Sequential enolboration/hydroformylation/aldol addition: a new one-pot cascade reaction for the regio- and diastereoselective formation of carbocyclic quaternary centres from acyclic olefins

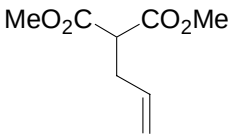
Mark D. Keränen and Peter Eilbracht

Fachbereich Chemie, Organische Chemie I, Universität Dortmund, Otto-Hahn-Str. 6, D-44227 Dortmund, Germany

Supporting information & experimental data

General Methods. All air-sensitive reactions were performed under an argon atmosphere using distilled solvents where required. Triethylamine (Et_3N) was distilled from calcium hydride (CaH_2). All other reagents were commercially purchased and used without further purification. NMR spectra were measured using $CDCl_3$ as the solvent and internal standard. Hydroformylation/aldol addition reactions were carried out in autoclaves - 250 mL PTFE insert or 70 mL stainless steel - with specially designed heating and stirring mantles.

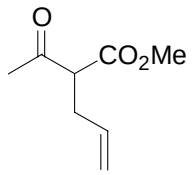
Dimethyl 2-allyl-malonate (3)



To a suspension of 60 % NaH (11 g, 280 mmol) in 200 mL dry THF was added dropwise dimethyl malonate (33.0 g, 250 mmol). After addition was complete, the mixture was stirred for 15 min at RT before allyl bromide (30.25 g, 250 mmol) was added dropwise. After 2 h, the mixture was quenched by the slow addition of water, extracted with ether and washed with brine before being dried, concentrated and purified by flash chromatography (15:1 hexane/Et_2O) to give **3**

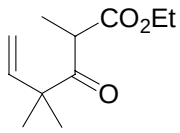
(37.1g, 215 mmol) in 86 % as a colourless oil. All spectra matched those reported in the literature.[1]

Methyl 2-acetyl-pent-4-enoate (4)



To a suspension of 60 % NaH (625 mg, 26 mmol) in 75 mL dry THF at 0 °C was added via syringe methyl 3-oxo-butyrate (2.3 g, 19.8 mmol). When addition was complete, the mixture was stirred for 15 min at 0 °C before allyl bromide (2.94 g, 24 mmol) was added dropwise. After 2 h, the mixture was quenched by the slow addition of sat. aq. NH_4Cl, extracted with ether and washed with brine before being dried, concentrated and purified by Kugelrohr distillation (70 °C @ 1 mbar) to give **4** (2.0 g, 12.9 mmol) in 65 % as a nearly colourless oil. All spectra matched those reported in the literature.[2]

Ethyl 2,4,4-trimethyl-3-oxo-hex-5-enoate (5)



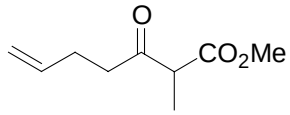
(A) A mixture of zinc dust (19.6 g, 0.3 mol), $AlCl_3$ (4 g, 30 mmol) and ethyl cyano acetate (10.6 mL, 90 mmol) was stirred in 200 mL of dry THF at 0 °C. After 15 minutes, a solution of prenyl bromide (11.53 mL, 0.1 mol) in 15 mL THF was added dropwise. After addition was complete, the reaction was left to warm to RT and was stirred overnight, after which 200 mL of 2 N HCl was added to the

(1) Ma, S.; Xu, B.; Ni, B. *J. Org. Chem.* **2000,** *65,* 8532.
(2) Welch, S. C.; Assercq, J. M.; Loh, J. P.; Glase, S. A. *J. Org. Chem.* **1987,** *52,* 1440.

reaction mixture, and stirring was continued for another 15 min. The reaction was filtered and washed with sat. aq. $NaHCO_3$ (3 x 100 mL) and brine (1 x 100 mL) before being dried, concentrated and purified by column chromatography (5:1 CH_2Cl_2/hexane) to give 11. 2 g (61 %) of ethyl 4,4-dimethyl-3-oxo-hex-5-enoate as a pale-yellow oil. All spectra matched those reported in the literature.[3]

(B) To a stirring mixture of ethyl 4,4-dimethyl-3-oxo-hex-5-enoate (1.0 g, 5.4 mmol) and methyl iodide (0.3 mL, 5.4 mmol) in 20 mL of acetone at RT was added at once 0.75 g (5.4 mmol) K_2CO_3 and the mixture was stirred overnight. The mixture was then extracted with ether and washed with sat. aq. $NaHCO_3$ solution before being dried and concentrated to give the methylated ketoester **5** (0.92 g, 4.6 mmol) in 85 % (52 % over both steps) as a yellow oil which required no further purification. **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 1.20 (m, 6H, 2x*CH*$_3$); 1.26 (m, 6H, 2x*CH*$_3$); 3.89 (q, *J* = 6 Hz, 1H, RC(O)C*(H)*CO_2Et); 4.09 (q, *J* = 6 Hz, 2H, ROC*H*$_2$$CH_3$); 5.21 (dd, *J* = 10, 20 Hz, 2H, *H*$_2$C=CHR); 5.81 (dd, *J* = 10, 20 Hz, 1H, H_2C=C*H*R). **^{13}C-NMR** (125 MHz, $CDCl_3$) δ 13.9 (α-*C*H_3), 14.8 (RCO_2CH_2*Me*), 23.3 (2x*Gem-C*H_3), 46.8 (C_q), 51.8 (R_2*C*HCH_3), 61.1 (RCO_2*C*H_2Me), 115.3 (C=C), 141.4 (C=C), 170.6 (*C*O_2Et), 208.6 (*C*=O). **FTIR** ($CDCl_3$ film): 2977, 1751, 1685, 1249, 910, 743 cm^{-1}. **HR-EIMS** anal. calc. for $C_{11}H_{19}O_3$ $[M + H]^+$: 199.1334; anal. found: 199.1359

Methyl 2-methyl-3-oxo-hept-6-enoate (6)



(A) To a stirring mixture of 1.2 g (50 mmol) NaH in 100 mL dry THF cooled to 0 °C was added 3.48 g (30 mmol) methyl 3-oxo-butyrate via syringe. When addition was complete, the mixture was stirred for 30 min at 0 °C before 11.7 mL

(3) Hiyashi, Y.; Orikasa, S.; Tanaka, K.; Kanoch, K.; Kiso, Y. *J. Org. Chem.* **2000,** *65,* 8402.

of *n*-BuLi (2.5 M in hexane) was added over 10 min via syringe. The mixture was stirred for another 10 min before allyl bromide (3.99 g, 33 mmol) was added and the mixture was allowed to warm to RT while stirring (approx. 15 min). The reaction was then quenched via the slow addition of sat. aq. NH_4Cl (100 mL), extracted with ether and washed with brine before being dried, concentrated and purified by Kugelrohr distillation to give methyl 3-oxo-hept-6-enoate (3.9 g, 25.0 mmol) in 85 % yield as a pungent, light-yellow oil which was immediately taken on to the subsequent reaction without purification.

(B) To a stirring RT acetone solution (20 mL) of methyl 3-oxo-hept-6-enoate (3.9 g, 25.0 mmol), methyl iodide (0.40 mL, 6.4 mmol) and 885 mg (6.4 mmol) K_2CO_3 were added at once and the mixture was stirred overnight. The mixture was then extracted with ether and washed with brine before being dried and concentrated to give the methylated ketoester **6** in 89 % (76 % over both steps) as a yellow oil which required no further purification. All spectra matched those reported in the literature.[4]

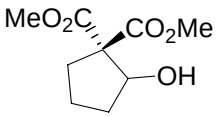
Procedure for enolboration/hydroformylation/aldol addition (Method A)

Et_3N (1.05 eq. to carbonyl compound) was pre-complexed under an argon atmosphere with (*cy*-hex)$_2$BCl (1.05 eq.) in dry CH_2Cl_2 (5 mL) at 0 °C for 15 min. The unsaturated carbonyl compound in approx. 1 mL of solvent was then added slowly via syringe and the enolboration was allowed to stir for an additional 30 min. The mixture was simply transferred into the autoclave containing 0.9 mol % $Rh(CO)_2(acac)$, 10-15 mL of solvent and 1.8 mol % XANTPHOS ligand. The autoclave was then pressurized to 60 bar with equal pressures of CO and H_2 ***!!!CAUTION! DEADLY GAS!!!*** and heated overnight to 80 °C. Upon cooling the autoclave to RT, the reaction mixture was removed and concentrated under reduced pressure. Enough MeOH was added to dissolve the solid residue (~25 mL) along with 2 mL of conc. pH 7 phosphate buffer and 1 mL of 30 % H_2O_2, and the reaction was allowed to stir overnight before being extracted with

(4) Stork, G.; Winkler, J. D.; Saccomano, N. A. *Tetrahedron Lett.* **1983,** *24,* 465.

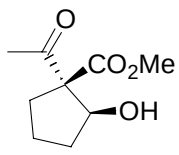
ether (100 mL), washed with sat. aq. $NaHCO_3$ (1x75 mL), dried and concentrated prior to further purification when necessary via flash chromatography or Kugelrohr distillation.

Dimethyl 2-hydroxy-cyclopentane-1,1-dicarboxylate (7) via Method A



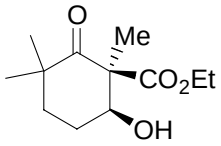
The reaction was performed according to **method A** with 500 mg (2.9 mmol) **3** using 6 mg (0.9 mol %) $Rh(CO)_2(acac)$ catalyst and 24 mg (1.8 mol %) XANTPHOS, with the autoclave being subjected to a pressure of 60 bar (30:30) CO/H_2 and temperature of 80 ^oC for 18 h. Buffered oxidative workup as described above resulted in a 51 % yield of **7** (294 mg, 1.45 mmol) as a pale-yellow oil requiring no further purification. **Anal. Calc.** for $C_9H_{14}O_5$: C: 53.5 %; H 7.0 %. Anal found: C: 53.6 %; H: 7.0 %. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 1.64 (m, 2H, $CH_2R(C\mathit{H_2})CH_2R$); 1.85 (m, 1H, $CH_2R(C\mathit{H}H)CHC_q(OH)$); 2.05 (m, 1H, $CH_2R(CH\mathit{H})CH(OH)R$); 2.27 (m, 2H, $C_q(C\mathit{H_2})CH_2R$); 3.64 (s, 3H, $CO_2C\mathit{H_3}$); 3.66 (s, 3H, $CO_2C\mathit{H_3}$); 4.53 (t, J = 5 Hz, 1H, $C_qC\mathit{(H)}(OH)CH_2R$). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 20.0 ($\mathit{C}H_2$), 30.8 ($\mathit{C}H_2$), 32.6 ($\mathit{C}H_2$), 48.9 ($CO_2\mathit{Me}$), 52.5 ($CO_2\mathit{Me}$), 64.7 (C_q), 77.2 ($R_2\mathit{C}HOH$), 169.3 ($C_q\mathit{C}O_2Me$), 171.0 ($C_q\mathit{C}O_2Me$). **FTIR** (neat): 3501 (broad), 2952, 2856, 1731, 1436, 1274, 1091. **HR-FABMS** anal. calc. for $C_9H_{15}O_5$ $[M + H]^+$: 203.0920; anal. found: 203.0910.

Methyl 1-acetyl-2-hydroxy-cyclopentanecarboxylate (8) via Method A



The reaction was performed according to **method A** with 250 mg (1.6 mmol) of **4** using 4 mg (0.9 mol %) $Rh(CO)_2(acac)$ catalyst and 16 mg (1.8 mol %) XANTPHOS, with the autoclave being subjected to a pressure of 60 bar (30:30) CO/H_2 and temperature of 80 ^oC for 16 h. Buffered oxidative workup as described above resulted in a 50 % yield of **8** (150 mg, 0.8 mmol) as the sole product in a 1.6:1 ratio of diastereoisomers as a fragrant, volatile yellow oil requiring no further purification. **^{1}H-NMR** (400 MHz, $CDCl_3$) *Major diastereoisomer:* δ 1.45-1.92 (m, 4H, $RCH_2CH_2CH(OH)R$); 2.02 (m, 2H, $C_q(CH_2)CH_2R$); 2.15 (s, 3H, *Ac*); 3.69 (s, 3H, $C_qCO_2CH_3$) 4.65 (t, *J* = 8 Hz, 1H, $C_qCH(OH)CH_2R$). *Minor diastereoisomer:* δ 2.13 (s, 3H, *Ac*); 3.72 (s, 3H, $C_qCO_2CH_3$); 4.51 (t, *J* = 6 Hz, 1H, $C_qCH(OH)CH_2R$). **^{13}C-NMR** (100 MHz, CDCl3) *Major diastereoisomer:* δ 24.0 (CH_2), 25.3 (CH_2), 28.5 (Ac), 38.3 (CH_2), 52.5 (CO_2Me), 66.5 (C_q), 76.3 (*C*HOH), 173.6 (CO_2Me), 200.2 (*C*=O). *Minor diastereoisomer:* δ 26.2 (Ac), 52.7 (CO_2Me), 77.4 (R_2CHOH). **FTIR** (neat): 3411 (broad), 2933, 2856, 1720, 1711, 1258, 1063, 733. **HR-FABMS** anal. calc. for $C_9H_{15}O_4$ $[M + H]^+$: 187.0970; anal. found: 187.0950

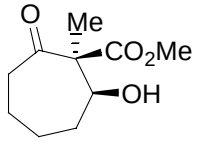
Ethyl 6-hydroxy-1,3,3-trimethyl-2-oxo-cyclohexanecarboxylate (9) via Method A



The reaction was performed according to **method A** with 50 mg (0.25 mmol) **5** using 0.6 mg (0.9 mol %) $Rh(CO)_2(acac)$ and 3 mg (1.8 mol %) XANTPHOS in 10 mL CH_2Cl_2 at 60 bar (30:30) CO/H_2 and temperature of 80 °C for 18 h. Buffered oxidative workup as described above resulted in 47 mg (0.205 mmol) of **9** as a 2.5:1 mixture of diastereoisomers in 82 % yield as a viscous, pale-yellow oil requiring no further purification. **^{1}H-NMR** (400 MHz, $CDCl_3$) *Major diastereoisomer:* δ 1.14 (m, 3H, $CH_3C_qCH_3$); 1.20 (t, *J* = 8 Hz, 3H,

$RCO_2CH_2CH_3$); 1.24 (m, 3H, $CH_3C_qCH_3$); 1.27 (s, 3H, α-CH_3); 1.61-1.69 (m, 3H, $C_qCH_2CH_{eq}H_{ax}R$); 1.87 (m, 1H, $C_qCH_2CH_{eq}H_{ax}R$); 3.58 (t, *J* = 6 Hz, 1H, $CH_2RC(H)(OH)R$); 4.10 (q, *J* = 8 Hz, 2H, $RCO_2CH_2CH_3$). Minor diastereoisomer: δ 1.29 (s, 3H, α-CH_3); 3.95 (q, *J* = 8 Hz, 2H, $RCO_2CH_2CH_3$). **^{13}C-NMR** (100 MHz, $CDCl_3$) Major diastereoisomer: δ 13.9 (α-CH_3), 14.8 (RCO_2CH_2Me), 24.02 (*Gem*-CH_3), 24.05 (*Gem*-CH_3), 25.4 (CH_2), 27.7 (CH_2), 48.4 (Me_2-C_q), 61.1 ($CO_2CH_2CH_3$), 62.8 (α-C_q), 70.3 (R_2CHOH), 170.6 (RCO_2Et), 211.3 (C=O). Minor diastereoisomer: δ 14.7 (CH_3), 61.3 (RCO_2CH_2Me), 170.5 (CO_2Et). **FTIR** (neat): 3364 (broad), 2932, 2856, 1758, 1685, 1239, 1023. **HR-FABMS** anal. calc. for $C_{12}H_{19}O_4$ $[M - H]^+$: 227.1283; anal. found: 227.1259

Methyl 2-hydroxy-1-methyl-7-oxo-cycloheptanecarboxylate (10) via Method A



The reaction was performed according to **method A** with 232 mg (1.37 mmol) **6** using 3 mg (0.9 mol %) $Rh(CO)_2(acac)$ catalyst and 15 mg (1.8 mol %) XANTPHOS, with the autoclave being subjected to a pressure of 60 bar (30:30) CO/H_2 and temperature of 80 ^oC for 18 h. Buffered oxidative workup as described above resulted in an 89 % yield of **10** (243 mg, 1.2 mmol) as a fragrant clear-yellow oil requiring no further purification in a 6:1 ratio of diastereoisomers. **^{1}H-NMR** (400 MHz, $CDCl_3$) Major diastereoisomer: δ 1.35 (s, 3H, α-CH_3); 1.80 (dq, *J* = 4, 12 Hz, 2H, $R(O)CCH_2C(H_2)R$); 2.09 (m, 1H, $RH_2CCH_2CHHCH(OH)R$); 2.37 (m, 3H, $RH_2CCH_2CHHCH(OH)R$); 2.55 (dt, *J* = 4, 12 Hz, 2H, $R(O)CC(H_2)CH_2R$); 3.69 (s, 3H, RCO_2CH_3); 4.15 (m, 1H, $RC(H)(OH)R$). Minor diastereoisomer: δ 1.47 (s, 3H, α-CH_3); 3.71 (s, 3H, RCO_2CH_3). **^{13}C-NMR** (100 MHz, $CDCl_3$) Major diastereoisomer: δ 17.6 (α-CH_3), 25.4 (CH_2), 27.6 (CH_2), 35.4 (CH_2), 39.5 (CH_2), 52.5 (CO_2Me), 61.2 (C_q), 78.9 (R_2CHOH), 172.8 (CO_2Me),

207.1 (*C*=O). *Minor diastereoisomer:* δ 17.8 (α-CH_3), 52.6 (CO_2*Me*). **FTIR** ($CDCl_3$ film): 3500 (broad), 2935, 1712, 1453, 1255, 910, 733. **HR-FABMS** anal. calc. for $C_{10}H_{17}O_4$ $[M + H]^+$: 201.1127; anal. found: 201.1112

26 Jan 2004
F:\KEMIA\NMR\MK-419\10\001.ESP

Spectrum's Parameters

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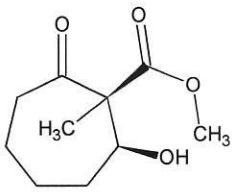

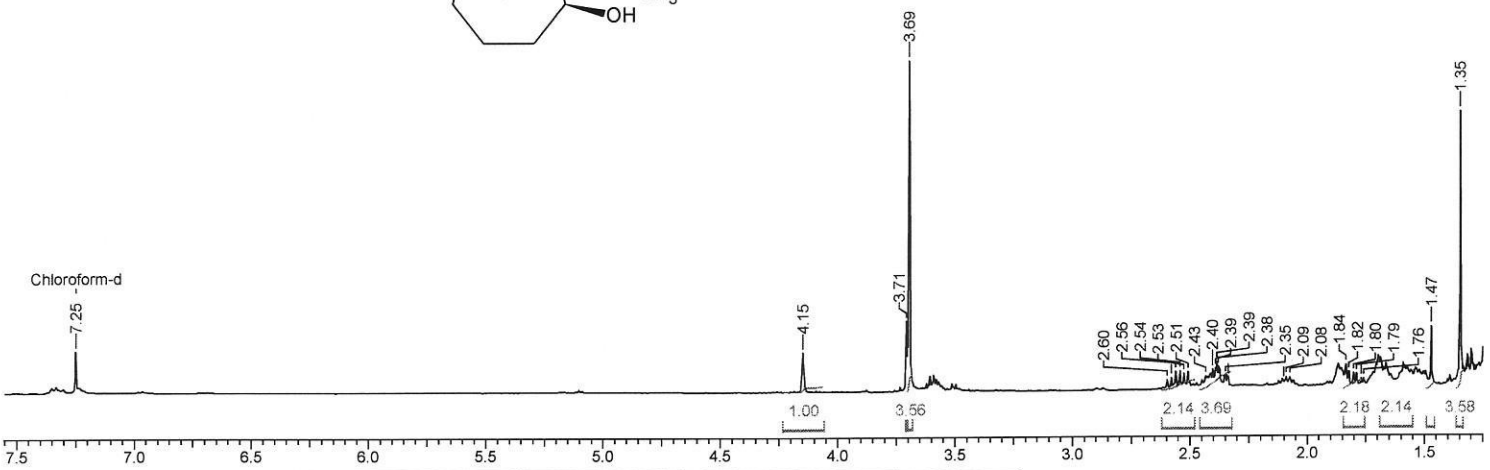

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2	1.47	0.189	10	2.09	0.039	18	2.40	0.062	26	3.69	1.000
3	1.76	0.033	11	2.10	0.026	19	2.43	0.042	27	3.71	0.213
4	1.77	0.032	12	2.34	0.039	20	2.51	0.054	28	4.15	0.117
5	1.79	0.048	13	2.35	0.043	21	2.53	0.051	29	7.25	0.125
6	1.80	0.048	14	2.37	0.062	22	2.54	0.058			
7	1.82	0.053	15	2.38	0.071	23	2.56	0.055			
8	1.84	0.075	16	2.39	0.085	24	2.58	0.037			

No.	Annotation	(ppm)
1	Chloroform-d	7.25

26 Jan 2004F:\KEMIA\NMR\MK-419\11\001.ESP

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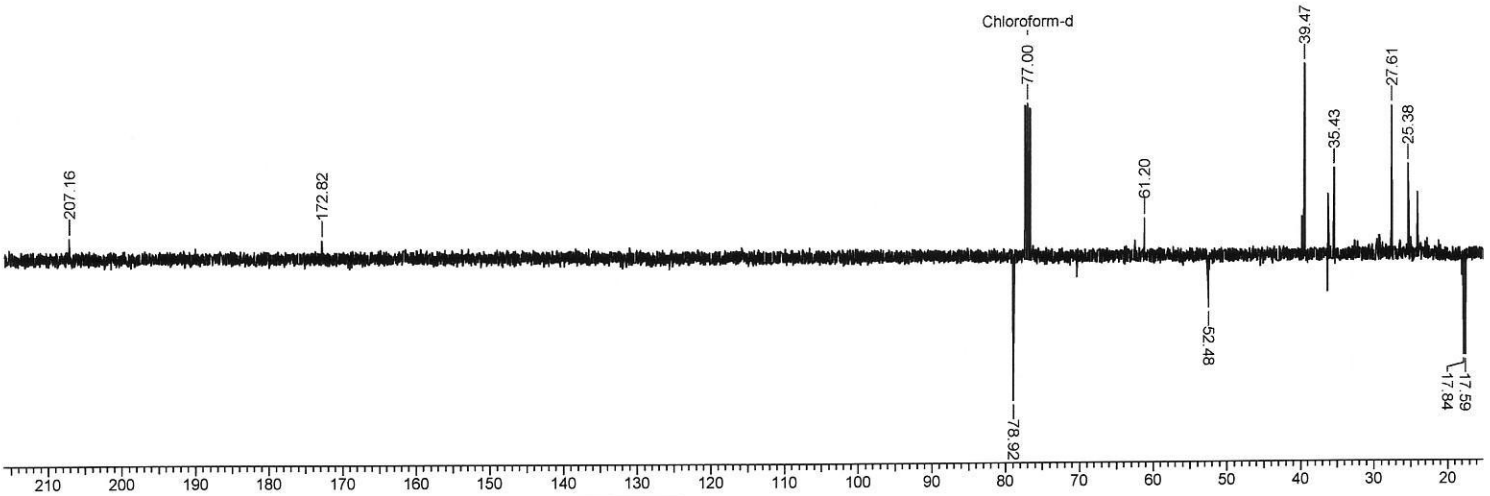

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4	25.38	0.465	11	78.92	-0.769
5	27.61	0.774	12	172.82	0.096
6	35.43	0.446	13	207.16	0.109
7	39.47	1.000			

No.	Annotation	(ppm)
1	Chloroform-d	77.00

STANDARD PROTON PARAMETERS

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INOVA-600 "eden"

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Mixing 0.800 sec
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Width 6000.6 Hz
64 repetitions
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DATA PROCESSING
Line broadening 1.0 Hz
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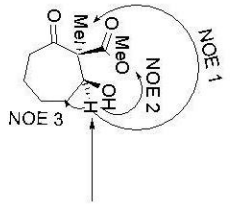
6:1 mixture of diastereoisomers



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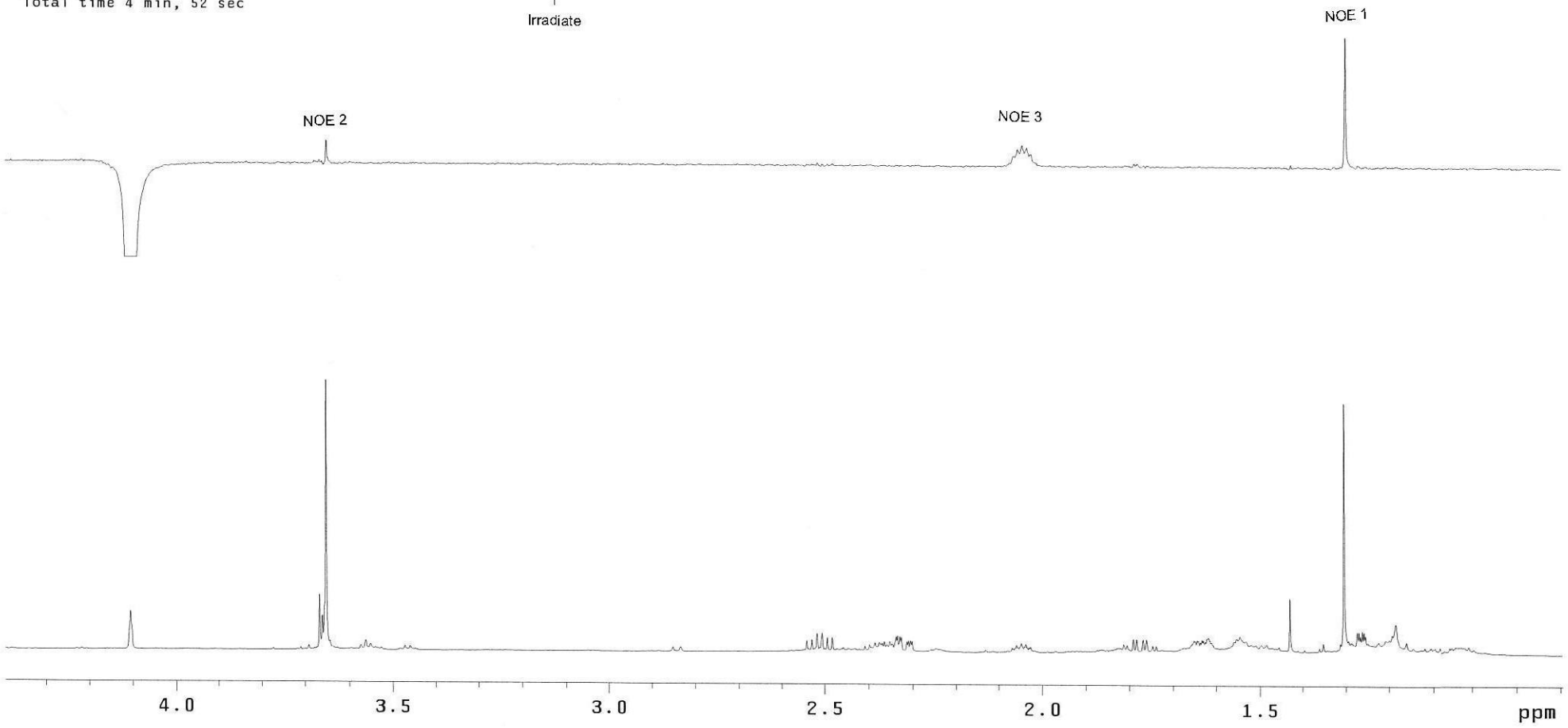

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INOVA-600 "eden"

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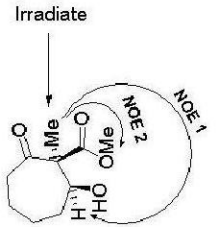
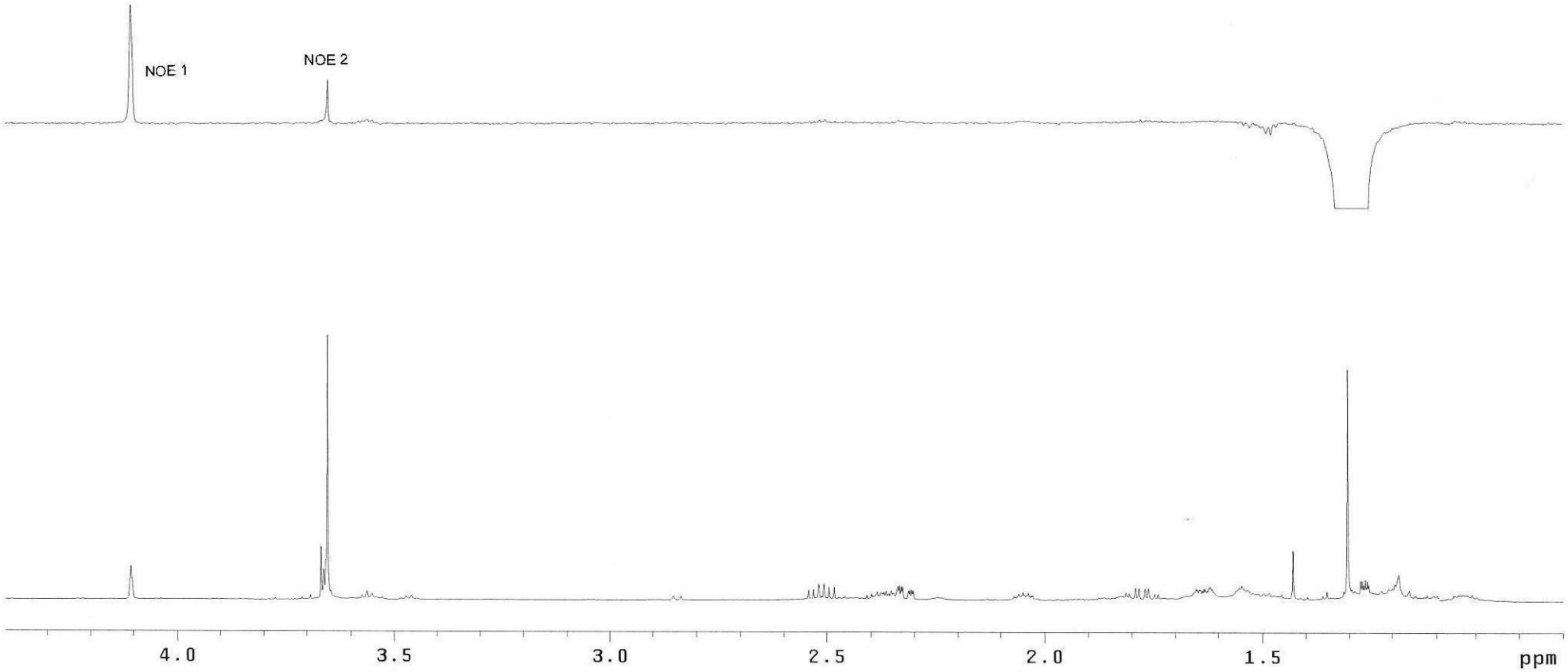


major diastereoisomer



MK419-noe2_20Jan2004

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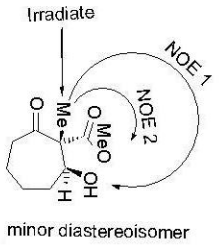
Pulse Sequence: NOESY1D

Solvent: CDCl3
Temp. 27.0 C / 300.1 K
INOVA-600 "eden"

Relax. delay 1.000 sec
Pulse 90.0 degrees
Mixing 0.800 sec
Acq. time 1.888 sec
Width 6000.6 Hz
64 repetitions
OBSERVE H1, 599.8311865 MHz
DATA PROCESSING
Line broadening 1.0 Hz
FT size 32768
Total time 4 min, 40 sec



minor diastereoisomer