The Synthesis of a "Smoothened" Cholesterol: 18,19-Dinorcholesterol

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Supporting Information

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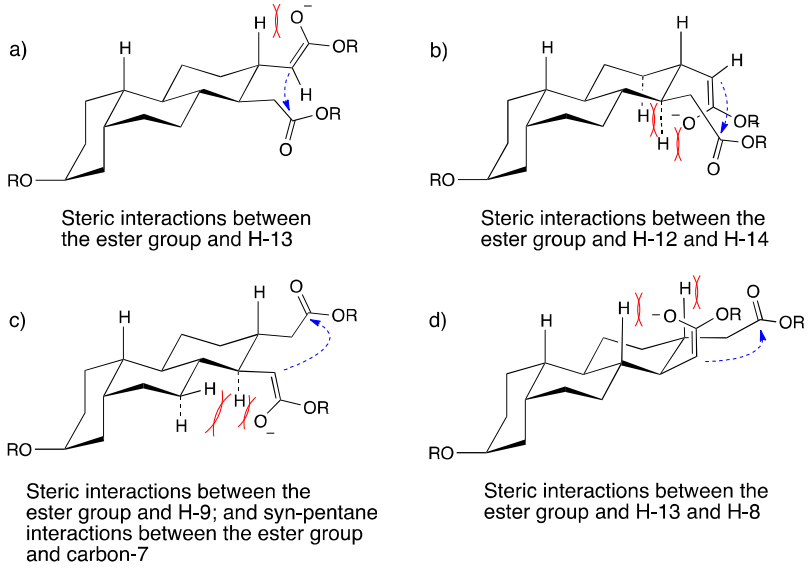
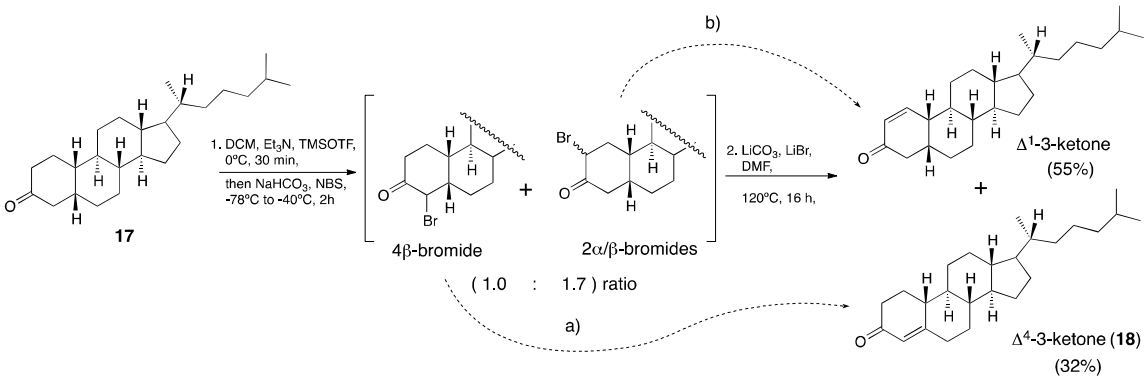
Scheme S1.[a]



[a]Illustration of possible intermediates in the Dieckmann Condensation. Intermediate (a) is rationalized to be the least sterically hindered intermediate and therefore the more stable intermediate. Accordingly, the product that comes from intermediate (a) is the β-ketoester that corresponds to our desired compound **4**; which we obtained as the sole product.

Scheme S2.[a]

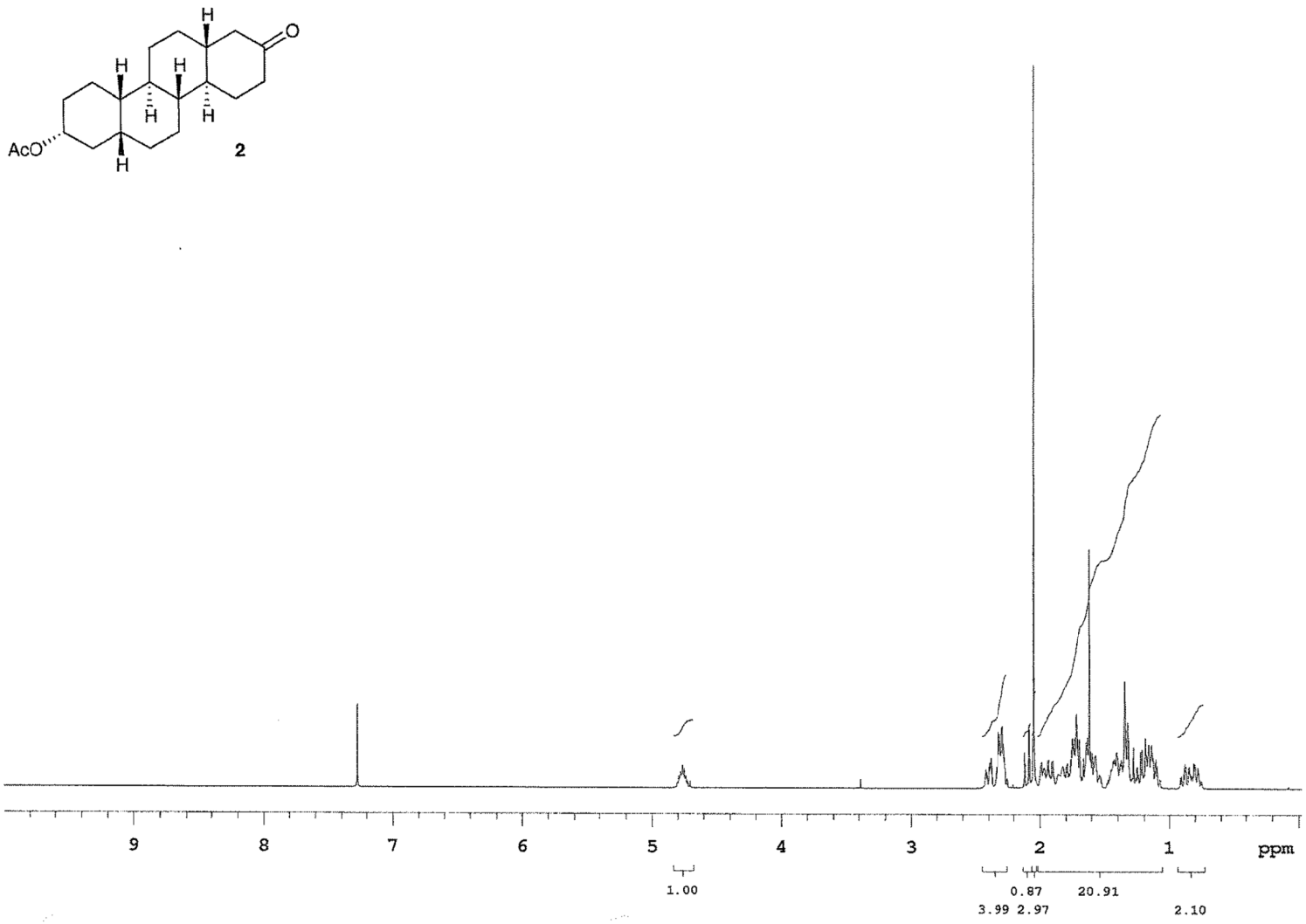


[a]Mechanism of double bond reintroduction. The bromination of compound **17** was found to consistently yield a 1:1.7 mixture of 4β:2α/β bromide intermediates (as detected by ^{1}HNMR, ref 25 in main text). It is postulated that from these intermediates, elimination of the: a) 4β-bromide leads to the formation of the desired Δ^4-3-ketone (**18**); and b) 2α/β-bromides leads to the formation of the undesired Δ^1-3-ketone, as these enones are also obtained in a 1:1.7 ratio (32%:55%), mirroring that of the intermediate bromides.

1. ^{1}HNMR and ^{13}CNMR Spectra of Compounds 1-18

General Remarks

All NMR spectra were recorded in $CDCl_3$, at either 400 MHz (^{1}H) or 100 MHz (^{13}C). Compounds **11-13** contain an additional 2D NMR (COSY), recorded in $CDCl_3$ at 400 MHz. Chemical shifts (δ) were reported downfield from internal Me_4Si (δ: 0.00).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O
H
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9
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2
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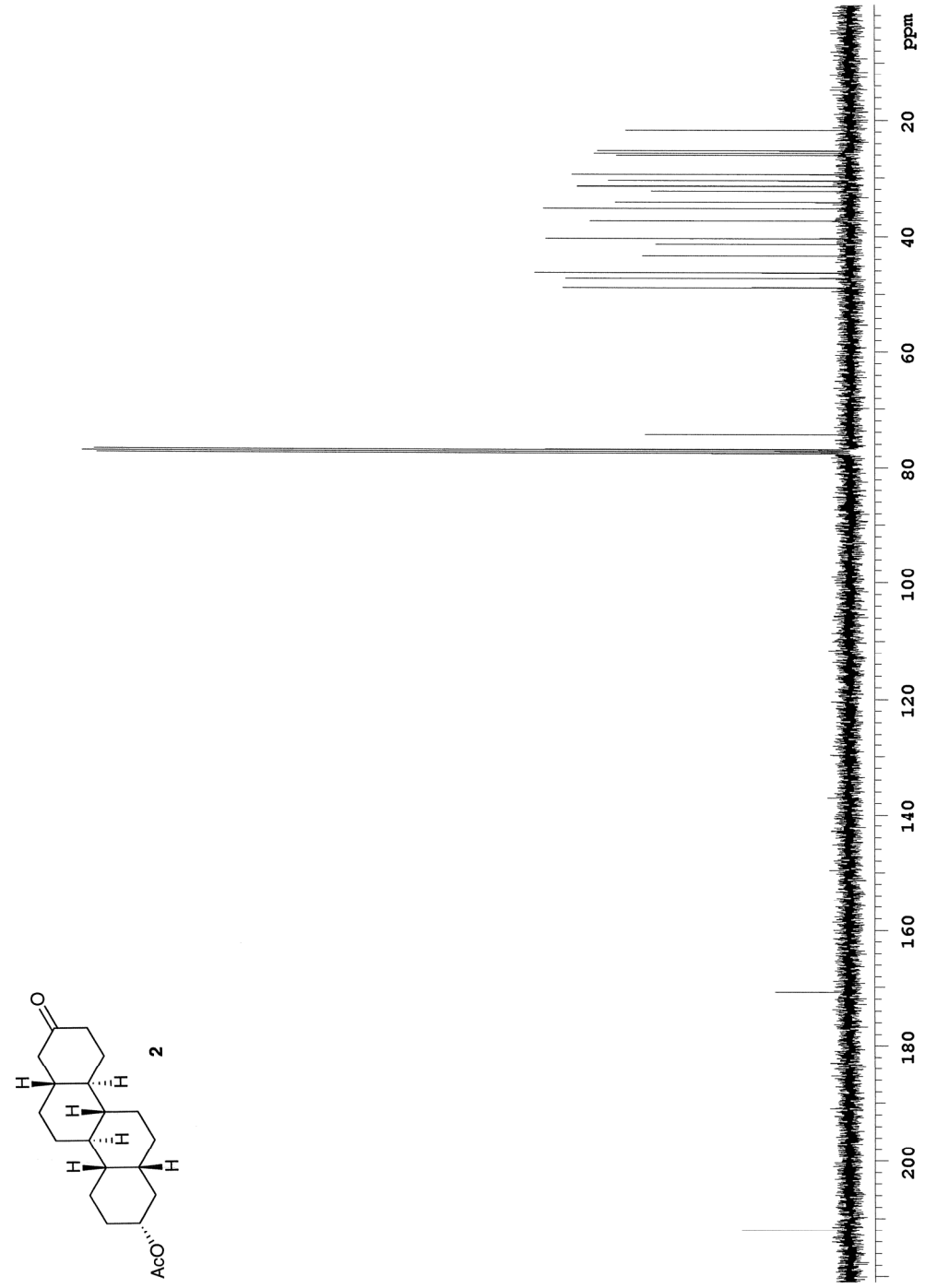
0.87
20.91
2.10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H
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H
H
H
H
AcO
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120
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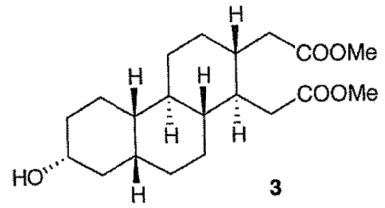
80
60
40
20
ppm



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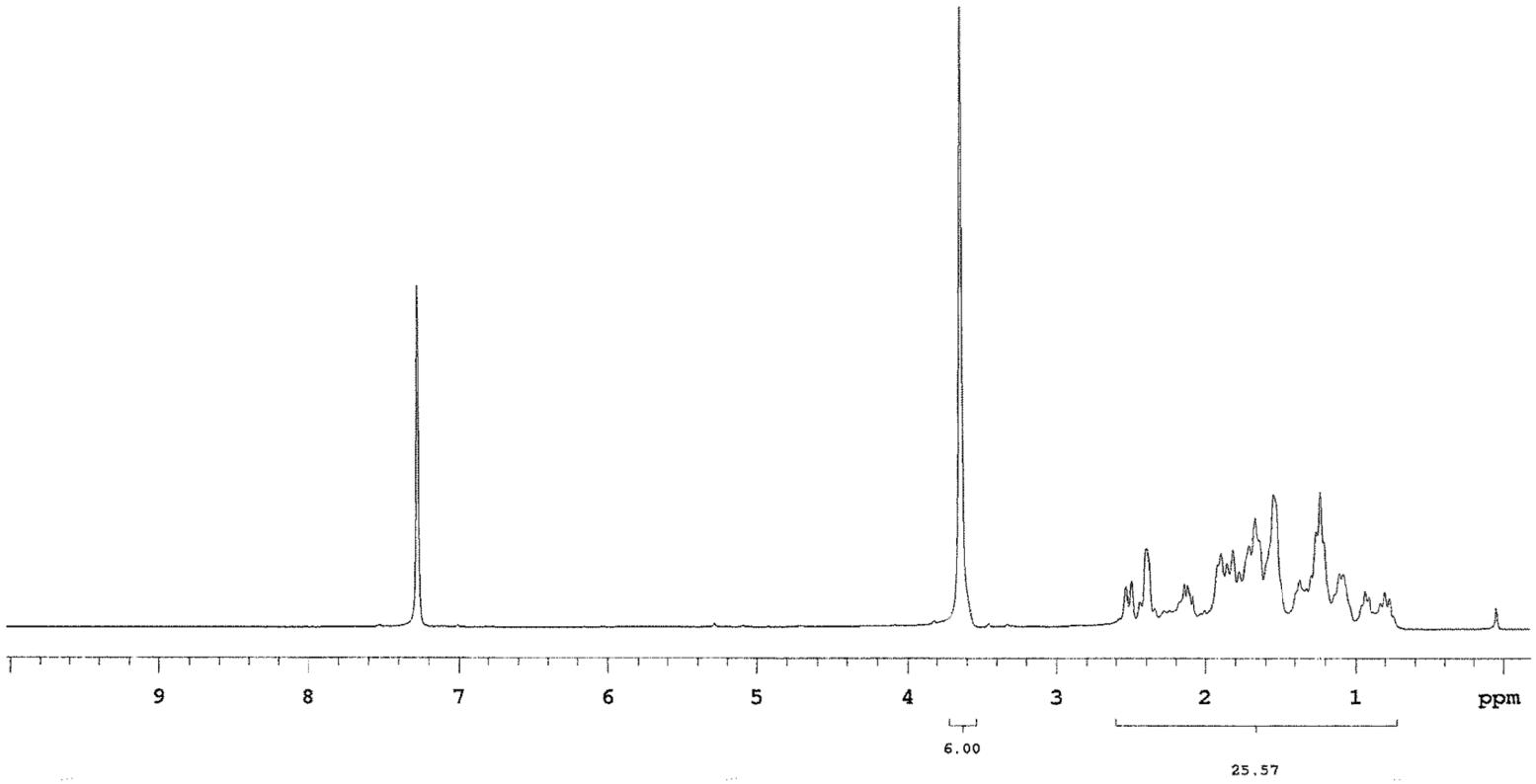

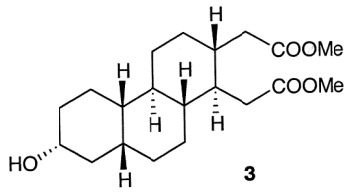

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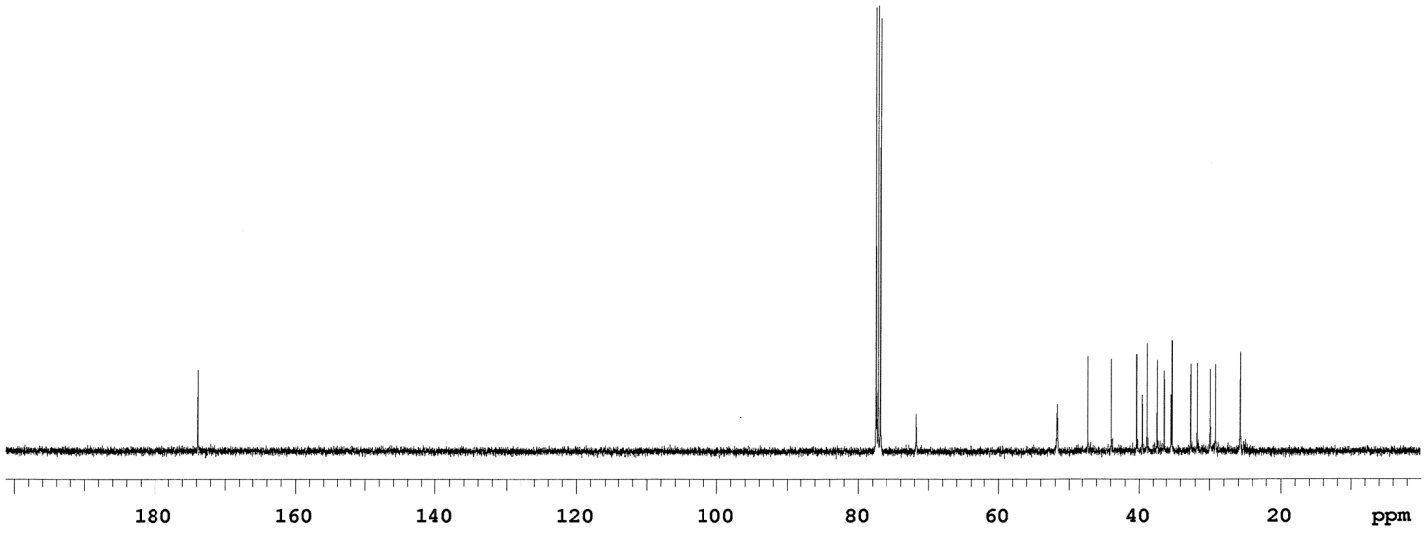

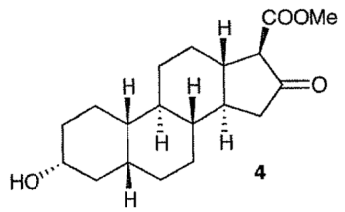

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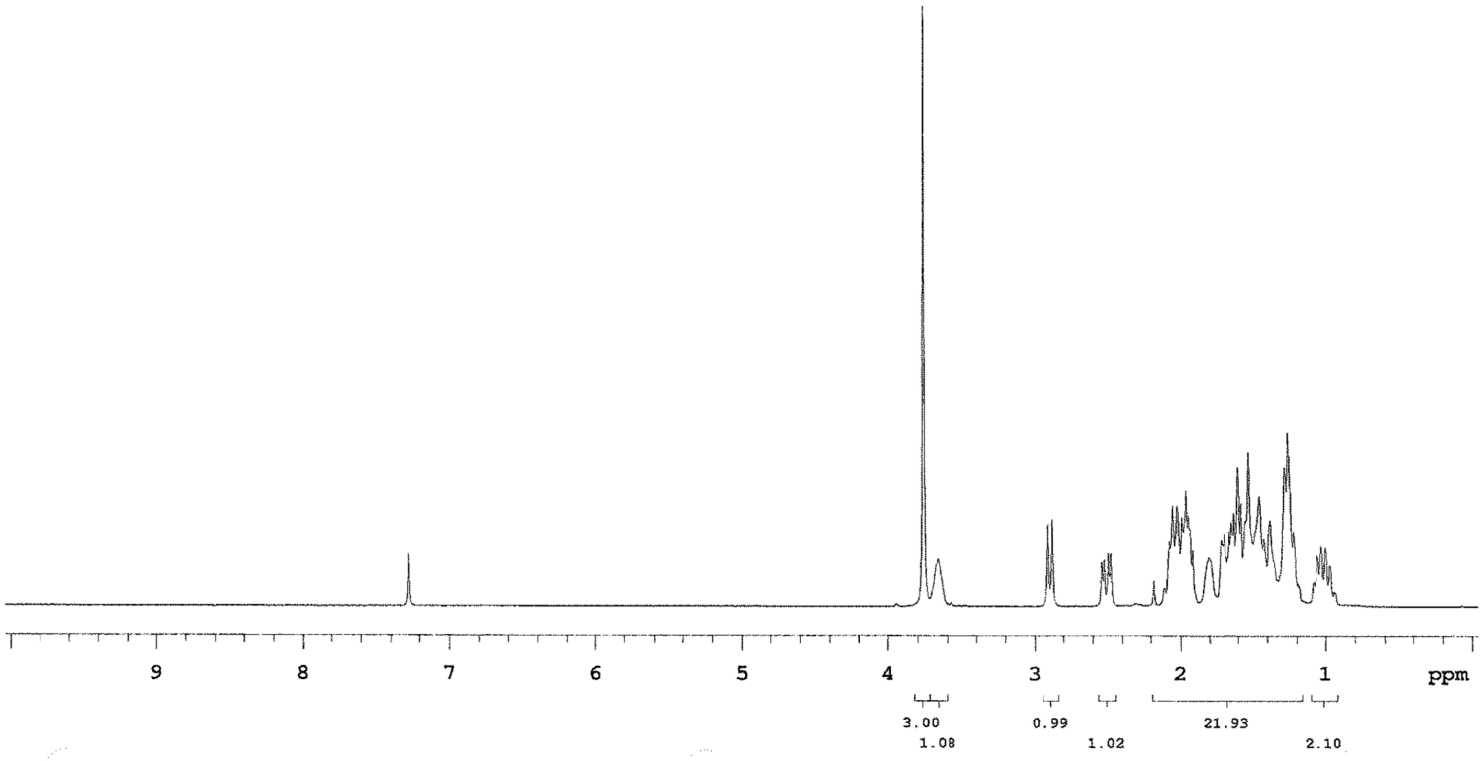

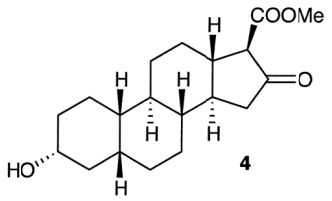

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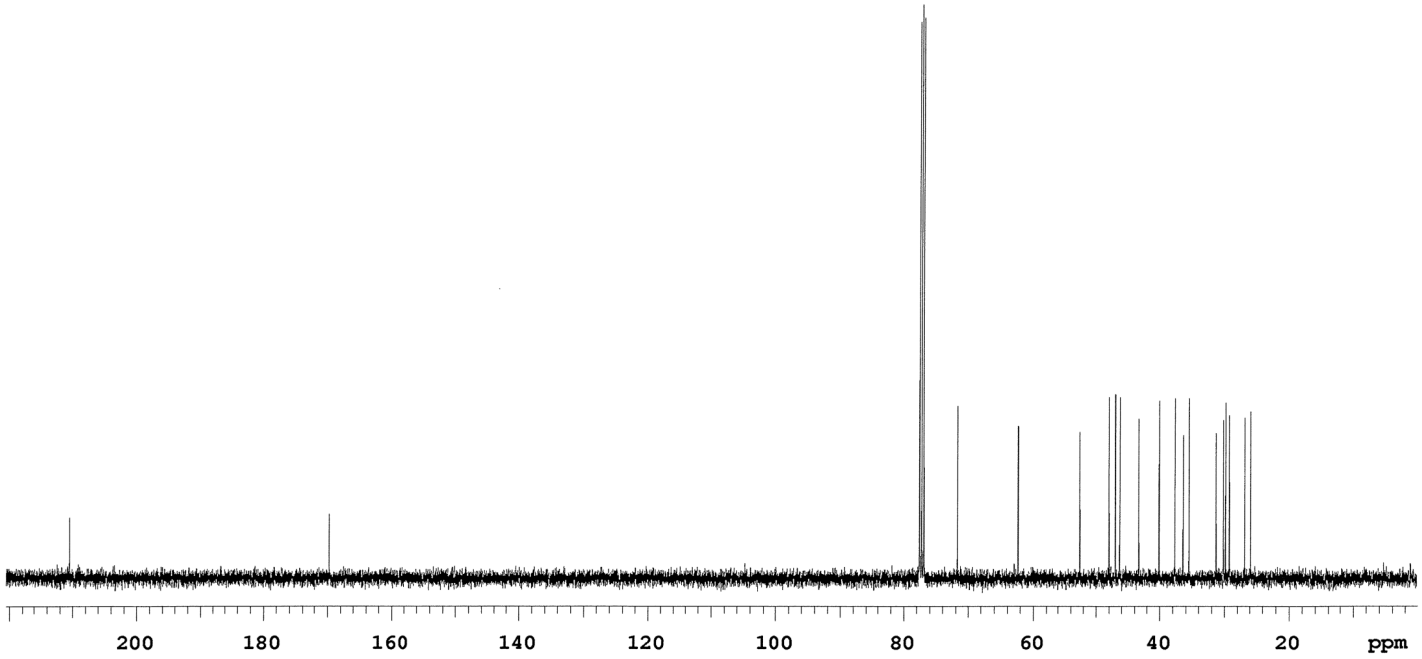

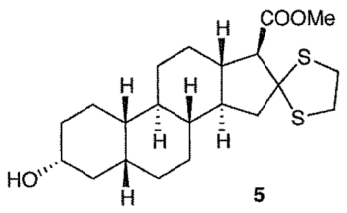
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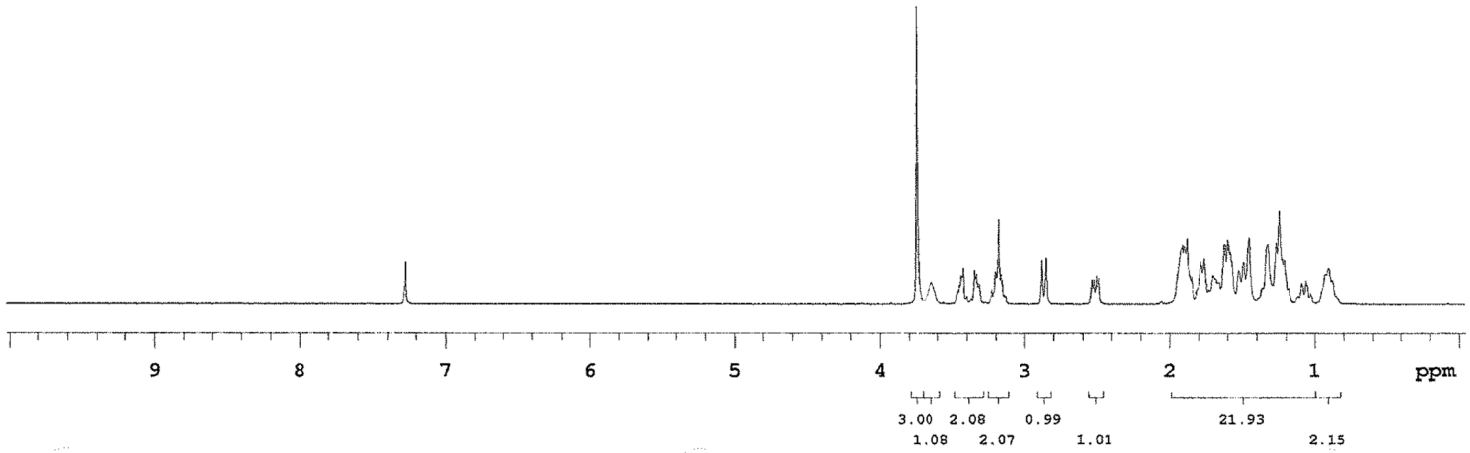
S
H
H
H
H
HO
H

5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7
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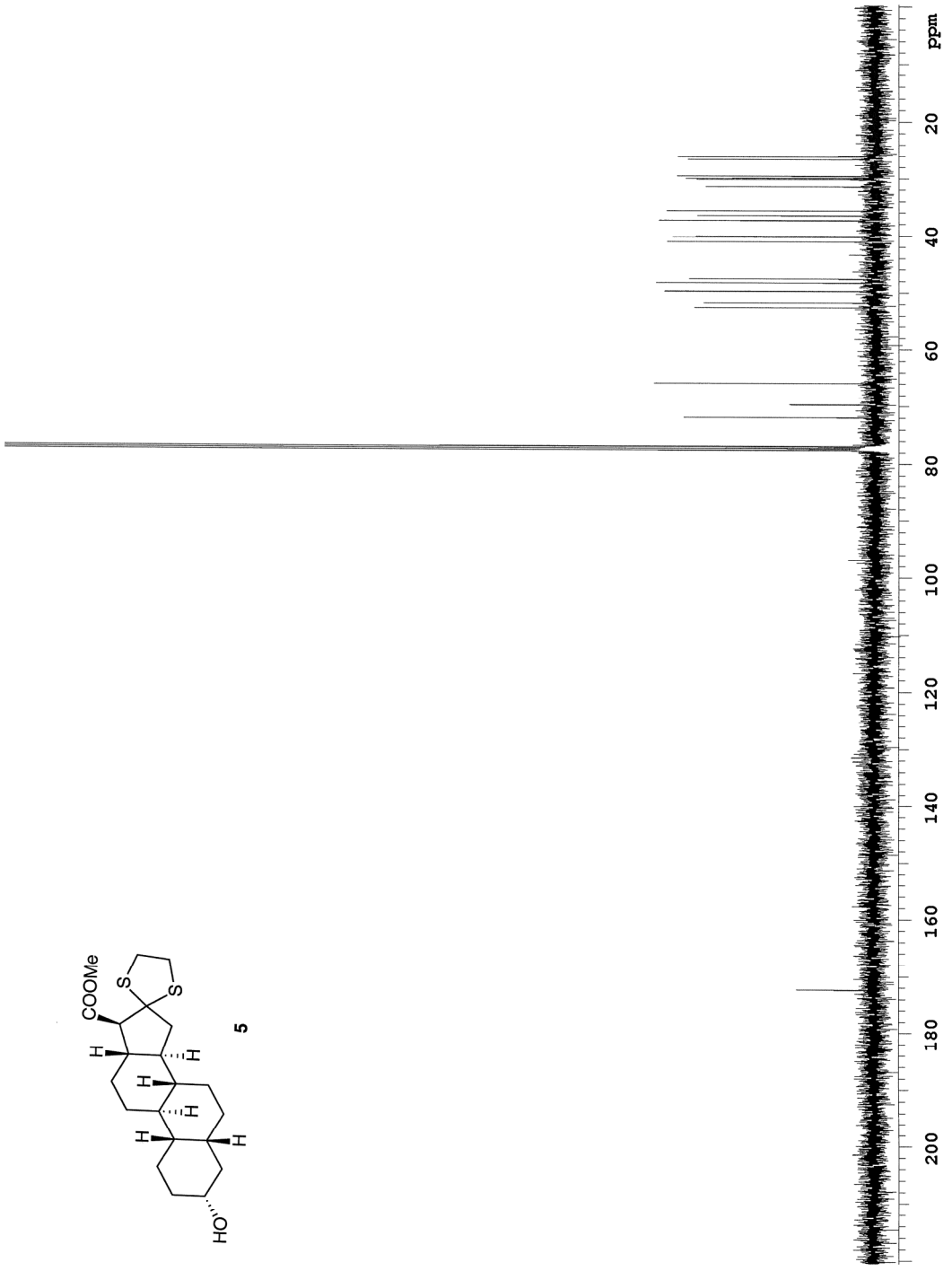
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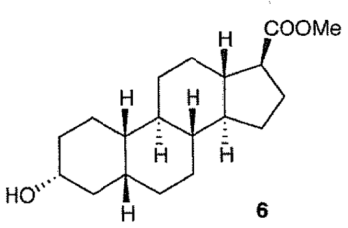

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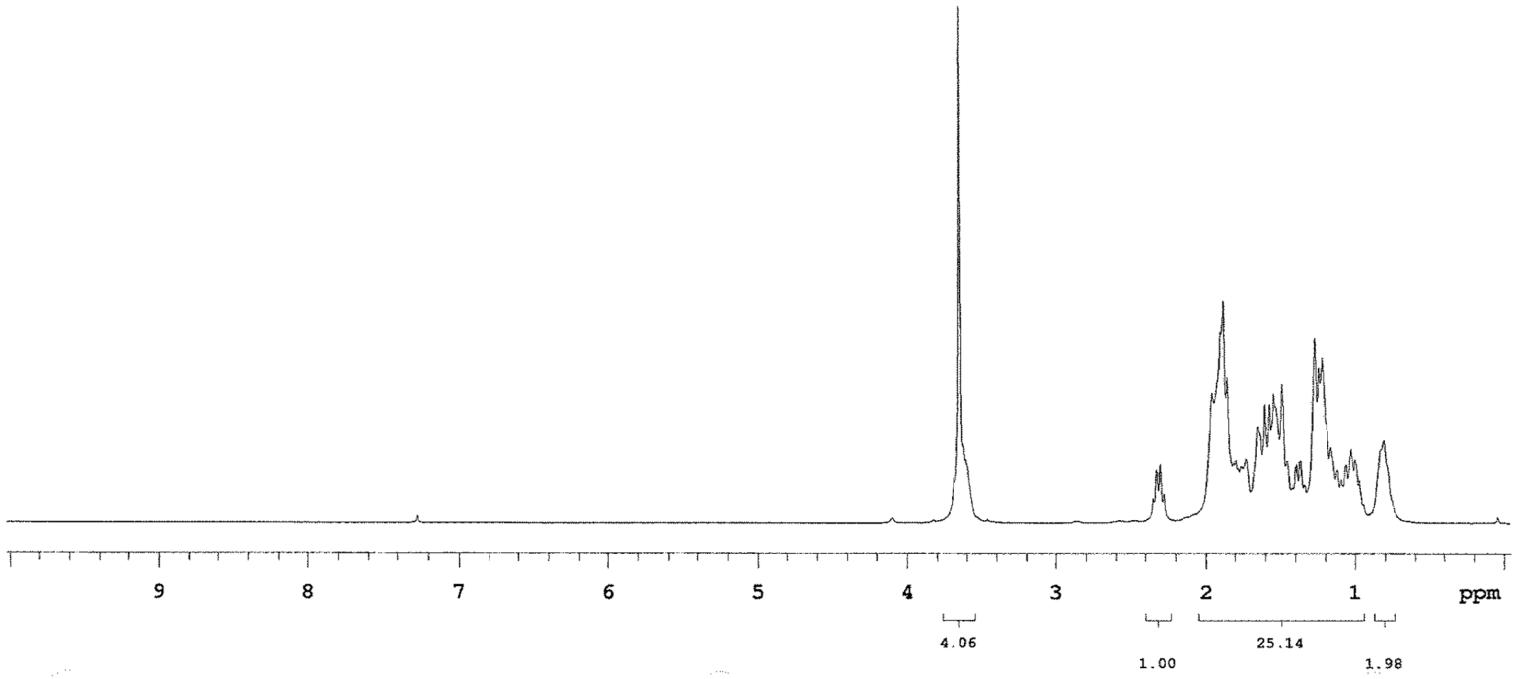

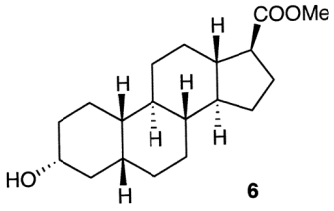

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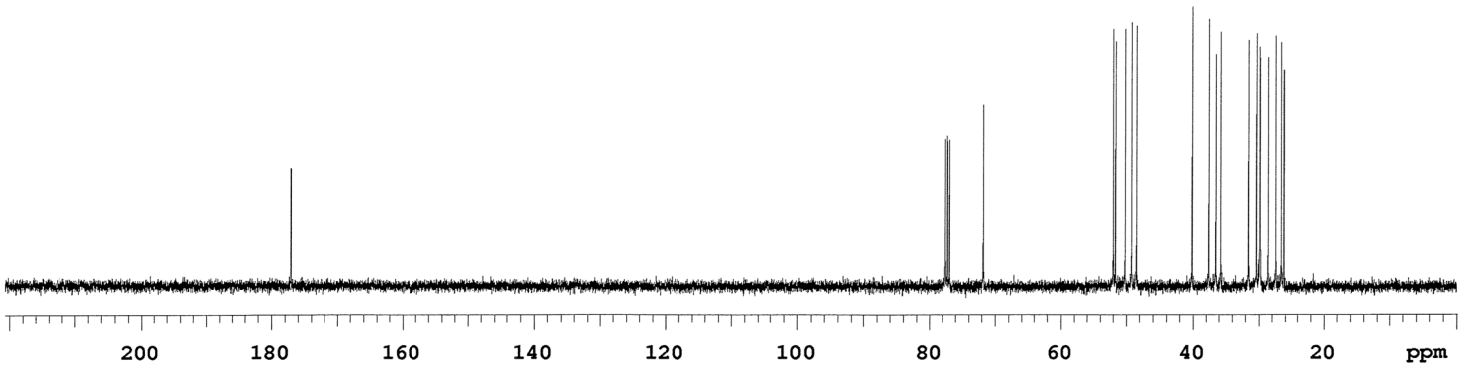

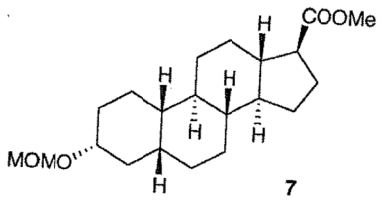
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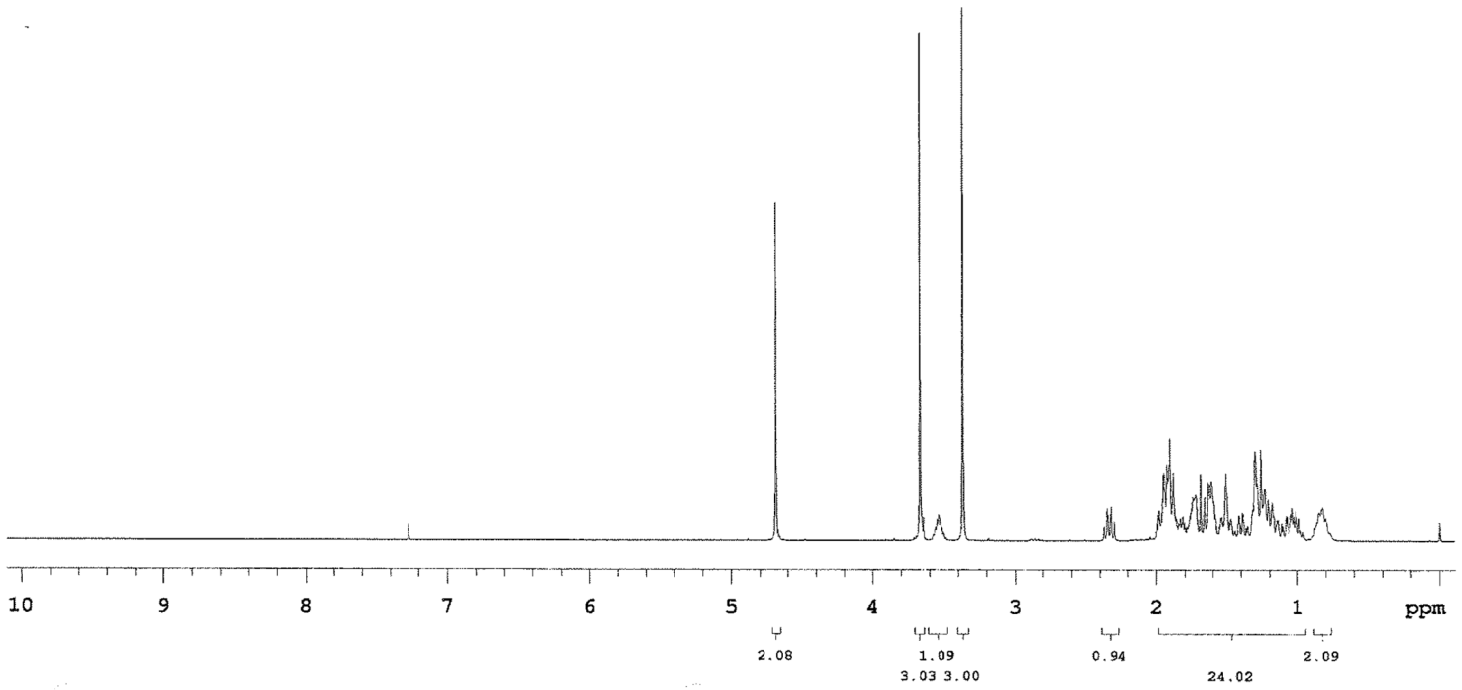
H
H
H
H
H
H
MOMO

7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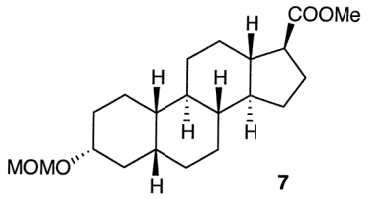

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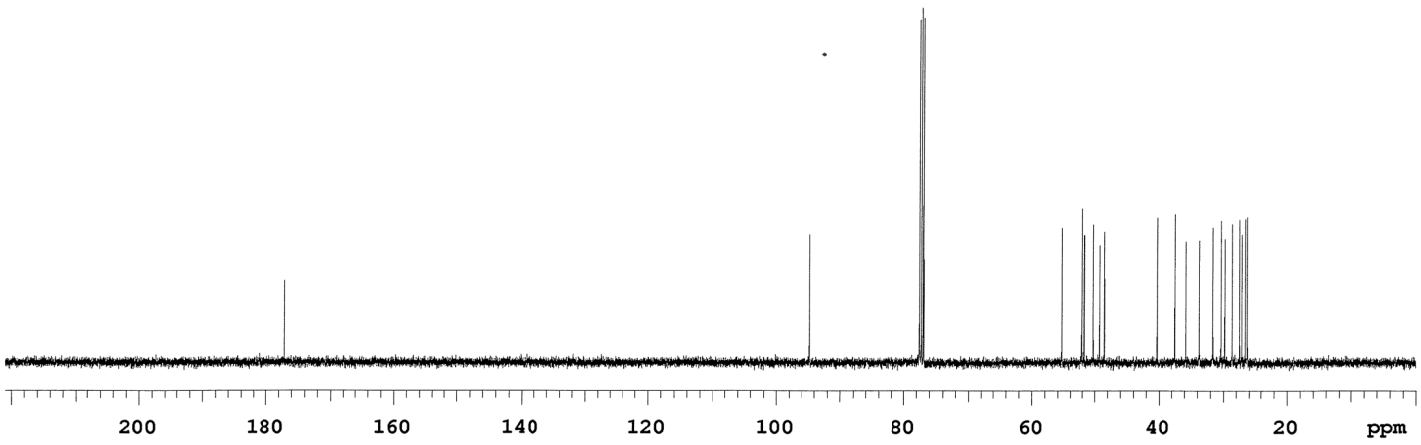

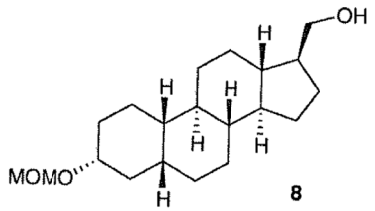

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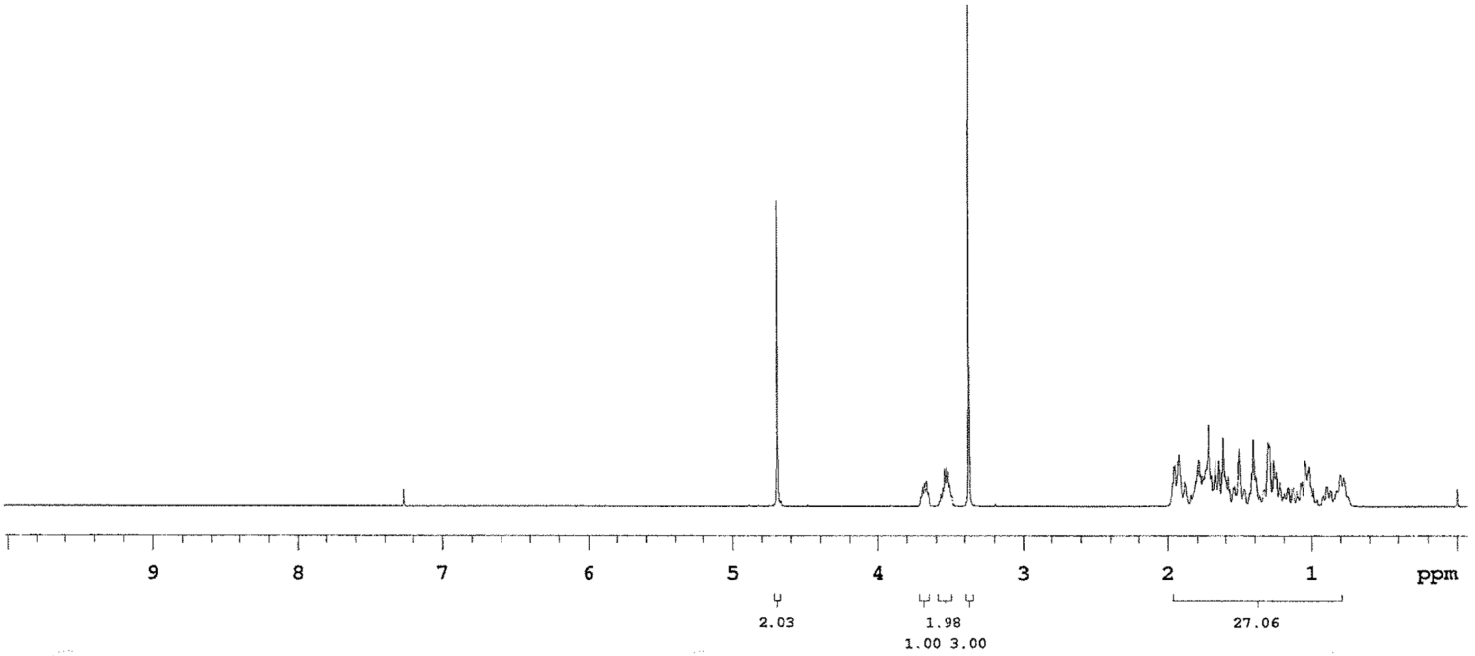

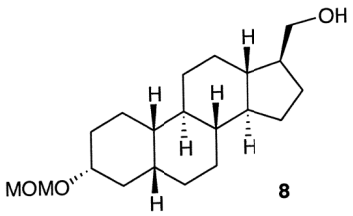

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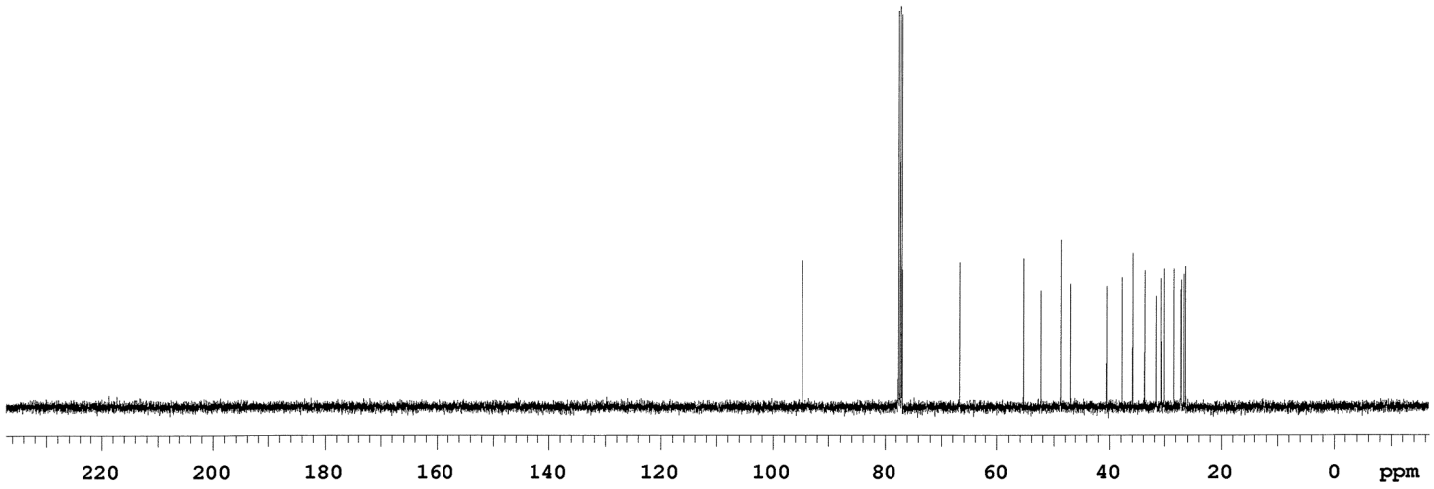

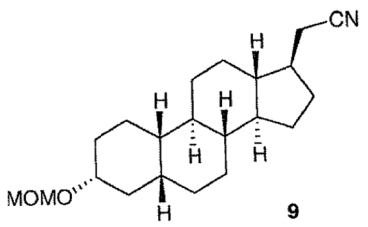

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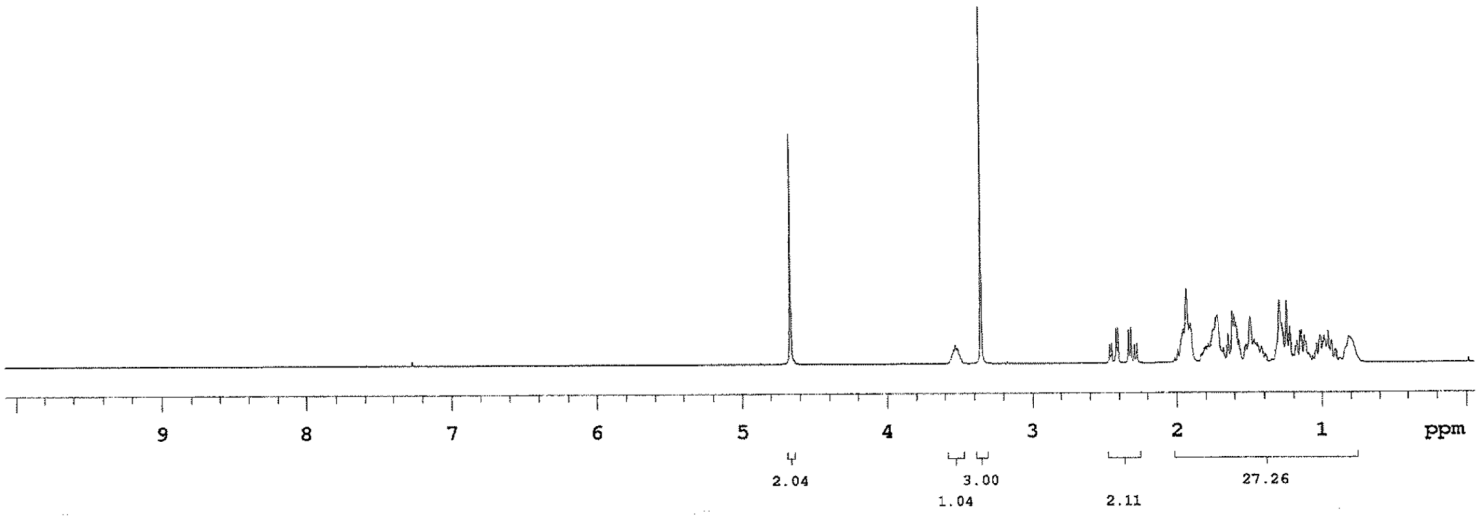

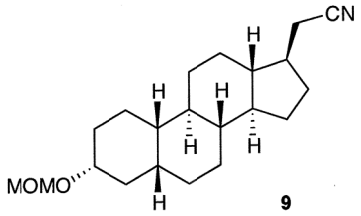

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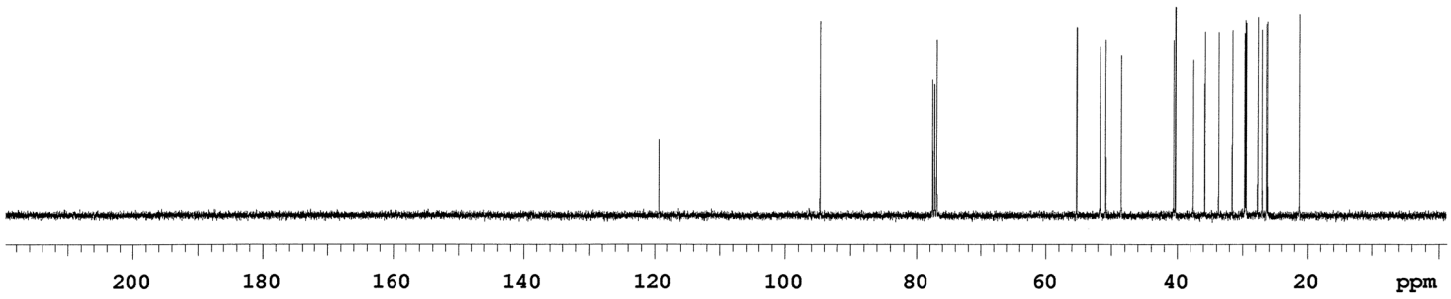

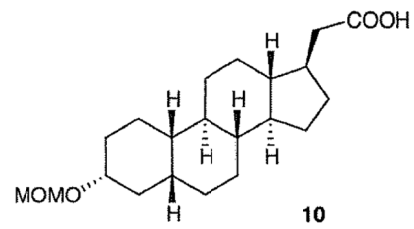
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H
H
H
H
MOMO
H

10

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8
7
6
5
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2
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1.02
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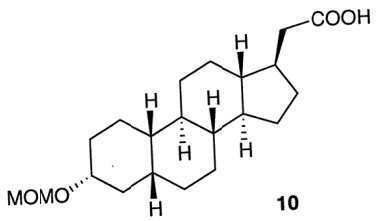

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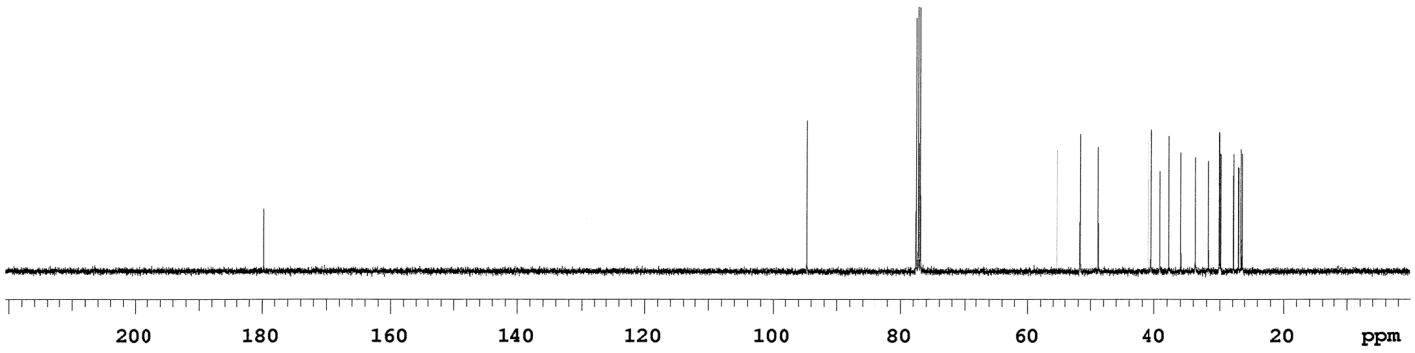

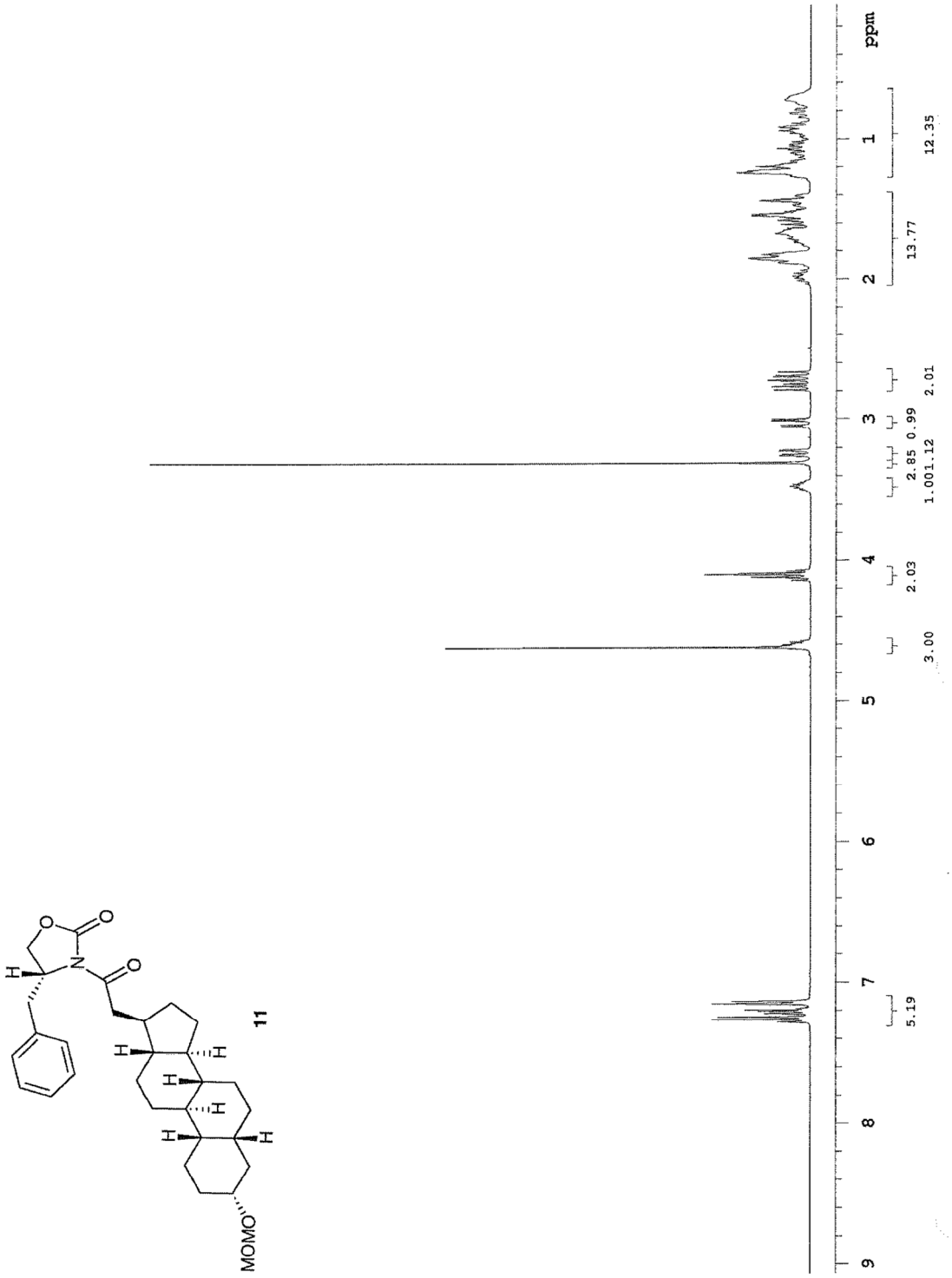
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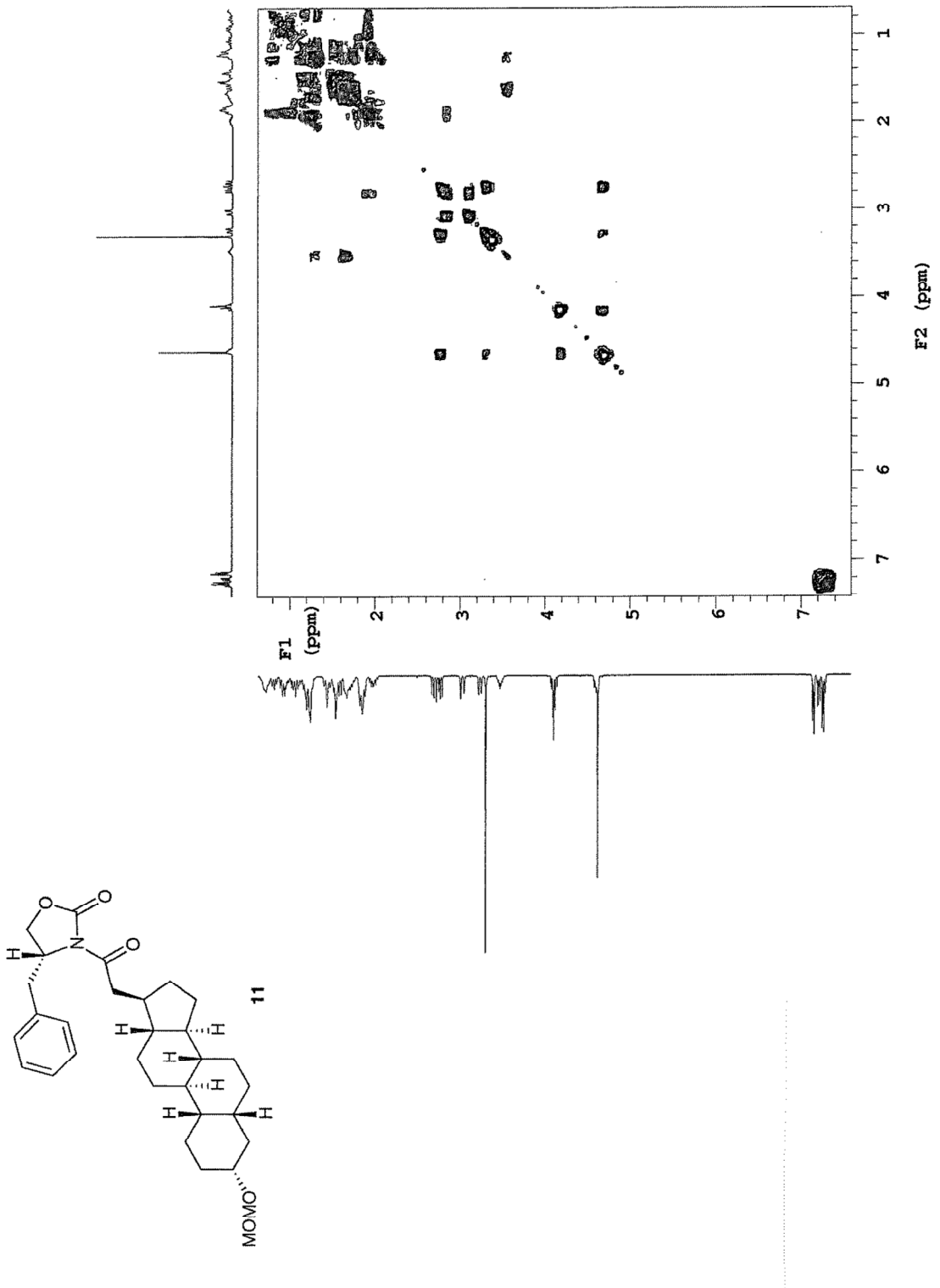
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F2 (ppm)
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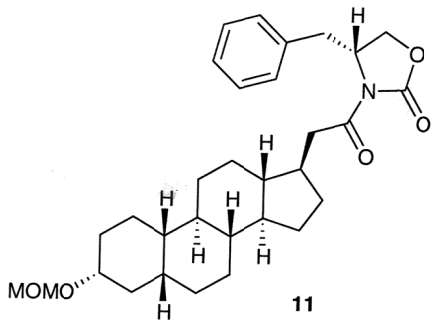

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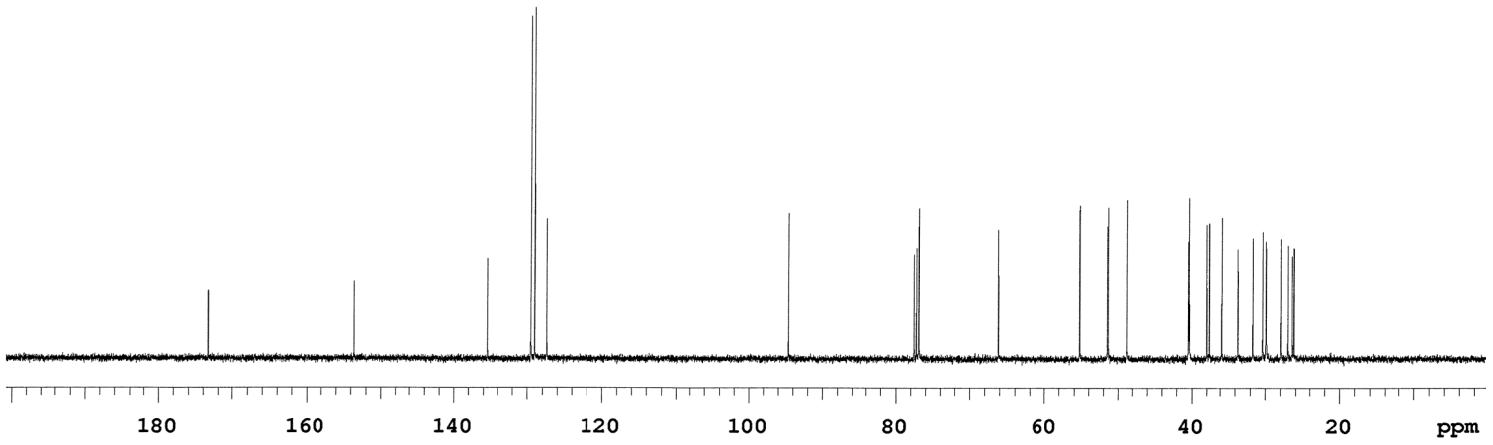

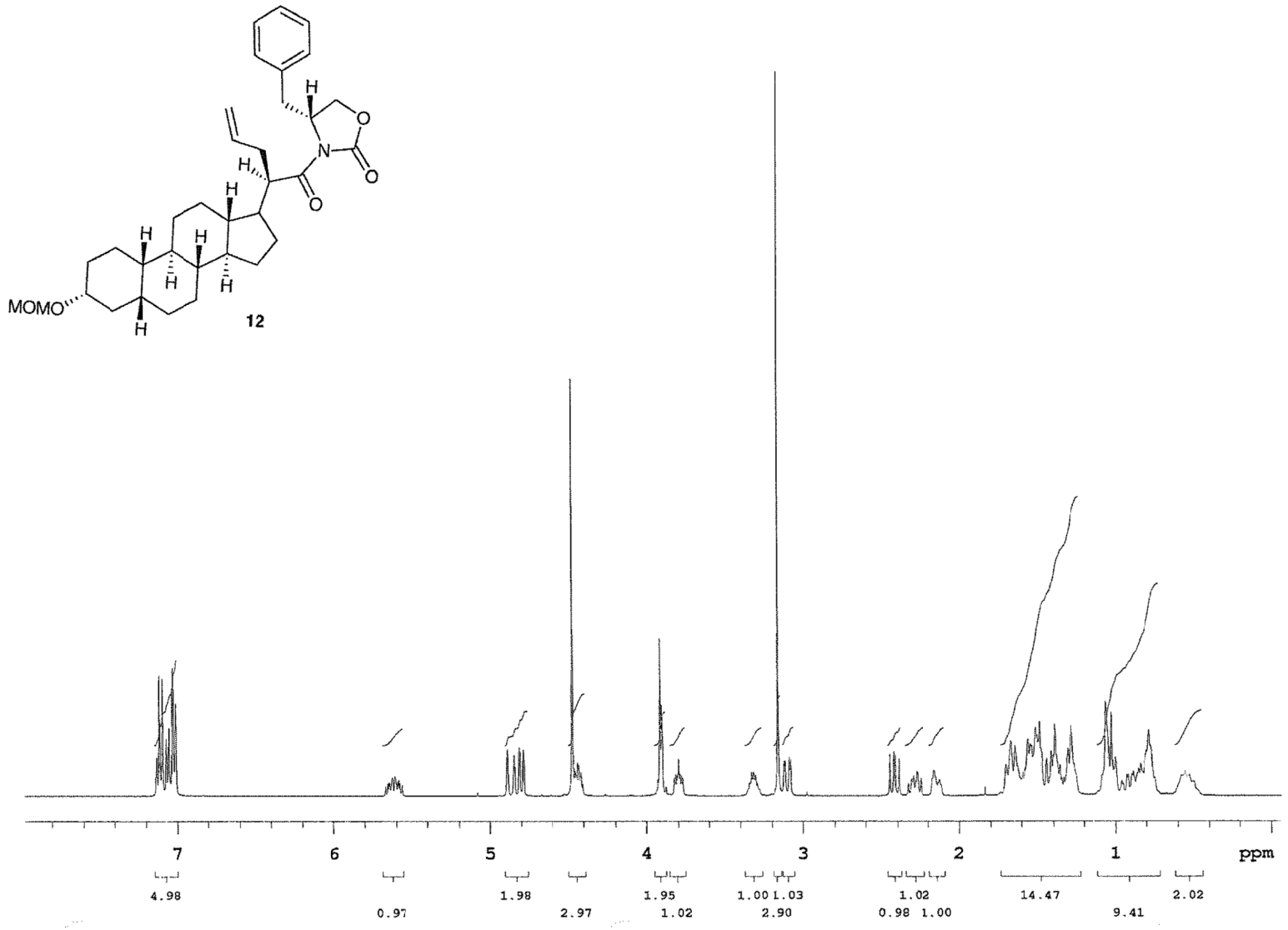
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5
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1
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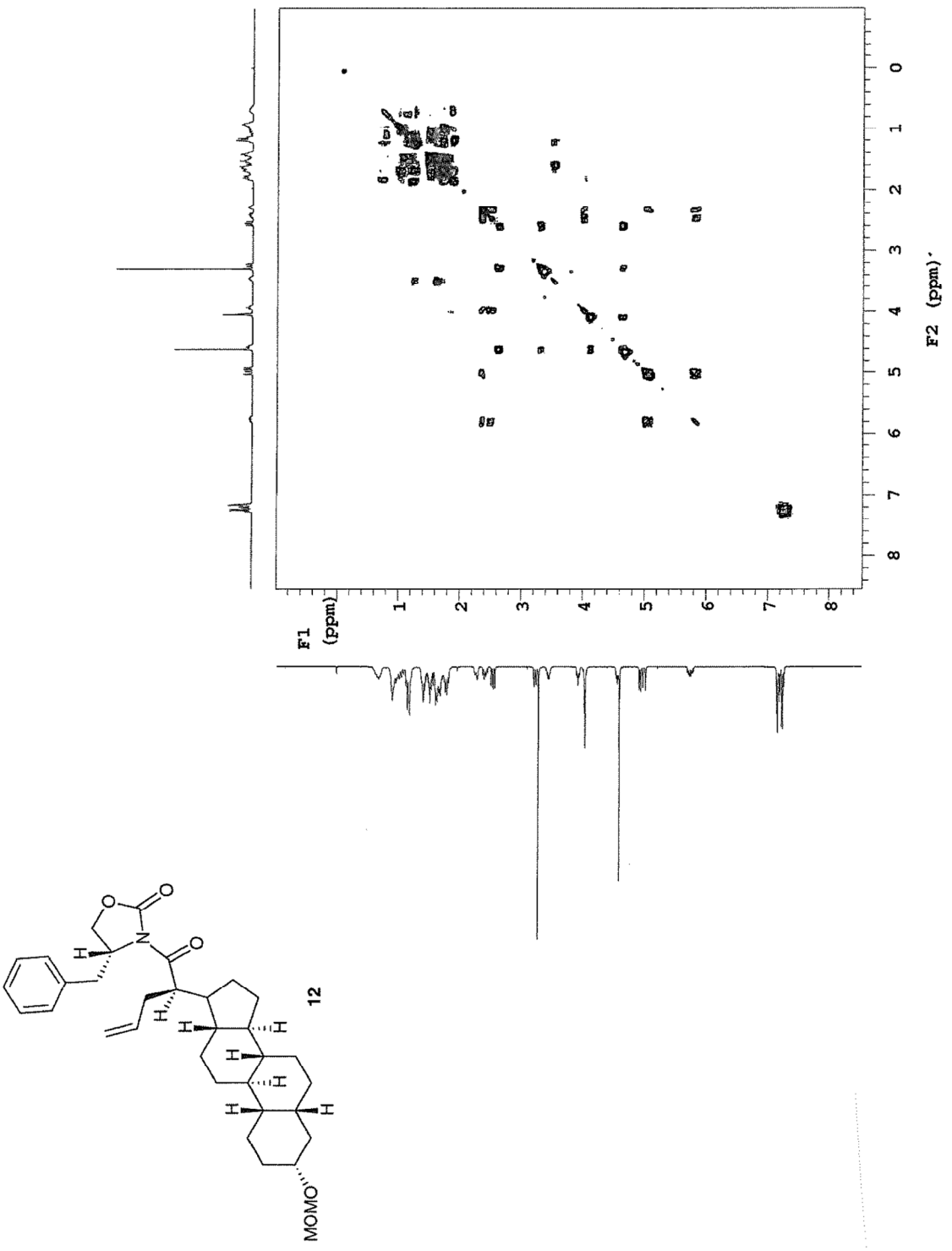
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F2 (ppm)
MOMO
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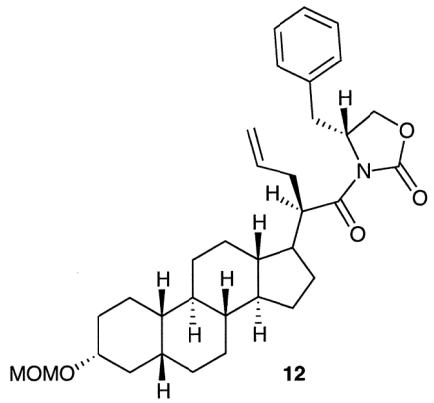
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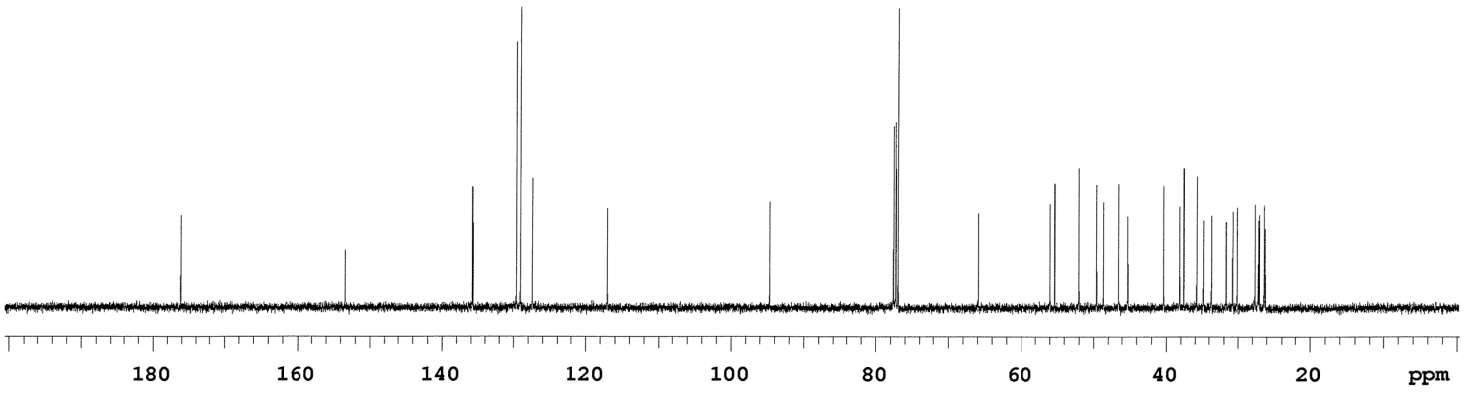
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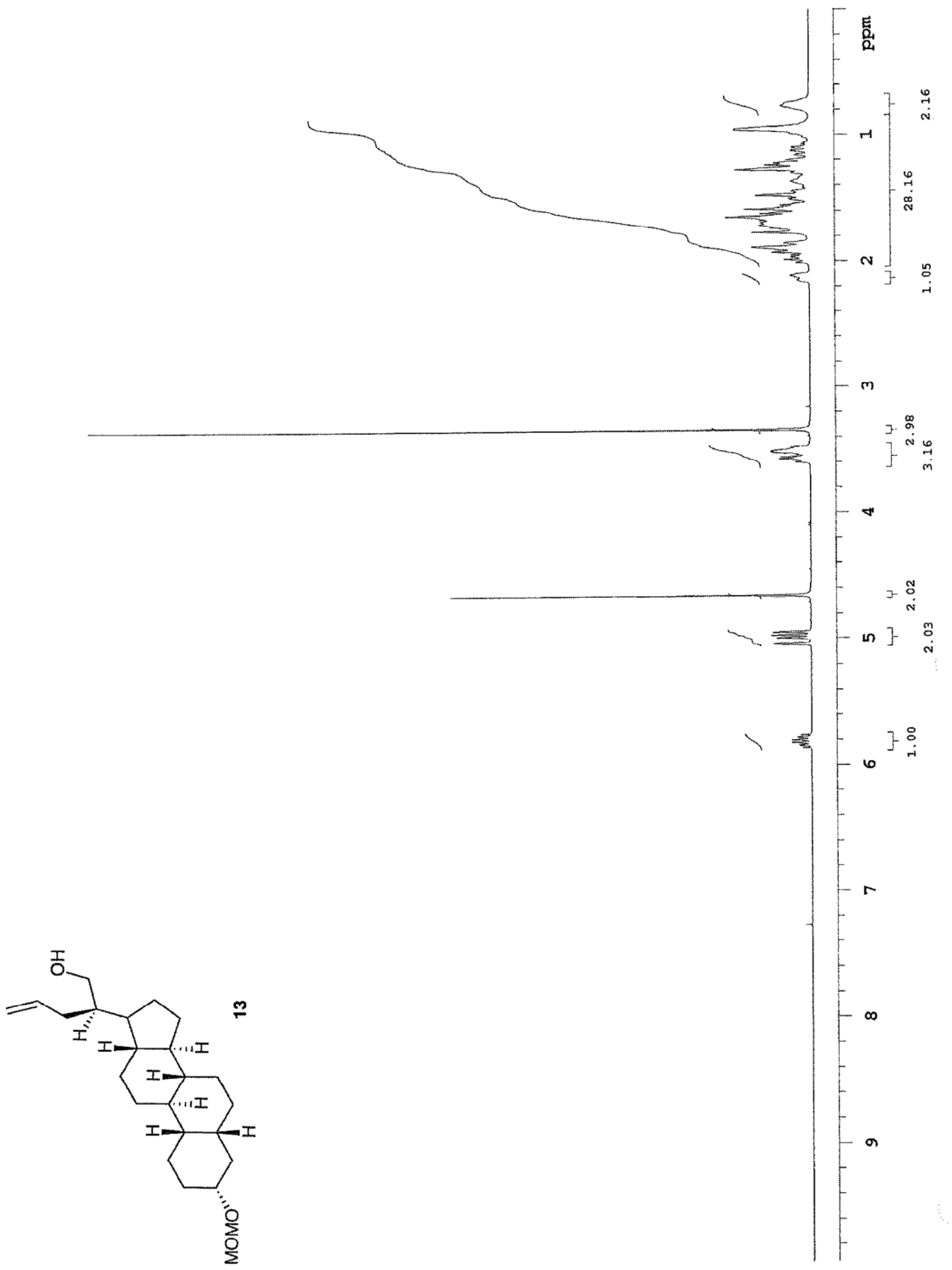
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H
H
H
H
H
H
H
MOMO
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7
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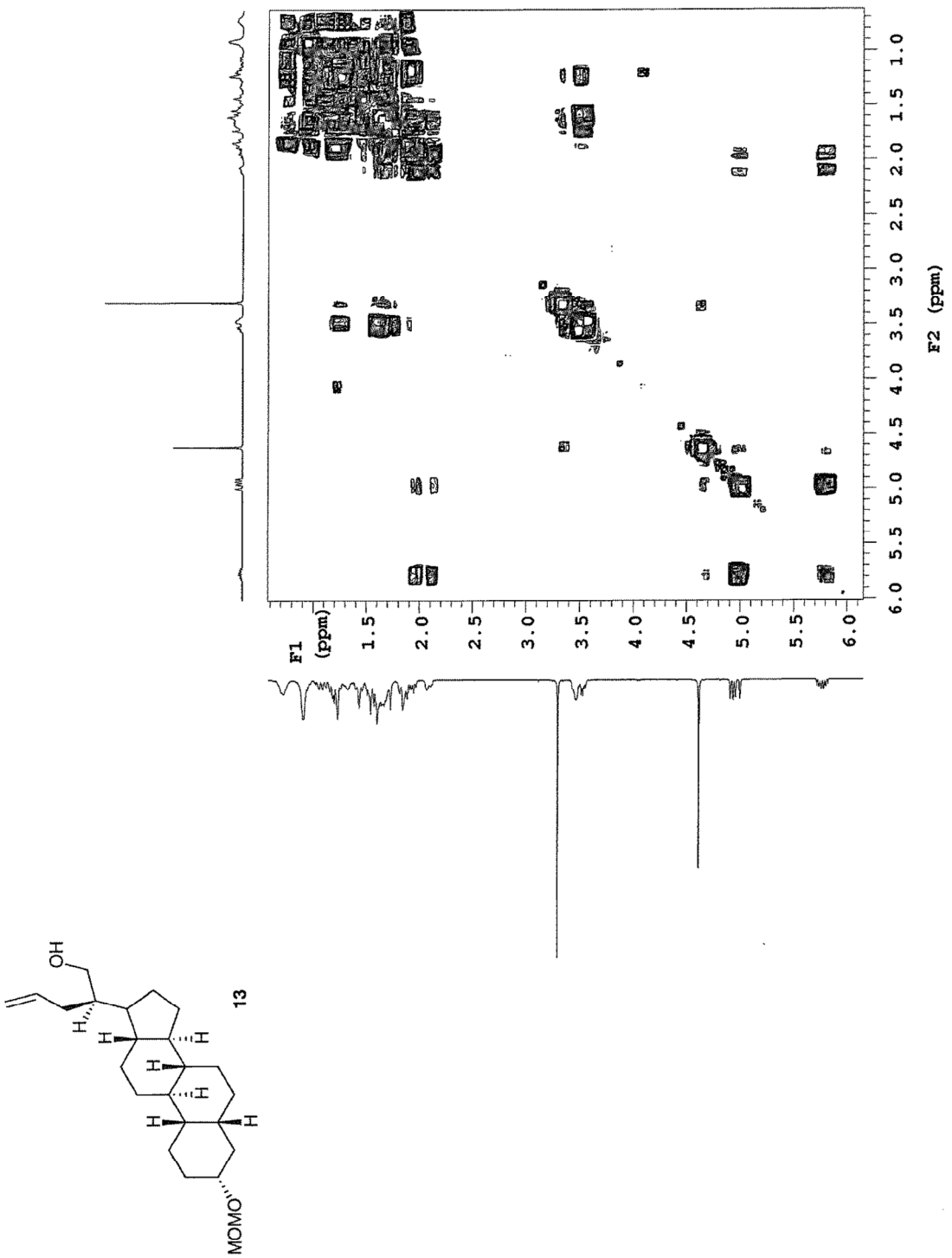
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H
H
H
H
H
H
H
MOMO
13
F1 (ppm)
1.5
2.0
2.5
3.0
3.5
4.0
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5.5
6.0
6.0
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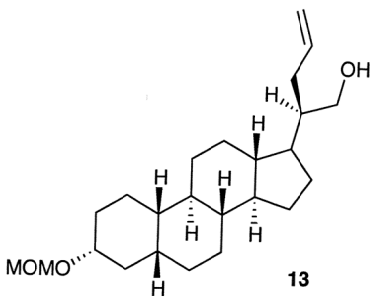
1.0
F2 (ppm)



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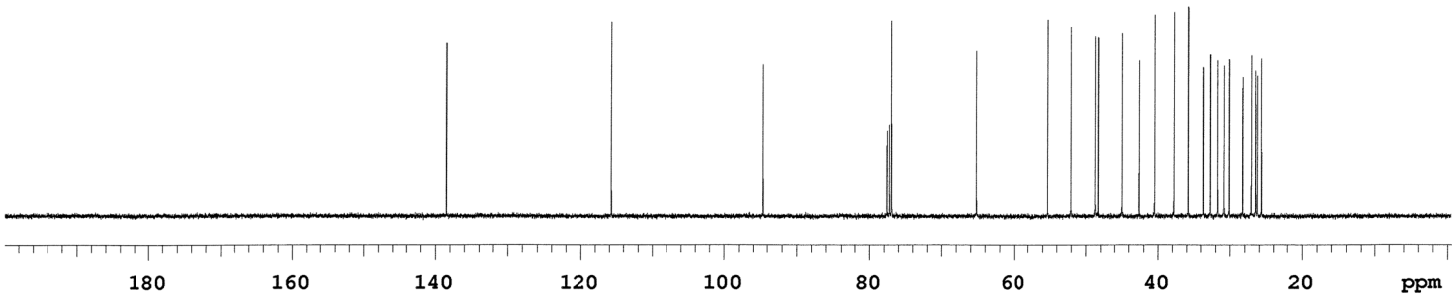

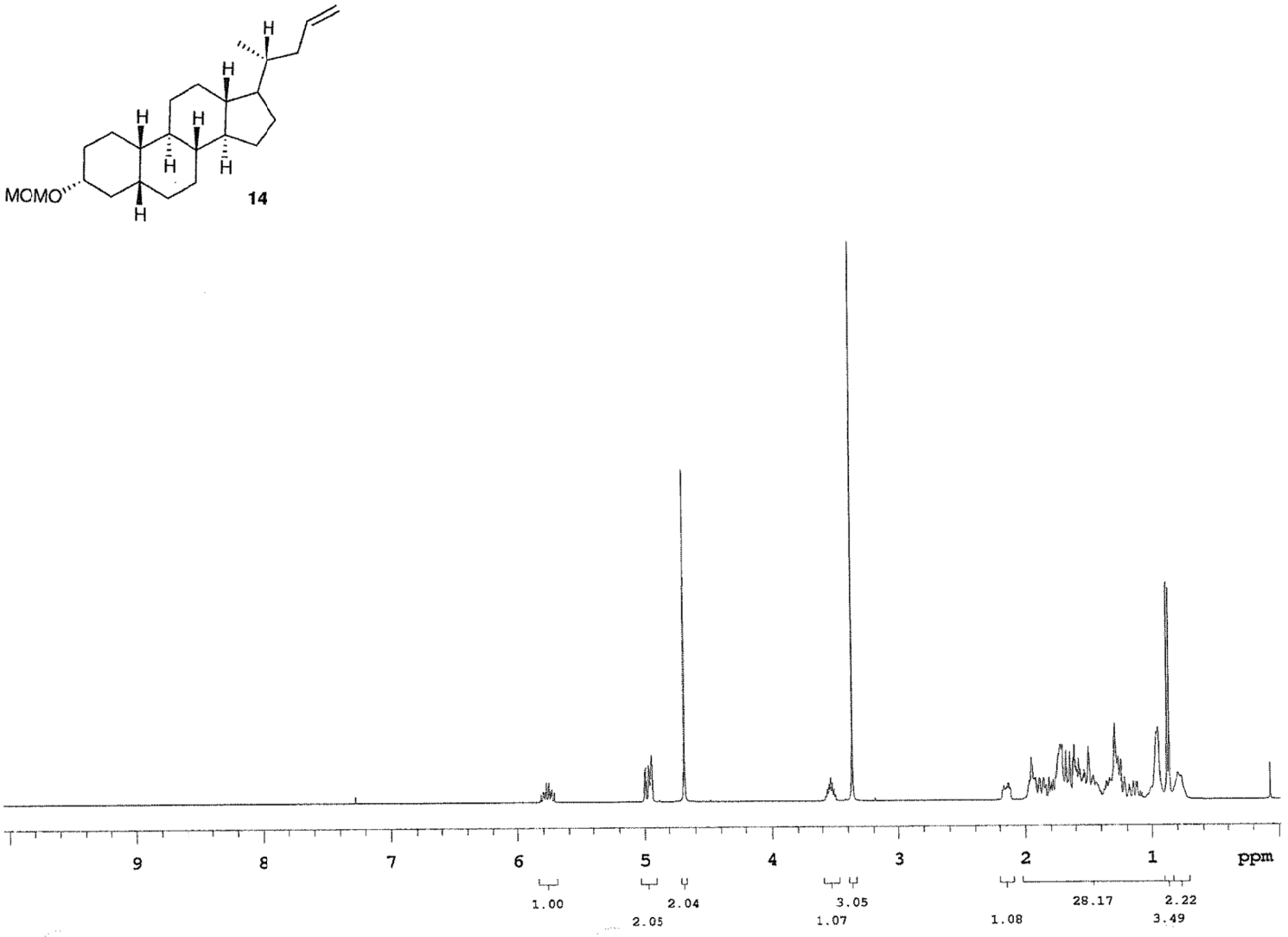
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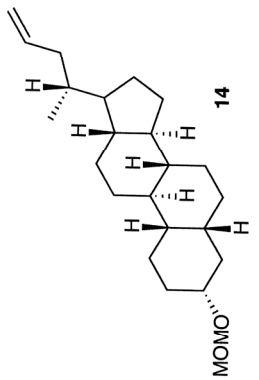

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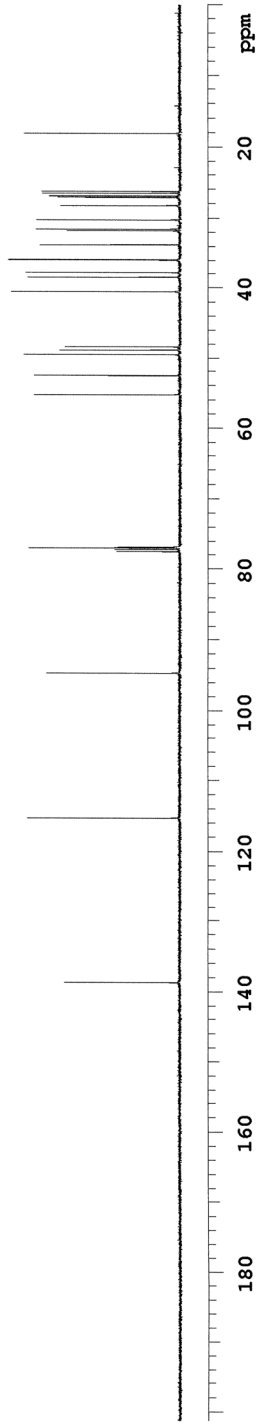

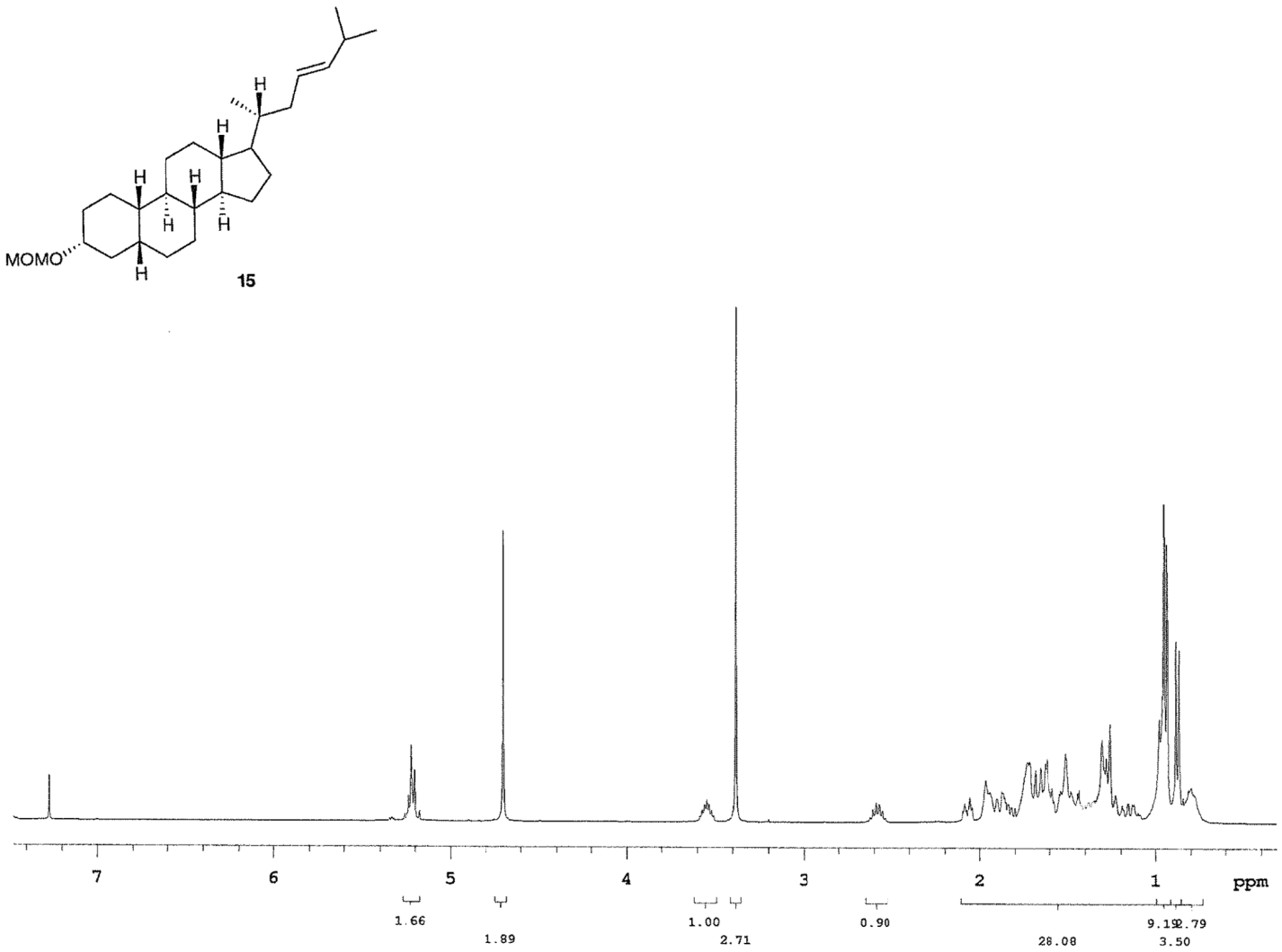
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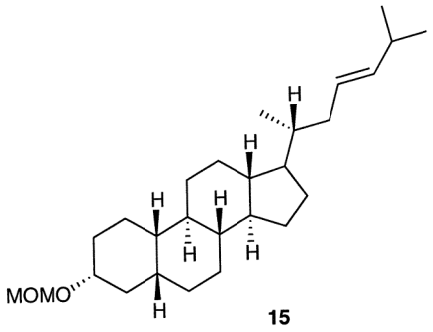

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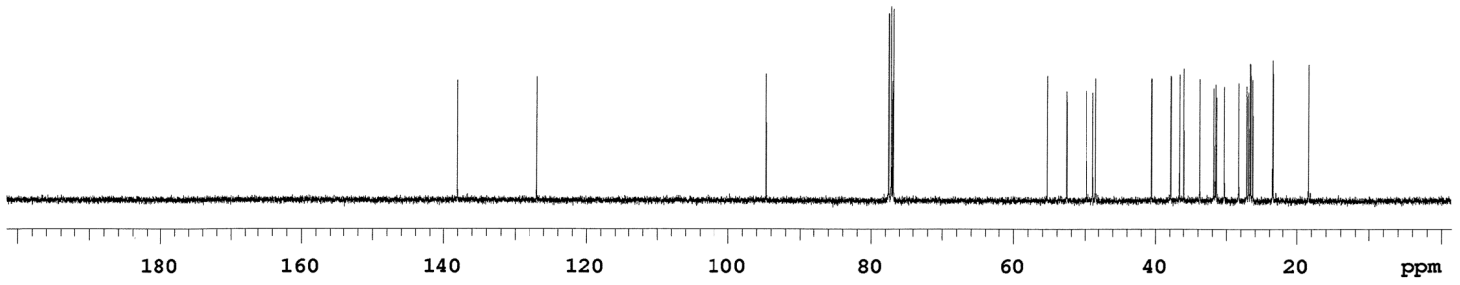

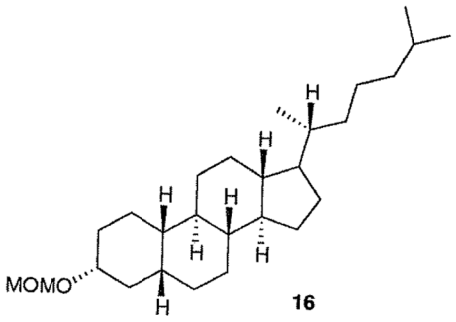

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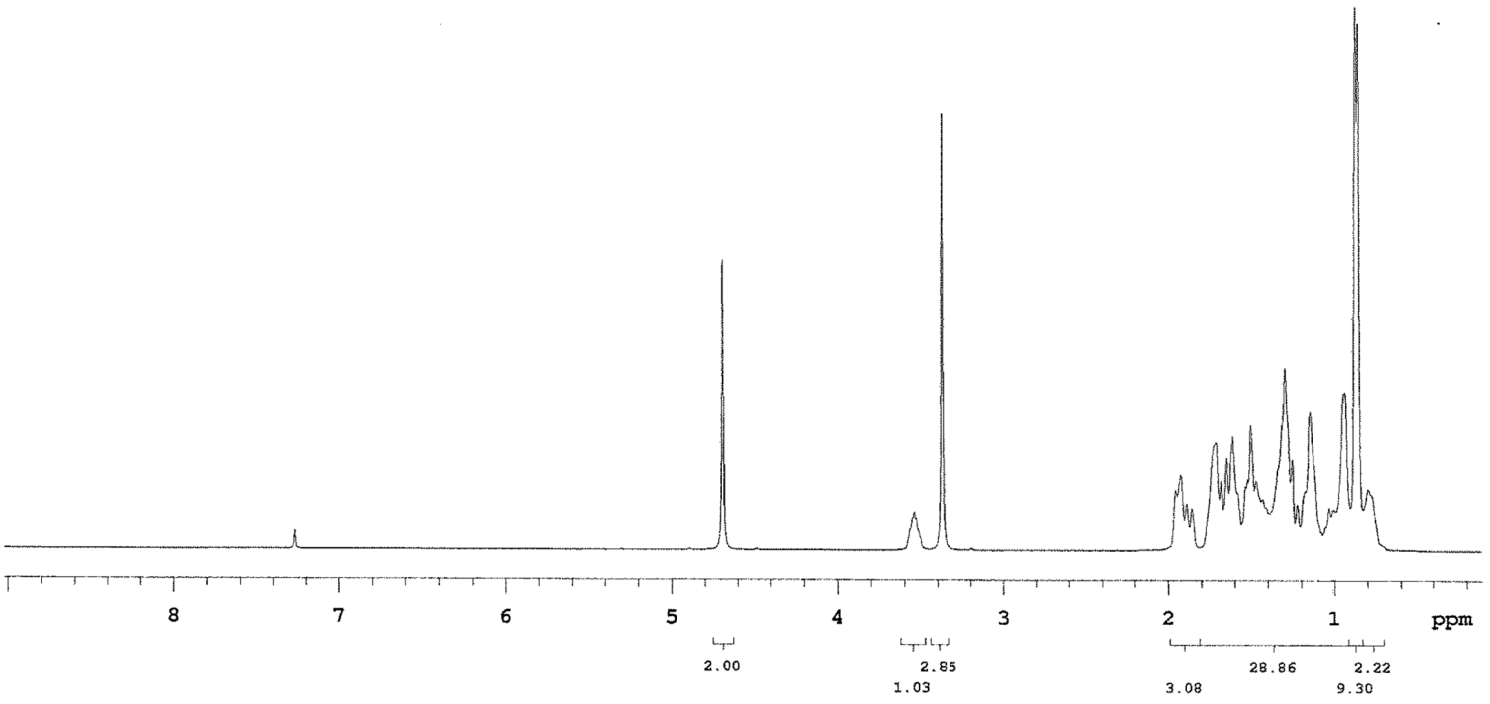

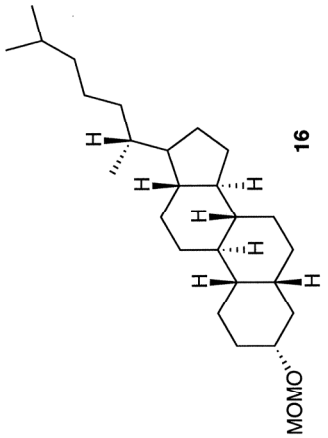
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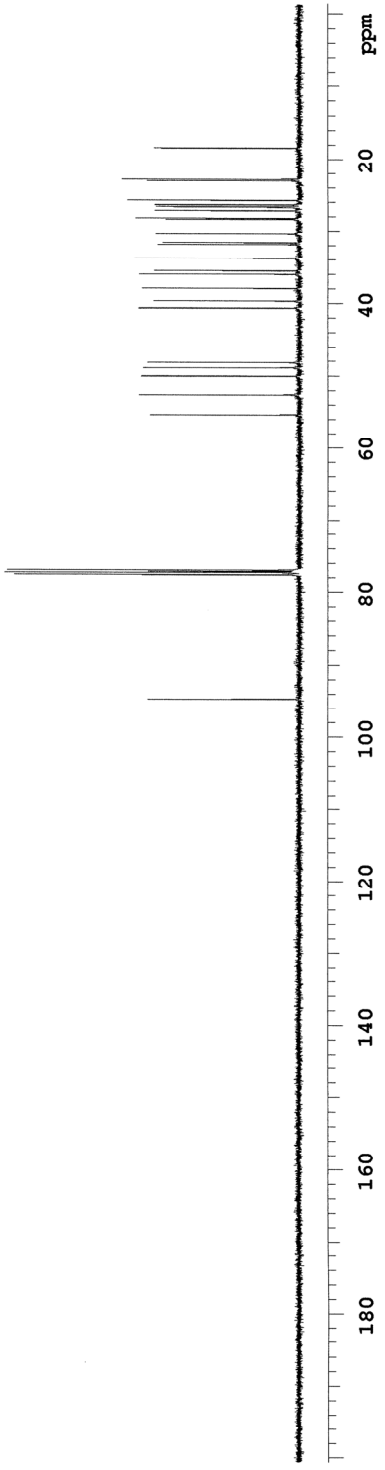
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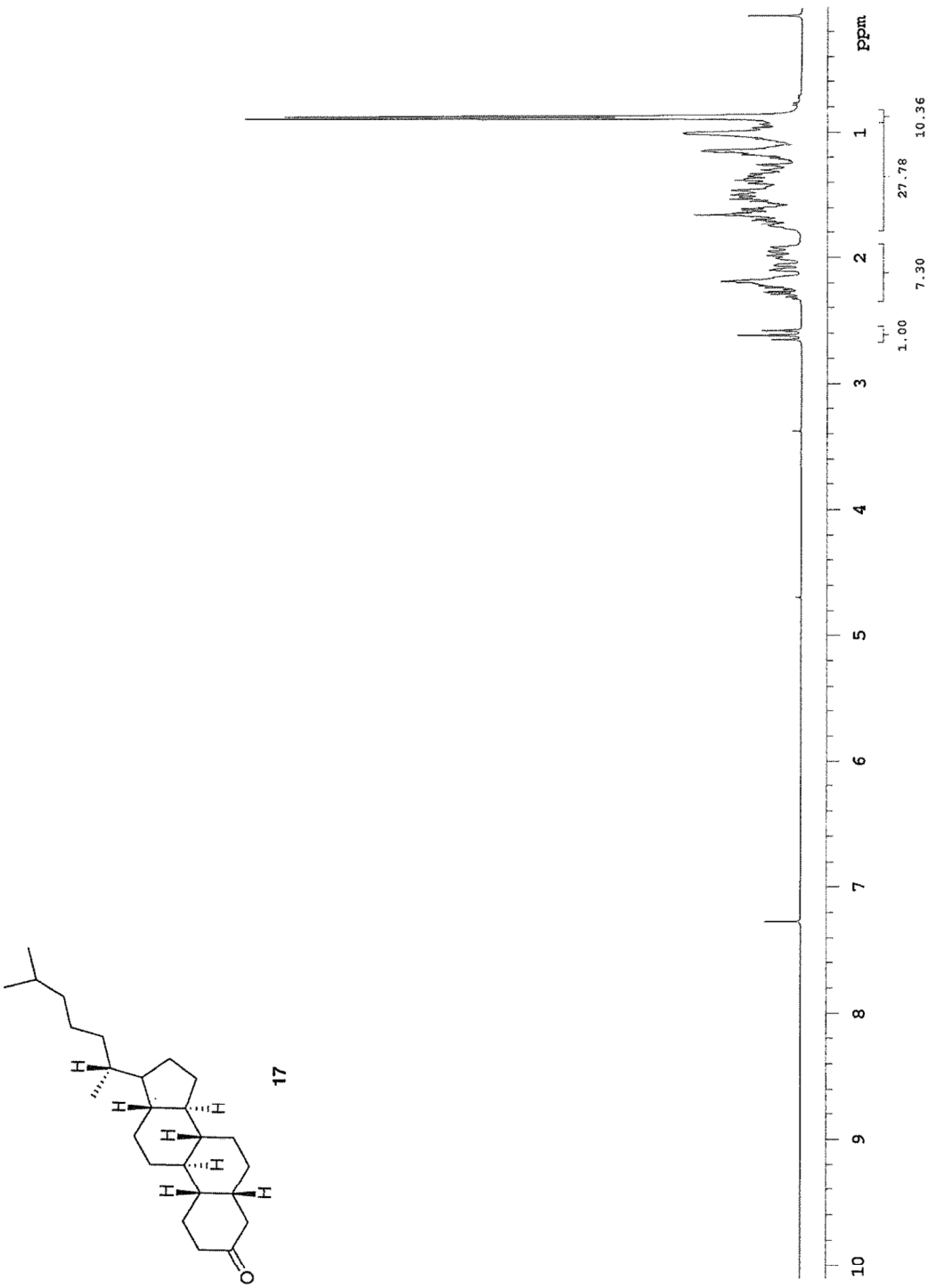
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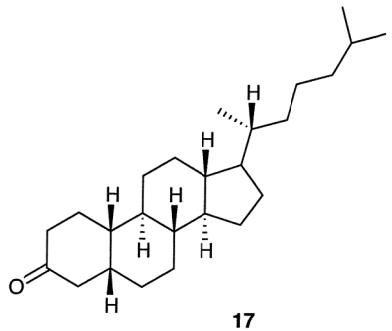

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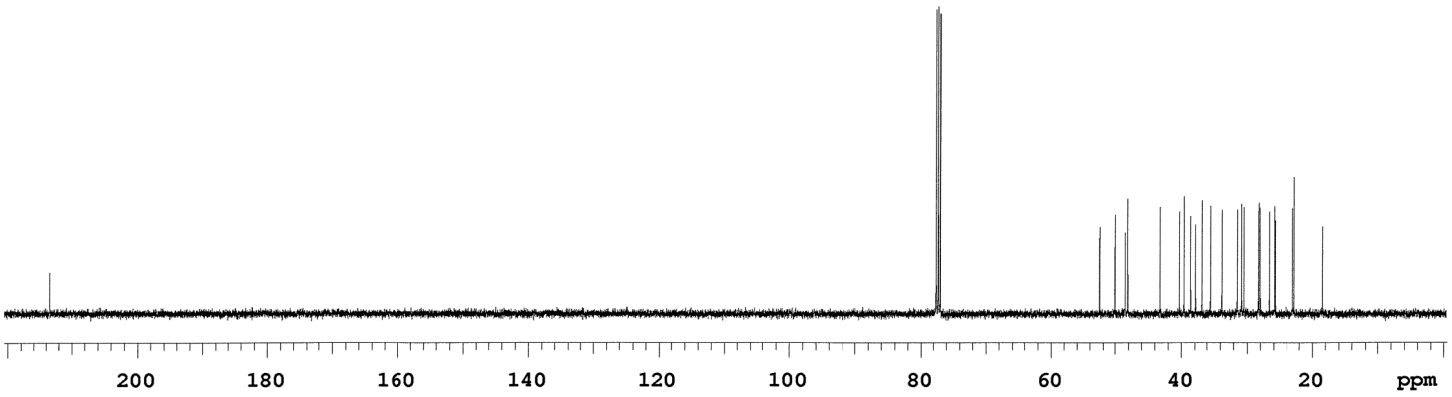

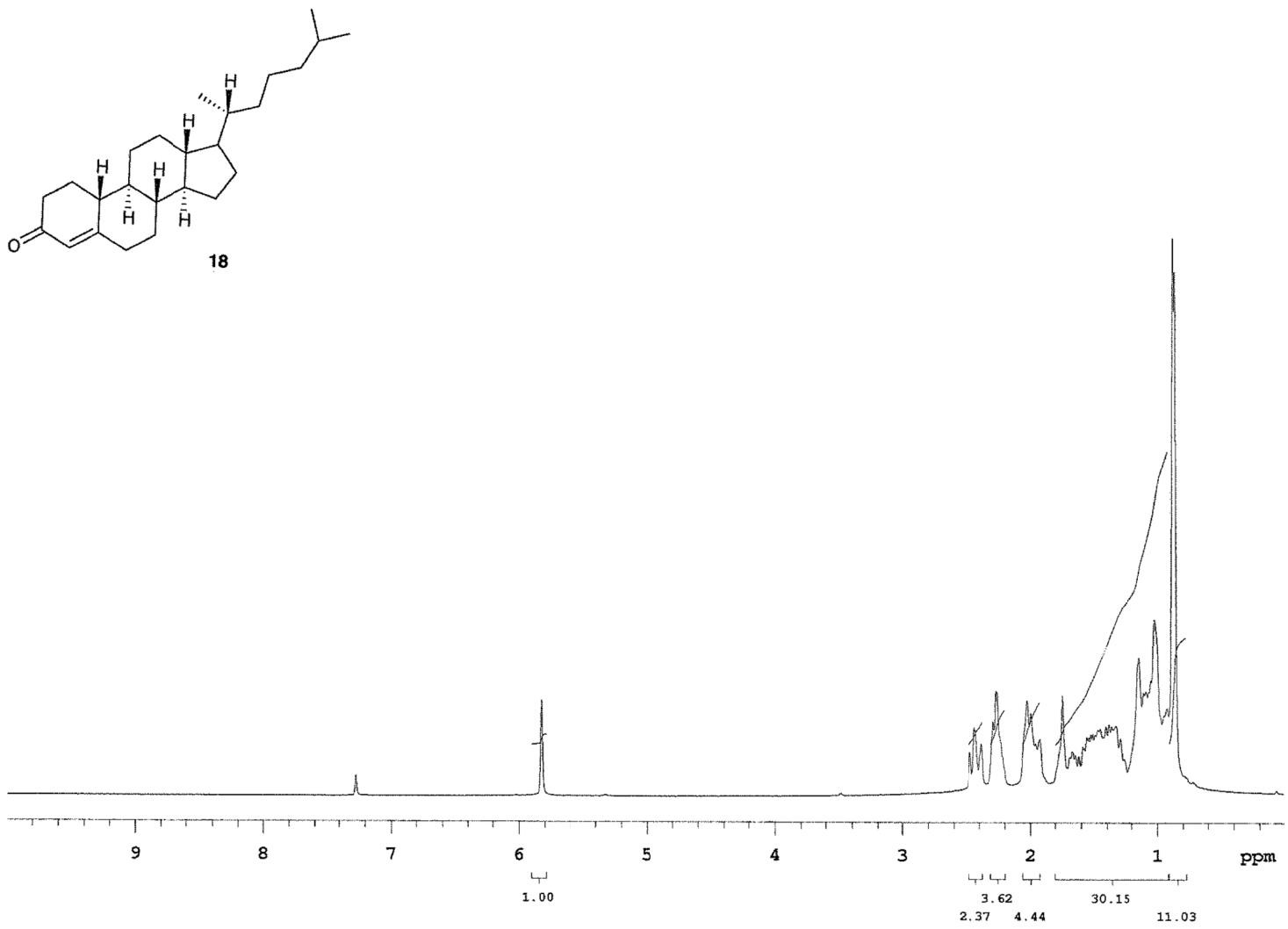
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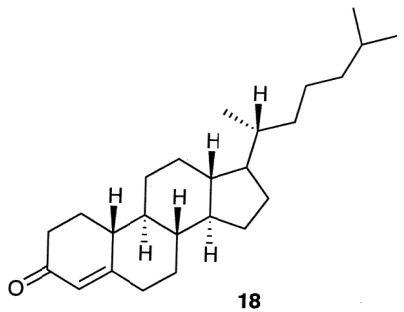

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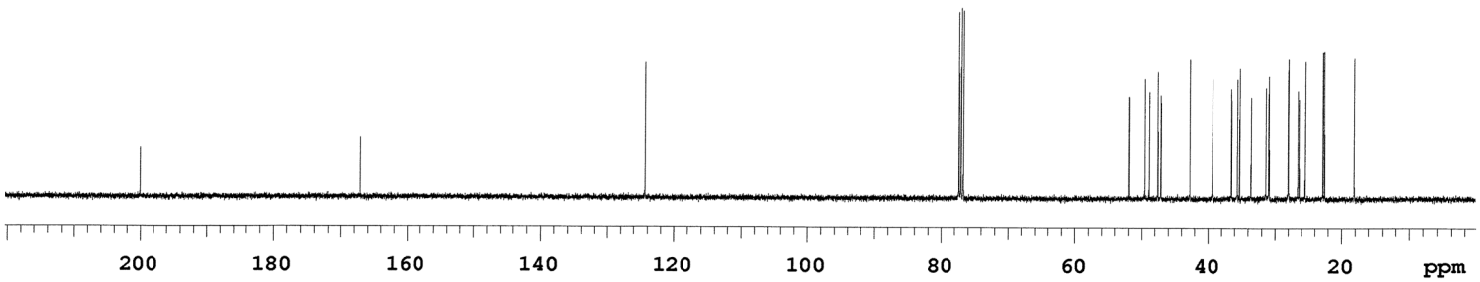

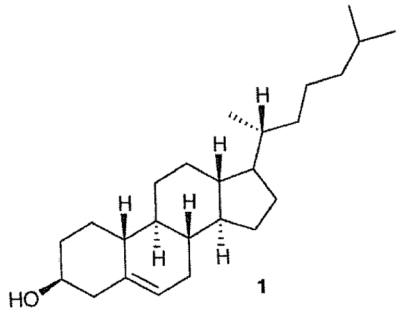
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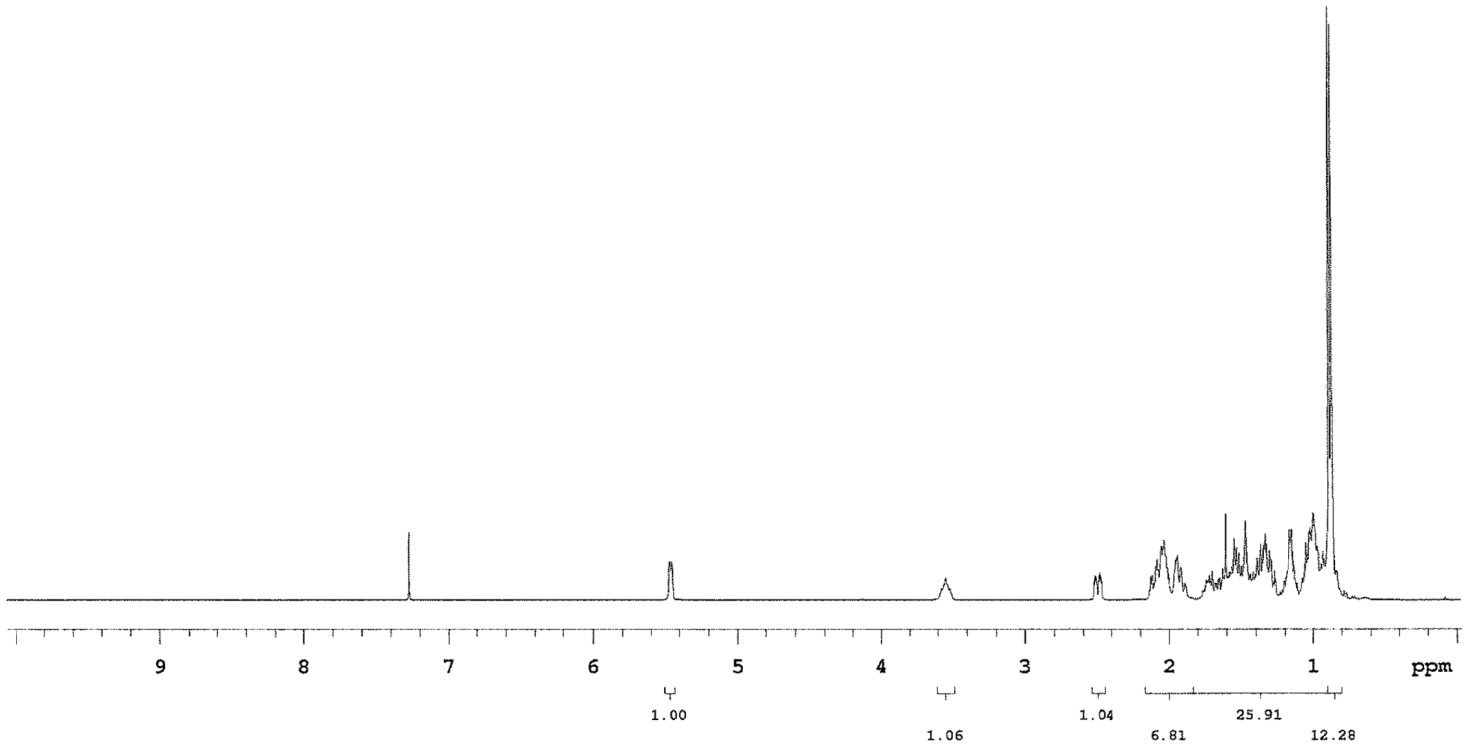
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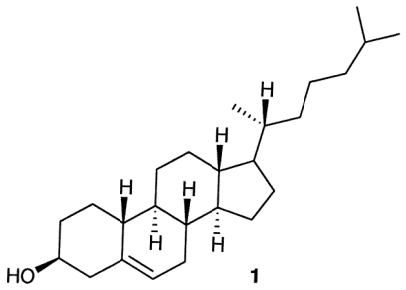

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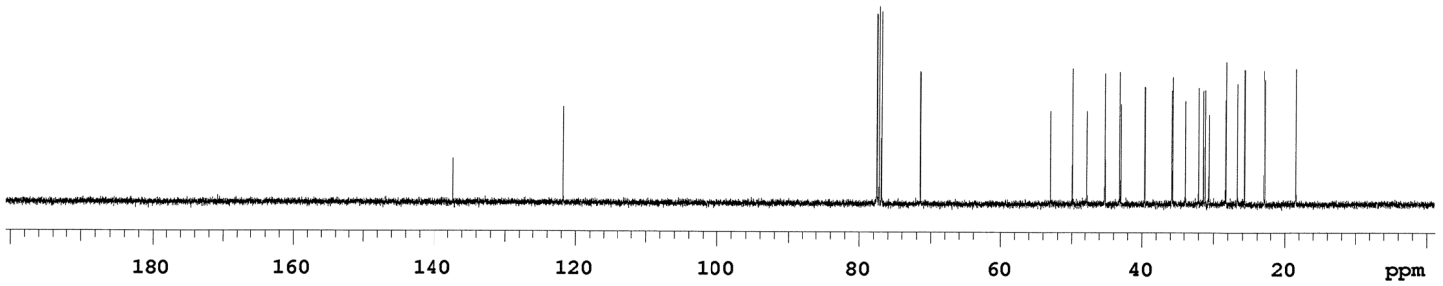

2. X-Ray Data for compounds 4 and 13

General Remarks

Crystals of appropriate dimension were obtained by slow evaporation of EtOAc/Hexanes. Crystals of approximate dimensions were mounted on MitGen cryoloops in random orientations. Preliminary examination and data collection were performed using a Bruker X8 Kappa Apex II Charge Coupled Device (CCD) Detector system single crystal X-Ray diffractometer equipped with an Oxford Cryostream LT device. All data were collected using graphite monochromated Mo Kα radiation (λ= 0.71073 Å) from a fine focus sealed tube X-Ray source. Preliminary unit cell constants were determined with a set of 36 narrow frame scans. Typical data sets consist of combinations of ϖ and ϕ scan frames with typical scan width of 0.5° and counting time of 15 seconds/frame at a crystal to detector distance of 4.0 cm. The collected frames were integrated using an orientation matrix determined from the narrow frame scans. Apex II and SAINT software packages (*Reference: Bruker Analytical X-Ray, Madison, WI, 2010*) were used for data collection and data integration. Analysis of the integrated data did not show any decay. Final cell constants were determined by global refinement of reflections harvested from the complete data set. Collected data were corrected for systematic errors using SADABS (*Reference: Bruker Analytical X-Ray, Madison, WI, 2010*) based on the Laue symmetry using equivalent reflections.

Structure solution and refinement were carried out using the SHELXTL- PLUS software package (*Reference: Sheldrick, G.M. (2008). Acta Cryst. A64,112-122*). The structure was solved by direct methods and refined successfully in the space groups, $P2_1$ and I2 respectively for Compunds **4** and **13**. Full matrix least-squares

refinements were carried out by minimizing $\Sigma w(F_o^2-F_c^2)^2$. The non-hydrogen atoms were refined anisotropically to convergence. All hydrogen atoms were treated using appropriate riding model (AFIX m3). Absolute structure determination resulted in unreliable Flack x paramters using Parson's method (*Reference: Parsons, S. & Flack, H. (2004). Acta Cryst.,A, s61.*)

Summary of Data for Compound 4

CCDC 984002

Compound Name: Formula: C19 H28 O4

Unit Cell Parameters: a 7.2917(12) b 12.210(2) c 9.9260(17) P21

Projection view with 50% thermal ellipsoids:

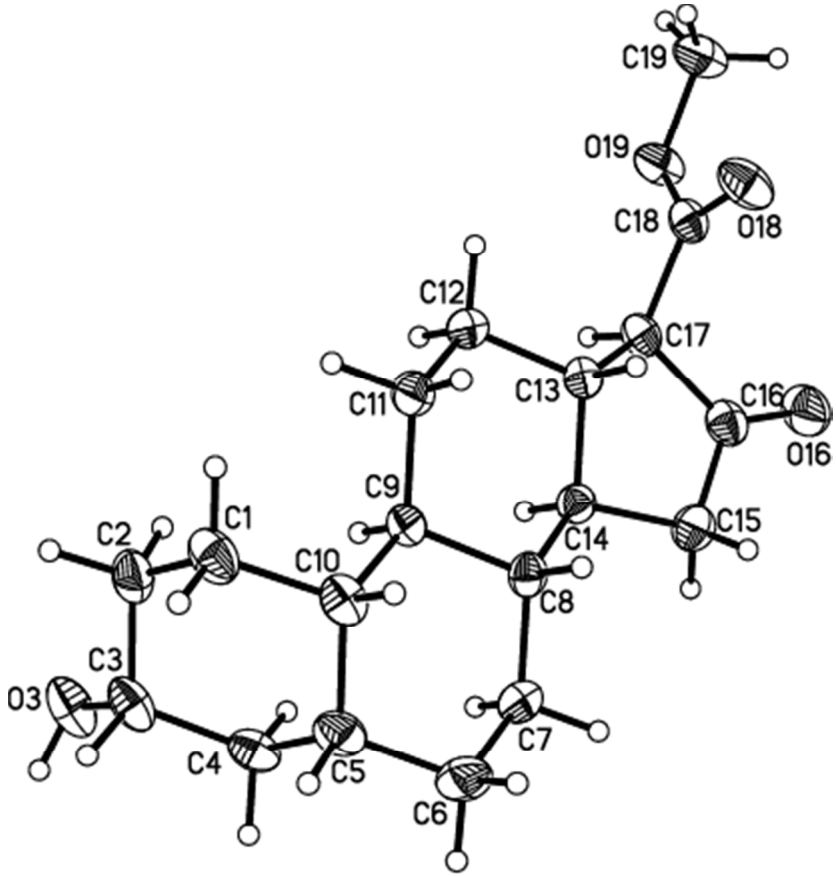

Table S1. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for compound **4**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(3)	8877(2)	3444(1)	8808(1)	39(1)
O(16)	7344(2)	11381(1)	9379(1)	42(1)
O(18)	9242(2)	11482(1)	6604(1)	38(1)
O(19)	11785(2)	11346(1)	8538(1)	33(1)
C(1)	7428(3)	5117(1)	5488(2)	33(1)
C(2)	8717(3)	4478(1)	6742(2)	32(1)
C(3)	7553(3)	3908(1)	7562(2)	31(1)
C(4)	6193(2)	4689(1)	7969(2)	30(1)
C(5)	4938(2)	5360(1)	6720(2)	30(1)
C(6)	3628(2)	6158(2)	7173(2)	36(1)
C(7)	4746(2)	7098(1)	8044(2)	30(1)
C(8)	5947(2)	7704(1)	7268(2)	24(1)
C(9)	7298(2)	6911(1)	6820(2)	22(1)
C(10)	6174(2)	5955(1)	5942(2)	28(1)
C(11)	8517(3)	7522(1)	6046(2)	31(1)
C(12)	9688(2)	8446(1)	6939(2)	30(1)
C(13)	8341(2)	9217(1)	7364(2)	24(1)
C(14)	7132(2)	8618(1)	8151(2)	23(1)
C(15)	6104(3)	9565(1)	8638(2)	32(1)
C(16)	7519(3)	10500(1)	8882(2)	29(1)
C(17)	9210(2)	10153(1)	8372(2)	25(1)
C(18)	10036(2)	11071(1)	7724(2)	26(1)
C(19)	12695(3)	12230(2)	8017(2)	40(1)

Summary of Data for Compound 13

CCDC 984003

Formula: C24 H40 O3□

Unit Cell Parameters: a 15.9947(8) b 6.2325(2) c 21.7799(8) I2

Projection view with 50% probability ellipsoids:

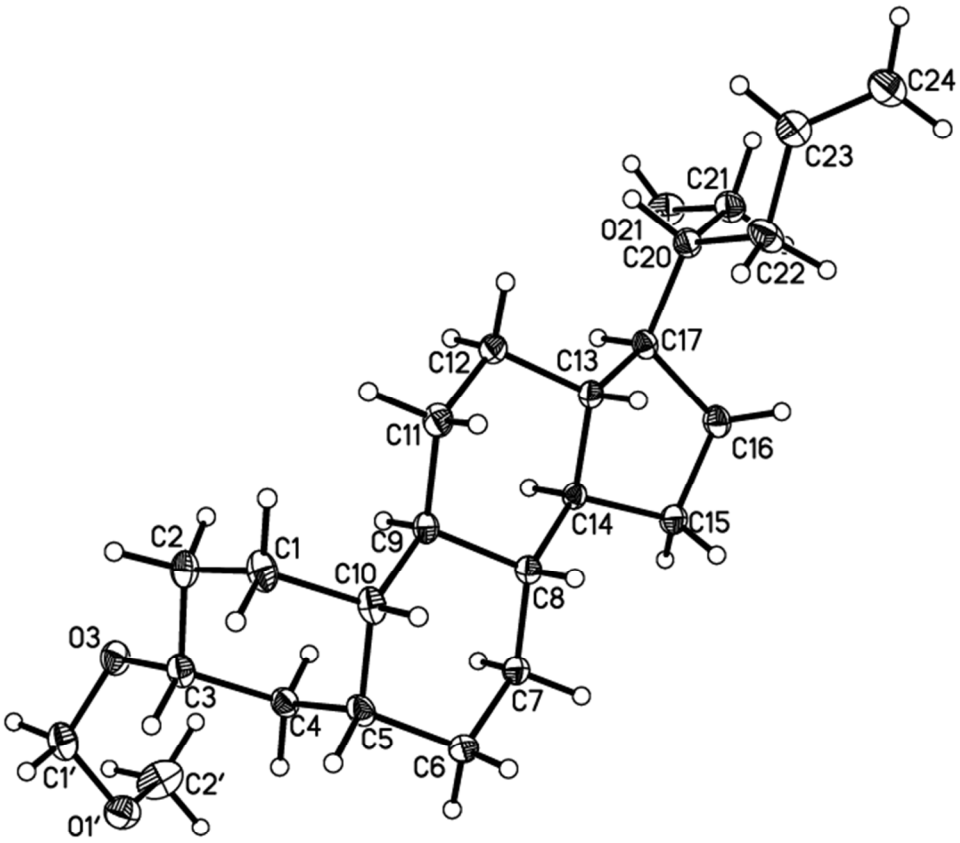

Table S2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for compound **13**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(3)	3639(1)	4757(2)	8631(1)	20(1)
O(1')	4062(1)	6203(3)	9629(1)	24(1)
O(21)	-1551(1)	11189(2)	5747(1)	24(1)
C(1)	1750(1)	1197(3)	8161(1)	20(1)
C(1')	4279(1)	4907(4)	9147(1)	24(1)
C(2)	2556(1)	2461(3)	8114(1)	19(1)
C(2')	3979(2)	8409(4)	9460(1)	31(1)
C(3)	2906(1)	3531(3)	8727(1)	17(1)
C(4)	2238(1)	4924(3)	8955(1)	16(1)
C(5)	1445(1)	3602(3)	9013(1)	17(1)
C(6)	782(1)	4899(3)	9282(1)	18(1)
C(7)	345(1)	6549(3)	8822(1)	16(1)
C(8)	-26(1)	5532(3)	8198(1)	13(1)
C(9)	654(1)	4266(3)	7918(1)	14(1)
C(10)	1066(1)	2574(3)	8387(1)	16(1)
C(11)	276(1)	3290(3)	7287(1)	18(1)
C(12)	-170(1)	4940(3)	6823(1)	17(1)
C(13)	-826(1)	6166(3)	7112(1)	13(1)
C(14)	-430(1)	7181(3)	7728(1)	12(1)
C(15)	-1155(1)	8553(3)	7897(1)	17(1)
C(16)	-1685(1)	9228(3)	7263(1)	18(1)
C(17)	-1264(1)	8087(3)	6761(1)	14(1)
C(20)	-1846(1)	7617(3)	6142(1)	16(1)
C(21)	-2196(1)	9695(3)	5832(1)	21(1)
C(22)	-2576(1)	6081(4)	6201(1)	23(1)
C(23)	-3025(1)	5210(3)	5597(1)	21(1)
C(24)	-3842(1)	5375(4)	5387(1)	24(1)