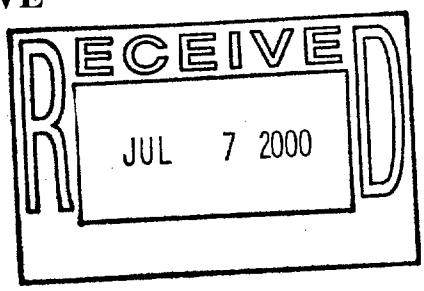
ol000180h

APPROACHES TO THE FULLY FUNCTIONALIZED DEF RING SYSTEM OF RISTOCETIN A VIA HIGHLY SELECTIVE RUTHENIUM-PROMOTED S_NAr REACTION



Anthony J. Pearson* and Jung-Nyoung Heo

Department of Chemistry, Case Western Reserve University, Cleveland, OH 44106

ajp4@po.cwru.edu

SUPPLEMENTARY MATERIAL

Experimental

(*S*)-*N*-(Benzyloxycarbonyl)-1-(3-benzyloxy-5-methoxy-4-methyl-phenyl)-2-hydroxyethylamine (11). To a solution of benzyl carbamate (380 mg, 2.51 mmol, 3.1 equiv) in 1-propanol (5 mL) was added an aqueous solution of NaOH (99 mg, 2.47 mmol, 3.05 equiv) in H_2O (6 mL), followed by *t*-butyl hypochlorite (268 mg, 2.47 mmol, 3.05 equiv). After 5 min a solution of $(DHQ)_2PHAL$ (32 mg, 0.04 mmol, 5 mol %) in 1-propanol (4 mL) was added to the above solution. Styrene **10** (206 mg, 0.81 mmol) dissolved in ethyl ether (3 mL) was then added, followed by $K_2OsO_2(OH)_4$ (12 mg, 0.032 mmol, 4 mol %). The resulting emulsion was stirred at rt for 1h until the mixture became a clear light yellow solution. The reaction was cooled to 0 °C and quenched with saturated Na_2SO_3 solution (10 mL) and further stirred for 15 min. The mixture was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with water (15 mL), brine (15 mL), dried ($MgSO_4$), and concentrated to provide the crude mixture of regioisomers (1°/2° alcohol = 4/1). Flash chromatography (2:3 EtOAc/hexanes) gave 227 mg (66%) of the desired 1° alcohol **11** as a colorless solid and 57 mg (17%) of the 2° alcohol. For 1° alcohol: mp 115-118 °C; R_f = 0.20 (2:3 EtOAc/hexanes); $[\alpha]^{25}_D$ +25.5 (*c* 1.0 , $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.44-7.31 (m, 10H), 6.52 (s, 1H), 6.47 (s, 1H), 5.53 (bs, 1H), 5.11 (s, 2H), 5.04 (s, 2H), 4.77 (s, 1H), 3.83 (d, 2H, J = 3.9 Hz), 3.80 (s, 3H), 2.13 (s, 3H), 2.02 (bs, 1H); ^{13}C NMR($CDCl_3$, 50 MHz) δ 158.8, 157.7, 156.6, 137.8, 137.4, 136.3, 128.6, 128.3, 127.9, 127.3, 114.8, 103.4, 102.2, 70.4, 67.2, 66.6, 57.7, 55.8, 8.5; IR (KBr) 3335, 1693, 1592, 1539, 1267, 1138 cm^{-1}; HRMS (EI) *m/z* 421.1879 for M^+ (421.1889 calcd for $C_{25}H_{27}NO_5$).

(*S*)-*N*-(Benzyloxycarbonyl)-(3-benzyloxy-5-methoxy-4-methylphenyl)-glycine (12). A solution of alcohol **11** (248 mg, 0.59 mmol) in acetone (5.0 mL) at 0 ℃ was added to an aqueous 5% $NaHCO_3$ (1.5 mL). This colloidal mixture was treated with KBr (10 mg, 0.08 mmol, 0.14 equiv) and TEMPO (98 mg, 0.62 mmol, 1.05 equiv) sequentially. Sodium hypochlorite (2.0 mL, 1.2 mmol, 2.0 equiv, 4-6% chlorine) was added slowly for 10min. The mixture was stirred at 0 °C for 2.5h, and then concentrated *in vacuo*. The residue was treated with H_2O (10 mL) and washed with diethyl ether (2 x 10 mL). The aqueous solution was acidified to pH = 6 with 10% aqueous citric acid solution and extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with H_2O (20 mL), brine (20 mL), dried ($MgSO_4$), and concentrated to give 182 mg (71%) of phenylglycine **12** as a white solid: mp 148-150 °C; R_f = 0.27 (10% MeOH/$CHCl_3$); $[\alpha]^{25}_D$ +94 (*c* 1.0 , EtOH); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 12.88 (bs, 1H), 8.06 (d, 1H, *J* = 8.4 Hz), 7.47-7.31 (m, 10H), 6.84 (s, 1H), 6.72 (s, 1H), 5.09 (d, 1H, *J* =8.4 Hz), 5.06 (s, 4H), 3.76 (s, 3H), 2.00 (s, 3H); ^{13}C NMR(Acetone-d_6, 50 MHz) δ 172.6, 159.5, 158.5, 156.7, 138.6, 138.2, 136.8, 129.4, 129.3, 128.9, 128.8, 128.7, 128.5, 115.0, 105.5, 104.2, 71.0, 67.1, 59.4, 56.2, 8.8; IR (KBr) 3390, 1740, 1679, 1602, 1542, 1432, 1246, 1142, 1059 cm^{-1}; HRMS (EI) *m/z* 435.1683 for M^+ (435.1682 calcd for $C_{25}H_{25}NO_6$).

***N*-Methyl (2*R*)-2-[(*S*)-1-[((benzyloxy)carbonyl)amino]-1-(3-benzyloxy-5-methyl-4-methylphenyl)methylcarboxamido]-2-(3,5-dihydroxy-4-methoxyphenyl)ethanamide (14).** To a solution of the *N*-methyl azidoacetamide **13** (52 mg, 0.12 mmol) in THF-MeOH (2 mL/2 mL) was added 10% Pd/C (14 mg) and 6N HCl (60 μL, 0.36 mmol, 3.0 equiv). The suspension was stirred under 1 atm H_2 (balloon) for 12h. The mixture was filtered through Celite and evaporated. The residue was chased with anhydrous diethyl ether (20 mL) and dried under vacuum to provide the crude amine hydrochloride as a light green film.

(*S*)-arylglycine **12** (52 mg, 0.12 mmol, 1.0 equiv), HOAt (25 mg, 0.18 mmol, 1.5 equiv), and EDCI (35 mg, 0.18 mmol, 1.5 equiv) were sequentially added to a solution of the above amine hydrochloride in DMF-CH_2Cl_2 (1.5 mL/1.5 mL), followed by TMP (32 μL, 0.24 mmol, 2.0 equiv) at 0 °C. The mixture was stirred at 0 ℃ for 3h, and then at rt for 17h. The mixture was diluted with EtOAc (30 mL) and washed with 1M $NaHSO_4$ (2 x 10 mL), saturated aqueous $NaHCO_3$ (2 x 10 mL), H_2O (10 mL), and brine (20 mL). The organic phase was dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography (80% → 90% EtOAc/hexanes, gradient elution) to afford 70 mg (91%) of

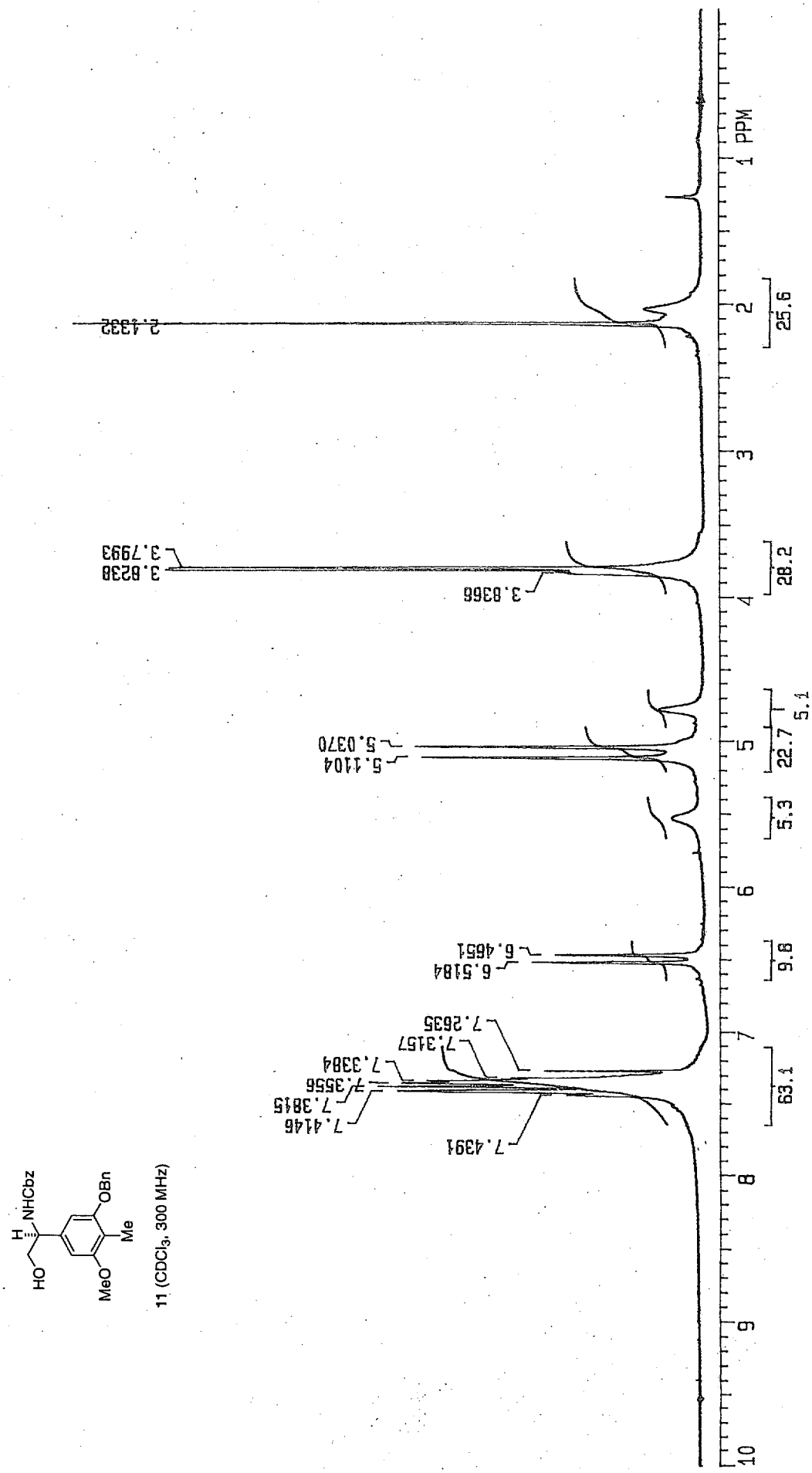
the dipeptide **14** as a white solid: R_f = 0.56 (1:9 MeOH/$CHCl_3$); $[\alpha]^{25}_D$ -18.5 (*c* 0.2, MeOH); ^{1}H NMR (CD_3CN, 300 MHz) δ 7.42-7.31 (m, 11H), 6.81 (s, 2H), 6.68 (s, 1H), 6.61 (bs, 1H), 6.59 (s, 1H), 6.40 (bs, 1H), 6.24 (s, 2H), 5.21 (d, 1H, *J* = 7.5 Hz), 5.07-5.05 (m, 3H), 4.97 (s, 2H), 3.71 (s, 3H), 3.68 (s, 3H), 2.63 (d, 3H, *J* = 4.8 Hz), 2.02 (s, 3H); ^{13}C NMR (Acetone-d_6 + CD_3OD, 50 MHz) δ 170.8, 170.2, 158.1, 157.2, 156.2, 137.3, 136.7, 135.9, 135.0, 133.0, 128.0, 127.5, 127.4, 127.3, 127.2, 113.6, 106.4, 103.8, 102.6, 69.7, 66.1, 59.2, 58.6, 56.9, 54.7, 25.0, 7.2; FABHRMS (NBA/PEG246) *m/z* 666.2447 for M^+ + Na (666.2427 calcd for $C_{35}H_{37}N_3O_9Na$).

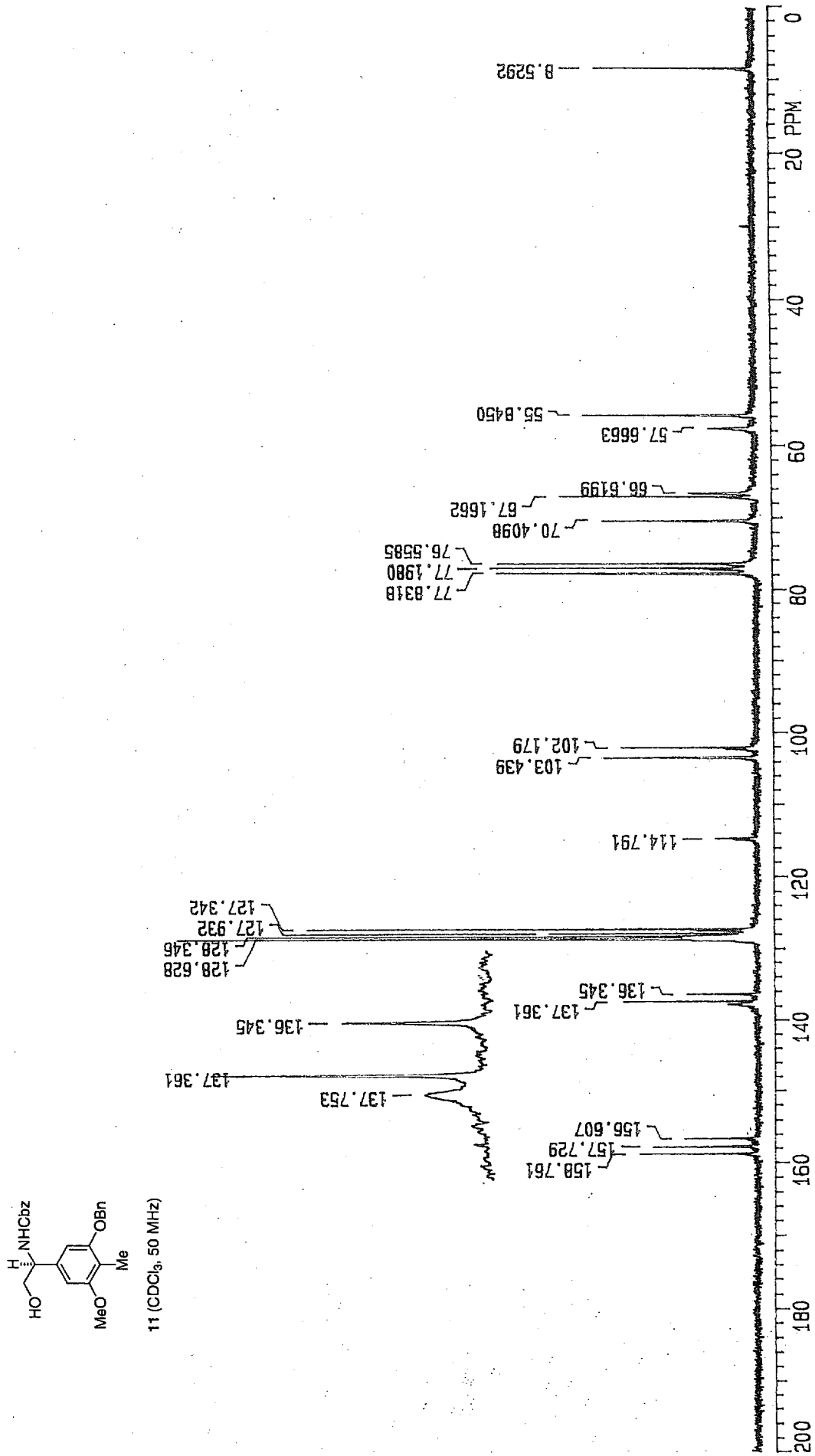
(η^5-2,4-Cyclopentadien-1-yl) {*N*-methyl (2*R*)-2-[(*S*)-1-((1*R*, 2*R*)-1-((*tert*-butyloxycarbonyl)amino)-2-(*tert*-butyldimethylsilyloxy)-2-((1,2,3,4,5,6,-h)-4-chlorophenyl)ethylcarboxamido)-1-(3-benzyloxy-5-methoxy-4-methylphenyl)methylcarboxamido]-2-(3,5-dihydroxy-4-methoxyphenyl)ethanamido} ruthenium(II) hexafluorophosphate (16). To a solution of the dipeptide **14** (44 mg, 0.068 mmol) in MeOH/THF (1.5 mL/1.5 mL) was added 10% Pd/C (13 mg) and 6N HCl (34 μL, 0.21 mmol, 3.0 equiv). The suspension was stirred under 1 atm H_2 (balloon) for 20h. The mixture was filtered through Celite and evaporated. The residue was chased with anhydrous diethyl ether (20 mL) and dried under vacuum to provide the crude amine hydrochloride as a light yellow film. This amine hydrochloride was dissolved in DMF (1.5 mL), and the arylserine-ruthenium complex **15** (60 mg, 0.082 mmol, 1.2 equiv) and HATU (52 mg, 0.14 mmol, 2.0 equiv) was sequentially added at 0 °C. To this was added TMP (20 μL, 0.15 mmol, 2.0 equiv) and stirred at 0 °C for 3h, and then at rt for 19h. The solution was diluted with CH_2Cl_2 (30 mL) and washed with 1M $NaHSO_4$ (2 x 10 mL), saturated aqueous $NaHCO_3$ (2 x 10 mL), H_2O (10 mL), and brine (20 mL). The organic phase was dried (Na_2SO_4), and concentrated. The residue dissolved in CH_3CN (0.5 mL) was treated with diethyl ether/hexanes (30 mL/10 mL) and sonicated to precipitate the brown solid for 20 min. This was filtered, washed with diethyl ether (20 mL), and dried to provide 72 mg (92%) of the tripeptide ruthenium complex **16** as a brown powder: ^{1}H NMR (Acetone-d_6 + CD_3OD, 300 MHz) δ 8.39 (d, 1H, *J* = 6.6 Hz), 7.93 (d, 1H, *J* = 4.8 Hz), 7.73 (d, 1H, *J* = 6.9 Hz), 6.79 (d, 1H, *J* = 6.0 Hz), 6.62 (d, 1H, *J* = 6.3 Hz), 6.54-6.43 (m, 6H), 6.20 (d, 1H, *J* = 5.7 Hz), 5.59 (s, 5H), 5.55 (d, 1H, *J* = 2.7 Hz), 5.23 (d, 1H, *J* = 3.0 Hz), 5.18 (d, 1H, *J* = 6.6 Hz), 4.71 (d, 1H, *J* = 4.8 Hz), 3.75 (s, 3H), 3.70 (s, 3H), 2.79 (d, 3H, *J* = 4.5 Hz), 1.98 (s, 3H), 1.38 (s, 9H), 0.96 (s, 9H), 0.27 (s, 3H), 0.18 (s, 3H); ^{13}C NMR (CD_3CN, 50 MHz) δ 172.5, 170.8, 169.4, 159.9, 156.9, 156.8, 151.7, 135.9, 135.4, 133.5, 113.5, 108.7, 107.6, 106.3, 105.6, 102.0, 87.6, 87.2, 85.3, 83.8, 83.7, 81.5, 72.1,

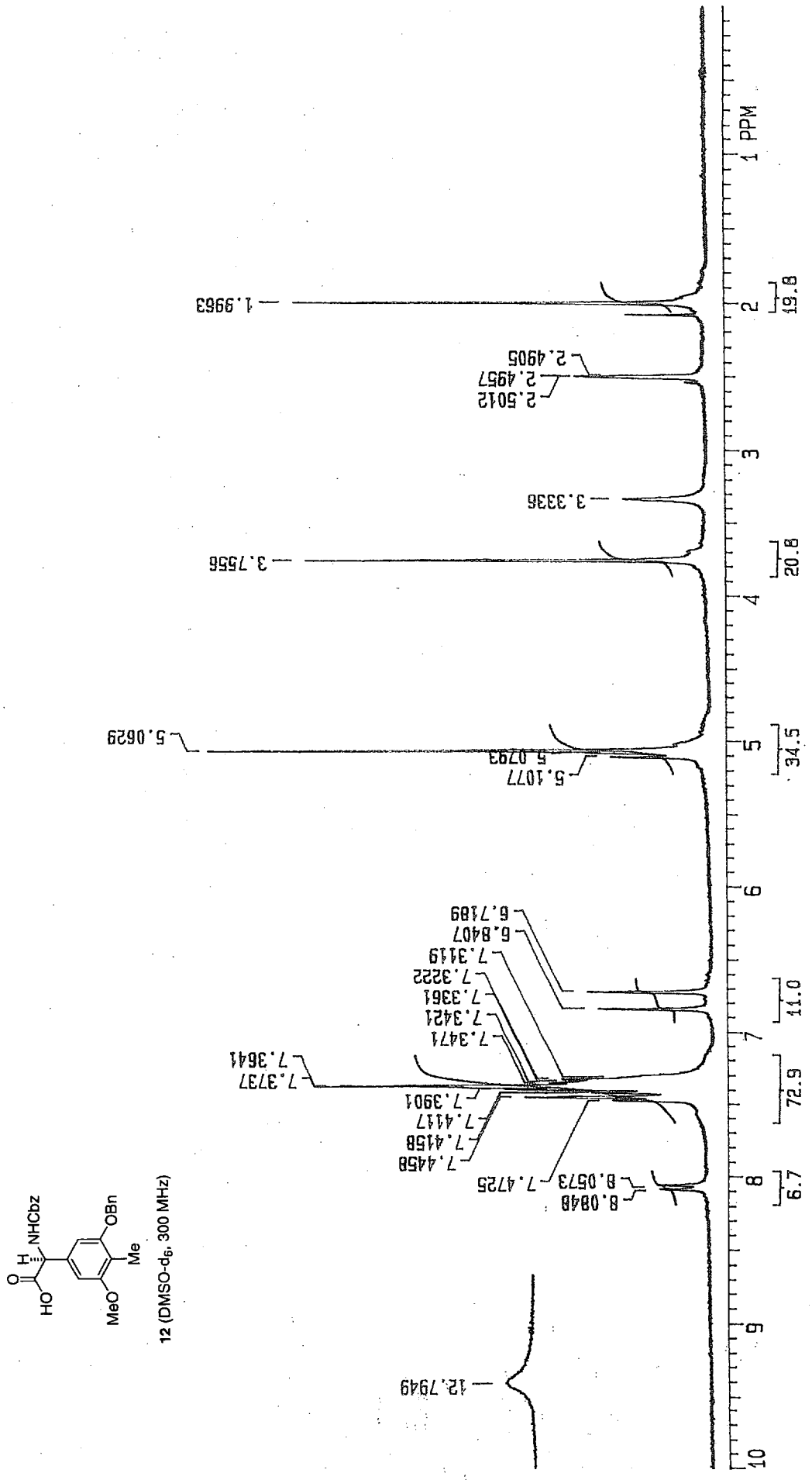
62.6, 60.8, 58.9, 58.2, 56.4, 28.4, 27.0, 26.0, 18.4, 8.5, -4.4, -4.8; FABHRMS (NBA/PEG246/NaI) *m/z* 997.2760 for $M^+ - PF_6$ (997.2760 calcd for $C_{45}H_{60}ClN_4O_{11}SiRu$).

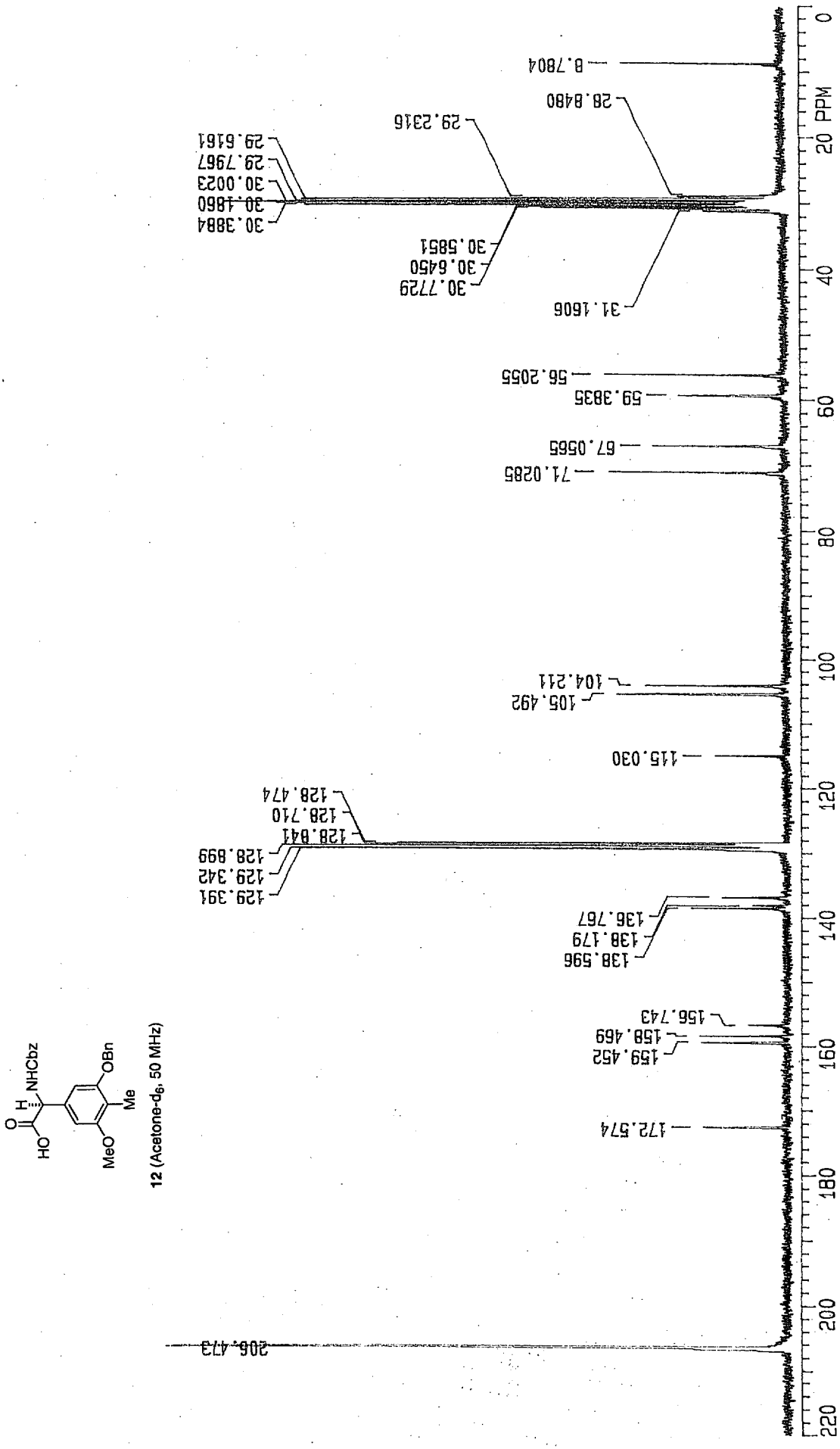
***N*-Methyl (8*R*,11*S*,14*R*,15*R*)-14-[*N*-[(*tert*-Butoxy)carbonyl] amino]-15-(*tert*-butyldimethylsilyloxy)-10,13-dioxo-5-hydroxy-4-methoxy-11-(3-benzyloxy-5-methoxy-4-methylphenyl)-2-oxa-9,12-diazatricyclo-[14.2.2.1^{3,7}]heneicosa-3,4,7(21),16,18,19-hexaene-8-carboxamide (4).** To the tripeptide ruthenium complex **16** (40 mg, 0.035 mmol) in DMF (7.0 mL, 5 mM) was added Cs_2CO_3 (57 mg, 0.175 mmol, 5.0 equiv) under argon atmosphere at room temperature. After 4h the mixture was diluted with CH_2Cl_2 (20 mL) and washed with 1M $NaHSO_4$ (2 x 10 mL), H_2O (2 x 10 mL), and brine (2 x 10 mL). The organic phase was dried (Na_2SO_4), and concentrated.

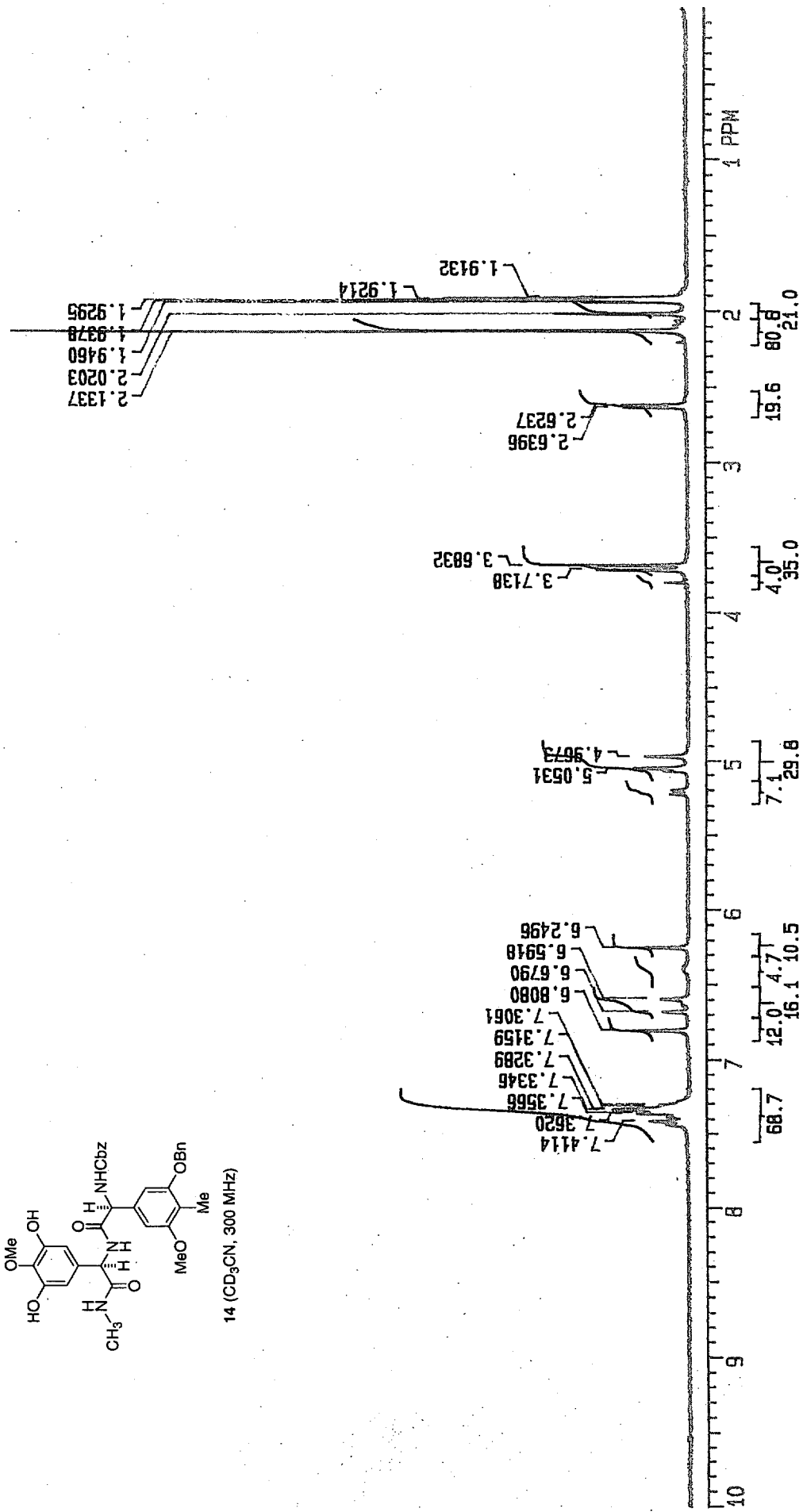
The residue was dissolved in 20 mL of CH_3CN, degassed with Ar for 20 min, and photolyzed (Rayonet, 350 nm) for 24h. The solution was concentrated and purified by chromatography (50 → 80% EtOAc/hexanes, gradient elution) to obtain 17 mg (61%) of the cyclized product **4** as a white solid: R_f = 0.42 (80% EtOAc/hexanes); $[\alpha]^{25}_D$ -19.1 (*c* 0.47, MeOH); ^{1}H NMR (Acetone-d_6, 300 MHz) δ 8.41 (s, 1H), 8.21 (s, 1H), 8.04 (d, 1H, *J* = 9.9 Hz), 7.71 (d, 1H, *J* = 8.1 Hz), 7.46 (d, 1H, *J* = 3.9 Hz), 7.35 (dd, 2H, *J* = 8.4, 2.4 Hz), 7.23 (dd, 2H, *J* = 8.7, 2.1 Hz), 6.95 (dd, 2H, *J* = 8.4, 2.4 Hz), 6.65 (d, 1H, *J* = 1.8 Hz), 6.54 (s, 2H), 5.75 (s, 1H), 5.67-5.63 (m, 2H), 5.34 (bs, 1H), 5.25 (d, 1H, *J* = 7.2 Hz), 4.76 (bs, 1H), 3.98 (s, 3H), 3.79 (s, 3H), 2.67 (s, 3H, *J* = 4.8 Hz), 2.02 (s, 3H), 1.47 (s, 9H), 0.99 (s, 9H), 0.22 (s, 3H), 0.13 (s, 3H); ^{13}C NMR (Acetone-d_6, 50 MHz) δ 170.3, 169.7, 169.6, 159.8, 157.8, 156.9, 156.8, 155.0, 151.7, 137.7, 137.1, 136.9, 134.7, 129.8, 127.6, 123.7, 123.0, 112.5, 108.9, 107.8, 106.5, 100.6, 80.4, 74.0, 63.0, 61.4, 58.4, 57.5, 56.1, 28.7, 26.5, 26.3, 19.0, 8.5, -4.7, -4.8; FABHRMS (NBA/PEG246) *m/z* 795.3652 for MH^+ (795.3636 calcd for $C_{40}H_{55}N_4O_{11}Si$).

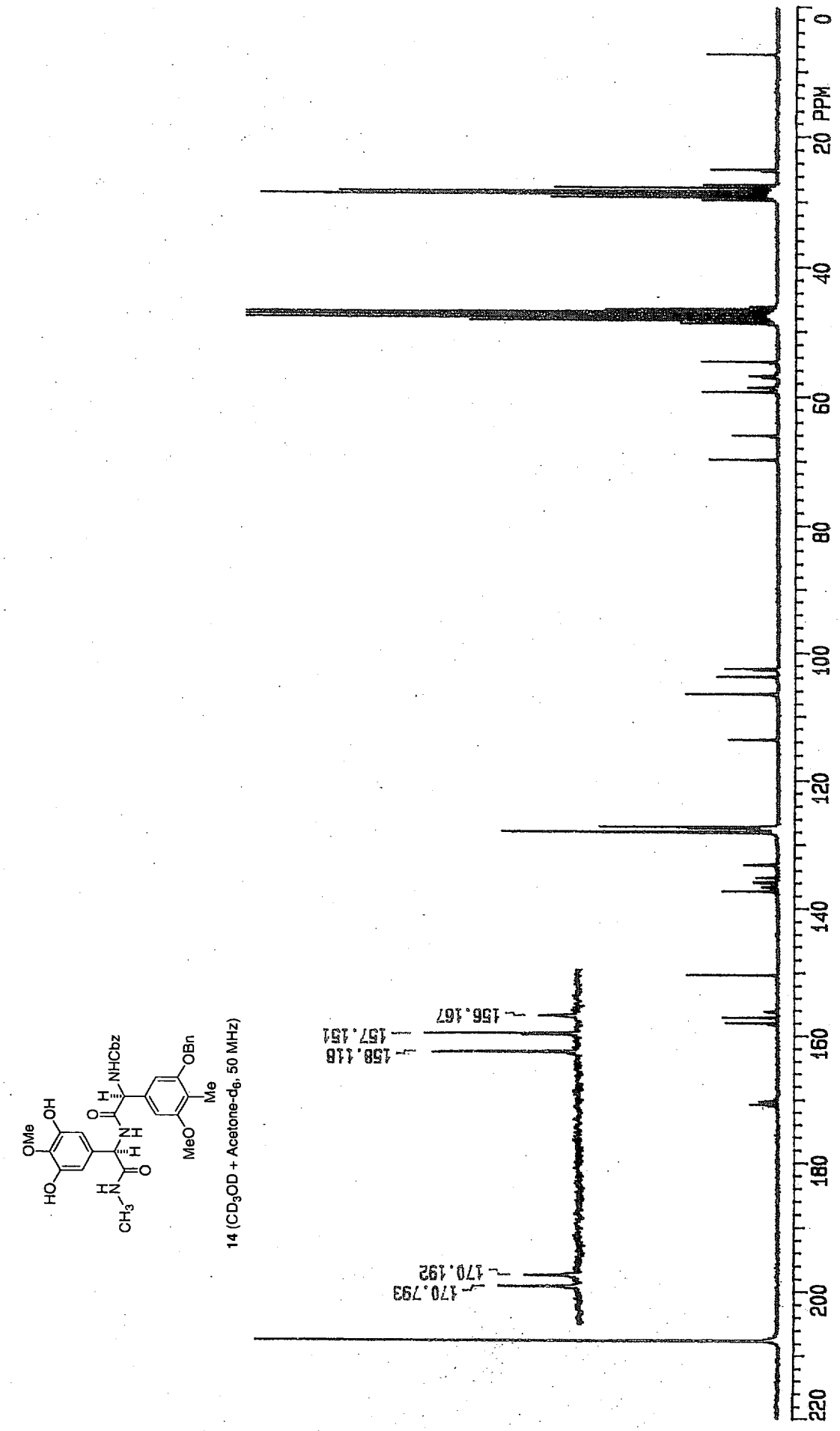

11 (CDCl3, 300 MHz)
HO
NHCbz
H
MeO
OBn
Me
2.1332
3.7993
3.8238
3.8366
5.0370
5.1104
6.4651
6.5184
7.2635
7.3157
7.3384
7.3556
7.3815
7.4146
7.4391
1 PPM
25.6
28.2
22.7
5.1
5.3
9.8
63.1

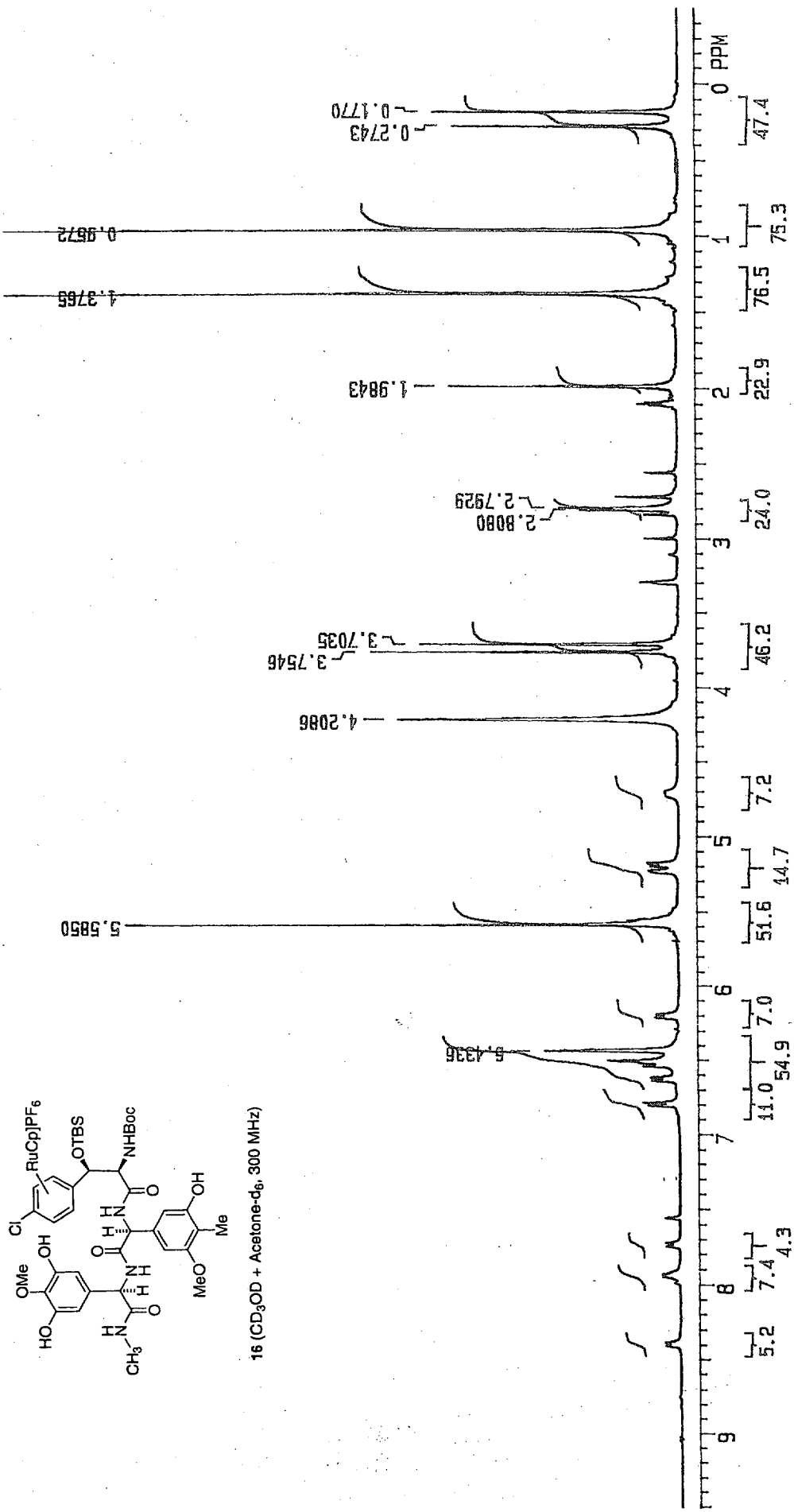


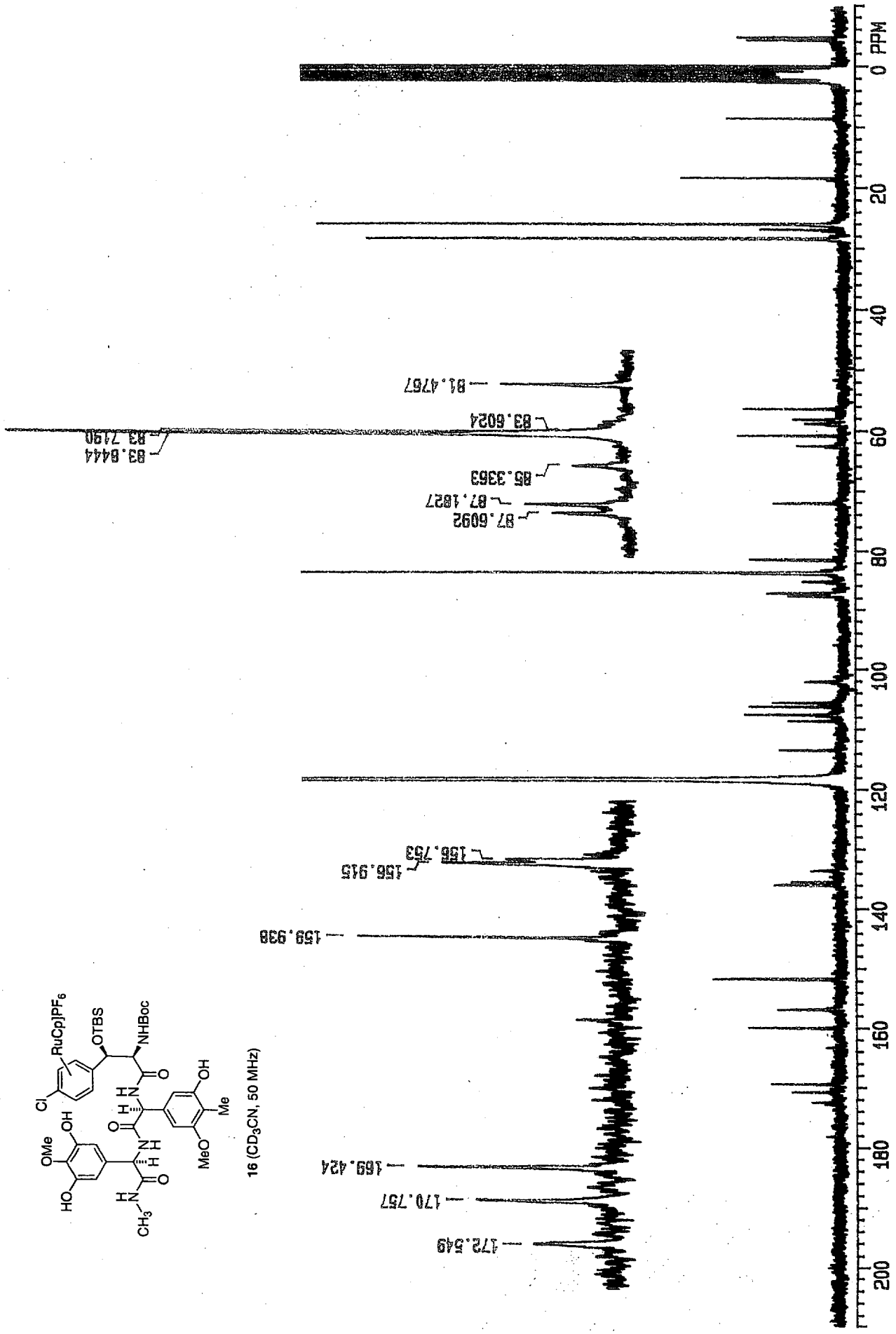

12 (DMSO-d6, 300 MHz)
NHCbz
OBn
Me
MeO
HO
O
1.9963
2.4905
2.4957
2.5012
3.3336
3.7556
5.0629
5.0793
5.1077
6.7189
6.8407
7.3119
7.3222
7.3361
7.3421
7.3471
7.3641
7.3737
7.3901
7.4117
7.4158
7.4458
7.4725
8.0573
8.0848
12.7949
1 PPM
19.8
20.8
34.5
11.0
72.9
6.7

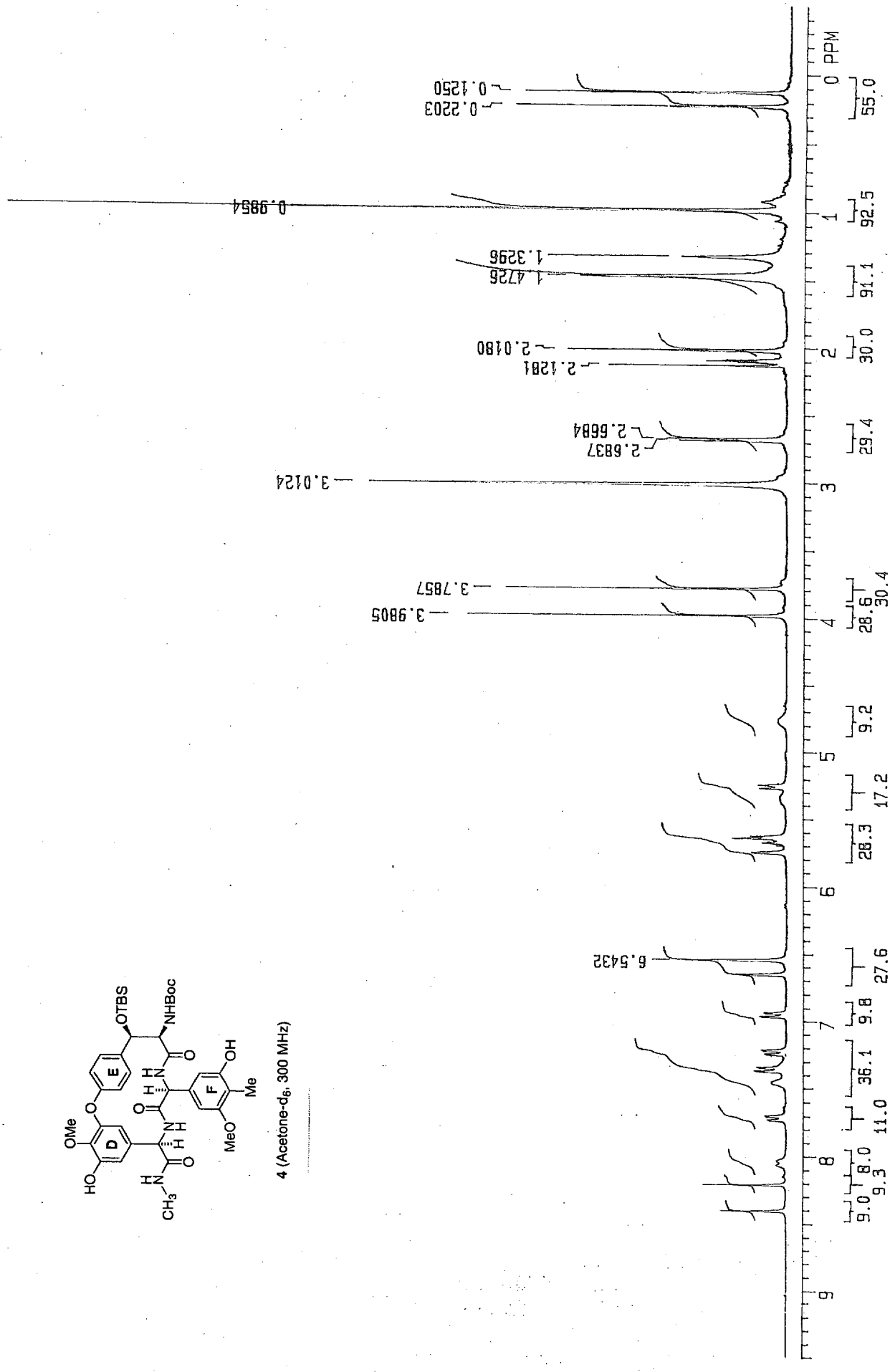

8.7804
28.8480
29.2316
29.6161
29.7967
30.0023
30.1860
30.3884
30.5851
30.6450
30.7729
31.1606
56.2055
59.3835
67.0565
71.0285
104.211
105.492
115.030
128.474
128.710
128.841
128.899
129.342
129.391
136.767
138.179
138.596
156.743
158.469
159.452
172.574
206.473
0
20
40
60
80
100
120
140
160
180
200
220
PPM
NHCbz
OBn
Me
MeO
HO
O
12 (Acetone-d6, 50 MHz)




156.167
157.151
158.118
170.192
170.793
0
20 PPM
40
60
80
100
120
140
160
180
200
220
OMe
OH
HO
NHCbz
OBn
Me
MeO
CH3
14 (CD3OD + Acetone-d6, 50 MHz)






0.1250
0.2203
0.9854
1.3296
1.4726
2.0180
2.1281
2.6837
2.6884
3.0124
3.7857
3.9805
6.5432
0 PPM
55.0
92.5
91.1
30.0
29.4
30.4
28.6
9.2
17.2
28.3
27.6
9.8
36.1
11.0
8.0
9.3
9.0
OTBS
NHBoc
OMe
HO
MeO
Me
OH
E
D
F
CH3
4 (Acetone-d6, 300 MHz)