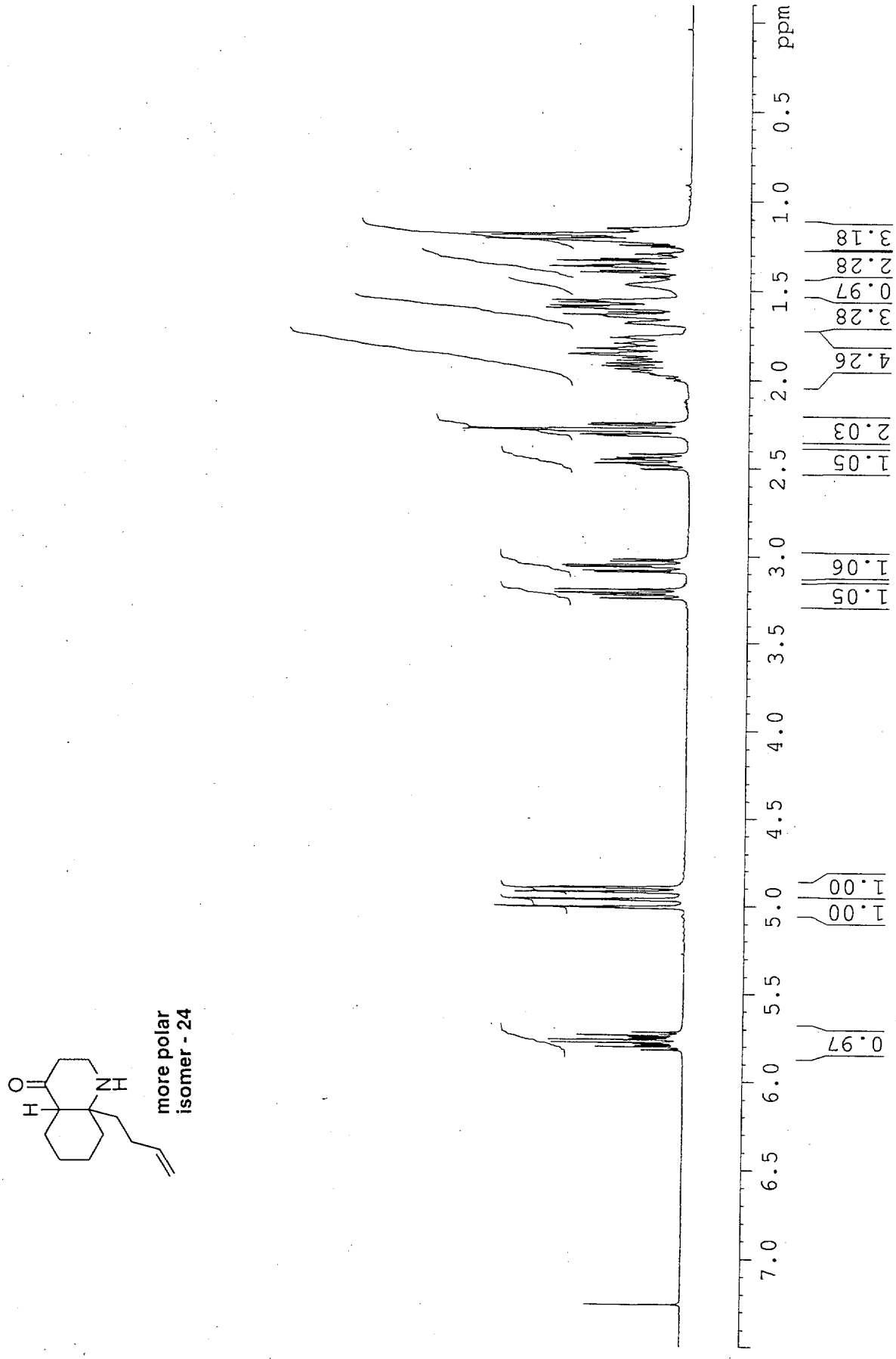
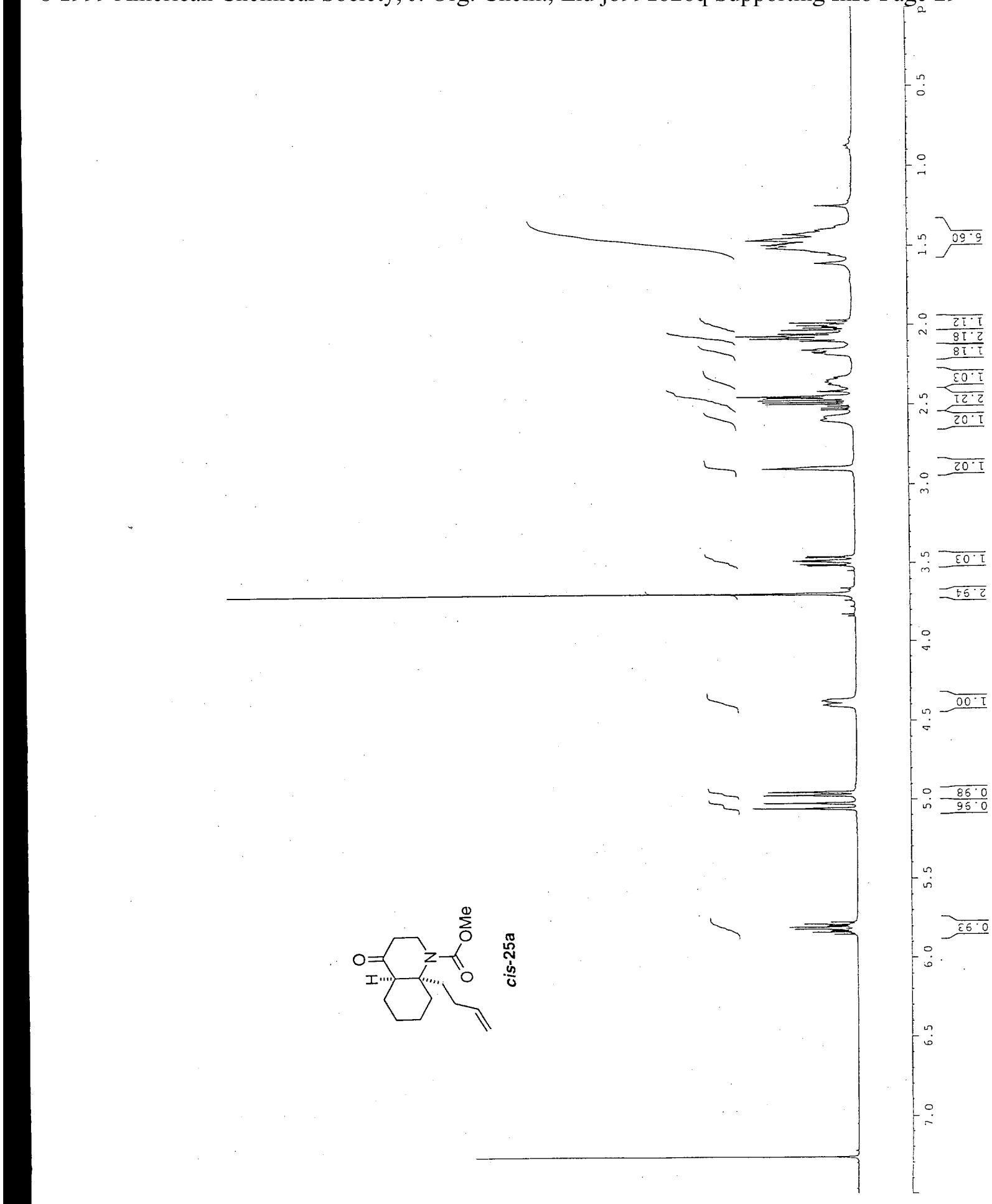
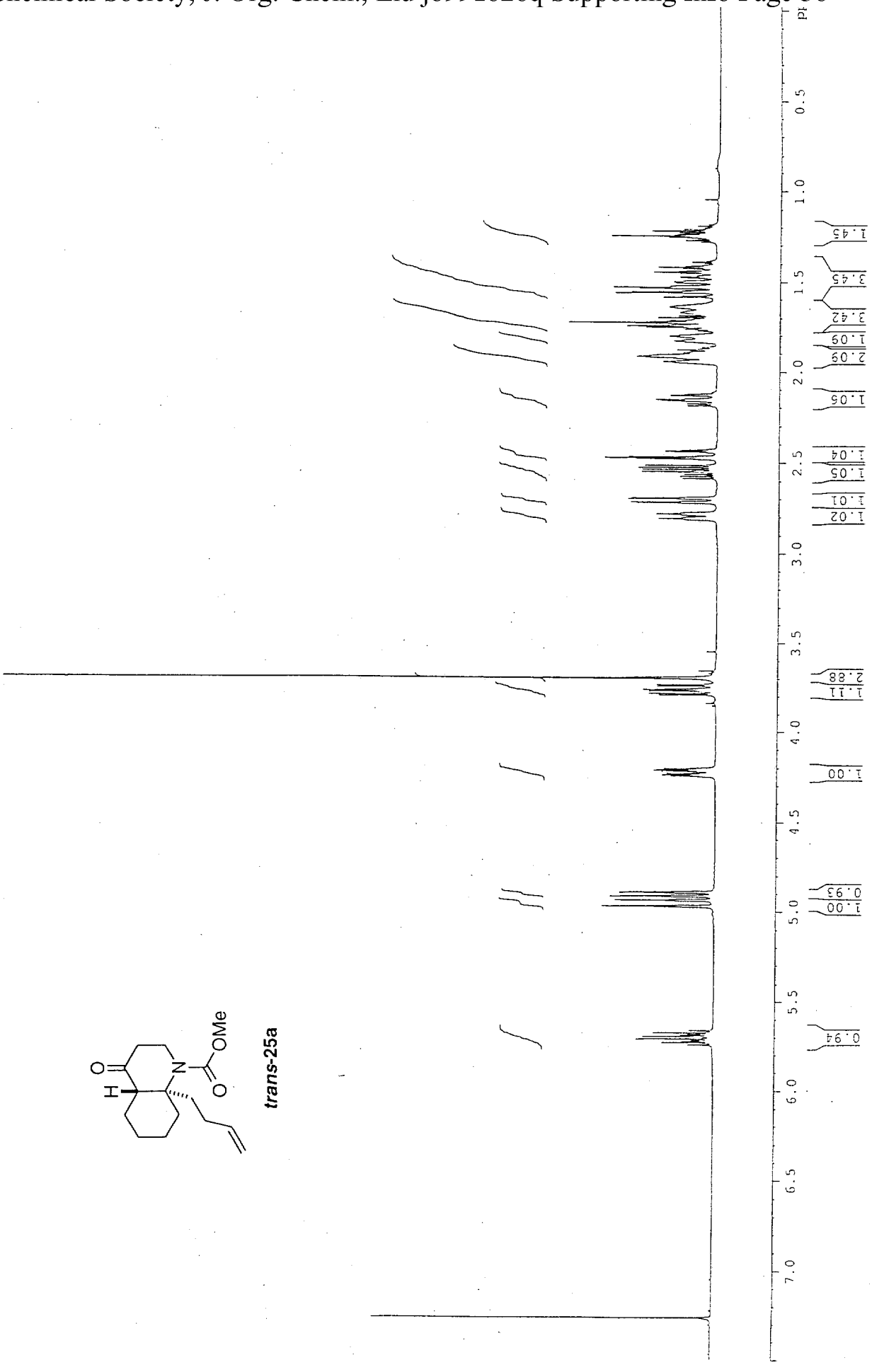
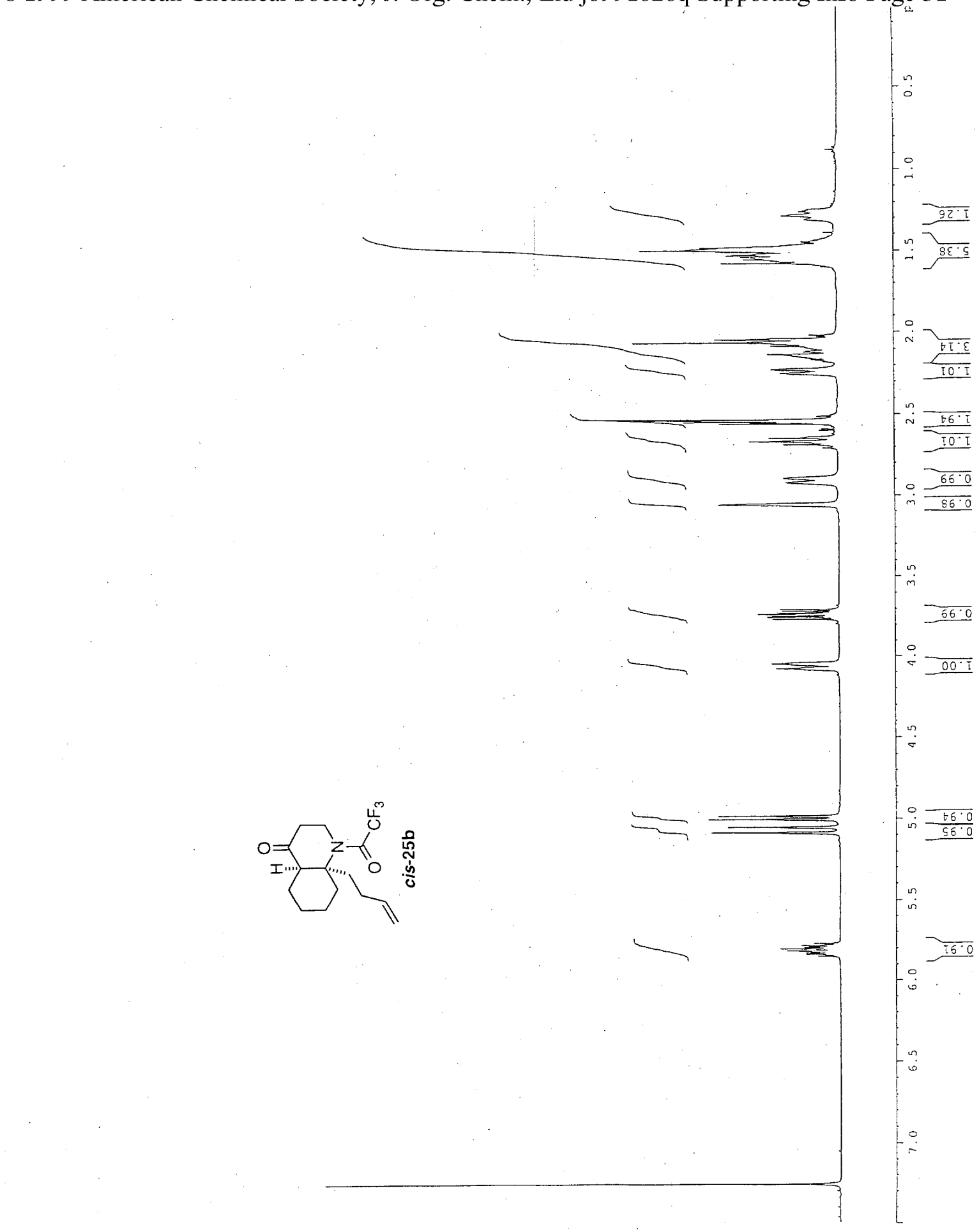
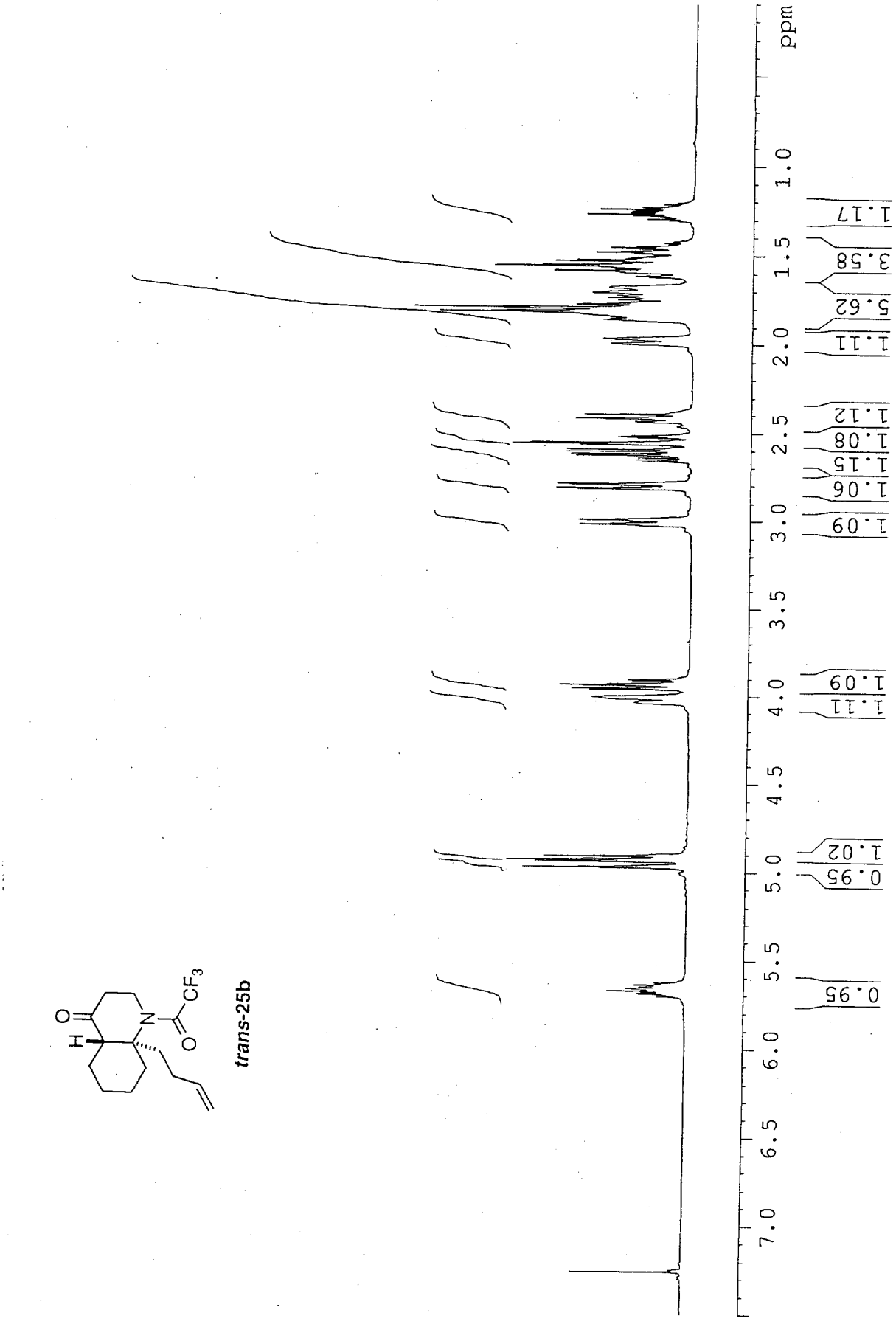
0.94
0.84
less polar
isomer - 24
O
H
N
H



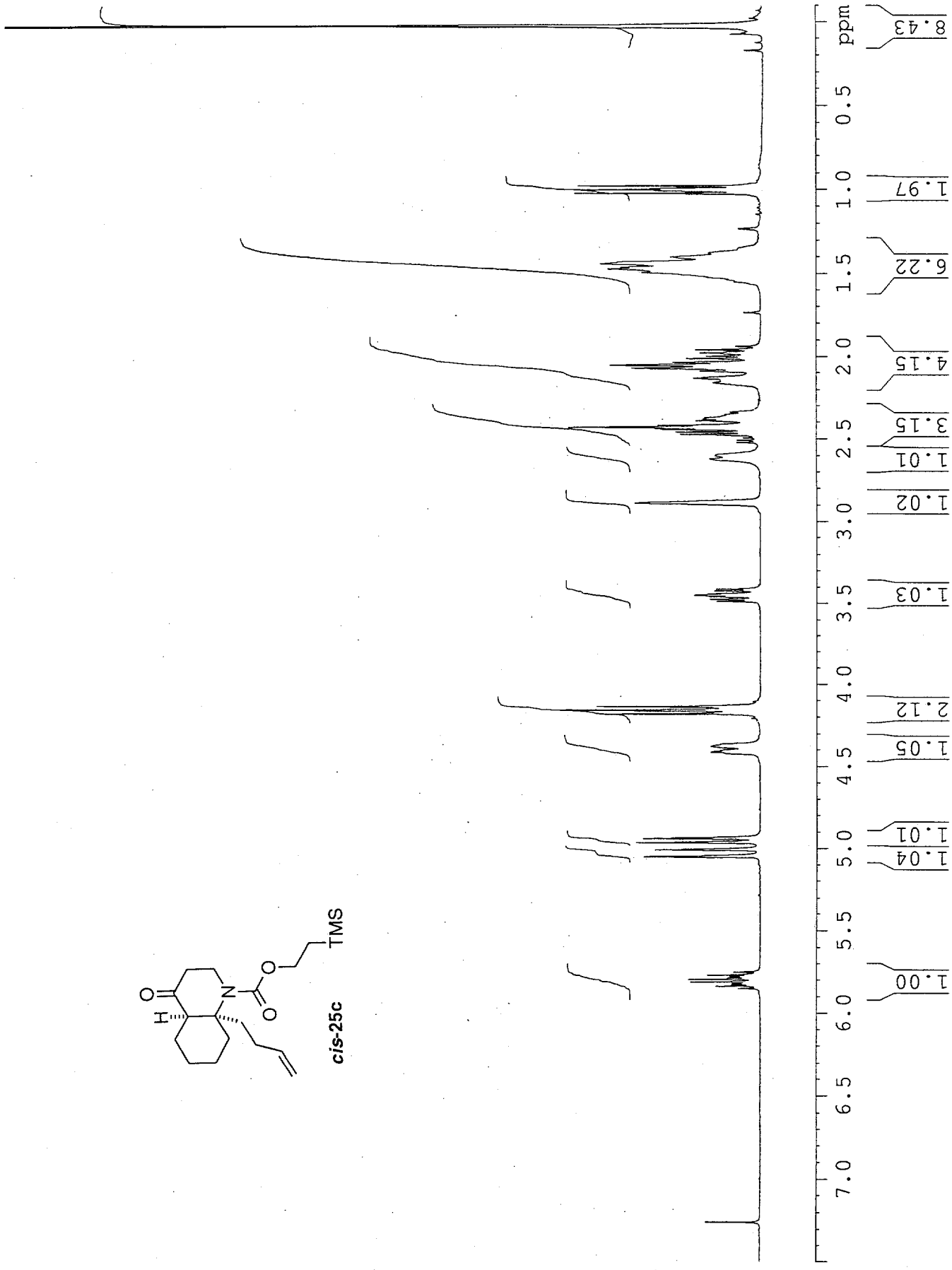


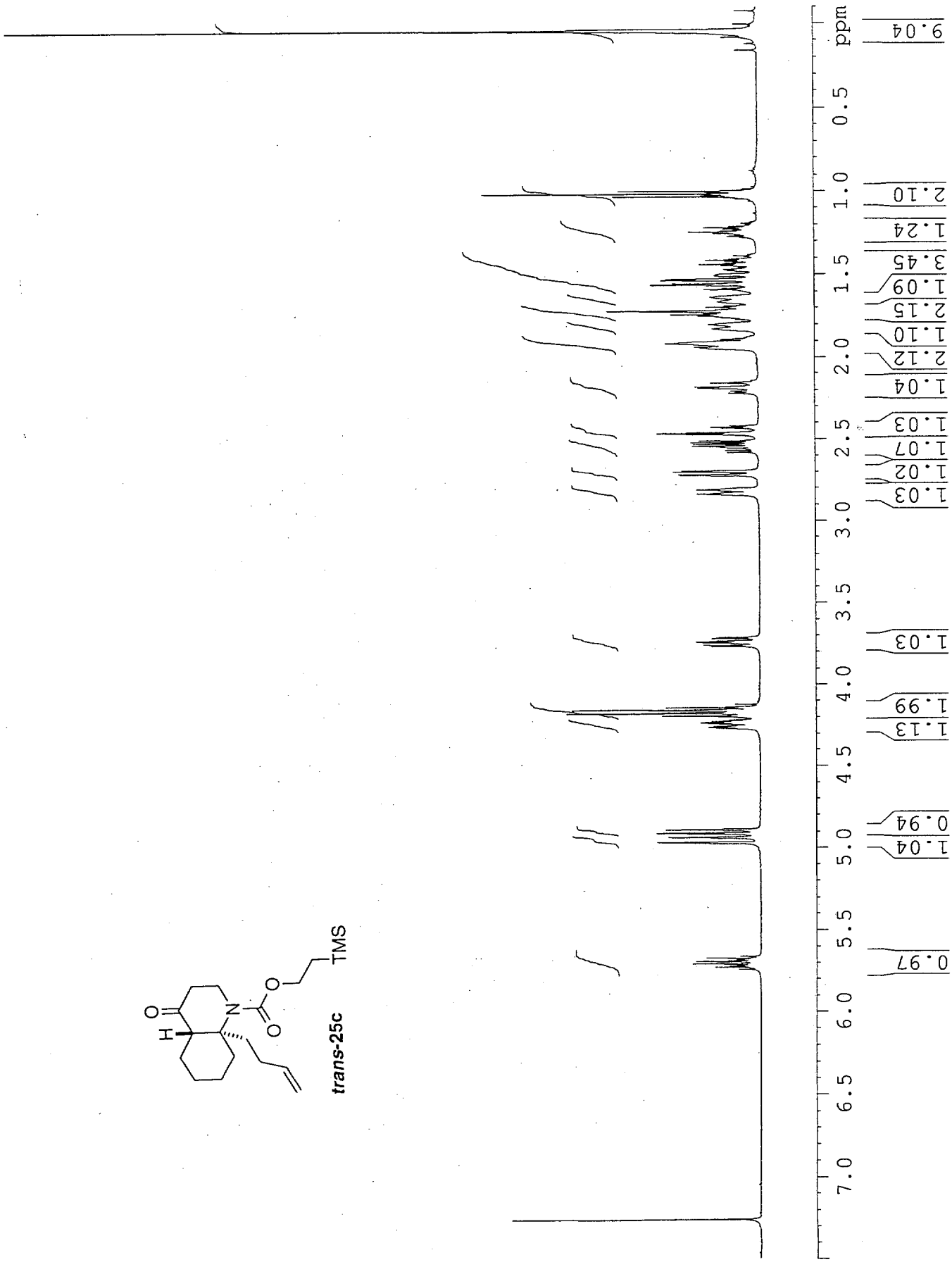


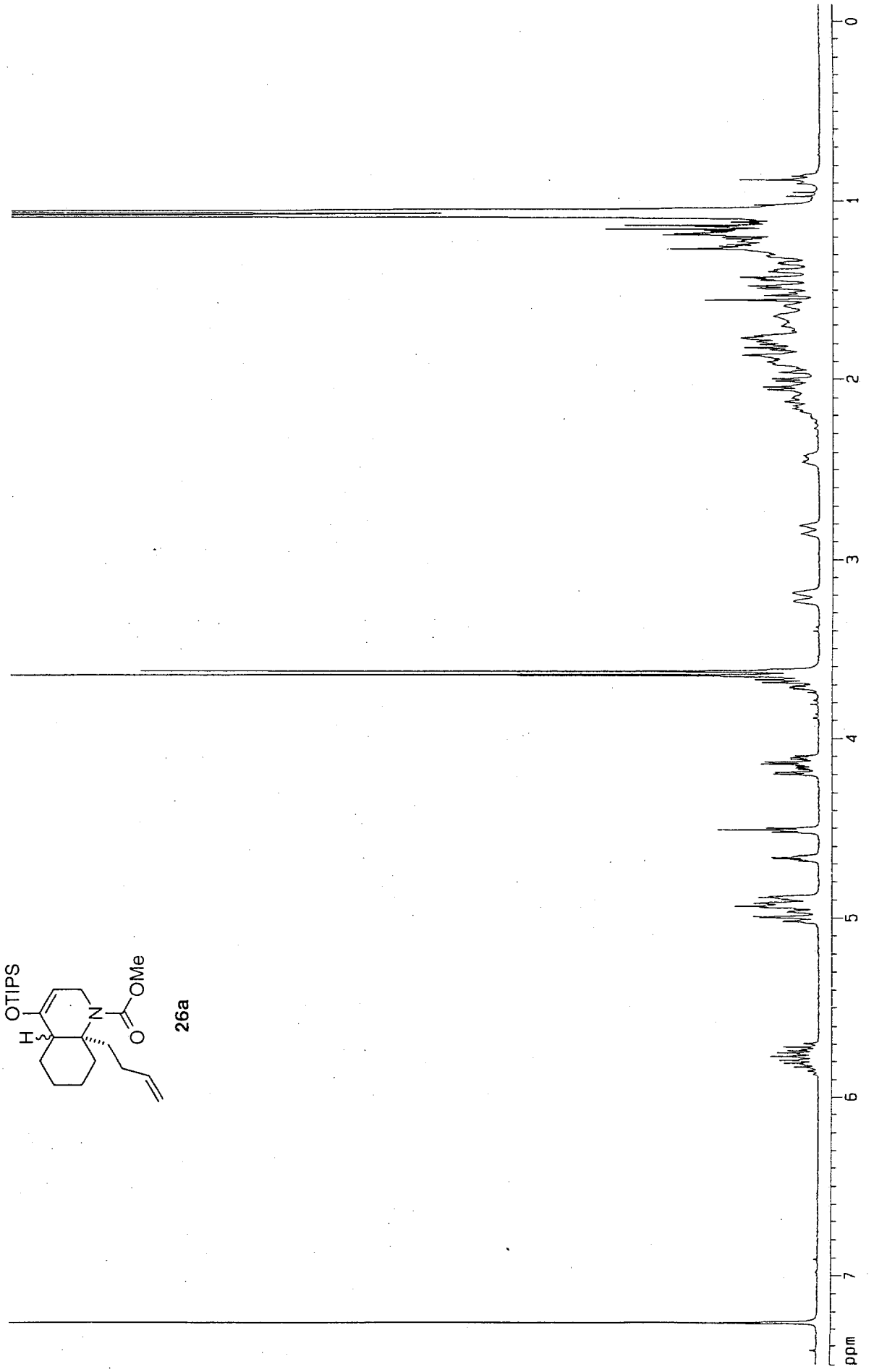


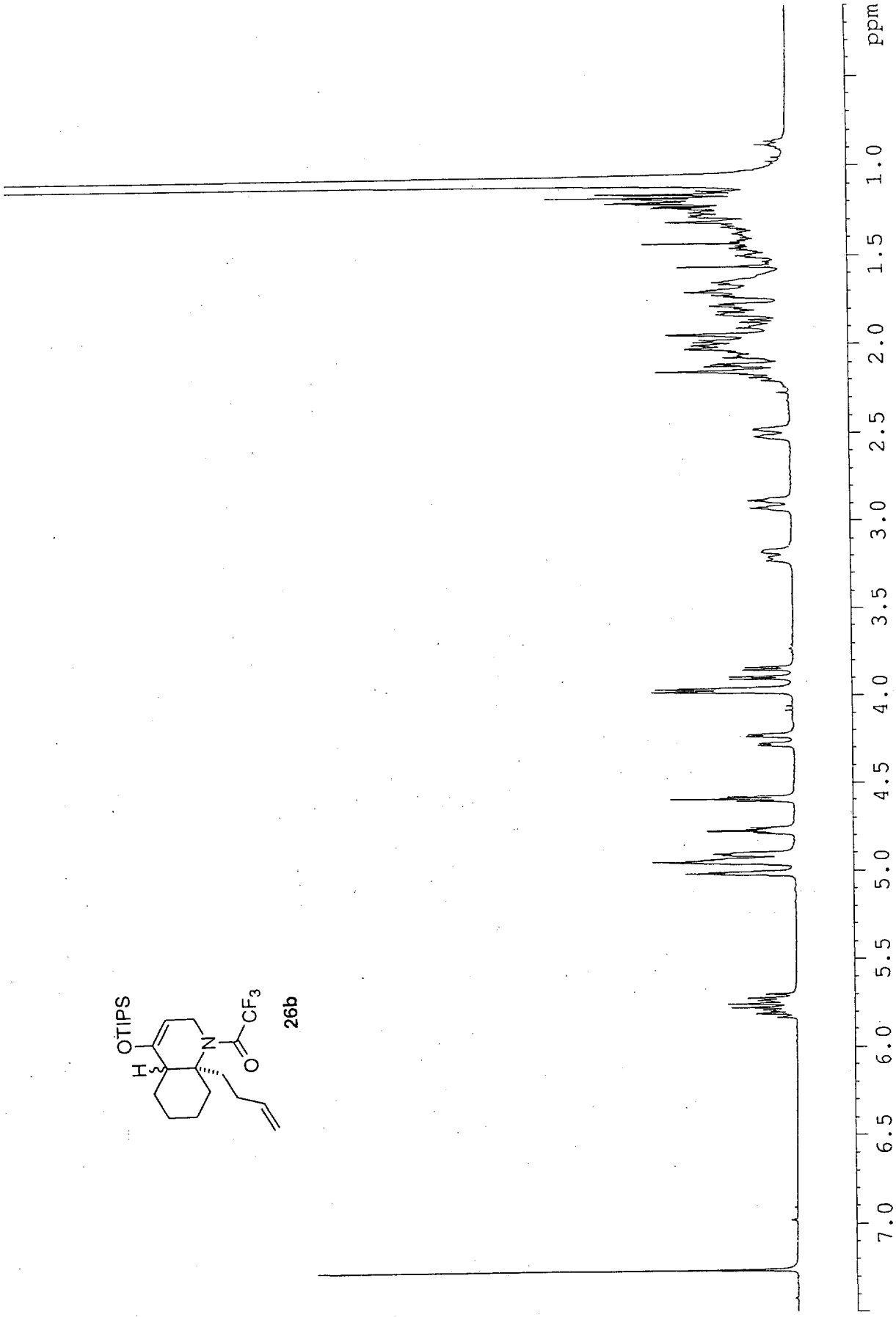


trans-25b

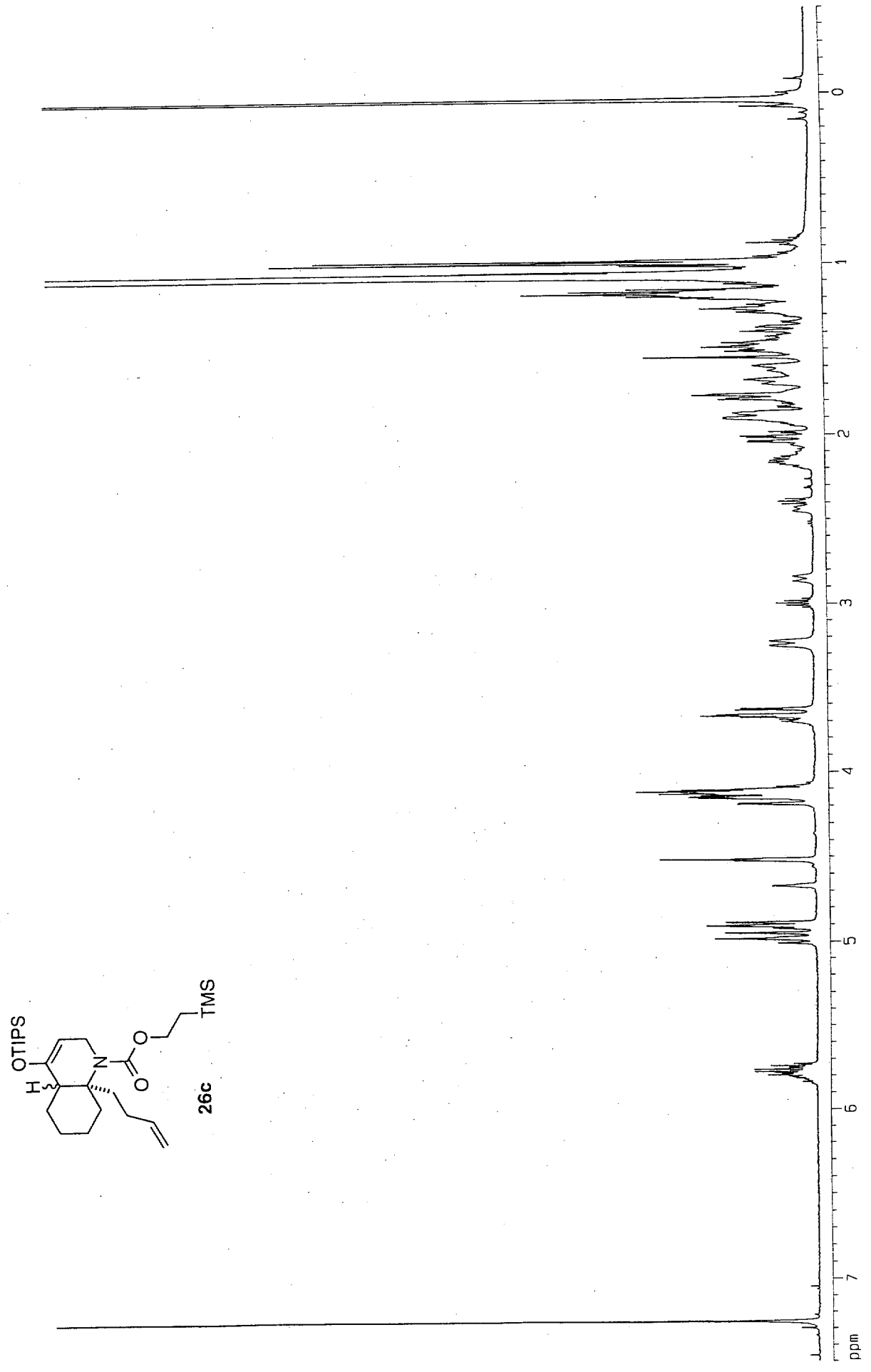


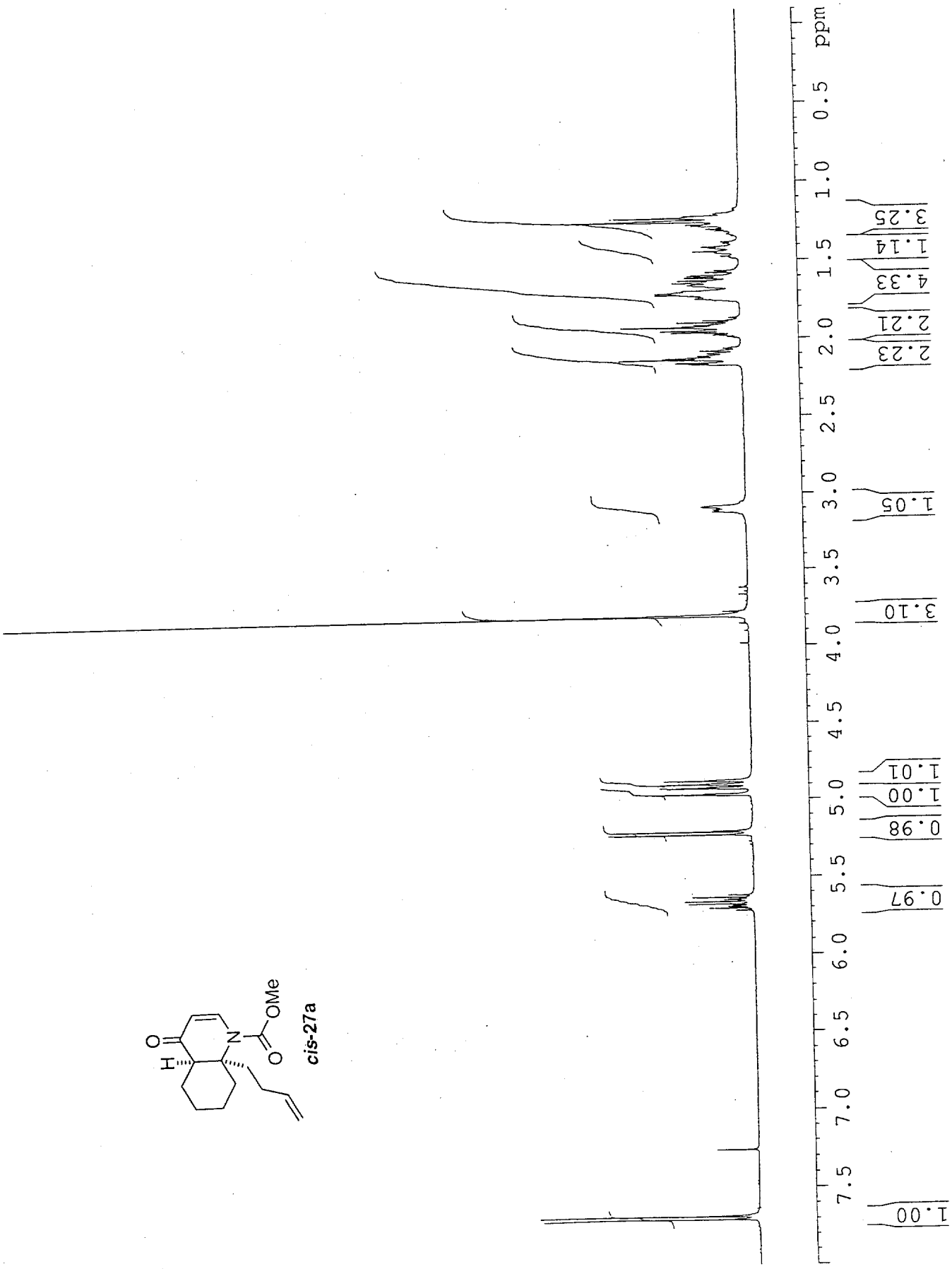




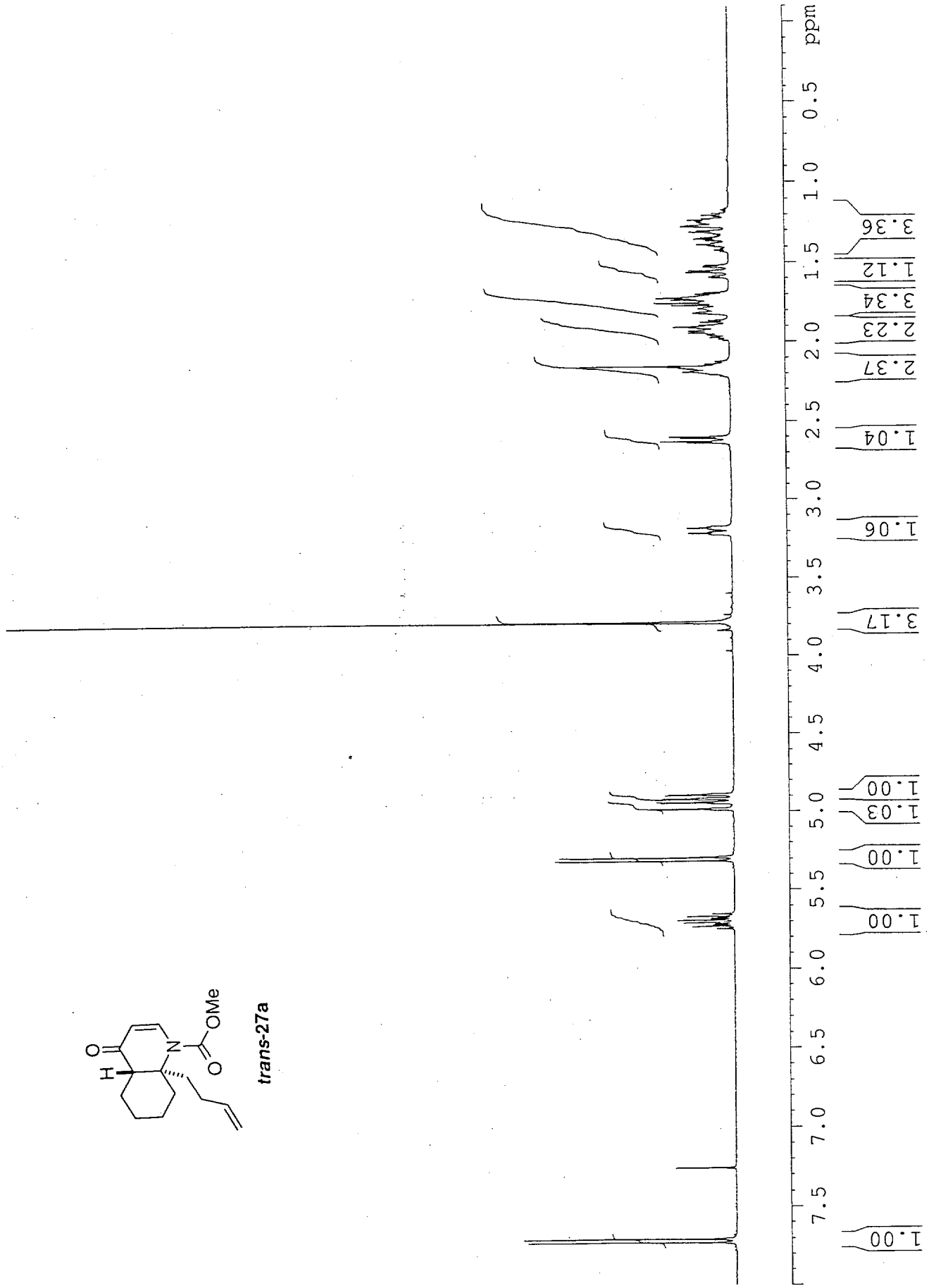


26b

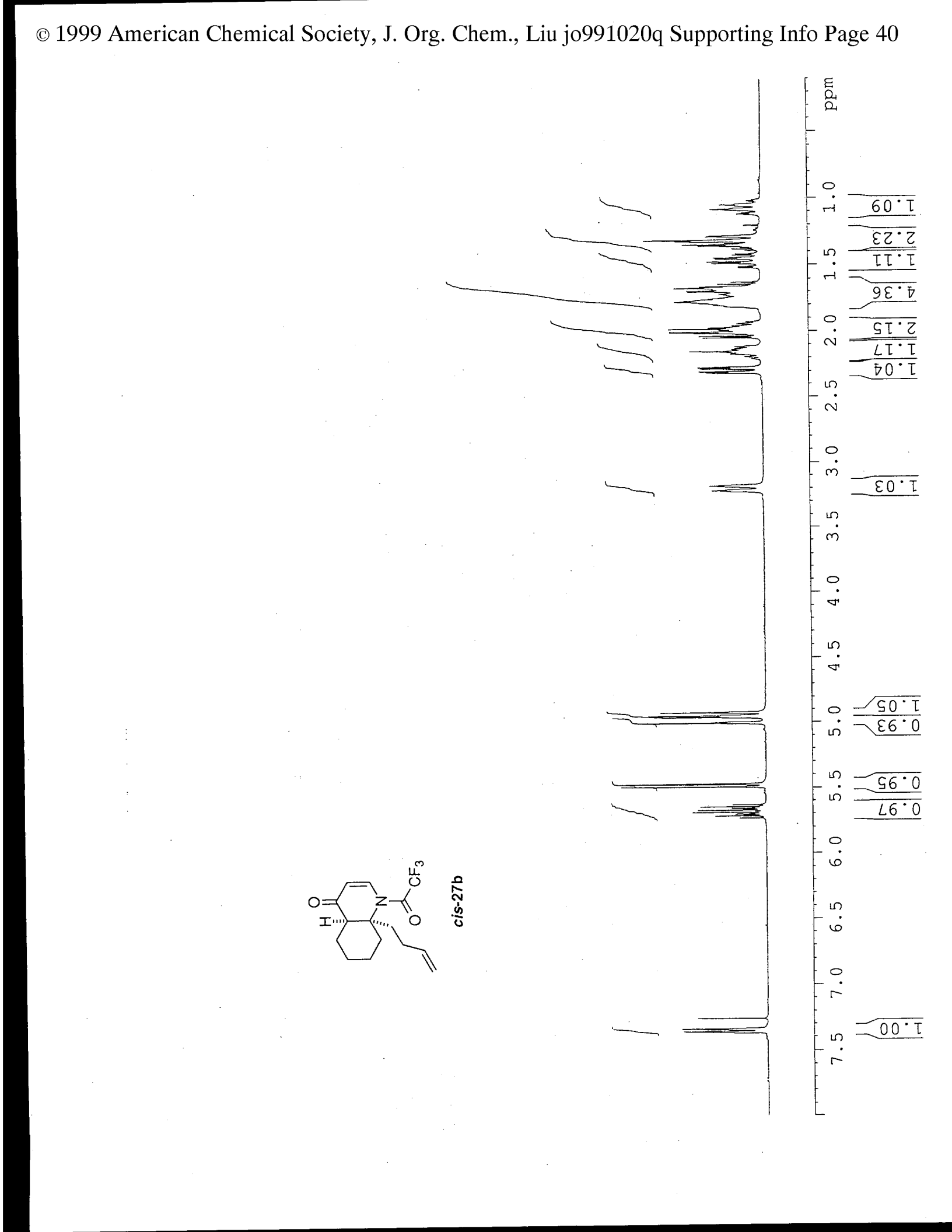




cis-27a



trans-27a



cis-27b