

A chiral pool approach towards enantiopure building blocks for naturally occurring hydroporphyrins

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Dedicated to Gordon W. Gribble on Occasion of his 85th Birthday

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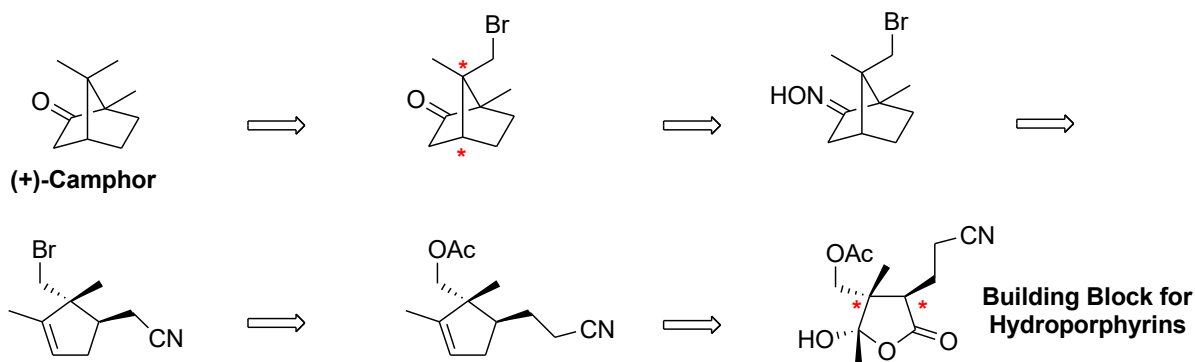
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Abstract

A chiral pool synthesis of a potential common building block for the marine pigment bonellin, chlorophyll *a*, and other naturally occurring hydroporphyrins, as well as for vitamin B₁₂, was accomplished starting from (+)-camphor *via* (+)-9-bromocamphor. A second-order Beckmann rearrangement of the latter provided access to the key cyclopentene intermediate.



Keywords: (+)-Camphor, chiral pool, enantiopure building blocks, hydroporphyrins, corrins, second order Beckmann rearrangement

Introduction

In both landmark total syntheses of vitamin B₁₂, (+)-camphor served as the starting material for the construction of rings C and D of the corrin macrocycle.¹⁻⁶ Camphor was also employed as a homochiral starting point for all four ring subunits in an unfinished synthetic approach toward vitamin B₁₂.⁷⁻⁹ The camphor-derived ring C building block for vitamin B₁₂ was furthermore successfully utilized as a ring D precursor in the total synthesis of bonellin (Figure 1).¹⁰⁻¹¹

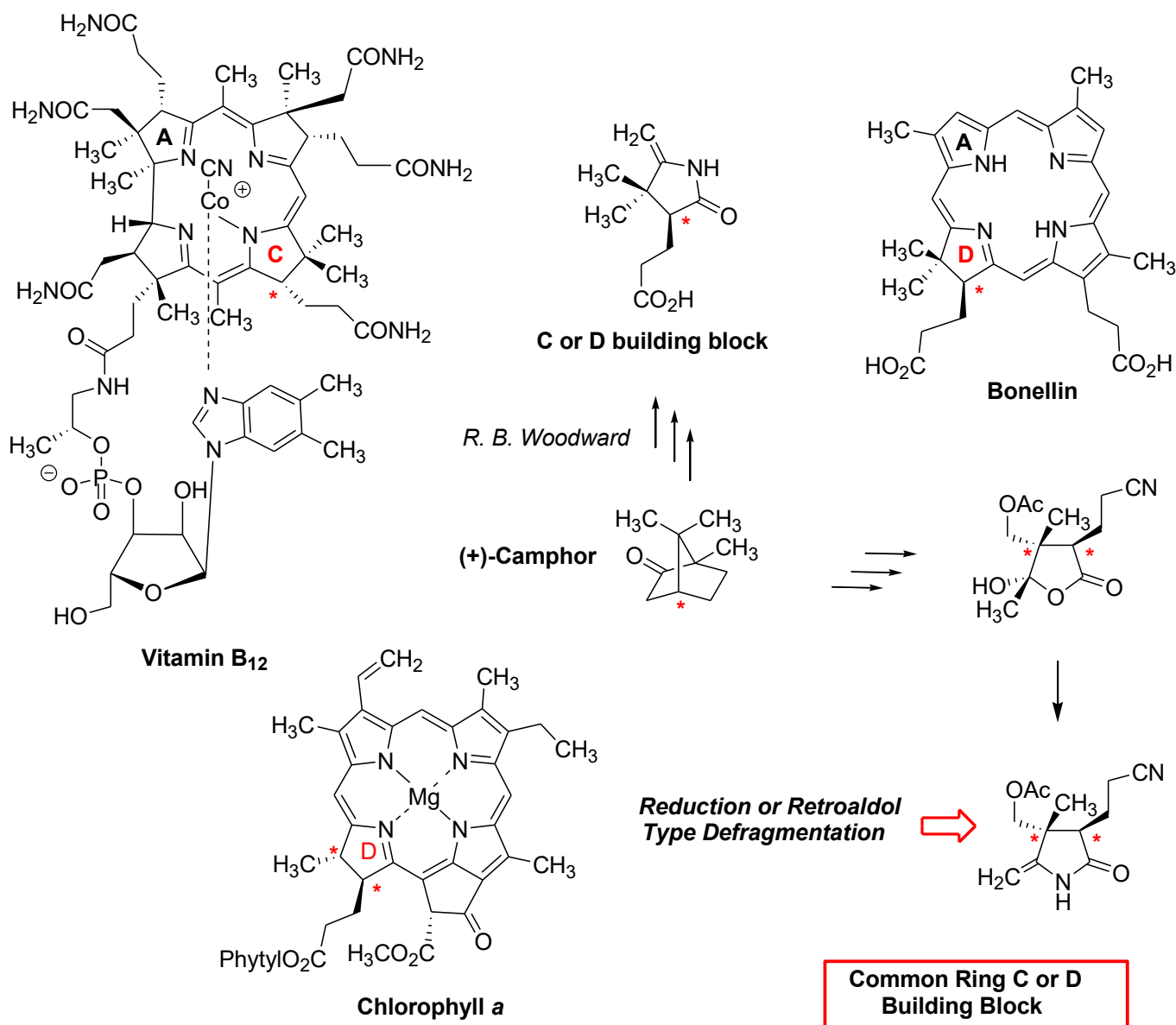
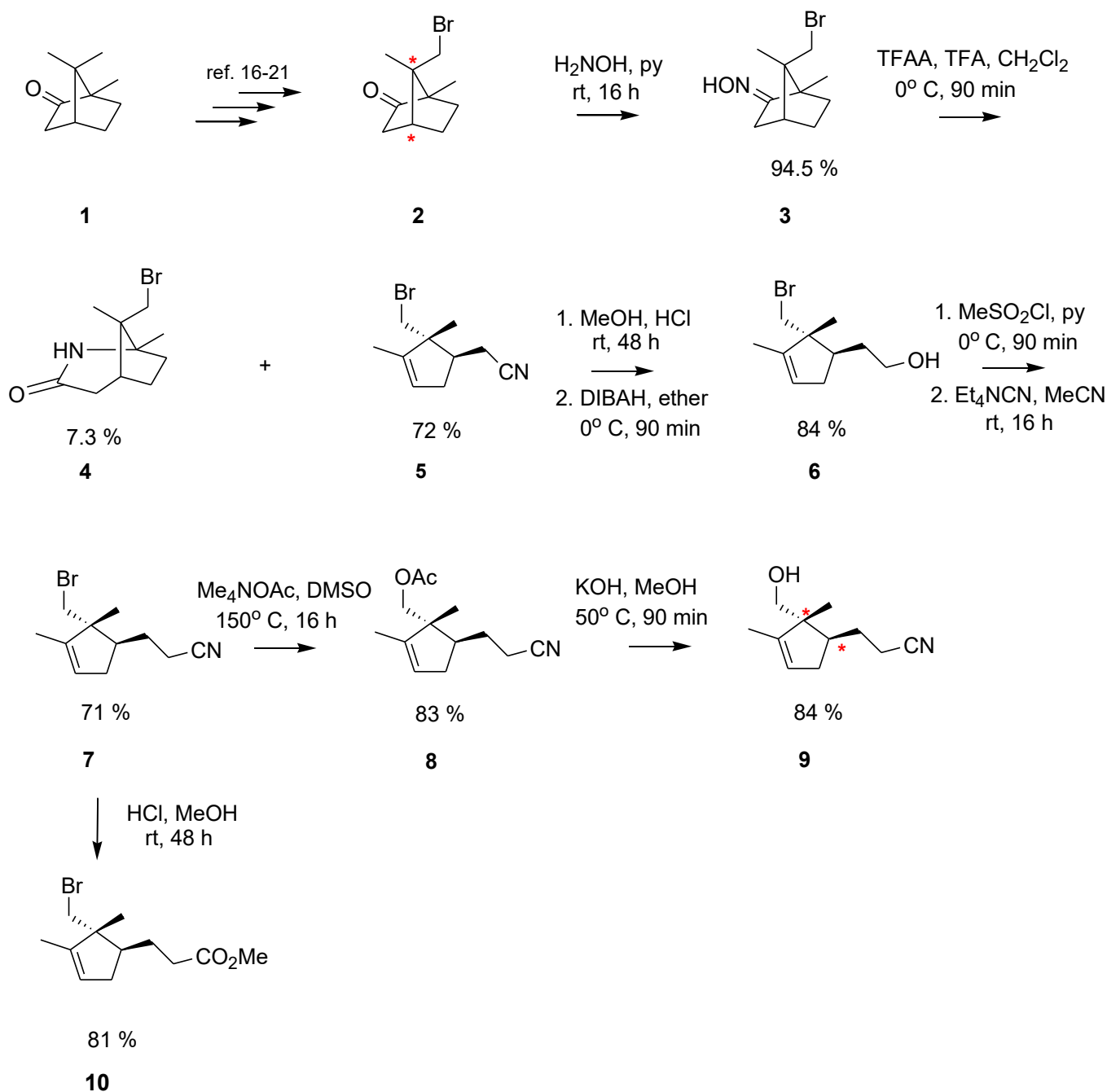


Figure 1. A novel common building block for rings C and D for vitamin B₁₂, bonellin and chlorophyll *a*

The total syntheses of several naturally occurring hydroporphyrins, including bonellin and chlorophyll *a*, require homochiral building blocks to establish the characteristic peripheral substitution patterns of these macrocycles.¹²⁻¹⁴ A common ring D building block for bonellin and chlorophyll *a* featuring a geminal acetoxymethyl-methyl substitution pattern was envisioned. This arrangement was expected to guarantee the stereochemical integrity of the adjacent chiral center bearing the trans-oriented propionitrile chain (Figure 1).

In the final stages of the synthesis, the acetoxymethyl group could either be removed completely by a retro-aldol-type fragmentation to furnish the substitution pattern characteristic of ring D in chlorophyll *a*, or the acetoxy function could be reductively removed to install the second methyl group required for ring D of bonellin.

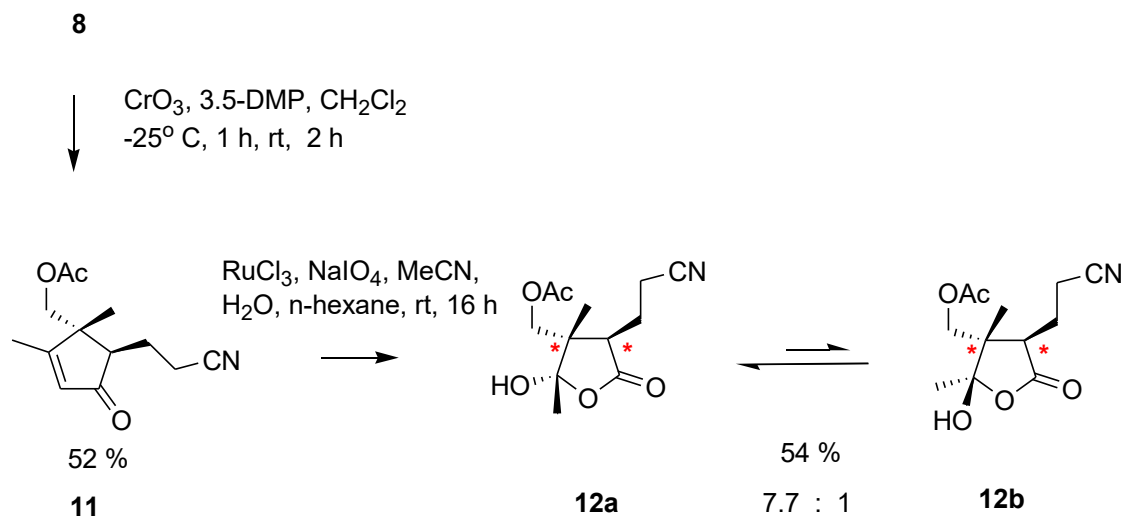
Results and Discussion



Scheme 1. Synthesis of homochiral cyclopentene intermediates from (+)-(1*R*,4*R*)-camphor (**1**) *via* (+)-(1*R*,4*R*,7*R*)-9-bromo-camphor (**2**).

Preparation of (+)-9-bromocamphor **2** from (+)-camphor **1**¹⁵ was achieved in 62% overall yield using modified literature procedures (Scheme 1).¹⁶⁻²¹ The oxime **3**, required for the subsequent Beckmann rearrangement, was obtained in nearly quantitative yield. As anticipated, the subsequent second-order Beckmann rearrangement afforded predominantly the desired cyano-cycloalkene **5**, along with a minor amount of the conventional lactam **4**.²¹ The mixture of rearrangement products was readily separated by a single crystallization.

The propionitrile side chain of the target compounds was installed by homologation of the acetonitrile moiety in cyclopentene **5**. Conversion of nitrile **5** into the corresponding methyl ester was followed by reduction with DIBAL-H to give alcohol **6**. Subsequent mesylation and nucleophilic substitution with tetraethylammonium cyanide furnished the cyclopentene propionitrile **7**. This sequence proved particularly straightforward with respect to simplicity of the reaction conditions and reagents while delivering a good overall yield. Treatment of propionitrile **7** with methanol/HCl converted the nitrile into the corresponding methyl propionate **10**. However, for the subsequent steps of the synthesis the nitrile function was retained as a convenient ester equivalent. Nucleophilic S_N2 displacement of the bromide in cyclopentene propionitrile **7** required relatively harsh conditions owing to the neopentyl position of the leaving group. Nevertheless, the substitution with tetramethylammonium acetate proceeded in excellent yield to afford cyclopentene acetate **8** (Scheme 2). Cyclopentene acetate **8** served as a suitable substrate for allylic oxidation at the ring position using the chromium trioxide–3,5-dimethylpyrazole complex, delivering enone **11** (Scheme 2).²² This compound provided direct entry to hydroporphyrin building block **12**. Alkaline hydrolysis of the acetate group of **8** furnished the corresponding hydroxymethyl derivative **9**, which was further elaborated toward an alternative hydroporphyrin building block **15** (Scheme 3).

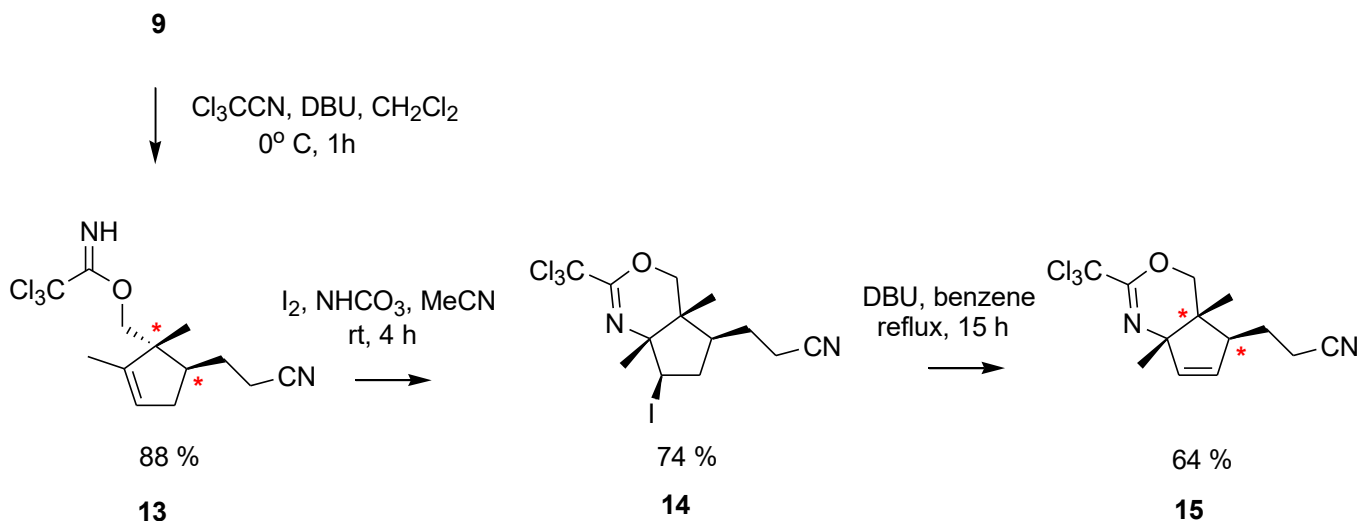


Scheme 2. Preparation of hydroporphyrin building block **12** by oxidation and cleavage of cyclopentene intermediate **8**.

Ring cleavage of cyclopentenone **11** was best accomplished by oxidation with a catalytic amount of ruthenium trichloride in the presence of excess sodium periodate (Scheme 2).²³⁻²⁴ The initially formed α -ketoaldehyde underwent further oxidation with decarboxylation, generating a carboxylate function. The resulting carboxylic acid and the adjacent keto group form an equilibrium mixture of the tautomeric pseudo-acids **12a** and **12b**, with the cis-diastereomer **12a** as the major isomer (cis orientation of hydroxy and acetoxymethyl groups at C-2).

and C-3) (**12a/12b**: 7.7:1). Previous studies have shown that treatment of such intermediates with ammonia furnishes the desired ring C/D building blocks.

In an alternative route (Scheme 3), the hydroxymethyl function of cyclopentene **9** was converted by trichloroacetonitrile into the trichloro-acetimidate **13**. Iodo-imidation under classical conditions of the iodolactonization then afforded bicyclic iodo-imidate **14**. Base-induced elimination of iodine yielded cyclopentene **15**. Subsequent oxidative cleavage of the endocyclic double bond and hydrolysis of the oxazine ring are expected to provide the required carboxylate functions and amino group for a hydroporphyrin building block.



Scheme 3. Preparation of a potential hydroporphyrin building block **15** by iodoimidation and elimination of cyclopentene intermediate **9**.

Conclusions

A chiral pool approach toward building blocks for vitamin B_{12} and hydroporphyrins such as bonellin and chlorophyll *a* (Figure 1) has been explored. Starting from (+)-camphor **1**, oxime **3** of (+)-9-bromocamphor **2** was converted *via* a second-order Beckmann rearrangement into the key cyclopentene intermediate **5** (Scheme 1). Bromide displacement and homologization of the acetonitrile side chain furnished cyclopentene propionitriles **8** and **9** in high overall yields (21% and 18%, respectively) on a multigram scale. These intermediates were further transformed into the advanced hydroporphyrin precursors **12** and **15** *via* two complementary routes (Schemes 2 and 3).

Experimental Section

General. Starting materials were prepared either according to literature procedures or were purchased from Fluka, Merck, Acros Organics or Sigma Aldrich and used without further purification. All solvents were purified and dried by standard methods. All reactions were carried out under argon. Melting points are not corrected. TLC: Silica gel plates (Riedel de Haen, silica gel 60 F 254; Macherey-Nagel, Polygram SIL G/UV 254). HPLC: Knauer 64.00, refractometer detection; Li Chrosorb RP 18 (Merck). Column chromatographic separations

were performed on silica gel (SiO₂, ICN Biomedicals, 32-63 µm, 60 Å). Optical Rotation: Perkin-Elmer 243 polarimeter. IR: Perkin-Elmer Paragon 500 FT-IR spectrometer, Perkin Elmer IR spectrophotometer 1310 and Thermo Scientific Nicolet iS10 FT-IR spectrometer with diamond window-ATR. NMR: Bruker DPX-200 AVANCE, Bruker WH 360 and Bruker 600 AVANCE neo. All chemical shifts were referenced to TMS lock signal. Exact assignment of proton signals in ¹H NMR spectra was obtained from two-dimensional H,H-COSY and NOESY experiments. Multiplicity and assignment of ¹³C signals was obtained from corresponding DEPT experiments. MS: Finnigan MAT 8222, MAT 95, MAT 95 XL, AMT CH7A spectrometer [E (70 eV), CI and DCI (NH₃, 8 mA/s)]. HRMS: Finnigan MAT 8222 spectrometer according peak matching method. Elemental analyses: Microanalytical Laboratories Beller (Göttingen).

(1R,4R,7R)-7-Bromomethyl-1,7-dimethyl-bicyclo[2.2.1]heptan-2-on (2)¹⁶⁻²¹ prepared from (+)-camphor (1) *via* (+)-(1R,3S,4S)-3-bromocamphor and (+)-(1R,3S,4S,7R)-3.9-dibromocamphor. To **(+)-(1R,3S,4S,7R)-3.9-dibromocamphor** (60 g, 0.194 mol), dissolved in dry dichloromethane (240 mL), was added zinc powder (42 g, 0.643 mol). With stirring, a weak stream of HBr was passed through the reaction mixture for 3.5 h and stirring was continued for an additional 30 min. Excess zinc and precipitated zinc bromide were removed by filtration through a pleated filter and thoroughly washed with dichloromethane. The filtrate was transferred into a separatory funnel and washed twice with water (2 x 200 mL) and with brine (200 mL). The organic phase was neutralized with saturated sodium bicarbonate solution (200 mL) and dried by filtration through cotton. After removal of the solvent, light yellow crystals were obtained, which were recrystallized from petroleum ether. **(+)-9-Bromocamphor 2** (CAS: RN 10293-09-1) was obtained as colorless needles. Yield (36.8 g, 83 %). Mp 95 - 97 °C. (Lit.¹⁸ 93-95 °C). IR (KBr, $\tilde{\nu}_{\text{max}}$, cm⁻¹): 2970, 2900, 2860 (CH), 1720 s (CO), 1746s (CO carbonate, ester), 1470, 1440, 1420, 1410, 1370, 1300, 1265, 1235, 1205, 1195, 1145, 1070, 1055, 1030, 1010, 940, 920, 900, 860. ¹H NMR (360 MHz, CDCl₃): δ_{H} 0,97 [3H, s, H₃C-C(1)], 1,0 [3H, s, H₃C-C(7)], 1,40-1,54 [2H, m, H₂C(6)], 1,66-1,76 [1H, m, HHC(5)], 1,90-1,99 [2H, m, HHC(5) and endo-HHC(3)], 2,32-2,39 [1H, m, exo-HHC(3)], 2,49 [t, 1H, HC(4)], 3,23 [1H, d, *J* 10,1 Hz, HHBrC-C(7)], 3,60 [1H, d, *J* 10,1 Hz, HHBrC-C(7)]. ¹³C-NMR (90.5 MHz, CDCl₃): δ_{C} 9.5 [q, H₃C-C(7)], 16.5 [q, H₃C-C(1)], 26.2 [t, C(5)], 29.4 [t, C(6)], 39.9 (t, -CH₂Br), 40.9 [d, C(4)], 42.5 [t, C(3)], 51.5 [s, C(1)], 58.3 [s, C(7)], 207.0 [s, CO(2)]. EI-MS (70 eV, direct inlet 20 °C): *m/z* (%) 232 (11 M⁺, ⁸¹Br), 230 (12, M⁺, ⁷⁹Br), 188 (25), 186 (27), 109 (48), 108 (55), 107 (82), 95 (41), 81 (100), 69 (38), 67 (42), 55 (24), 41 (38).

N-[(1R,4R,7R)-7-Bromomethyl-1,7-dimethyl-bicyclo[2.2.1]heptan-2-yliden}-hydroxylamin (3). To hydroxylamine hydrochloride (10.5 g, 0.151 mol) in dry pyridine (35 mL) was added 9-bromocamphor **2** (5 g, 21.6 mmol) and the mixture was stirred at rt under argon for 16 h. After removal of pyridine in *vacuo* of rotary evaporator, to the remaining crystalline residue was added water (30 mL) and the pH value was adjusted to 1 using half-concentrated HCl. The mixture was thoroughly extracted with diethyl ether (5 x 30 mL). The combined organic phases were dried by filtration through cotton wool and the diethyl ether was evaporated in *vacuo*. The residue was dried in *vacuo*. Isothermal recrystallization from diethyl ether/*n*-hexane yielded pure 9-bromocamphor oxime **3** as colorless needles. Yield (5.02 g, 94.5%). Mp 133-134 °C (diethylether/*n*-hexane). IR (KBr, $\tilde{\nu}_{\text{max}}$, cm⁻¹): 3300 (s, OH), 3160, 2980 (CH), 2975 (s), 2920 (s), 2880 (s), 1690 (w, C=N), 1490, 1450, 1440 (s), 1390, 1385, 1310, 1280, 1250, 1210, 1190, 1150, 1120, 1105, 1090, 1080, 1050, 1020, 1005, 955, 930 (s), 910, 860, 830. ¹H-NMR (360 MHz, CDCl₃): δ_{H} 1.00 [3H, s, H₃C-C(1)], 1.05 [3H, s, H₃C-C(7)], 1.31-1.42 (1H, m, HHC(6)], 1.55-1.62 [1H, m, HHC(6)], 1.73-1.95 [2H, m, H₂C(5)], 2.09 [1H, d, *J* 14.3 Hz, H₂C(6)], 2.32 [1H, m, HC(4)], 2.55 (2H, m, *J* 14,3 Hz, H₂C(3)], 3.24 (1H, d, *J* 10,1 Hz, HHBrC-C(7)], 3.58 (1H, d, *J* 10.1 Hz, HHBrC-C(7)], 8.18 (1H, s, NOH). ¹³C-NMR (90.5 MHz, CDCl₃): δ_{C} 11.4 [q, H₃C-C(7)], 16.1 [q, H₃C-C(1)], 26.5 [t, C(5)], 32.2 [t, C(3)], 32.4 [t, C(6)], 39.3 (t, -CH₂Br), 41.9 [d, C(4)], 52.6 [s, C(1)], 52.7 [s, C(7)], 169.1 [s, C=NOH]. MS (EI, 70eV, direct inlet, 80 °C): *m/z* (%) 247 (9, M⁺, ⁸¹Br), 245 (10, M⁺, ⁷⁹Br), 166 (35), 89 (22), 58 (10), 45

(100). $[\alpha]_D^{20} + 75.1^\circ$, $c = 1.6$ in MeOH. Microanalysis for $C_{10}H_{16}BrNO$ (246.147): calcd. C 48.80, H 6.55, Br 32.46, N 5.69; found C 48.85, H 6.59, Br 32.55, N 5.72.

2-[(1*R*,2*R*)-2-Bromomethyl-2,3-dimethyl-cyclopent-3-en-1-yl]-acetonitrile (5) and (1*R*,4*R*,8*R*)-8-Bromomethyl-1,8-dimethyl-2-azabicyclo[3.2.1]octan-3-on (4). To 9-bromocamphor oxime **3** (15 g, 61 mmol) in dichloromethane (15 mL) was added dropwise trifluoroacetic anhydride (15 mL) at 0 °C during 90 min. The mixture was stirred at 0 °C for 2 h, and then trifluoroacetic acid (15 mL) was added dropwise at rt over 10 min. After the exothermic reaction had subsided, stirring was continued for 16 h at rt. All volatile components were removed in vacuo of the rotary evaporator at 50 °C. The dark brown residue was dissolved in diethyl ether (200 mL) and carefully washed for neutralization with a saturated sodium bicarbonate solution. The organic layer was washed once with saturated sodium chloride solution and dried by filtration through cotton wool. After removal of the solvent, 13.7 g of a dark brown mixture of desired product **5** and by-product **4** was obtained. To remove the by-product **4**, the crude mixture was stored overnight in a deep freezer, during which the lactam by-product **4** crystallized from the mixture. The main product **5** was filtered off from the crystals. The crystalline by-product was washed with *n*-hexane, dried in vacuo and characterized. Purification of crude main product by Kugelrohr distillation in *vacuo* at 90 - 100 °C yielded nitrile **5** as a colorless oil.

5: Yield (10.1 g, 72%). TLC (SiO₂, petrol ether/EtOAc = 3 : 1): R_f 0.37. IR (KBr, $\tilde{\nu}_{max}$, cm⁻¹): 3020, 2960 (s), 2920 (s), 2840 (s), 2230 (CN), 1440, 1420 (s), 1365, 1245, 1160, 1090, 1050, 1030, 1005, 930, 800. ¹H NMR (360 MHz, CDCl₃): δ_H 1.05 [3H, s, H₃C-C(2)], 1.65 [3H, s, H₃C-C(3)], 2.02-2.13 [1H, m, HC(1)], 2.32-2.38 [1H, dd, HHC(5)], 2.47-2.55 [1H, dd, HHC(5)], 2.56-2.65 (1H, m, -CHHCN), 2.69-2.78 (1H, m, -CHHCN), 3.39, 3.48 (2H, 2d, AB-system, J_{AB} 12 Hz, -CH₂Br), 5.39 [1H, s, HC(4)]. ¹³C-NMR (90.5 MHz, CDCl₃): δ_C 12.4 [q, H₃C-C(2')], 17.5 [q, H₃C-C(3')], 18.6 (t, -CH₂-CN), 35.5 [t, H₂C(5')], 40.8 [d, HC(1')], 41.6 (t, -CH₂Br), 51.5 [s, C(2')], 119.1 (s, CN), 124.2 [d, HC(4')], 143.4 [s, C(3')]. MS (EI, 70eV, direct inlet, 20 °C): m/z (%) 229 (8, M⁺, ⁸¹Br), 227 (8, M⁺, ⁷⁹Br), 134 (100), 107 (17), 93 (40), 79 (10). $[\alpha]_D^{20} + 27.1^\circ$, $c = 2.1$ in MeOH. HRMS (ESI, *i*-PrOH): calcd for (C₁₀H₁₄N⁷⁹Br + Na) 250.0202; found 250.0199.

4: Yield (1.1 g, 7.3 % by-product). Mp 168-169 °C. IR (KBr, $\tilde{\nu}_{max}$, cm⁻¹): 3180 (NH), 3160, 2950 (s), 2920, 2900, 2870, 1670 (s, CO), 1460, 1445, 1395 (s), 1390, 1315, 1300, 1250, 1240, 1220, 1200, 1180, 1170 (8s), 1110, 1100, 1060, 1045, 1010, 955, 945, 910, 860, 820. ¹H-NMR (360 MHz, CDCl₃): δ_H 1.14 [3H, s, H₃C-C(8)], 1.19 (3H, s, H₃C-C(1)), 1.54-1.60, 1.89-2.12 [4H, 2 m, H₂C(6) and H₂C(7)], 2.22, 2.56 [2H, 2d, H₂C(4)], 2.45 (1H, t, HC(5)], 3.38 (2H, AB-system, -CH₂Br), 6.49 [1H, s (br), NH]. MS (EI, 70eV, direct inlet, 80 °C): m/z (%) 247 (1, M⁺, ⁸¹Br), 245 (1, M⁺, ⁷⁹Br), 166 (72, M⁺-Br), 149 (37), 134 (27), 123 (29), 110 (100), 93 (33), 81 (48), 70 (69), 67 (26), 60 (46), 55 (23), 42 (46). $[\alpha]_D^{20} - 44.1$, $c = 1.15$ in MeOH. Microanalysis for $C_{10}H_{16}BrNO$ (246.147): calcd. C 48.80, H 6.55, Br 32.46, N 5.69; found C 48.90, H 6.51, Br 34.35, N 5.72.

Methyl 2-[(1*R*,2*R*)-2-bromomethyl-2,3-dimethylcyclopent-3-en-1-yl]-acetate (5a). Nitrile **5** (5.05 g, 22.2 mmol) in methanol/HCl (100 mL, 25 % solution) was stored under Ar at rt for 48 h. The solution was then concentrated in *vacuo* of a rotary evaporator to a small volume (ca. 20 mL). The resulting crystalline slurry was taken up in dichloromethane (100 mL), transferred to a separatory funnel, and washed twice with water (2 x 50 mL) and with brine (2 x 50 mL). After drying by filtration through cotton wool, the solvent was evaporated in *vacuo*. The remaining yellow oil was purified by Kugelrohr distillation in *vacuo* at 100 -110 °C to yield methyl ester **5a** as a colorless oil. Yield (5.13 g, 87 %). TLC (SiO₂, petrol ether/EtOAc = 3:1): R_f 0.49. IR (KBr, $\tilde{\nu}_{max}$, cm⁻¹): 3020, 2960 (s), 2940, 2920, 1735 (s, CO), 1420 (s), 1360, 1295, 1245, 1195, 1170, 1150, 1095, 1005, 920, 880, 800. ¹H-NMR (200 MHz, CD₃COCD₃): δ_H 0.98 [3H, s, H₃C-C(2)], 1.67 (3H, s, H₃C-C(3)], 1.89 -1.97 (1H, m, HC(1)], 2.28-2.35 [1H, dd, ³*J* 15.0 Hz, ²*J* 10.1 Hz, HHC(5)], 2.48-2.55 (2H, dd, ³*J* = 15.1 Hz, ²*J* 5.2 Hz, HHC(5) and HHC-CO₂Me], 2.47-2.83 (1H, m, HHC-CO₂Me), 3.40 (2H, AB-system, -CH₂Br), 3.69 (3H, s, -OCH₃), 5.39 [1H, s, HC(4)]. ¹³C-NMR (90.5 MHz, CDCl₃): δ_C 12.5 [q, H₃C-C(2')], 17.5 [q, H₃C-C(3')], 21.5 (q, -OCH₃), 35.5 [t, H₂C(5')], 35.8 (t,

-CH₂-CO₂Me), 40.7 [d, HC(1')], 41.7 (t, -CH₂Br), 51.5 [s, C(2')], 119.1 (s, CN), 124.8 [d, HC(4')], 143.6 [s, C(3')], 173.5 (s, -CO-). MS (EI, 70eV, direct inlet, 30 °C): *m/z* (%) 262 (1, M⁺, ⁸¹Br), 260 (1, M⁺, ⁷⁹Br), 167 (6), 107 (10), 73 (100), 44 (82). [α]_D²⁰ + 29.7°, *c* = 3.7 in CHCl₃. HRMS (EI): calcd for (C₁₁H₁₇⁷⁹BrO₂) 260.04119; found 260.04048.

2-[(1*R*,2*R*)-2-Bromomethyl-2,3-dimethyl-cyclopent-3-en-1-yl]-ethan-1-ol (6). To methyl ester **5a** (4.65 g, 17.9 mmol) in anhydrous diethyl ether (90 mL) DIBAH (40 mL, 1 M solution in *n*-hexane = 40 mmol) was added dropwise under Ar at 0 °C. The mixture was stirred in an ice bath for 75 min and the reaction was quenched by cautious addition of solid sodium sulfate decahydrate. The suspension was stirred for 60 min. All insoluble components were filtered off, and the filtrate was washed with brine (50 mL). The organic layer was dried over sodium sulfate, filtered off and the solvent evaporated in *vacuo*. The obtained yellow oil (4.07 g) was purified by Kugelrohr distillation in *vacuo* at 90 -100 °C. The alcohol **6** was obtained as a viscous colorless oil. Yield (3.99 g, 97 %). IR (KBr, $\tilde{\nu}_{\max}$, cm⁻¹): 3300 (br, OH), 3020, 2960 (s), 2920 (s), 2900, 2820, 1440, 1430, 1360, 1240, 1060, 1045, 1010, 920, 835, 800. ¹H-NMR (360 MHz, CDCl₃): δ_H 0.98 [3H, s, H₃C-C(2')], 1.55 (2H, m, -CH₂-OH), 1.68 [3H, s, H₃C-C(3')], 1.70-1.80 (2H, m, -CH₂CH₂OH), 2.38-2.47 [2H, m, H₂C(5')], 3.40 (2H, AB-system, -CH₂Br), 3.63-3.78 (2H, m, -CH₂CH₂OH), 5.40 [1H, s, HC(4)]. ¹³C-NMR (90.5 MHz, CDCl₃): δ_C 12.5 [q, H₃C-C(2')], 17.5 [q, H₃C-C(3')], 33.3 (t, -CH₂-CH₂OH), 35.5 [t, H₂C(5')], 40.9 [d, HC(1')], 41.8 (t, -CH₂Br), 51.6 [s, C(2')], 62.1 (t, -CH₂OH), 124.0 [d, HC(4')], 144.2 [s, C(3')]. MS (EI, 70eV, direct inlet, 30 °C): *m/z* (%) 234 (8, M⁺ ⁸¹Br), 232 (8) (9, M⁺, ⁷⁹Br), 139 (64), 121 (27), 107 (21), 95 (100), 79 (29), 41 (26). 139 (64), 121 (27), 107 (21), 95 (100), 79 (29), 41 (26). [α]_D²⁰ + 34.7°, *c* = 1.7 in MeOH. HRMS (EI): calcd for (C₁₀H₁₇⁷⁹BrO) 232.04628; found 232.04696.

3-[(1*S*,2*R*)-2-Bromomethyl-2,3-dimethyl-cyclopent-3-en-1-yl]-propionitrile (7). To a mixture of alcohol **6** (1.80 g, 7.7 mmol) and of methanesulfonyl chloride (0.98 g, 8.6 mmol) was added anhydrous pyridine (2.5 mL) with stirring at 0 °C under a nitrogen atmosphere. The resulting crystalline slurry was stirred at 0 °C for 90 min and the reaction was quenched by addition of ice cold 10% hydrochloric acid (50 mL). The mixture was extracted three times with diethyl ether (3 x 50 mL). The organic phases were washed with water and saturated sodium bicarbonate solution. The combined organic layers were dried by filtration through cotton wool and the solvent was evaporated in *vacuo*. The mesylate was obtained as a colorless oil. Due to the low stability of **2-[(1*R*,2*R*)-2-Bromomethyl-2,3-dimethyl-cyclopent-3-en-1-yl]-ethan-1-*O*-methylsulfonate (6a)**, crude product was used without exhaustive characterization directly in the next reaction step. Yield (2.21 g, 92 %). IR (NaCl film, $\tilde{\nu}_{\max}$, cm⁻¹): 3000, 2940, 2900, 2805, 1440, 1430, 1420, 1340 (s), 1230, 1160 (s), 1005, 1010, 995, 960 (s), 945, 920 (s), 865, 835, 800. ¹H-NMR (360 MHz, CDCl₃): δ_H 0.9 [3H, s, H₃C-C(2')], 1.60 [3H, s, H₃C-C(3')], 1.82-1.94 (2H, m, -CH₂CH₂OH), 2.32-2.42 [2H, m, H₂C(5')], 2.98 (3H, s, -OSO₂CH₃) 3.29 – 3.39 (2H, AB-system, -CH₂Br), 4.14 – 4.29 (2H, m, -CH₂CH₂OMs), 5.32 [1H, s, HC(4)].

To mesylate **6a** (1.05 g, 3.38 mmol) in anhydrous acetonitrile (10 mL) was added dropwise over 10 min at 0 °C a solution of tetraethylammonium cyanide (1.05 g, 6.7 mmol) in acetonitrile (10 mL). The yellow mixture was stirred for 16 h under a nitrogen atmosphere. The solvent was removed in *vacuo* of the rotary evaporator, and the residue was distributed between diethyl ether (50 mL) and water (50 mL). The organic layer was separated and washed twice with water (2 x 30 mL) and with brine (2 x 30 mL), dried by filtration through cotton wool and the solvent evaporated in *vacuo*. The remaining yellow oil was purified by flash chromatography [SiO₂, ICN Biomedicals 32 – 63 μm, 60 Å, ether/EtOAc = 5 : 1]. After evaporation of the eluent a yellow oil was obtained, which was crystallized from diethyl ether/*n*-hexane, to give the nitrile **7** as colorless plates. Yield (626 mg, 77%). Mp 50 °C (Et₂O/*n*-hexane). TLC (SiO₂, petrol ether/EtOAc = 5 : 1): R_f 0.32. IR (KBr, $\tilde{\nu}_{\max}$, cm⁻¹): 3020, 2960 (s), 2920 (s), 2820, 2230 (m, CN), 1440 (s), 1420 (s), 1365, 1245, 1185, 1170, 1095, 1015, 930, 800. ¹H-NMR (360 MHz, CDCl₃): δ_H 0.99 [3H, s, H₃C-C(2')], 1.50-1.65 [1H, m, HHC-CH₂-CN], 1.66 [3H, s, H₃C-C(3')], 1.81-2.01 (2H, m, HHC-CH₂-CN, HHC(5')), 2.25-2.57 [4H, m, -CH₂CN, HC(1') and HHC(5')], 3.40 (2H, AB-system, -CH₂Br),

5.41 [1H, s, HC(4')]. ^{13}C -NMR (90.5 MHz, CDCl_3): δ_{C} 12.5 [q, $\text{H}_3\text{C}-\text{C}(2')$], 16.2 (t, $-\text{CH}_2-\text{CH}_2\text{CN}$), 17.4 [q, $\text{H}_3\text{C}-\text{C}(3')$], 26.6 (t, $-\text{CH}_2-\text{CH}_2-\text{CN}$), 34.9 [t, $\text{H}_2\text{C}(5')$], 41.6 (t, $-\text{CH}_2\text{Br}$), 44 [d, HC(1')], 51.7 [s, C(2')], 119.7 (s, CN), 124.3 [d, HC(4')], 144.2 [s, C(3')]. MS (EI, 70eV, direct inlet, 200 °C): m/z (%) 243 (19, $\text{M}^+ {}^{81}\text{Br}$), 241 (20, M^+ , ${}^{79}\text{Br}$), 162 (15, $\text{M}^+ - \text{Br}$), 148 (97, $\text{M}^+ - \text{CH}_2\text{Br}$), 133 (13), 121 (31), 107 (100), 91 (60), 79 (51). $[\alpha]_{\text{D}}^{20} + 42.3^\circ$, $c = 2.2$ in CHCl_3 . HRMS (EI): calcd for ($\text{C}_{11}\text{H}_{16}{}^{79}\text{BrN}$) 241.04661; found 241.0484 ($R = 10000$). Microanalysis for $\text{C}_{11}\text{H}_{16}\text{BrN}$ (242.158): calcd. C 54.56, H 6.66, Br 32.99, N 5.78; found C 54.61, H 6.64, Br 32.85, N 5.78.

3-[(1S,2R)-2-Acetoxymethyl-2,3-dimethyl-cyclopent-3-en-1-yl]-propionitrile (8). Nitrile **7** (1.03 g, 4.25 mmol) and tetramethylammonium acetate (1.70 g, 12.77 mmol) in dimethyl sulfoxide (15 mL) was heated at 150 °C under a nitrogen atmosphere for 16 h. After cooling, the dark brown reaction mixture was poured in 1 M HCl (60 mL) and extracted exhaustively with diethyl ether (5 x 60 mL). The combined ether phases were washed once with brine (100 mL), dried by filtration through cotton wool, and evaporated. The resulting brown oil was purified by Kugelrohr distillation in vacuo at 100 - 110 °C. The acetate **8** was obtained as a colorless oil. Yield (0.785 g, 83 %). TLC (SiO_2 , $\text{CH}_2\text{Cl}_2/\text{EtOAc} = 10 : 1$): R_f 0.61. IR (NaCl film, $\tilde{\nu}_{\text{max}}$, cm^{-1}): 3020, 2950 (s), 2920 (s), 2820, 2230 (m, CN), 1730 (s, C=O), 1460, 1440, 1365, 1230, 1150, 1120, 1035 (s), 1010, 990, 900, 800. ^1H -NMR (360 MHz, CDCl_3): δ_{H} 0.84 [3H, s, $\text{H}_3\text{C}-\text{C}(2')$], 1.62 [4H, s br, $\text{H}_3\text{C}-\text{C}(3')$ and $\text{HHC}-\text{CH}_2-\text{CN}$], 1.80-1.99 [2H, m, $\text{HHC}-\text{CH}_2\text{CN}$ and $\text{HHC}(5')$], 2.07 (3H, s, $\text{H}_3\text{C}-\text{CO}$), 2.19-2.55 [4H, m, $-\text{CH}_2\text{CN}$, HC(1') and $\text{HHC}(5')$], 3.94 (2H, AB-system, $-\text{CH}_2\text{OAc}$), 5.34 [1H, s, HC(4')]. ^{13}C -NMR (90.5 MHz, CDCl_3): δ_{C} 12.5 [q, $\text{H}_3\text{C}-\text{C}(2')$], 15.0 [q, $\text{H}_3\text{C}-\text{C}(3')$], 16.0 (t, $-\text{CH}_2-\text{CH}_2\text{CN}$), 20.6 (q, $-\text{OCH}_3$), 26.1 (t, $-\text{CH}_2-\text{CH}_2-\text{CN}$), 34.5 [t, $\text{H}_2\text{C}(5')$], 43.3 [d, HC(1')], 50.2 [s, C(2')], 68.2 (t, $-\text{CH}_2\text{OAc}$), 119.5 (s, CN), 123.4 [d, HC(4')], 144.2 [s, C(3')], 170.9 (s, $-\text{COMe}$). MS (EI, 70eV, direct inlet, 200 °C): m/z (%) 221 (4, M^+), 161 (21), 148 (100, $\text{M}^+ - \text{CH}_2\text{OAc}$), 119 (27), 107 (52), 91 (15), 43 (25). MS (ESI, positive, MeOH): m/z 465 [$2\text{M} + \text{Na}$] $^+$, 260 [$\text{M} + \text{K}$] $^+$, 244 [$\text{M} + \text{Na}$] $^+$. $[\alpha]_{\text{D}}^{20} + 35.7^\circ$, $c = 2.1$ in MeOH. HRMS (ESI, MeCN/ H_2O): calcd for ($\text{C}_{13}\text{H}_{19}\text{NO}_2 + \text{Na}$) 244.1308 ; found 244.1303.

3-[(1S,2R)-2-Hydroxymethyl-2,3-dimethyl-cyclopent-3-en-1-yl]-propionitrile (9). Acetate **8** (320 mg, 1.44 mmol) and KOH (108 mg, 1.93 mmol) in MeOH (2 mL) was stirred at 50 °C for 90 min. After cooling of the reaction mixture, a half-concentrated sodium chloride solution (5 mL) was added and the mixture was extracted with diethyl ether (3 x 10 mL). The combined organic phases were dried by filtration through cotton wool and the solvent was evaporated. The yellow residue was purified by Kugelrohr distillation at 115 - 120 °C to yield the hydroxy compound **9** as a colourless oil. Yield (190 mg, 84 %). TLC (SiO_2 , $\text{CH}_2\text{Cl}_2/\text{EtOAc} = 9 : 1$): R_f 0.4. IR (NaCl film, $\tilde{\nu}_{\text{max}}$, cm^{-1}): 3420 (s, OH), 3020, 2950 (s), 2920 (s), 2860, 2810, 2230 (m, CN), 1460, 1440 (s), 1430, 1370, 1290, 1270, 1245, 1200, 1160, 1140, 1110, 1035 (s), 1010 (s), 940, 910, 880. ^1H -NMR (360 MHz, CDCl_3): δ_{H} 0.8 [3H, s, $\text{H}_3\text{C}-\text{C}(2')$], 1.30 (1H, s br, HO-), 1.56–1.69 [1H, m, $-\text{HHC}-\text{CH}_2-\text{CN}$], 1.64 [3H, s, $\text{H}_3\text{C}-\text{C}(3')$], 1.82-1.96 [2H, m, $-\text{HHC}-\text{CH}_2\text{CN}$ and $\text{HHC}(5')$], 2.28-2.48 [4H, m, $-\text{CH}_2\text{CN}$, HC(1') and $\text{HHC}(5')$], 3.48 (2H, AB-system, $-\text{CH}_2\text{OH}$), 5.42 [1H, s, HC(4')]. ^{13}C -NMR (90.5 MHz, CDCl_3): δ_{C} 12.6 [q, $\text{H}_3\text{C}-\text{C}(3')$], 15.0 [q, $\text{H}_3\text{C}-\text{C}(2')$], 16.2 (t, $-\text{CH}_2-\text{CH}_2\text{CN}$), 26.1 (t, $-\text{CH}_2-\text{CH}_2-\text{CN}$), 34.1 [t, $\text{H}_2\text{C}(5')$], 41.9 [d, HC(1')], 54.5 [s, C(2')], 66.4 (t, $-\text{CH}_2\text{OH}$), 120.0 (s, CN), 124.1 [d, HC(4')], 144.3 [s, C(3')]. MS (ECI, direct inlet, 30 °C): m/z (%) positive : 196 (100, [$\text{M} + \text{NH}_4$] $^+$), 179 (20, M^+); negative: 178 (100, [$\text{M} + \text{H}$] $^+$). $[\alpha]_{\text{D}}^{20} + 43.4^\circ$, $c = 2.1$ in MeOH. HRMS (ESI, MeCN/ H_2O): calcd for ($\text{C}_{11}\text{H}_{17}\text{NO} + \text{Na}$) 202.1202 ; found 202.1200.

Methyl 3-[(1S,2R)-2-bromomethyl-2,3-dimethylcyclopent-3-en-1-yl]-propionate (10). To nitrile **7** (500 mg, 2.07 mmol) was added a solution of HCl in methanol (10 mL, 25%) and the mixture was stored under Ar at rt for 48 h. HCl and the solvent were evaporated. The crude residue was solved in dichloromethane (100 mL), transferred to a separatory funnel, washed with water (2 x 50 mL) and with brine (50 mL). After drying over anhydrous sodium sulfate, the solvent was evaporated. The remaining yellow oil was purified by Kugelrohr distillation in vacuo at 105 - 115 °C. The ester **10** was obtained as a colorless oil. Yield (461 mg, 81 %). TLC (SiO_2 , petrol ether/ $\text{EtOAc} = 3 : 1$): R_f 0.51. IR (NaCl film, $\tilde{\nu}_{\text{max}}$, cm^{-1}): 2910 (s), 2810, 1720 (s, C=O), 1420, 1350,

1340, 1230, 1185, 1155, 1090, 1055, 1005, 910, 880, 820, 800. $^1\text{H-NMR}$ (360 MHz, CDCl_3): δ_{H} 0.98 [3H, s, $\text{H}_3\text{C-C}(2')$], 1.50 – 1.58 [1H, m, $\text{HC}(1')$], 1.66 [3H, s, $\text{H}_3\text{C-C}(3')$], 1.76-1.81 (2H, m, $-\text{CH}_2\text{CH}_2\text{CO}_2\text{Me}$), 2.22-2.43 [4H, m, $-\text{CH}_2\text{CH}_2\text{CO}_2\text{Me}$ and $\text{H}_2\text{C}(5')$], 3.38 (2H, AB-system, $-\text{CH}_2\text{Br}$), 3.69 (3H, s, $\text{H}_3\text{CO}-$), 5.39 [1H, s, $\text{HC}(4')$]. MS (EI, 70 eV, direct inlet, 20 °C): m/z (%) 276 (1, M^+ , ^{81}Br), 274 (1, M^+ , ^{79}Br), 194 (30, $\text{M}^+ - \text{HBr}$), 181 (50), 119 (48), 107 (62), 101 (100), 91 (32), 79 (28), 55 (24), 41 (26). $[\alpha]_{\text{D}}^{20} + 68.3^\circ$, $c = 1.8$ in MeOH. HRMS (EI): calcd for $(\text{C}_{12}\text{H}_{19}^{79}\text{BrO}_2)$ 274.0568; found 274.0573 ($R = 10000$).

3-[(1S,2R)-2-Acetoxymethyl-2,3-dimethyl-5-oxo-cyclopent-3-en-1-yl]-propionitrile (11). To a suspension of CrO_3 (2.7 g, 27.0 mmol) in anhydrous CH_2Cl_2 (50 mL) was added, 3,5-dimethylpyrazole (2.7 g, 28.1 mmol) under nitrogen at -25°C . The mixture was stirred at -25°C for 30 min. Then, nitrile **8** (700 mg, 3.16 mmol) was added, and stirring was continued at -25°C for 1 h and at rt for 2 h. Aqueous NaOH (50 mL, 5 M) was added and the mixture was stirred at rt for 1 h. Then, the mixture was filtered through cotton wool into a separatory funnel. The CH_2Cl_2 phase was separated and washed with hydrochloric acid (30 mL, 10%). The two aqueous phases (containing NaOH and HCl) were separately extracted with ethyl acetate (2 x 30 mL). The totally combined organic phases were washed with hydrochloric acid (50 mL, 10%) and water (50 mL). The organic phases were dried by filtration through cotton wool and evaporated. The crude product was pre-purified by flash chromatography [SiO_2 , ICN Biomedicals 32 – 63 μm , 60 Å, EtOAc]. The obtained yellow oil was further purified by a second flash chromatography [SiO_2 , ICN Biomedicals 32 – 63 μm , 60 Å, diethyl ether/*n*-heptane = 2 : 1]. Evaporation of the eluent in vacuo of an oil pump yielded **11** as a colorless oil. Yield (390 mg, 52 %). TLC (SiO_2 , *n*-heptane/EtOAc = 1 : 1): R_f 0.58. IR (ATR, $\tilde{\nu}_{\text{max}}$, cm^{-1}): 2940, 2880, 2245 (m, CN), 1740 (s, C=O), 1693 (s, CO), 1620 (m), 1433, 1376, 1314, 1231 (s), 1164, 1141, 1090, 1042, 912, 863. $^1\text{H-NMR}$ (360 MHz, CDCl_3): δ_{H} 1.09 [3H, s, $\text{H}_3\text{C-C}(2')$], 1.76-1.89 (2H, m, $-\text{CH}_2\text{CH}_2\text{CN}$), 2.10-2.15 (6H, 2s, H_3CO and $\text{H}_3\text{C-C}(3')$), 2.39-2.46 [m, 1H, $\text{HC}(1')$], 2.77-2.85 (2H, m, $-\text{CH}_2\text{CH}_2\text{CN}$), 4.09 (2H, AB-system, $-\text{CH}_2\text{OAc}$), 5.92 (1H, s, $\text{HC}(4')$). $^{13}\text{C-NMR}$ (90 MHz, CDCl_3): δ_{C} 15.1 [t, $-\text{CH}_2\text{-CH}_2\text{-CN}$], 16.4 (q, $\text{H}_3\text{C-C}(2')$), 18.9 [t, $-\text{CH}_2\text{CH}_2\text{CN}$], 21.17 (q, $-\text{OCOCH}_3$), 23.3 [q, $\text{H}_3\text{C-C}(3')$], 49.8 [s, $\text{C}(2')$], 50.8 (d, $\text{HC}(1')$], 67.5 (t, $-\text{CH}_2\text{OAc}$), 120.0 (s, CN), 130.6 [d, $\text{HC}(4')$], 171.1 (s, $-\text{OCOMe}$), 179.7 [s, $\text{C}(3')$], 208.0 [s, $\text{CO}(5')$]. MS (EI, 70 eV, direct inlet, 200 °C): m/z (%) 235 (18, M^+), 182 (25, $\text{M}^+ - \text{CH}_2\text{CH}_2\text{CN}$), 164, (15), 163 (98, $\text{M}^+ - \text{CH}_2\text{OAc}$), 162 (13), 135 (19), 123 (100, $\text{M}^+ - \text{CH}_2\text{CH}_2\text{CN}$, $-\text{OAc}$), 122 (38), 107 (17), 43 (56). HRMS (EI): calcd for $(\text{C}_{13}\text{H}_{17}\text{NO}_3)$ 235.12084; found 235.12012 ($R = 10000$).

[(2S,3S,4R)-4-(2-Cyanoethyl)-2-hydroxy-2,3-dimethyl-5-oxo-tetrahydrofuran-3-yl]-methyl acetate (12a) and [(2R,3S,4R)-4-(2-Cyanoethyl)-2-hydroxy-2,3-dimethyl-5-oxo-tetrahydrofuran-3-yl]-methyl acetate (12b). To a mixture of ketone **11** (500 mg, 2.1 mmol) in acetonitrile/hexane (25 mL, 1 : 1) and sodium periodate (2 g, 9.3 mmol) in water (10 mL) was added ruthenium trichloride hydrate (35 mg, 0.16 mmol) at -10°C and the entire mixture was stirred at rt for 16 h. Isopropanol (2 mL) and water (25 mL) was added and the organic phase was separated. The aqueous layer was extracted with CH_2Cl_2 (20 mL). The combined organic phases were dried by filtration through cotton wool and evaporated. The obtained crude oil was pre-purified by chromatography by flash chromatography [SiO_2 , ICN Biomedicals 32 – 63 μm , 60 Å, EtOAc] to give a light-yellow oil. A second flash chromatography [SiO_2 , ICN Biomedicals 32 – 63 μm , 60 Å, diethyl ether/*n*-heptane = 2 : 1] removed the yellow impurity and yielded **12a/12b** as a colorless solid. Yield (290 mg, 54 %). TLC (SiO_2 , *cyclo*-hexane/EtOAc = 2 : 1): R_f 0.23. IR (ATR, $\tilde{\nu}_{\text{max}}$, cm^{-1}): 3280 (br, OH), 3000, 2975, 2950, 2885, 2254 (m, CN), 1762 (s, CO), 1698 (s, CO), 1458, 1405, 1385, 1286, 1258, 1210, 1088, 1043, 1028, 908, 871, 838. $^1\text{H-NMR}$ (601 MHz, CDCl_3): for **12a**: δ_{H} 1.03 [3H, s, $\text{H}_3\text{C-C}(3)$], 1.62 [3H, s, $\text{H}_3\text{C-C}(2)$], 1.80 (1H, dddd, J 13.7, 8.8, 7.8, 3.4 Hz, $-\text{CHHCH}_2\text{CN}$), 1.92 (1H, dddd, J 13.7, 11.1, 7.6, 5.0 Hz, $-\text{CHHCH}_2\text{CN}$), 2.12 (3H, s, $\text{H}_3\text{COO}-$), 2.78 (1H, ddd, J 17.1, 8.9, 7.6 Hz, $-\text{CH}_2\text{CHHCH}_2\text{CN}$), 2.85 (1H, ddd, J 17.0, 7.8, 5.0 Hz, $-\text{CH}_2\text{CHHCH}_2\text{CN}$), 2.96 [1H, dd, J 11.1, 3.3 Hz, $\text{HC}(4)$], 3.54 (1H, s, HO), 4.20 (1H, d, J 11.4 Hz, $-\text{CHHOAc}$), 4.31 (1H, d, J 11.4 Hz, $-\text{CHHOAc}$); for **12b**: δ_{H} 1.13 [3H, s, $\text{H}_3\text{C-C}(3)$], 1.59 [3H, s, $\text{H}_3\text{C-C}(2)$], 1.80-1.92 (2H, m, $-\text{CH}_2\text{CH}_2\text{CN}$), 2.10 (3H, s, $\text{H}_3\text{COO}-$), 2.59 [1H, dd, $\text{HC}(4)$], 2.73-2.85 (2H, m, $-\text{CH}_2\text{CH}_2\text{CN}$).

CH₂CH₂CN), 3.45 (1H, s, HO), 4.25 (2H, AB system, -CH₂OAc). ¹H-NMR (360 MHz, CDCl₃): δ_H 1.0 [3H, s, H₃C-C(3)], 1.62 [3H, s, H₃C-C(2)], 1.73 – 2.0 (2H, m, -CH₂CH₂CN), 2.13 (3H, s, H₃COO-), 2.7 -2.9 (2H, m, -CH₂CH₂CN), 2.95 [m, 1H, HC(4)], 3.9 (1H, s, HO), 4.2 – 4.3 (2H, AB-system, -CH₂OAc). ¹³C-NMR (90 MHz, CDCl₃): δ_C 15.1 [q, H₃C-C(3)], 15.2 (t, -CH₂CH₂CN), 22.1 (q, H₃C-CO-), 23.2 (t, CH₂-CH₂-CN), 24.1 [q, H₃C-C(2)], 44.9 [d, HC(4)], 48.2 [s, C(3)], 67.6 [t, -H₂C-C(3)], 107.2 [s, C(2)], 118.3 (s, CN), 173.4 (s, -COCH₃), 177.4 [s, C(5)]. HRMS (ESI, MeCN, H₂O): calcd for (C₁₂H₁₇NO₅ + Na): 278.0999; found 278.0994.

3-[(1S,2R)-2-Trichloroacetimido-oxymethyl-2,3-dimethyl-cyclopent-3-en-1-yl]-propionitrile (13). To alcohol **9** (370 mg, 2.07 mmol) in anhydrous CH₂Cl₂ (3 mL) was added trichloroacetoneitrile (373 mg, 2.6 mmol, 1.25 eq) and DBU (60 mg, 0.39 mmol) at 0°C under an argon atmosphere. The mixture was stirred for 1 h at 0°C. The solvent was evaporated and the residue was filtered through a short silica gel column (SiO₂, ICN Biomedicals 32 – 63 μm, 60 Å, CH₂Cl₂/EtOAc = 10 : 1). Evaporation of the eluent in vacuo of an oil pump yielded trichloroacetimido nitrile **13** as a colorless, viscous oil. Yield (590 mg, 88 %). TLC (SiO₂, CH₂Cl₂/EtOAc = 10 : 1) : R_f 0.58. IR (KBr, $\tilde{\nu}_{\max}$, cm⁻¹): 3310 (s, NH), 2940 (s), 2860 2805, 2220 (m, CN), 1650 (s, C=N), 1450, 1430, 1380, 1355, 1300, 1230, 1080, 1010, 955, 930, 820. ¹H-NMR (360 MHz, CDCl₃): δ_H 0.97 [3H, s, H₃C-C(2')], 1.60-1.70 [1H, m, HC(1')], 1.70 [3H, s, H₃C-C(3')], 1.89 - 2.08 (2H, m, -CH₂CH₂CN), 2.22 - 2.53 [4H, m, -CH₂CH₂CN and H₂C(5')], 4.11 (2H, AB-system, -CH₂OR), 5.36 [1H, s, HC(4')], 8.30 (1H, s br, NH). MS (EI, 70eV, direct inlet, 230 °C): *m/z* (%) 326 (4, M⁺), 324 (14), 322 (15, M⁺, ³⁵Cl), 186 (15), 161 (8), 148 (100), 133 (5), 121 (30), 107 (78), 91 (17), 79 (11). MS (CI, direct inlet, 75 °C) : *m/z* (%) positive : 327 (26), 325 (95), 323 (100, [M+H]⁺), 341 (8, [M+NH₄⁺]); negative : 357 (100, [M+Cl]⁻). [α]_D²⁰ + 54°, c = 1.1 in MeOH. HRMS (EI) : calcd for (C₁₃H₁₇³⁵Cl₃N₂O) 322.0406 ; found 322.0388 (R = 10000).

3-[(1S, 6R, 7S, 9R)-1,6-Dimethyl-3-trichloromethyl-9-iodo-2-aza-4-oxabicyclo[4,3,0]non-2-en-7-yl]-propionitrile (14). Trichloroacetimido nitrile **13** (200 mg, 0.62 mmol), iodine (470 mg, 1.85 mmol) and sodium hydrogen carbonate (160 mg, 1.9 mmol) in acetonitrile (3 mL) was stirred under exclusion of light for 4 h. To the mixture was added dichloromethane (10 mL) and sodium thiosulfate (250 mg in 5 mL H₂O). The organic layer was separated, washed with water (2 x 5 mL), dried by filtration through cotton wool, and the solvent was evaporated. Flash chromatography [SiO₂, ICN Biomedicals 32 – 63 μm, 60 Å, petroleum ether/EtOAc = 2 : 1] of the crude product afforded after evaporation of the eluent a colorless oil, which on crystallization from diethylether/*n*-hexane yielded **14** as colorless needles. Yield (205 mg, 74 %). Mp 80 °C (*n*-hexane). TLC (SiO₂, petrol ether/EtOAc = 2 : 1) : R_f 0.38. HPLC (Li Chrosorb RP 18, MeOH/H₂O = 9 : 1, 1 mL/min, refractometer dedection) : t_R 3.7 min. IR (KBr, $\tilde{\nu}_{\max}$, cm⁻¹): 2940 (s), 2920 (s), 2860, 2220 (m, CN), 1655 (s, C=N), 1455, 1430, 1410, 1380, 1320, 1280, 1240 (s), 1220 (s), 1150, 1135, 1080, 1030, 1000, 920, 895, 830. ¹H-NMR (360 MHz, CDCl₃): δ_H 1.06 [3H, s, H₃C-C(6)], 1.50 [3H, s, H₃C-C(1)], 1.54 - 1.66 (1H, m, HC(7)), 1.82 – 1.92 [2H, m, -H₂C-CH₂-CN], 2.02 – 2.11 [1H, m, HHC(8)], 2.25 – 2.34 [1H, m, -H₂C-CHH-CN], 2.38 – 2.47 [1H, m, -H₂C-CHH-CN], 2.81 – 2.90 [1H, m, HHC(8)], 3.89 [1H, d *J* 11.7 Hz, HHC(5)], 4.10 [1H, d *J* 11.7 Hz, HHC(5)], 4.43 – 4.47 [1H, dd, *J* 7.5, *J* 8.5, HIC(9)]. ¹³C-NMR (90.5 MHz, CDCl₃): δ_C 14.7 [q, H₃C-C(6')], 16.2 [t, -CH₂-CH₂-CN], 26.4 [t, -CH₂CH₂CN], 27.8 [q, H₃C-C(1')], 32.5 [t, H₂C(8')], 40.7 [d, HIC(9')], 41.9 [s, C(6')], 42.0 [d, C(7')], 65.8 [s, C(1')], 68.6 [t, C(5')], 91.8 [s, -CCl₃], 118.7 [s, CN(1)], 150.6 [s, C(3')]. MS (EI, 70eV, direct inlet, 160 °C): *m/z* (%) 448 (2, M⁺ ³⁵Cl), 323 (20), 321 (95, M⁺ - I), 287 (22), 214 (32), 160 (97), 119 (100), 108 (74), 96 (42), 81 (44), 67 (43), 53 (42). MS (DCI, direct inlet) : *m/z* (%) positive : 453 (52), 451 (97), 449 (100, [M+H]⁺) ; negative: 483 (100, [M+Cl]⁻). [α]_D²⁰ + 86.2°, c = 0.6 in MeOH. HRMS (EI) : calcd for (C₁₃H₁₆³⁵Cl₃IN₂O) 447.9372 ; found 447.9373 (R = 10000).

3-[(1S, 6R, 7S)-1,6-Dimethyl-3-trichloromethyl-2-aza-4-oxabicyclo[4,3,0]-non-2,8-dien-7-yl]-propionitrile (15). Bicyclic iodide **14** (4.26 g, 9.48 mmol) and DBU (24.41 g, 0.19 mol) in anhydrous benzene (163 mL) was refluxed for 15 h. After cooling down to rt, diethyl ether (100 mL) was added and the mixture was washed with

7 N hydrochloric acid (150 mL). The aqueous layer was extracted with diethyl ether (3 x 50 mL). The combined organic phases, were washed with water (200 mL), dried by filtration through cotton wool and the solvent was evaporated. The crude product was purified by flash chromatography [SiO₂, ICN Biomedicals 32 – 63 µm, 60 Å, petroleum ether/EtOAc = 3 : 1]. The light-yellow oil was crystallized from diethyl ether/*n*-hexane to give **15** as colorless crystals. Yield: (1.94 g, 64 %). Mp 102 - 103 °C (diethylether/*n*-hexane). TLC (SiO₂, petrol ether/EtOAc = 2 : 1): R_f 0.33. HPLC (Li Chrosorb RP 18, MeOH/H₂O = 9 : 1, 1 mL/min, refractometer dedection) : t_R 3.2 min. IR (KBr, $\tilde{\nu}_{\max}$, cm⁻¹): 3040, 2990, 2970 (s), 2940 (s), 2895, 2860, 2225 (CN), 1620, 1470, 1450, 1430 (s), 1400, 1370, 1345, 1250, 1250, 1180, 1140, 1120, 1030, 1005, 990, 960, 950, 890, 855, 840, 820. ¹H-NMR (360 MHz, CDCl₃): δ_H 1.07 [3H, s, H₃C-C(6)], 1.30 [3H, s, H₃C-C(1)], 1.58 - 1.68 (1H, m, -HHC-CH₂-CN], 1.94 – 2.03 [1H, m, -HHC-CH₂-CN], 2.32 – 2.42 [2H, m, -CH₂-CH₂-CN], 2.46 – 2.54 [1H, m, HC(7)], 3.86 [1H, d *J* 10.5 Hz, HC(5)], 3.93 [1H, d *J* 10.5 Hz, HC(5)], 5.72 [1H, dd, *J* 6.0, *J* 2.5, HC(8)], 5.98 [1H, dd, *J* 6.0, *J* 1.75, HC(9)]. ¹³C-NMR (90.5 MHz, CDCl₃): δ_C 14.8 [q, H₃C-C(6')], 16.1 [t, -CH₂-CH₂-CN], 25.3 [q, H₃C-C(1')], 26.6 [t, -CH₂CH₂CN], 42.5 [s, C(6')], 49.1 [d, C(7')], 63.0 [s, C(1')], 72.8 [t, C(5')], 91.9 [s, -CCl₃], 119.0 [s, CN(1)], 129.3 [d, C(8')], 140.1 [d, C(9')], 150.6 [s, C(3')]. MS (EI, 70eV, direct inlet, 230 °C): *m/z* (%) 322 (3), 320 (3, M⁺, ³⁵Cl), 305 (5), 285 (100, M⁺ - Cl), 251 (10), 175 (12), 134 (15), 119 (34), 107 (11), 95 (13), 79 (19), 55 (11), 41 (14). [α]_D²⁰ HRMS (EI): calcd for (C₁₃H₁₅³⁵Cl₃N₂O) 320.02348 ; found 320.02353 (R = 10000).

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This manuscript has been corrected by the author, checked by the scientific editor, and contains all necessary changes.

Supplementary Material

A chiral pool approach towards enantiopure building blocks for naturally occurring hydroporphyrins

Jens Bahrs^a, Maria Stapelbroek-Möllmann^b, Steven Harold Bleckwedel^c, and Franz-Peter Montforts^{*c}

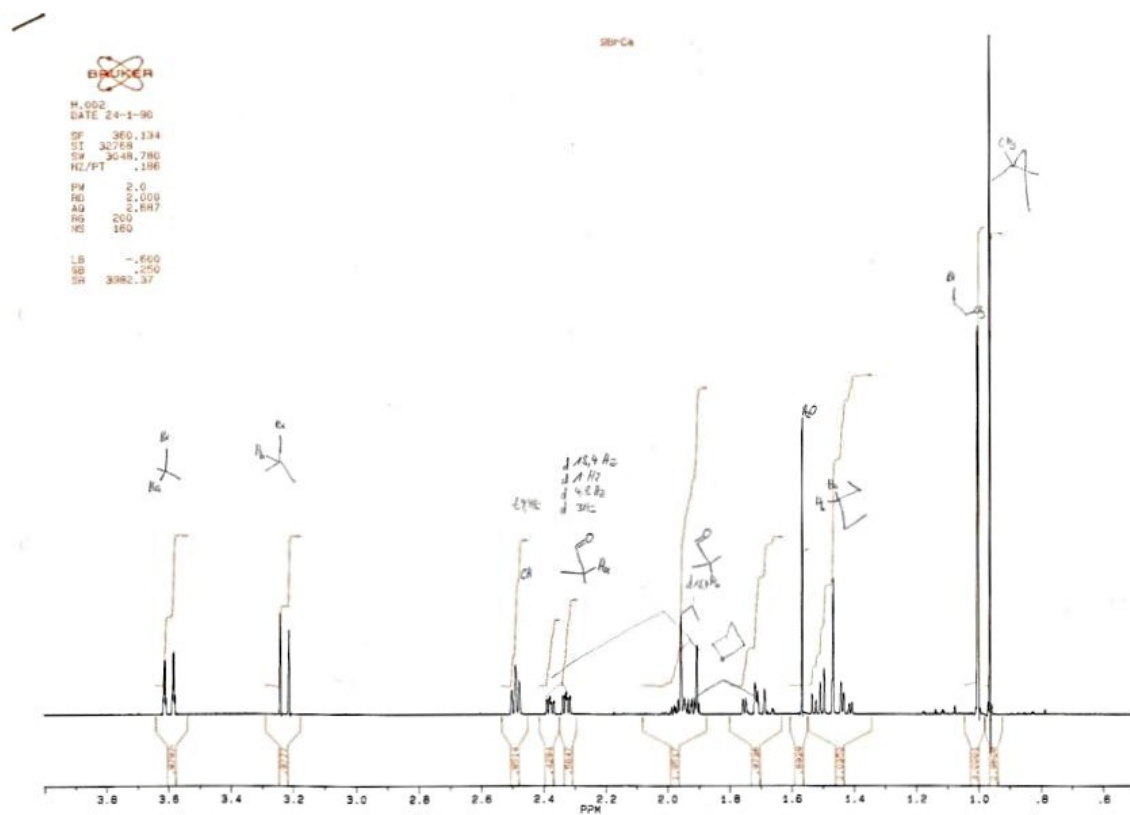
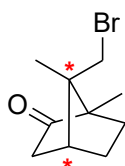
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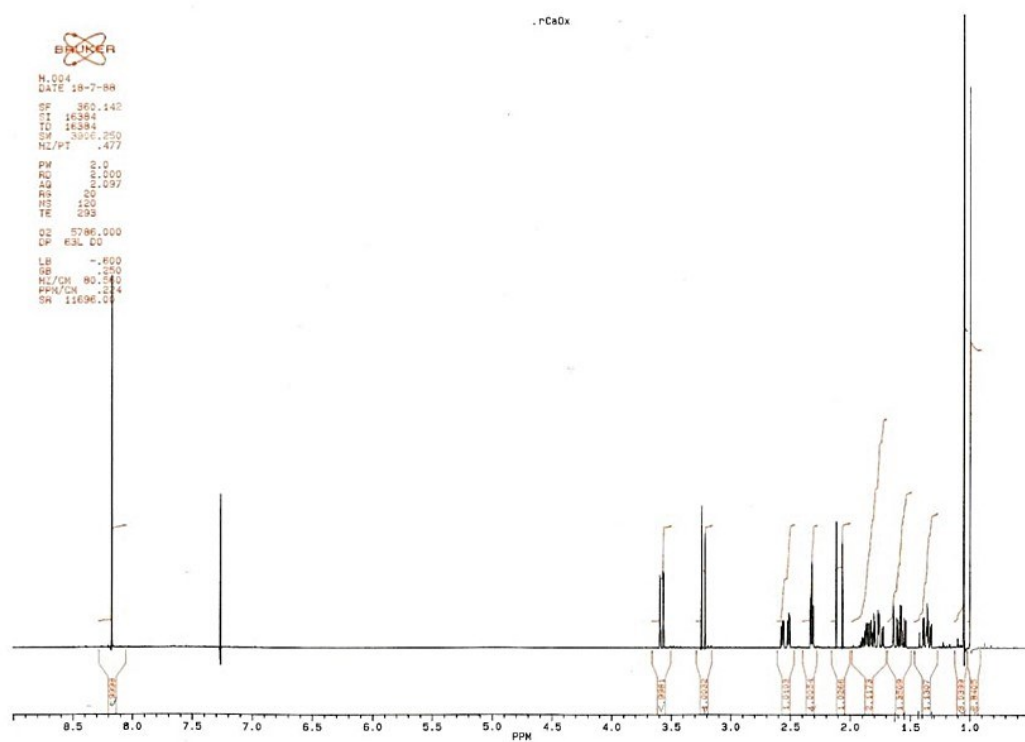
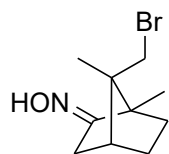
^bStandortentwicklungsgesellschaft Mansfeld-Südharz mbH, Ewald-Gnaustr. 1b,
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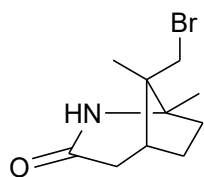
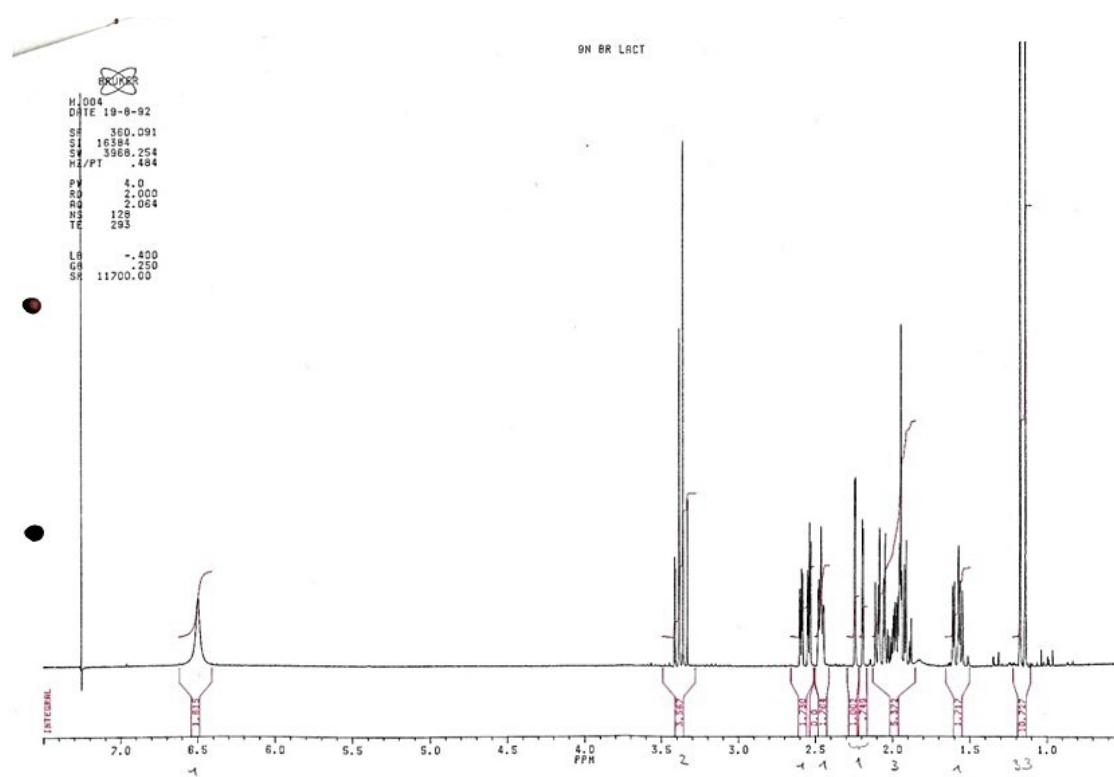
^cInstitute of Organic and Analytical Chemistry, FB2, University of Bremen, P.O. Box 33 04 40
28334 Bremen, Germany
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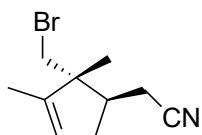
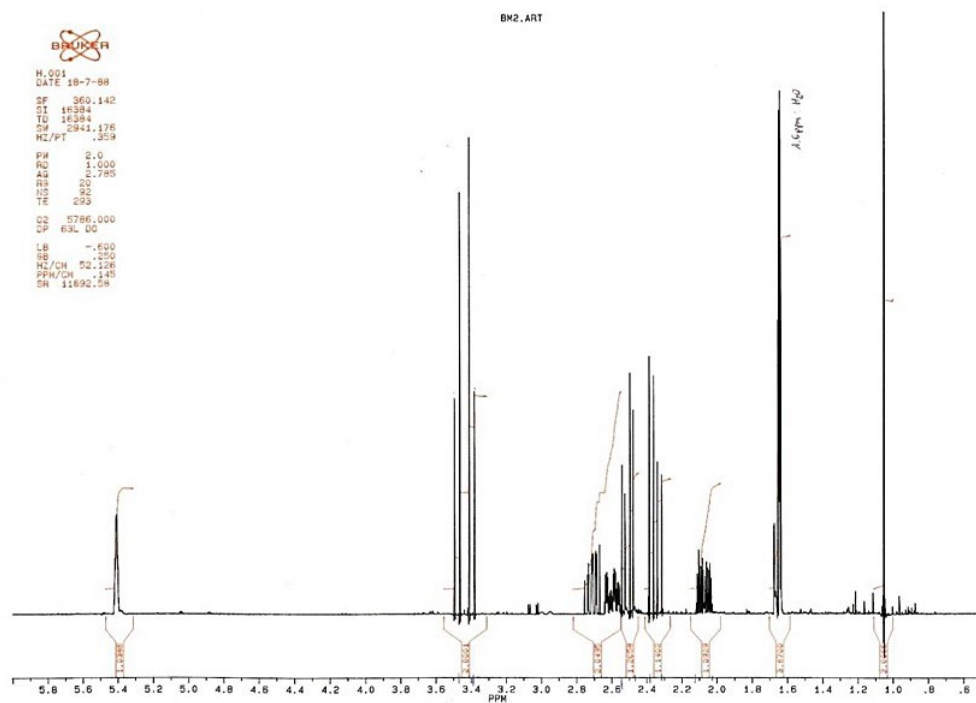
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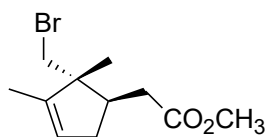
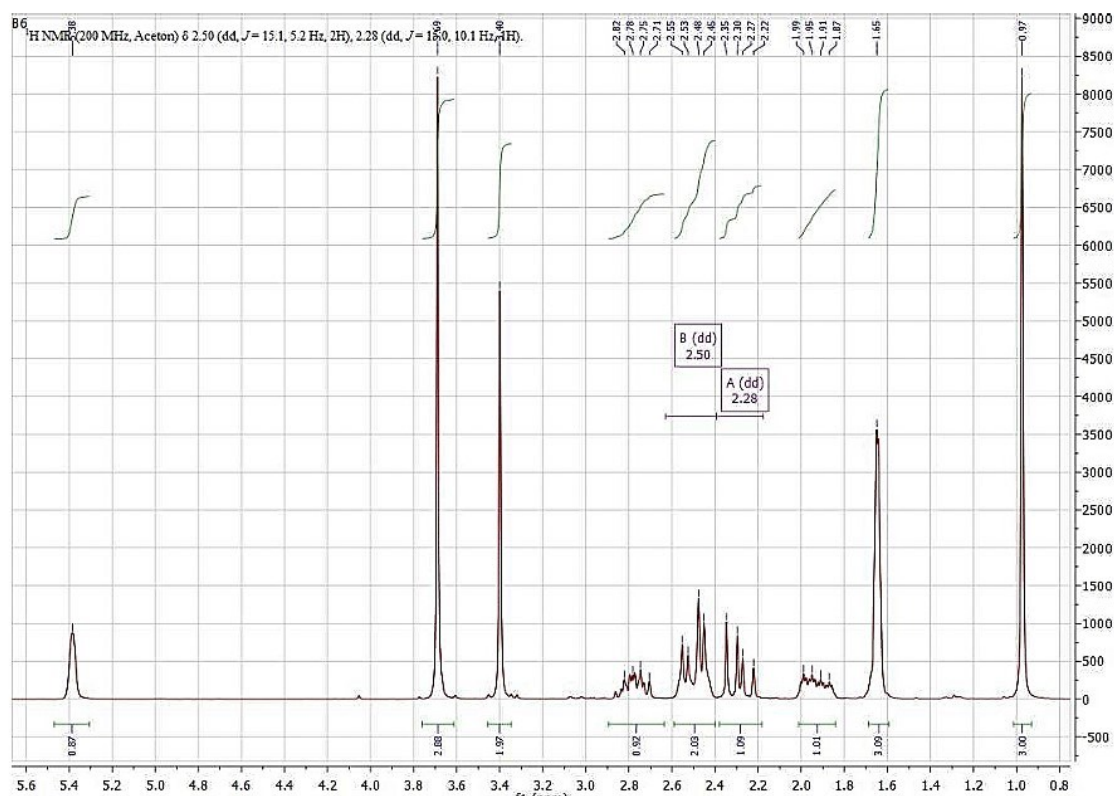
1. Compound 2	¹ H NMR spectrum	S1
2. Compound 3	¹ H NMR spectrum	S2
3. Compound 4	¹ H NMR spectrum	S3
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5. Compound 5a	¹ H NMR spectrum	S5
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10. Compound 9	¹ H NMR, ¹³ C NMR, HMBC, HSQC spectra	S10
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12. Compound 12a,b	¹ H NMR, 1D INEPT, ¹³ C NMR, COSY, HMBC, HSQC (360 MHz) and ¹ H NMR, NOESY (600 MHz) spectra	S12
13. Compound 15	¹ H NMR, ¹³ C NMR spectra	S13

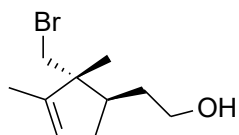
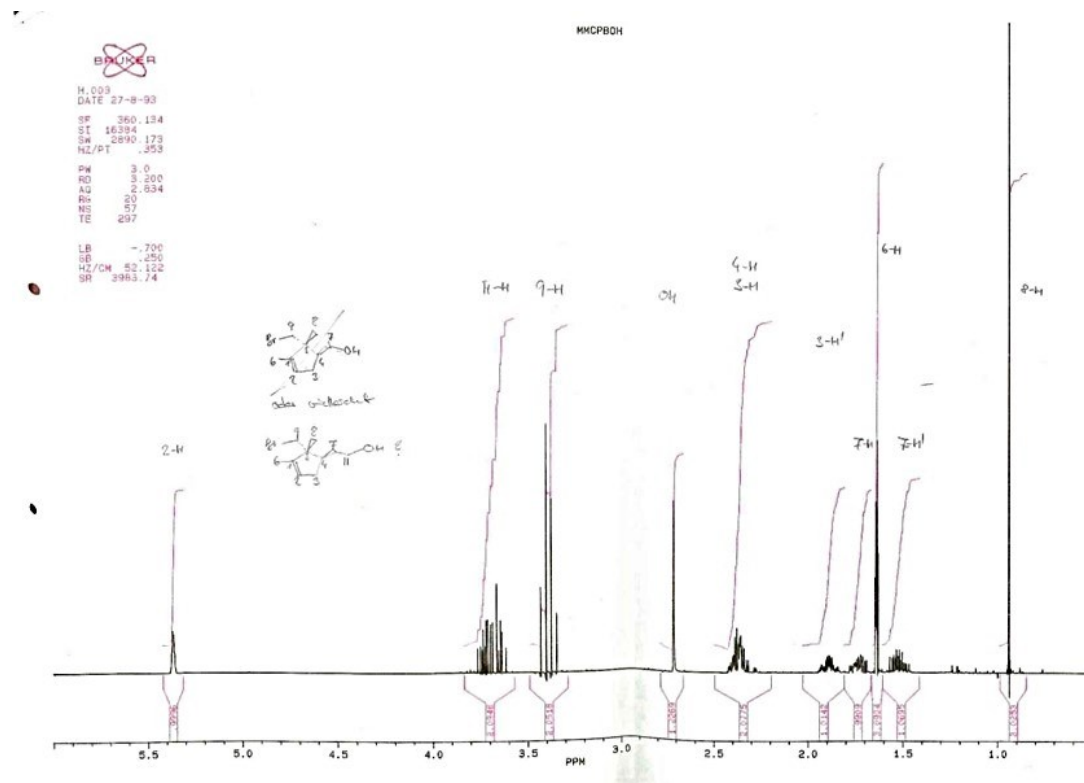


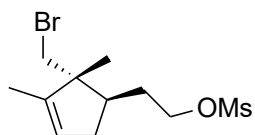
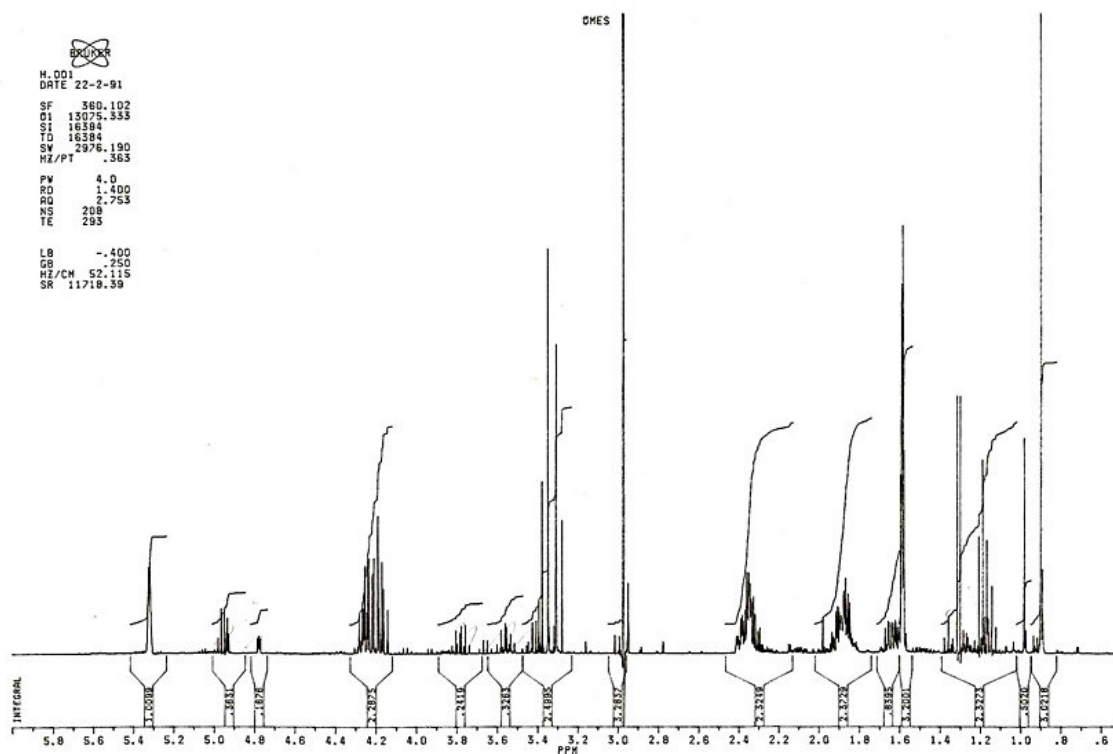


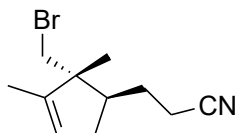
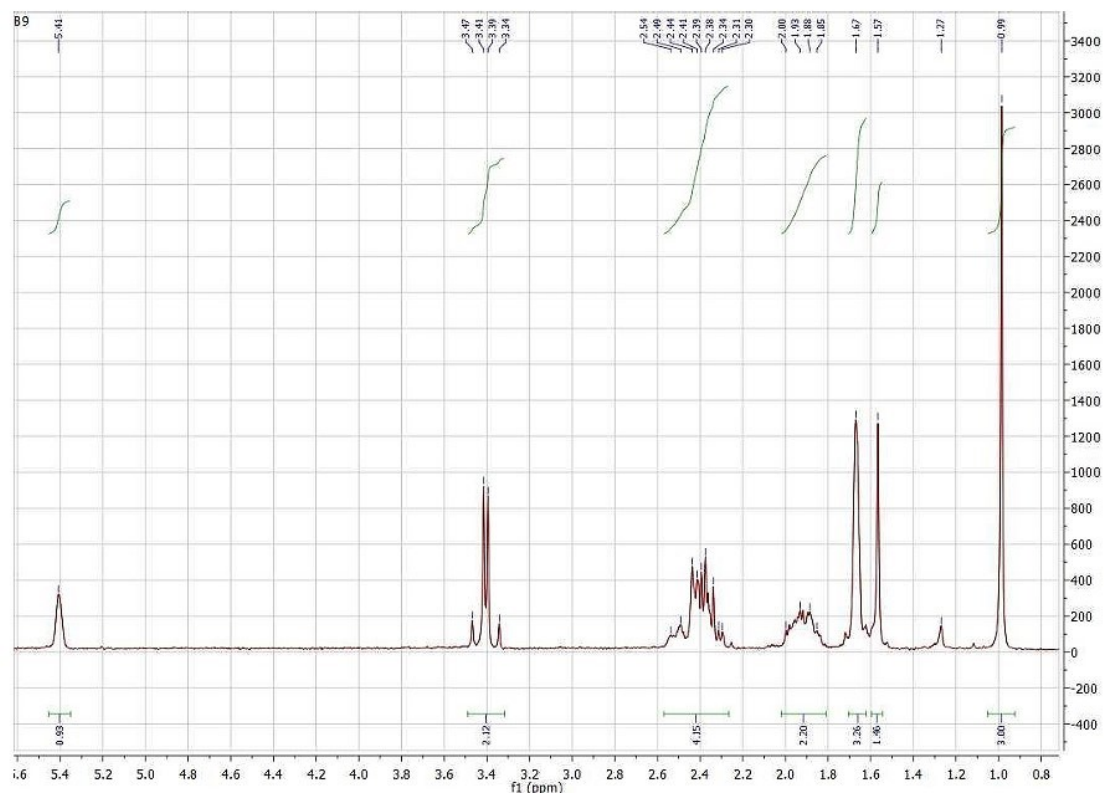
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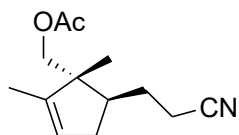
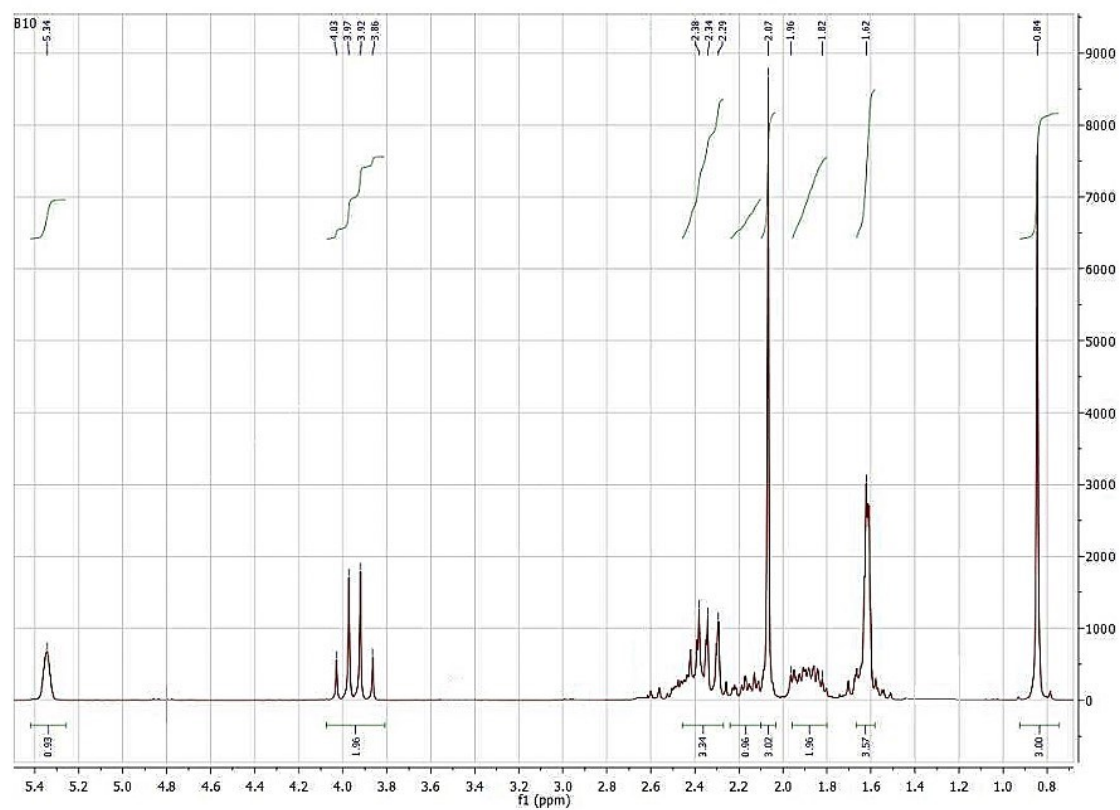
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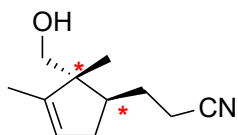
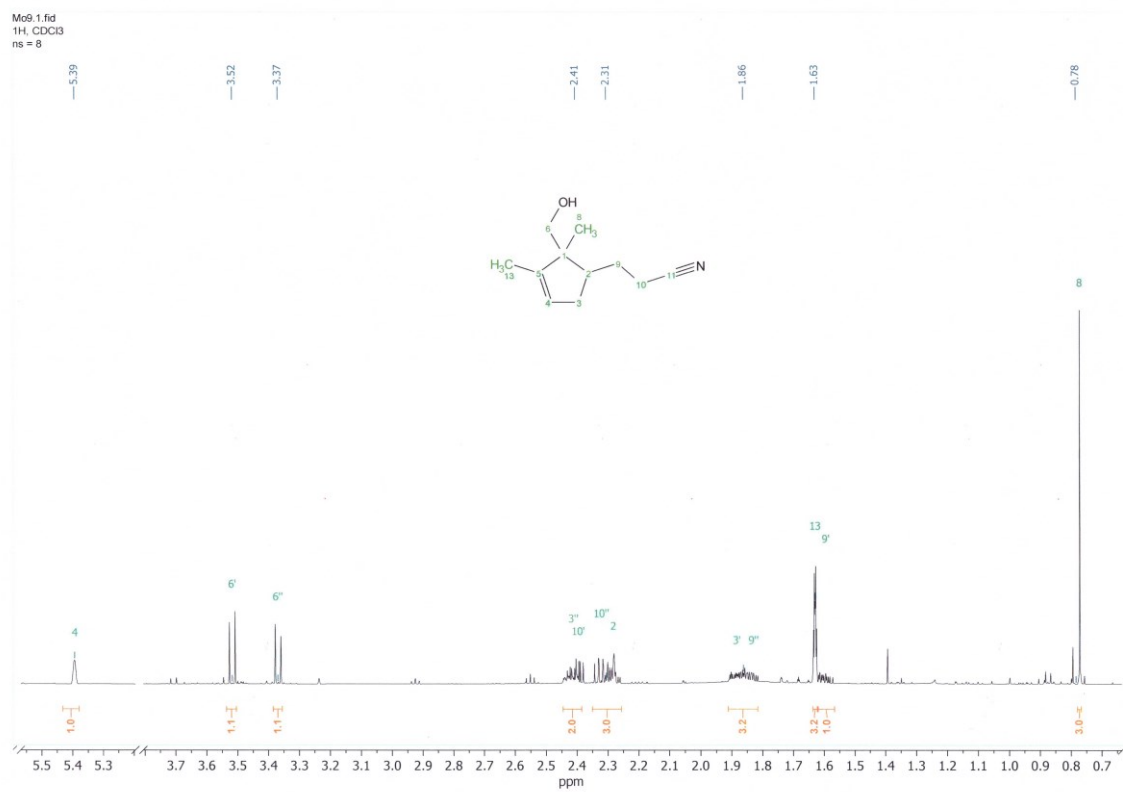
Compound 5a **^1H NMR (200 MHz, D_3COD_3)**

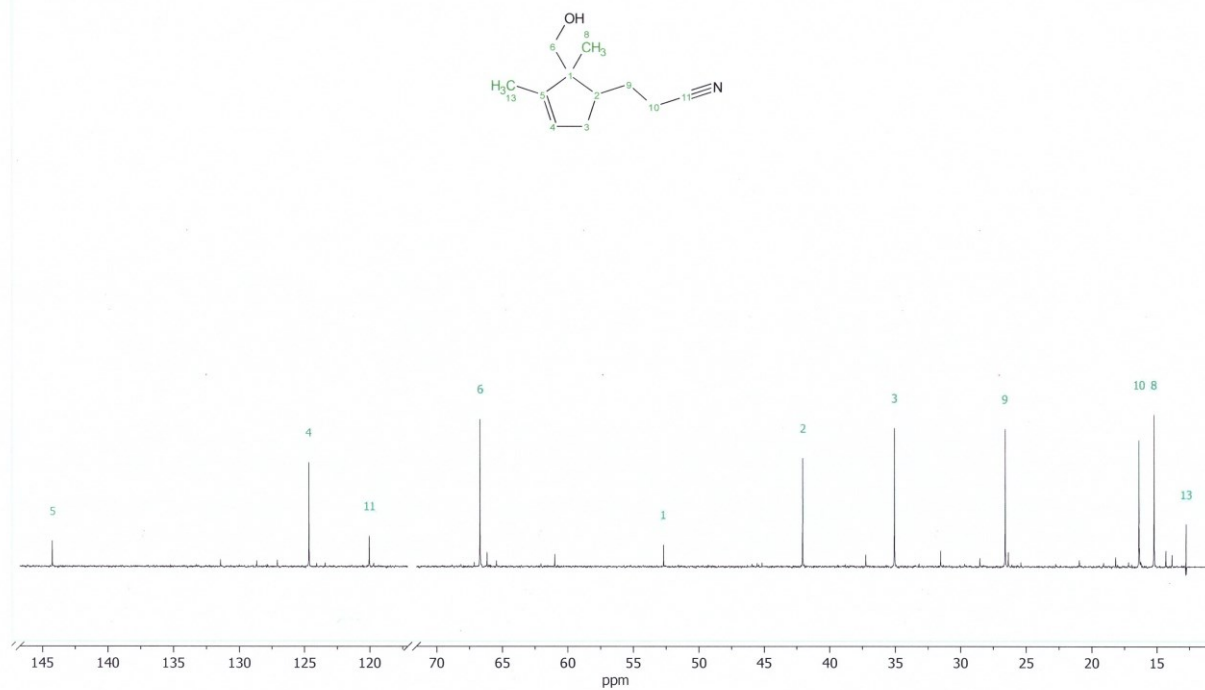
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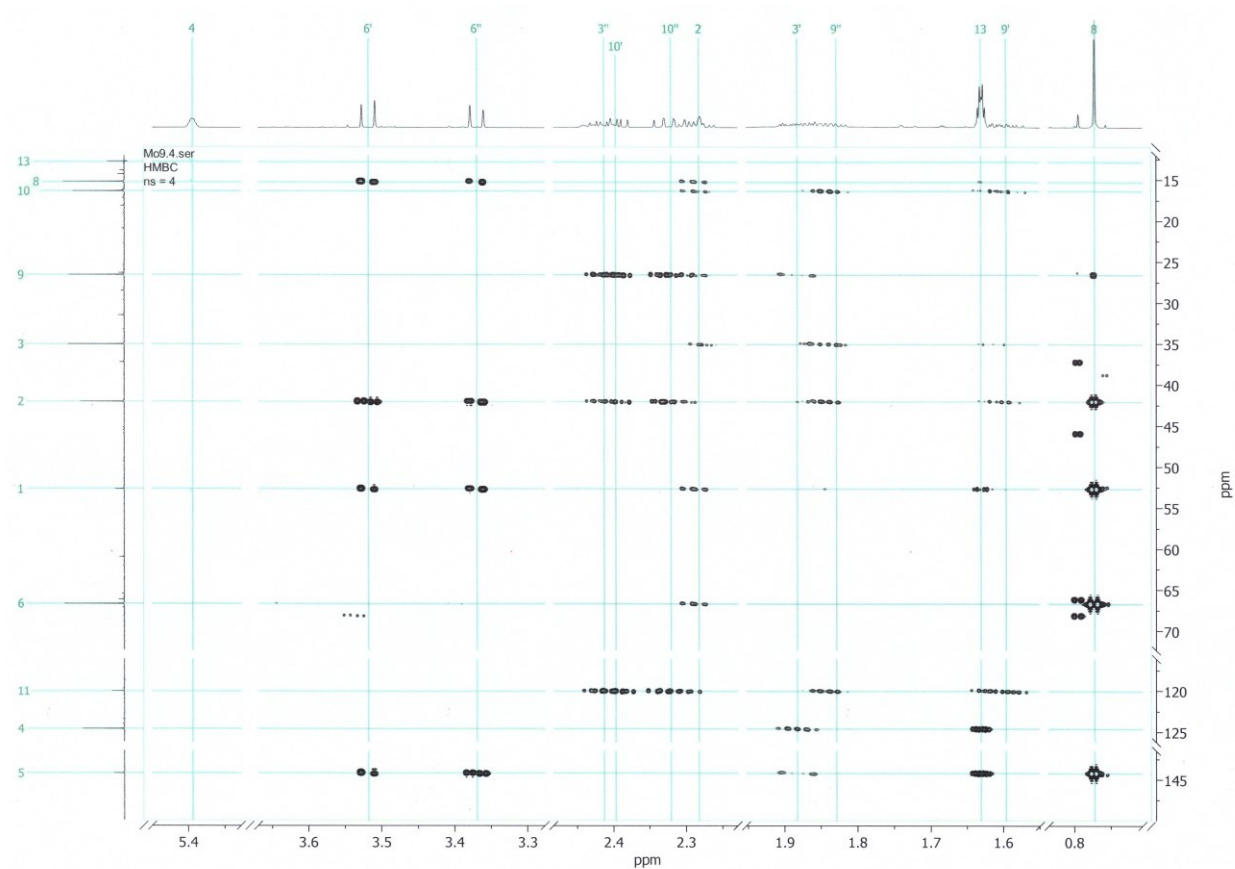
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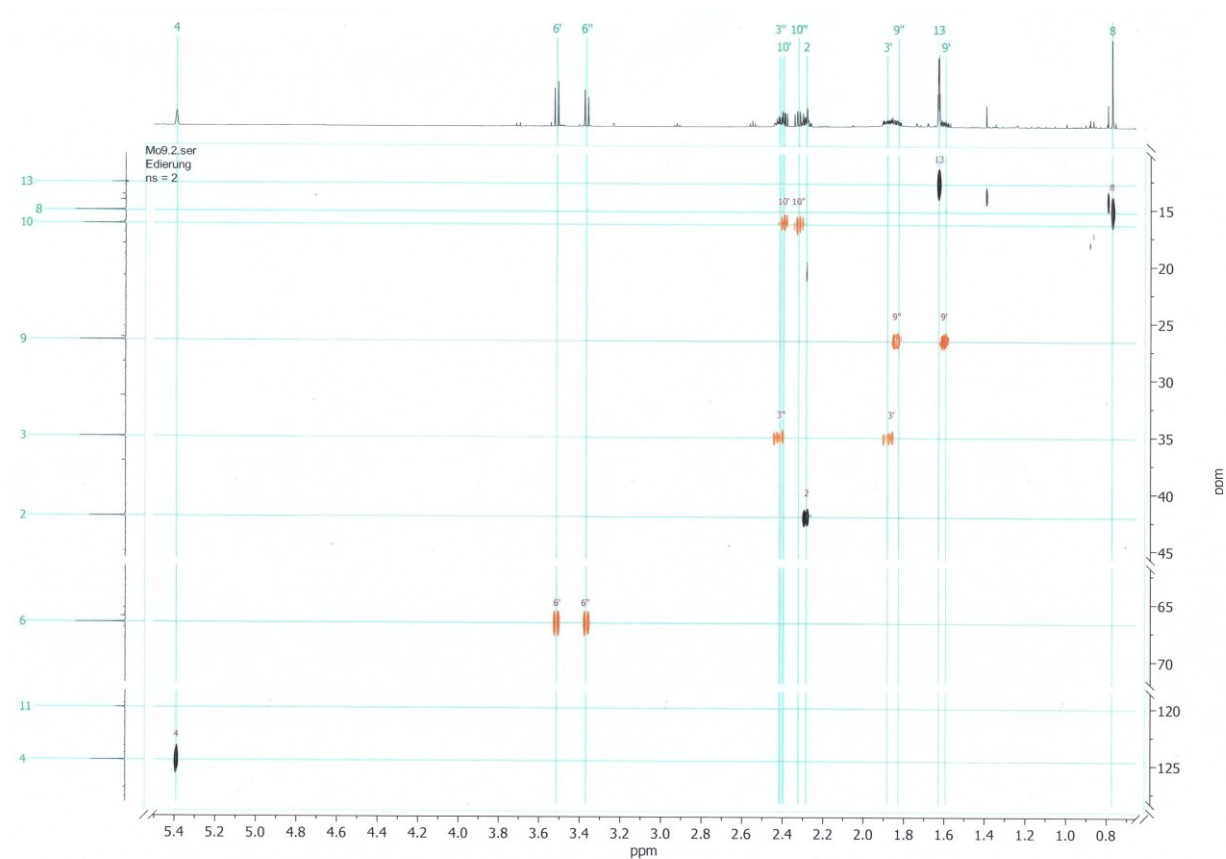
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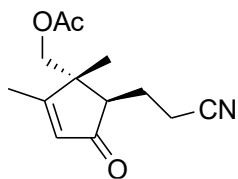
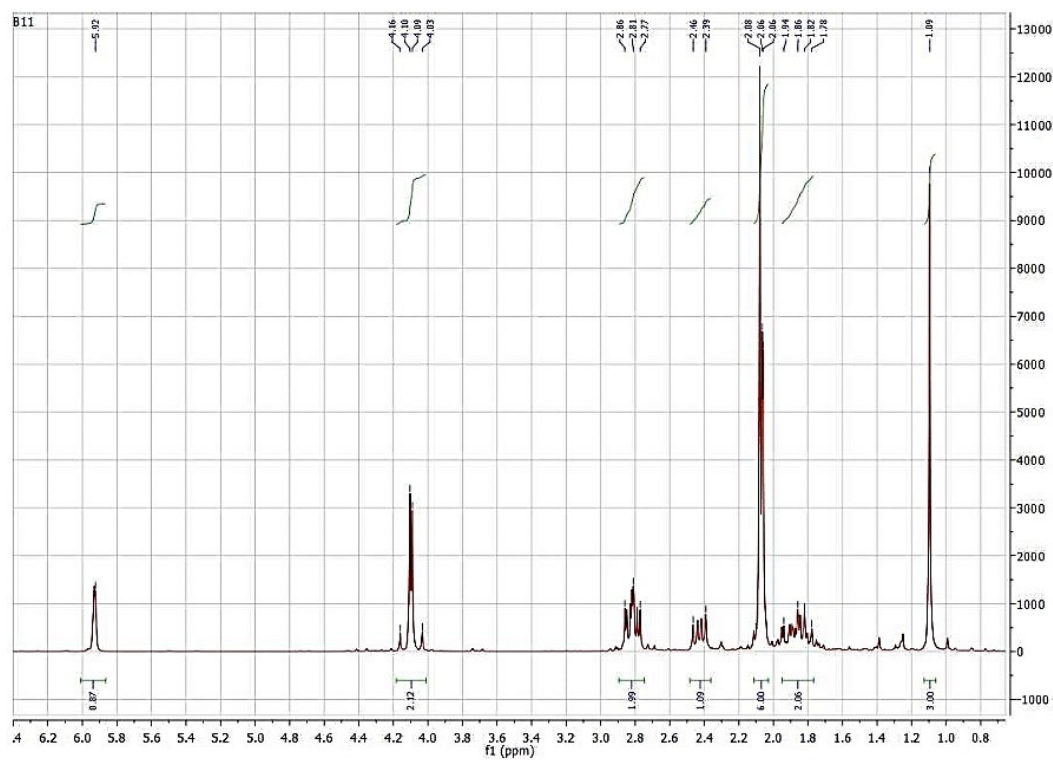
Compound 8 **^1H NMR (360 MHz, CDCl_3)**

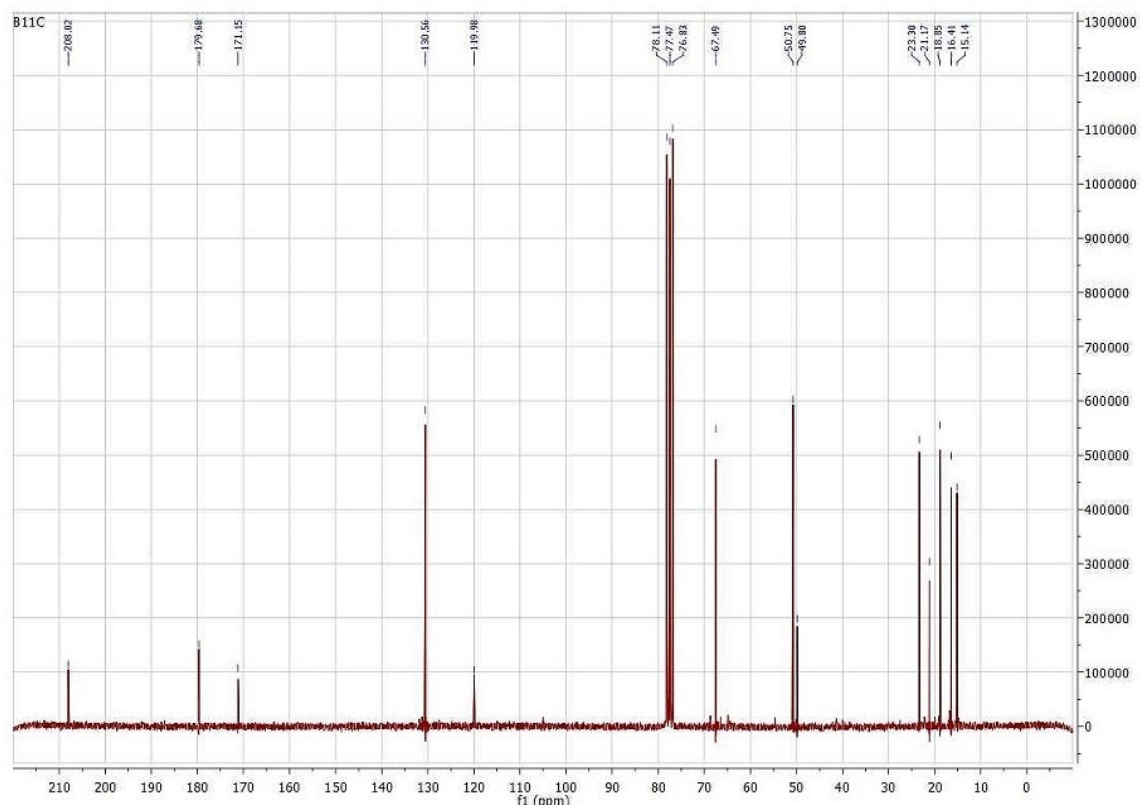
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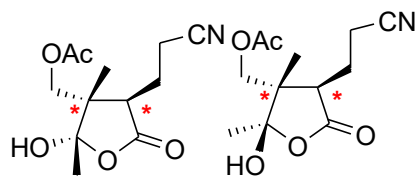
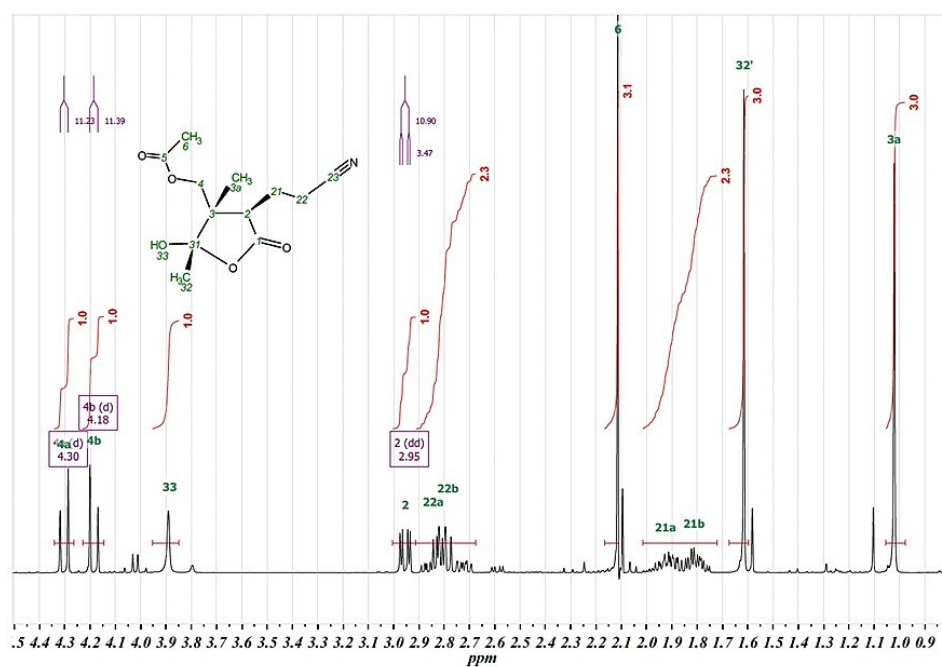
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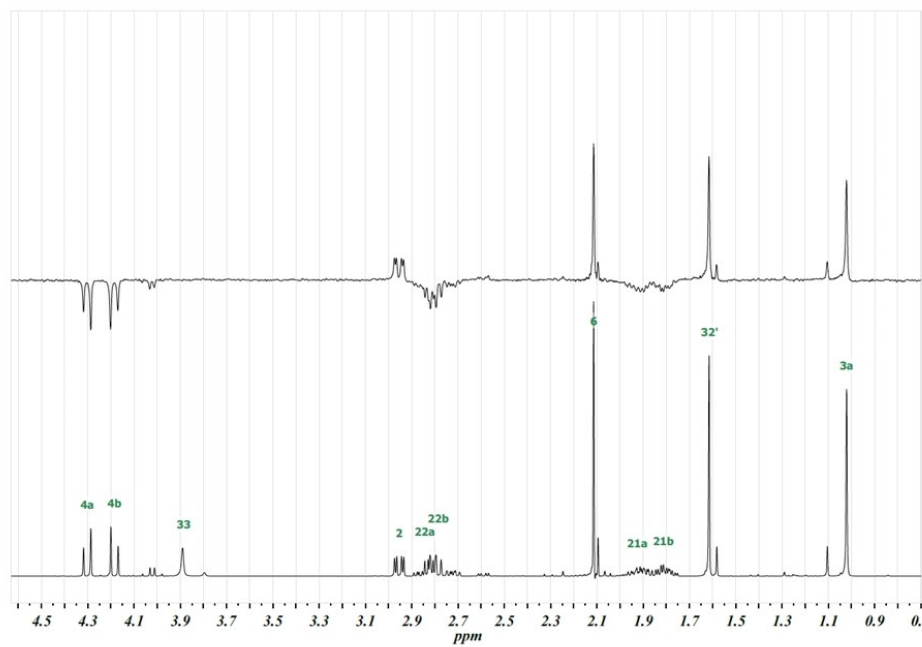
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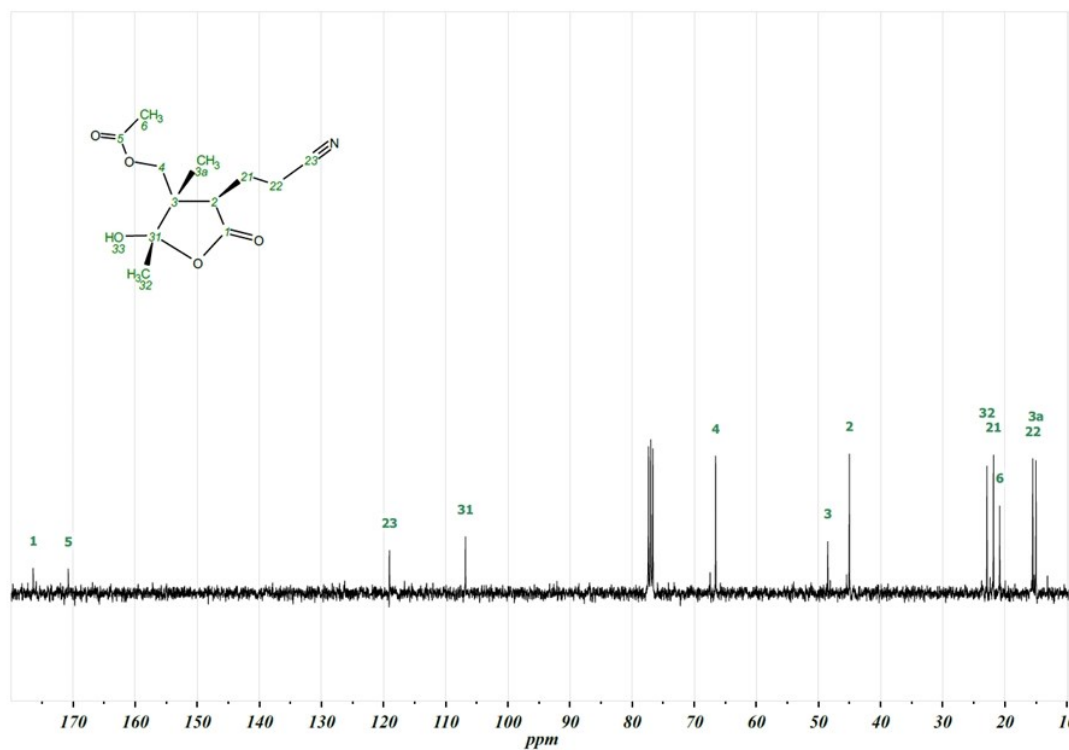
HSQC (600 MHz, CDCl₃, edited)

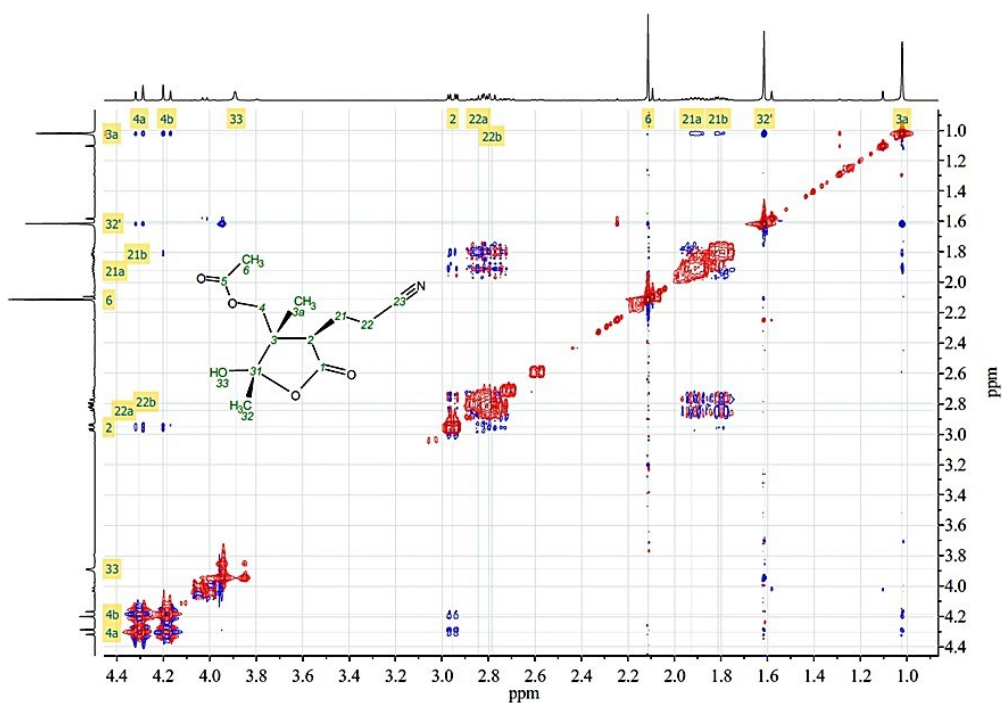
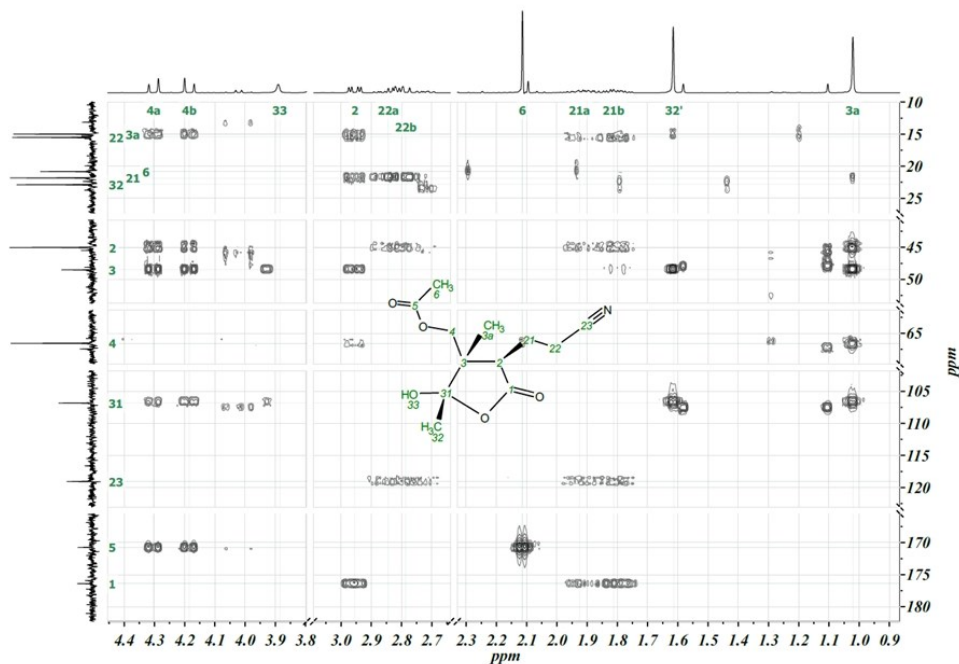
Compound 11**¹H NMR (360 MHz, CDCl₃)**

^{13}C NMR (90 MHz, CDCl_3)

Compound 12a,b**¹H NMR (360 MHz, CDCl₃)**

1D INEPT (360 MHz, CDCl₃)

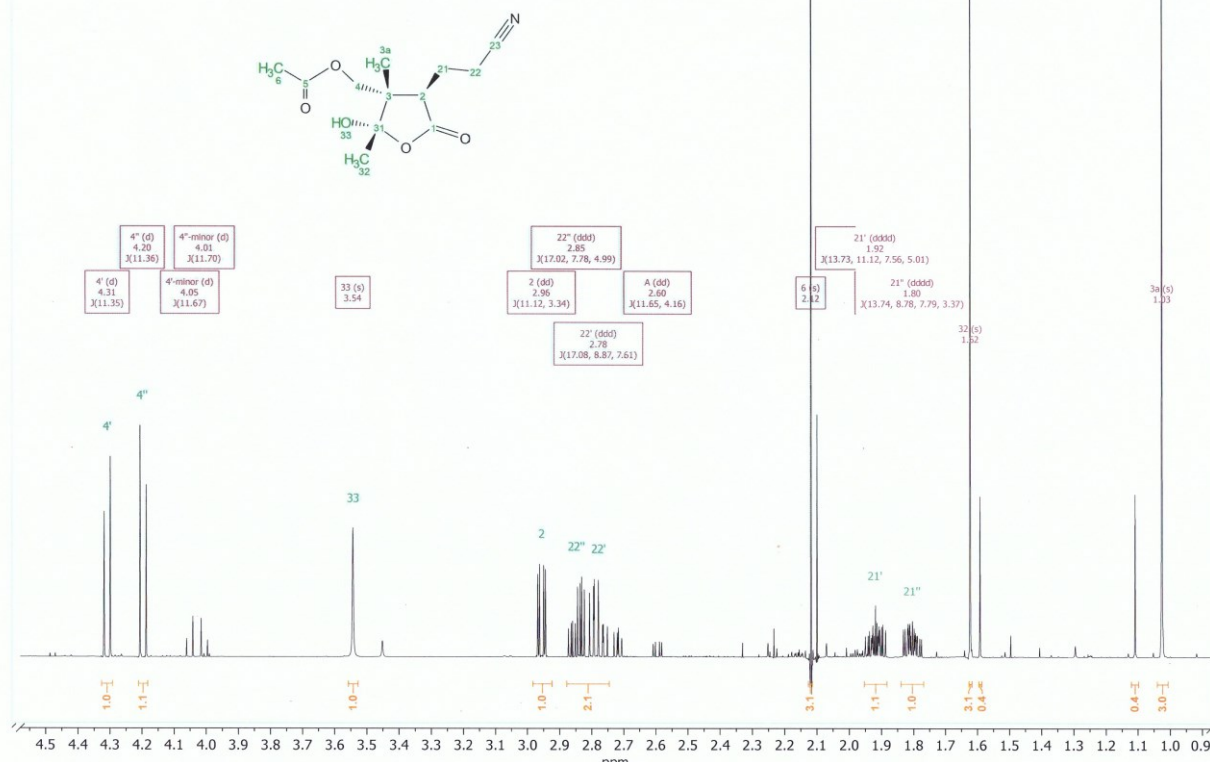
^{13}C NMR (90 MHz, CDCl_3)**COSY (360 MHz, CDCl_3)**

HMBC (360 MHz, CDCl₃)HSQC (360 MHz, CDCl₃)

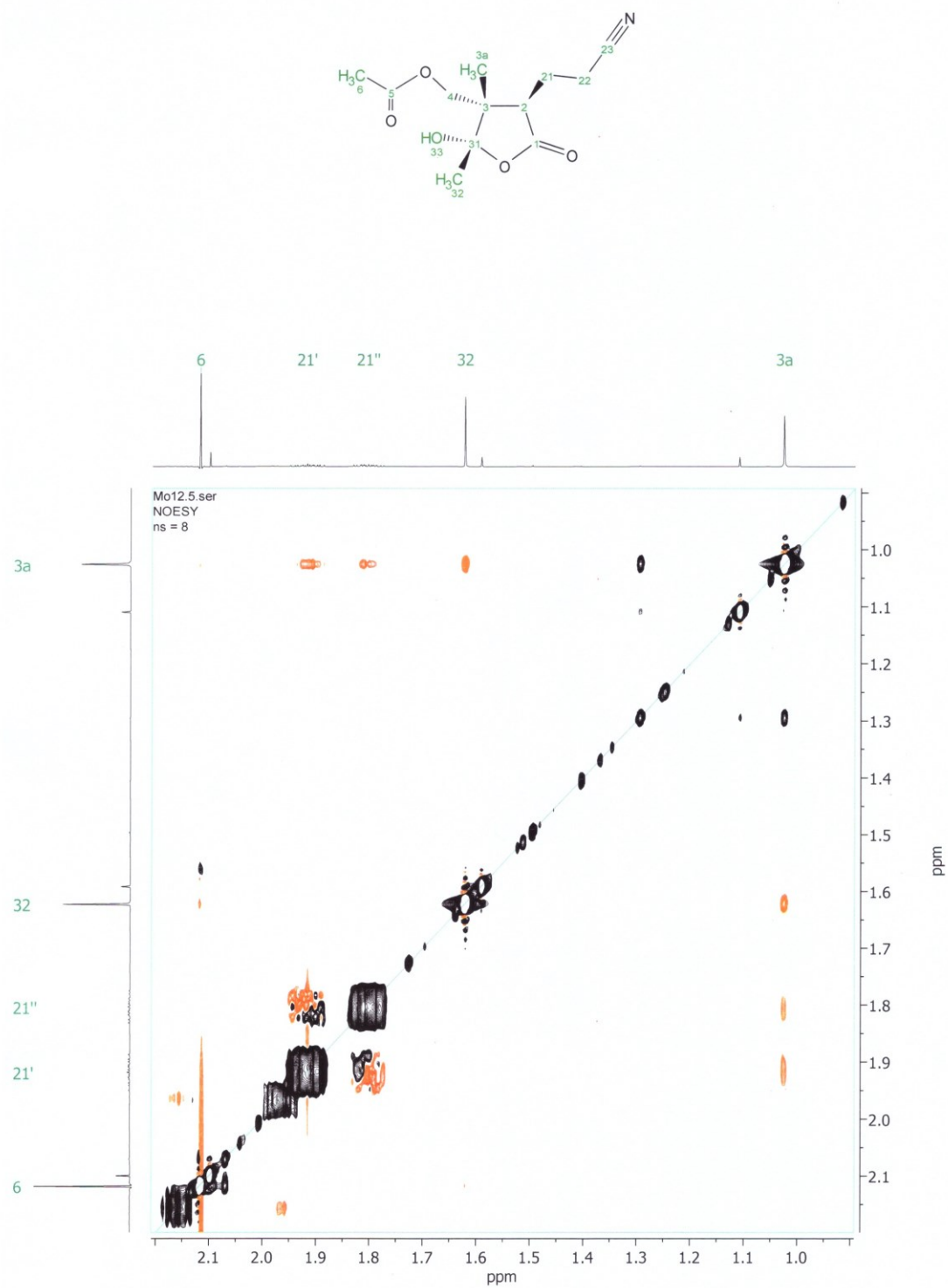


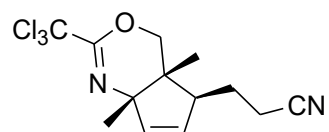
Mo12.1.fid
1H, CDCl3
ns = 8

¹H NMR (601 MHz, CDCl₃) δ 4.31 (d, *J* = 11.4 Hz, 2H, 4'), 4.20 (d, *J* = 11.4 Hz, 2H, 4''), 3.54 (s, 1H, 33), 2.96 (dd, *J* = 11.1, 3.3 Hz, 1H, 2), 2.85 (ddd, *J* = 17.0, 7.8, 5.0 Hz, 1H, 22'), 2.78 (ddd, *J* = 17.1, 8.9, 7.6 Hz, 1H, 22''), 2.12 (s, 3H, 6), 1.92 (dddd, *J* = 13.7, 11.1, 7.6, 5.0 Hz, 1H, 21'), 1.80 (dddd, *J* = 13.7, 8.8, 7.8, 3.4 Hz, 1H, 21''), 1.62 (s, 3H, 32), 1.03 (s, 3H, 3a).

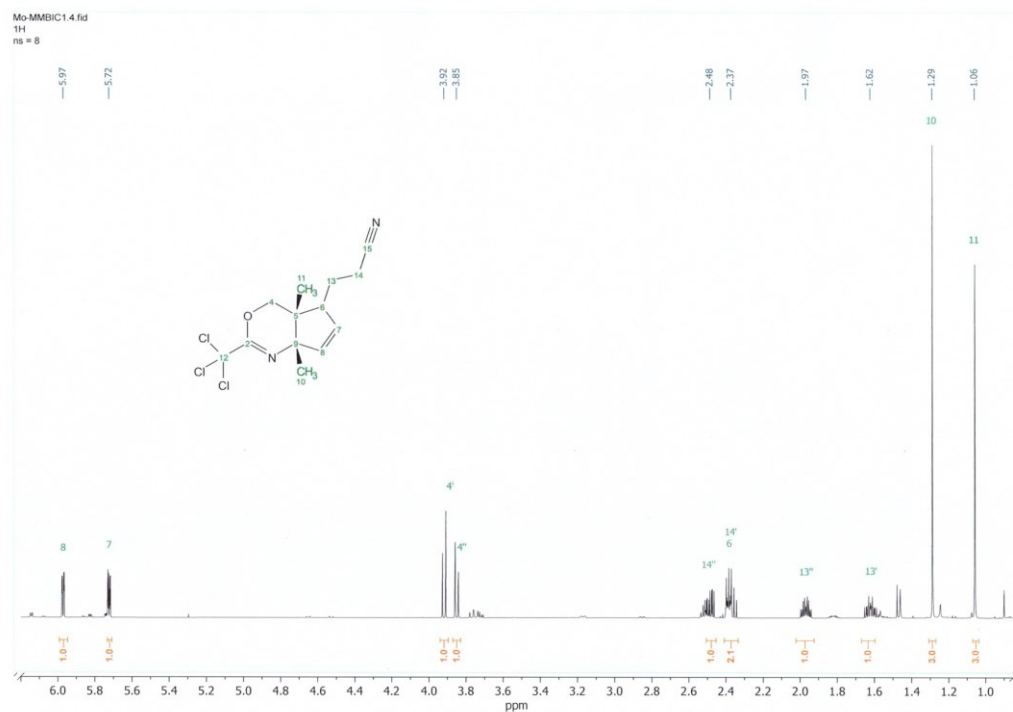


NOESY (600 MHz, CDCl₃)

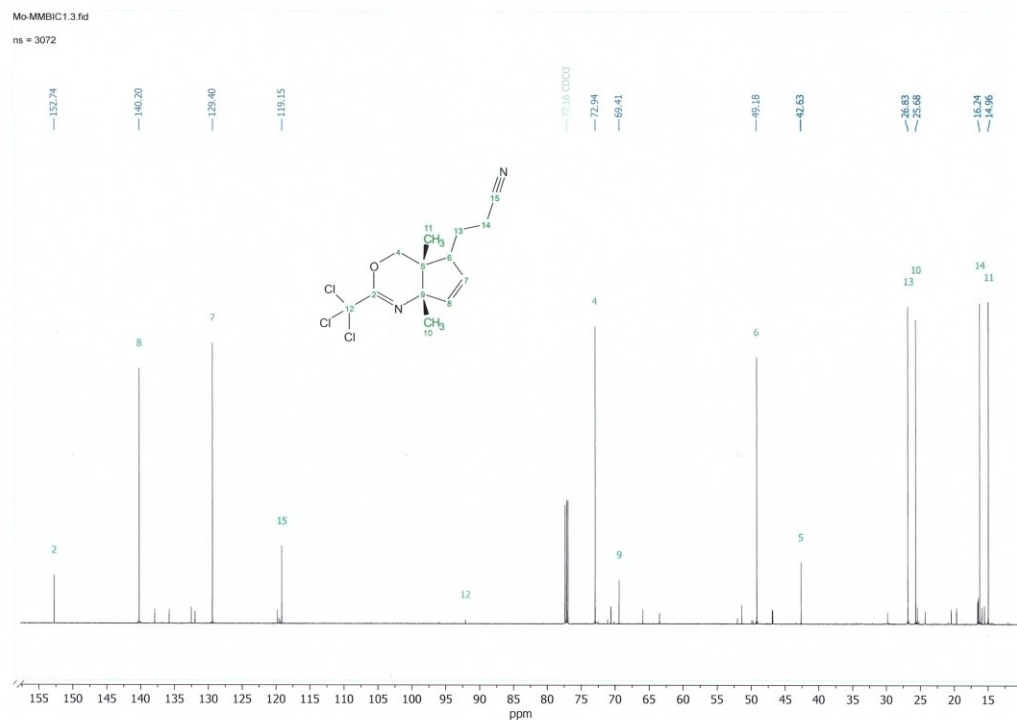
**Compound 15**



¹H NMR (600 MHz, CDCl₃)



¹³C NMR (150 MHz, CDCl₃)



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