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A TETRACARBONYL PAAL-KNORR APPROACH TO SEMICORRINS

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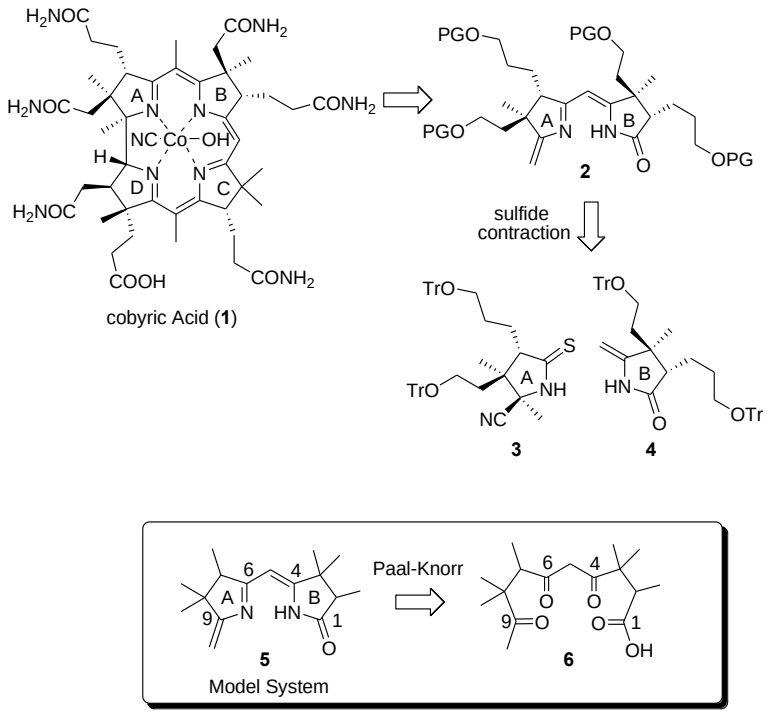
Abstract –A semicorrin model system was prepared *via* a novel twofold Paal-Knorr type cyclization of a tetracarbonyl precursor which was obtained from an aldol reaction between virtually identical partners, readily available from one and the same precursor.

INTRODUCTION

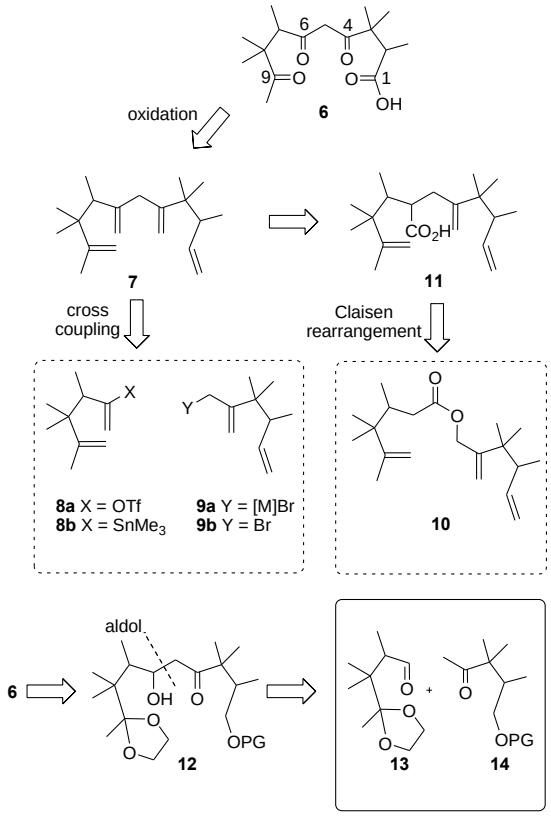
The syntheses of cobyric acid (**1**) by Woodward and Eschenmoser are true milestones in organic synthesis.[1] Despite extensive efforts[1h,2] no further synthesis has been accomplished over the last thirty years. In previous work we have developed a synthesis of the A-B-fragment **2** from monomers **3** and **4**.[2h] In continuation of this research we have been aiming for an approach to such semicorrinoids without taking recourse to the venerable *Eschenmoser* sulfide contraction.[3] More specifically, we opted for the incorporation of two nitrogen atoms into a tetra-carbonyl precursor in the last step. This double *Paal-Knorr* approach is new and was therefore tried on the stripped model system **5** (Scheme 1).



Scheme 1. Previous Retrosynthetic Disconnection[2h] and New Plan

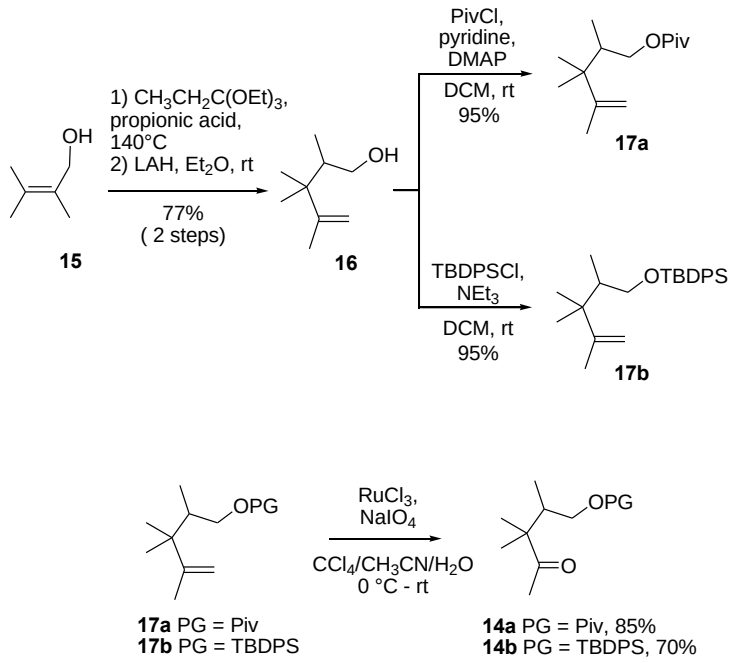
RESULTS AND DISCUSSION

Two different approaches to the tetracarbonyl precursor **6** were initiated. For instance, **6** was accessed *via* a global oxidation of tetra-olefin **7**, which we thought to prepare from fragments **8** and **9**. As outlined in Scheme 2, either fragment might be employed as an organometallic species (**8b**, **9a**) or as an electrophile (**8a**, **9b**) in transition-meta-mediated cross couplings. Several attempts were undertaken to achieve such a transformation, however, none was successful. Therefore, instead of the *intermolecular* coupling of the fragments, we used a Claisen rearrangement reaction, thus making the CC-bond formation by an *intramolecular* process. After extensive experimentation, the rearrangement of ester **10** to acid **11** could be achieved *albeit* in low yield. Moreover, the conversion of the carboxyl function into an *exo*-methylene group turned out to be rather messy. Therefore, we dropped the idea of the tetra-olefin precursor and turned to compound **12**, which was an obvious candidate for an aldol reaction between **13** and **14**. One major advantage of this approach lies in the possibility to capitalize on symmetry as the fragments **13** and **14** have identical carbon skeletons, though with different oxidation levels.



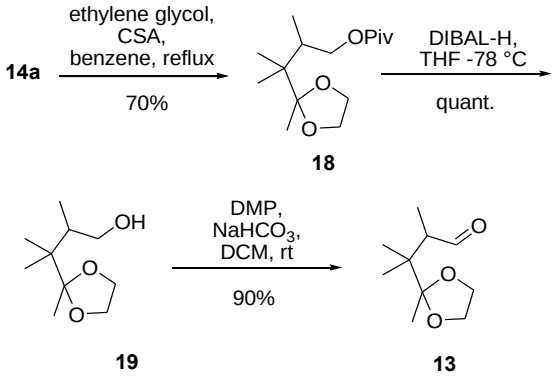
Scheme 2. Retrosynthetic Considerations.

The synthesis of ketone **14** started with a *Johnson-Claisen* rearrangement[4] of allylic alcohol **15**.[5] The crude ester was reduced to alcohol **16**, which was obtained in 77 % yield over 2 steps. After protecting the primary alcohol as a pivaloate (**17a**) or as a TBDPS ether (**17b**), oxidation with ruthenium (III) chloride and sodium periodate[6] led to methyl ketones **14a** and **14b** (Scheme 3).



Scheme 3. Synthesis of Ketones **14a** and **14b**.

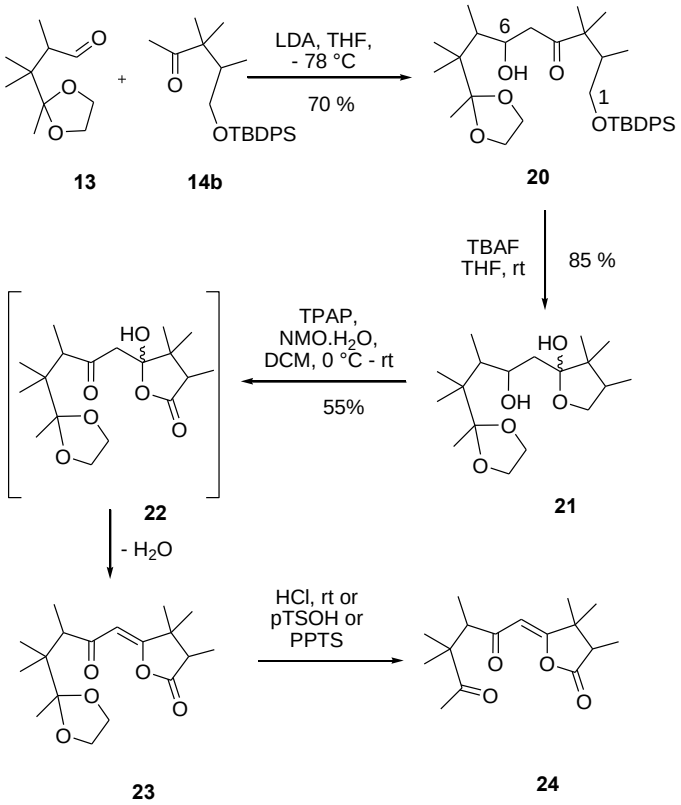
For the synthesis of aldehyde **13**, the carbonyl group in **14a** was ketalized and the pivaloyl group was removed with DIBAL-H to give alcohol **19**. The ketalization failed with the TBDPS-ether **14b**, which decomposed under acidic conditions. Oxidation of **19** with Dess-Martin periodinane (DMP) furnished aldehyde **13** in an overall yield of 63 % from ketone **14a** (Scheme 4).



Scheme 4. Synthesis of Aldehyde **13**.

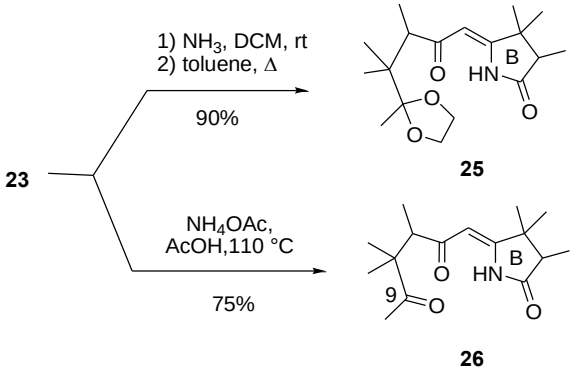
For the aldol reaction, ketone **14b** was deprotonated with 1.5 equivalents of LDA and treated with aldehyde **13** to give aldol adduct **20** in 70% yield. The subsequent deprotection of the silyl group was accomplished with TBAF in THF at room temperature and led to hemiketal **21**. Other deprotection conditions such as HF · pyridine in THF or ammonium fluoride in MeOH resulted in the elimination of the 6-hydroxy group. For the oxidation of **21** to the labile ketolactone **22**, best results were obtained using 10 mol% tetrapropylammonium perruthenate (TPAP) and 10 equivalents of *N*-methylmorpholine *N*-oxide

monohydrate ($NMO \cdot H_2O$) as a cooxidant in DCM at 0 °C.[7] Under these conditions water was eliminated to give enol lactone **23** directly. A number of other oxidation protocols (*e.g.* Dess-Martin periodinane or chromium reagents) led to decomposition. Next, the deprotection of the ketal function was investigated under acidic conditions (*e.g. p*-toluenesulfonic acid, 0.1 M HCl, AcOH), which, however, failed to give any defined product (Scheme 5).



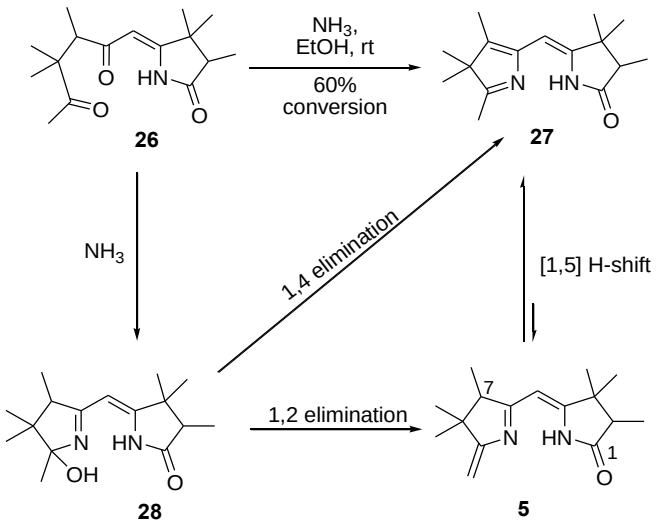
Scheme 5. Synthesis of Enol Lactone **23**.

Therefore, we decided to incorporate nitrogen into the ring B prior to ketal removal. Thus, lactone **23** was treated with ammonia followed by azeotropic removal of water to give pyrrolidinone **25**. Deprotection of the ketal group of **25** with acid failed. However, on heating **23** in acetic acid containing excess ammonium acetate (Scheme 6), 1,4-diketone **26** was obtained in good yield.



Scheme 6. Formation of pyrrolidinone **25** and 1,4-diketone **26**.

With 1,4-diketone **26** in hand the missing nitrogen was inserted into the A-ring with ammonia in ethanol at room temperature. The reaction was monitored by ^{1}H-NMR. After 16 h approximately 30% of the starting material was consumed and after additional 80 h 60% conversion was achieved. By thorough ^{1}H-NMR analysis the product was identified as semicorrin **27** (Scheme 7). Based on similar results by *Stevens*[8] and *Eschenmoser*,[9] we reason that 1,2-elimination of water from adduct **28** could have generated semicorrin **5**. Then, a [1,5] hydrogen shift leads to tautomer **27**, which could also have been formed from **28** *via* 1,4-elimination of water. In a related case, *Stevens et al* have observed[8] that the equilibrium between tautomers such as **27** and **5** is fully established, however, with inevitable epimerization at C-7. Nevertheless, epimerization is also observed in *Eschenmoser's* sulfide contraction,[1e-g] whereas, regrettably, this problem was not addressed in *Jacobi's* model studies.[2c-g]



Scheme 7. Synthesis of semicorrin **27**.

In conclusion, we have developed a twofold *Paal-Knorr* approach towards a semicorrin model system. Extension of this simple methodology to the synthesis of A-B-semicorrin **2** is ongoing and will be reported in due course.

EXPERIMENTAL

General

All reactions were carried out in flame-dried glassware under argon atmosphere. Solvents were purified by distillation over the agents indicated: Dichloromethane (DCM) (P_4O_{10}), Et_2O (Na), THF (Na), MeOH (Mg). NEt_3, diisopropylamine and TMSCl were distilled over CaH_2 prior to use. Pivaloyl chloride was purified by distillation prior to use. All commercially available compounds (Aldrich, FLUKA, Acros) were used without further purification. Monitoring of the reactions was carried out by thin layer chromatography (TLC) with E. Merck silica gel 60-F^{254} plates. Flash column chromatography was

performed with Merck silica gel (0.04-0.63 μm, 240-400 mesh) with ethyl acetate and hexane mixtures as eluent. NMR spectra were recorded on a Bruker Avance DRX 400 spectrometer. NMR spectra were measured in $CDCl_3$ or C_6D_6 solution and are referenced to ^1H, δ = 7.26; ^{13}C, δ = 77.16 ($CHCl_3$) and ^1H, δ = 7.15; ^{13}C, δ = 128.62 (C_6H_6) respectively. All ^1H and ^{13}C shifts are given in ppm (s = singlet; d = doublet; t = triplet; q = quadruplet; m = multiplet; bs = broad signal). Coupling constants *J* are given in Hz. Proton and carbon assignment was confirmed, when possible, by correlated spectroscopy (COSY, HSQC, HMBC). Stereochemical assignment was confirmed by NOESY experiments. IR spectra were recorded as thin films on a silicon disc on a Perkin-Elmer 1600 FT-IR spectrometer. Mass spectra were measured on a Micromass, trio 200 Fisions Instrument. High resolution mass spectra (HRMS) were performed with a Finnigan MAT 8230 with a resolution of 10000.

Starting Materials: 2,3-Dimethylbut-2-en-1-ol (**15**) was synthesized according to a previously published procedure.[5]

Synthesis of 2,3,3,4-tetramethylpent-4-en-1-ol (16)

A three neck round bottom flask equipped with a distillation apparatus was charged with 2,3-dimethylbut-2-en-1-ol (**15**) (17.3 g, 172 mmol, 1.00 eq), triethyl orthopropionate (745 mL, 3.75 mol, 22.0 eq) and propionic acid (1.00 mL, cat.). The resulting mixture was stirred at 140 °C for 2 h. After being cooled down to rt, 0.10 M HCl (200 mL) was added and the layers separated. The aqueous layer was extracted two times with Et_2O and the combined organic layer was washed sucessively with 0.10 M HCl, sat. aq. $NaHCO_3$ solution, water and brine. After drying over $MgSO_4$ and filtration, the solvent was removed *in vacuo*. Due to difficulties when subjected to distillation, the crude product was used directly in the next step. LAH (7.00 g, 184 mmol, 1.07 eq) was suspended in Et_2O (60 mL) and the crude ester, dissolved in Et_2O (160 mL), was added with stirring at such a rate that refluxing of the reaction mixture was maintained. After completion of the addition, the reaction mixture was stirred for additional 2 h at rt. The suspension was diluted with Et_2O (200 mL) and cooled down to 0 °C. H_2O (7 mL) was added cautiously, followed by 1 M NaOH (40 mL). After being stirred for 15 min vigorously at rt, the resulting mixture was filtered and the solvent was removed *in vacuo*. The crude product was purified by distillation at a reduced pressure to yield 18.8 g of alcohol **16** as a colorless oil (77% over 2 steps).

M_r = 142.24, $C_9H_{18}O$. bp 80 °C, 0.1 mbar. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 4.76 (m, 2H), 3.68 (dd, 1H, *J* = 10.7, 4.7 Hz), 3.28 (m, 1H), 1.81 (m, 1H), 1.75 (s, 3H), 1.00 (s, 3H), 0.98 (s, 3H), 0.89 (d, 3H, *J* = 6.9 Hz). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 153.4 (C), 109.9 (CH_2), 65.8 (CH_2), 41.5 (CH), 40.6 (C), 24.8 (CH_3), 22.7 (CH_3), 19.6 (CH_3), 12.5 (CH_3). **IR** ν_{max} 3346, 3091, 2970, 1635, 1455, 1376, 1362 cm^{-1}. **MS** (EI, 70 eV, 30 °C): *m/z*: 142, 127, 109, 97, 83, 69, 55. **HRMS** (70 eV, 30 °C): *m/z* calcd for $C_9H_{18}O$: 142.1354, found: 142.1358.

Synthesis of 2,2-dimethylpropionic acid 2,3,3,4-tetramethylpent-4-enyl ester (17a)

Pivaloyl chloride (3.80 mL, 30.9 mmol, 1.10 eq) was dissolved in DCM (60 mL) and treated with pyridine (2.72 mL, 33.7 mmol, 1.20 eq) with stirring at 0 °C. A solution of alcohol **16** (4.00 g, 28.1 mmol, 1.00 eq) and DMAP (cat.) in DCM (20 mL) was added slowly by a syringe. The resulting mixture was stirred at rt until completion (TLC). Sat. aq. NH_4Cl solution was added and the layers were separated. The aqueous layer was extracted three times with DCM and the combined organic layer was washed successively with 1 M HCl, sat. aq. $NaHCO_3$ solution and brine. After drying over $MgSO_4$, filtration and removal of the solvent *in vacuo*, the crude product was purified by column chromatography (hexane/EtOAc = 10:1) to yield **17a** (6.00 g, 95%) as a colorless oil.

M_r = 226.36, $C_{14}H_{26}O$. R_f = 0.6 (Hex/EE = 10:1). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 4.75 (m, 2H), 4.11 (dd, 1H, *J* = 10.8, 4.0 Hz), 3.72 (dd, 1H, *J* = 10.8, 8.9 Hz), 1.93 (m. 1H), 1.73 (s, 3H), 1.19 (s, 9H), 1.03 (s, 3H), 1.00 (s, 3H), 0.87 (d, 3H, *J* = 6.8 Hz). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 178.8 (C), 152.0 (C), 111.2 (CH_2), 67.3 (CH_2), 40.7 (C), 38.9 (C), 38.1 (C), 27.4 (CH_3, 3C), 24.2 (CH_3), 23.3 (CH_3), 19.5 (CH_3), 12.6 (CH_3). **IR** ν_{max} 3091, 2972, 1731, 1636, 1481, 1460, 1398, 1378 cm^{-1}. **MS** (EI, 70 eV, 30 °C): *m/z*: 226, 143, 124, 109, 83, 69, 57. **HRMS** (70 eV, 30 °C): *m/z* calcd for $C_{14}H_{26}O$: 226.1933, found: 226.1929.

Synthesis of 2,2-dimethylpropionic acid 2,3,3-trimethyl-4-oxo-pentyl ester (14a)

17a (6.00 g, 26.5 mmol, 1.00 eq) was dissolved in a mixture of CCl_4 (40 mL), MeCN (40 mL) and water (60 mL) and cooled to 0 °C. $NaIO_4$ (22.0 g, 106 mmol, 4.00 eq) and $RuCl_3$ (550 mg, 2.66 mmol, 0.10 eq) were added with stirring and the resulting mixture was stirred at rt until completion (TLC). After dilution with DCM and water, the layers were separated and the aqueous layer was extracted three times with DCM. After drying over $MgSO_4$, filtration and concentration under a reduced pressure, the residue was taken up in Et_2O and filtered through Celite®. The solvent was removed *in vacuo* and the crude product was purified by column chromatography (pentane/Et_2O = 10:1) to yield **14a** (5.14 g, 85%) as colorless oil.

M_r = 228.33, $C_{13}H_{24}O_3$, R_f = 0.35 (pentane/Et_2O = 10:1). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 4.03 (m, 1H), 3.79 (m, 1H), 2.25 (m, 1H), 2.15 (s, 3H), 1.18 (s, 9H), 1.09 (s, 3H), 1.07 (s, 3H), 0.89 (d, 3H, *J* = 6.9 Hz). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 213.1 (C), 178.7 (C), 66.6 (CH_2), 49.7 (C), 39.0 (C), 38.3 (CH), 27.3 (CH_3, 3 C), 25.5 (CH_3), 21.8 (CH_3), 20.9 (CH_3), 12.7 (CH_3). **IR** ν_{max} 2975, 1729, 1480, 1394, 1366 cm^{-1}. **MS** (EI, 70 eV, 30 °C): *m/z*: 228, 185, 126, 111, 83, 69, 57. **HRMS** (70 eV, 30 °C): *m/z* calcd for $C_{13}H_{24}O_3$: 228.1725, found: 228.1713.

Synthesis of 2,2-dimethylpropionic acid 2,3-dimethyl-3-(2-methyl-1,3-dioxolan-2-yl)butyl ester (18)

14a (5.00 g, 21.9 mmol, 1.00 eq), ethylene glycol (6.10 mL, 109 mmol, 5.00 eq) and CSA (cat.) in benzene (150 mL) were heated with stirring on a *Dean-Stark* trap at 110 °C for 4 h (TLC). After being

cooled down to rt, the reaction mixture was diluted with Et_2O and treated with sat. aq. $NaHCO_3$ solution. The layers were separated and the aqueous layer was extracted three times with Et_2O. The combined organic layer was washed with brine and dried over $MgSO_4$. After removal of the solvent *in vacuo*, the crude product was purified by column chromatography (hexane/EtOAc = 10:1) to yield **18** (4.20 g, 70%) as a colorless oil.

M_r = 272.38, $C_{15}H_{28}O_4$. R_f = 0.56 (hexane/EtOAc = 5:1). **^{1}H NMR** (400 MHz, C_6D_6): δ 4.82 (dd, 1H, *J* = 11.0, 3.7 Hz), 3.93 (dd, 1H, *J* = 11.0, 9.5 Hz), 3.40 (m, 4H), 1.98 (m, 1H), 1.2 (m, 12H), 1.05 (d, 3H, *J* = 6.8 Hz), 0.99 (s, 3H), 0.92 (s, 3H). **^{13}C NMR** (101 MHz, C_6D_6): δ 178.4 (C), 114.9 (C), 68.5 (CH_2), 65.4 (CH_2), 64.8 (CH_2), 44.7 (C), 39.4 (C), 39.2 (CH), 28.0 (CH_3, 3C), 22.8 (CH_3), 19.9 (CH_3), 18.8 (CH_3), 13.9 (CH_3). **IR** ν_{max} 2976, 2881, 1727, 1480, 1399, 1377, 1156 cm^{-1}. **MS** (EI, 70 eV, 30 °C): *m/z*: 257, 171, 109, 87. **HRMS** (70 eV, 30 °C): *m/z* calcd for $C_{14}H_{25}O_4$ (M - CH_3): 257.1753, found: 257.1761.

Synthesis of 2,3-dimethyl-3-(2-methyl-1,3-dioxolan-2-yl)butan-1-ol (19)

To a solution of **18** (4.20 g, 15.4 mmol, 1.00 eq) in DCM (100 mL) was added DIBAL-H (1.20 M in toluene, 28.5 mL, 33.9 mmol, 2.20 eq) with stirring at -78 °C. The resulting solution was stirred for 1 h (TLC) and then allowed to warm to rt. H_2O and 2 M NaOH solution were added and the layers were separated. The aqueous layer was extracted three times with DCM and the combined organic layer was washed with brine, dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* to yield alcohol **19** (2.90 g, quant.) as a colorless oil.

M_r = 188.26, $C_{10}H_{20}O_3$. R_f = 0.17 (Hex/EE = 5:1). **^{1}H NMR** (400 MHz, C_6D_6): δ 3.83 (m, 1H), 3.46 (m, 1H), 3.34 (m, 4H), 2.57 (bs, 1H), 1.75 (m, 1H), 1.22 (s, 3H), 0.99 (s, 3H), 0.91 (d, 3H, *J* = 7.0 Hz), 0.89 (s, 3H). **^{13}C NMR** (101 MHz, C_6D_6): δ 114.5 (C), 65.9 (CH_2), 65.1 (CH_2), 64.3 (CH_2), 44.4 (C), 42.3 (CH), 24.1 (CH_3), 19.9 (CH_3), 17.2 (CH_3), 14.2 (CH_3). **IR** ν_{max} 3417, 2982, 1455, 1374, 1221, 1158 cm^{-1}. **MS** (EI, 70 eV, 30 °C): *m/z*: 173, 158, 143, 127, 111, 99, 87, 69, 55. **HRMS** (70 eV, 30 °C): *m/z* calcd for $C_9H_{17}O_3$ (M – CH_3): 173.1178, found: 173.1175.

Synthesis of 2,3-dimethyl-3-(2-methyl-1,3-dioxolan-2-yl)butyraldehyde (13)

To a solution of alcohol alcohol **19** (1.10 g, 5.84 mmol, 1.00 eq) in DCM (60 mL) was added $NaHCO_3$ (2.45 g, 29.2 mmol, 5.00 eq) at 0°C. The resulting suspension was treated with stirring with DMP (3.22 g, 7.59 mmol, 1.30 eq) and stirring was continued at 0°C until completion (TLC). Et_2O was added and the suspension was treated with sat. aq. $NaHCO_3$ and sat. aq. $Na_2S_2O_3$ solution. After being vigorously stirred for 30 min at rt, the layers were separated and the aqueous layer was extracted three times with Et_2O. The combined organic layer was washed successively with sat. aq. $NaHCO_3$ solution, water and brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by column

chromatography (pentane/Et_2O = 5:1) to yield 980 mg of **13** (90%) as a colorless oil.

M_r = 186.25, $C_{10}H_{18}O_3$. R_f = 0.40 (hexane/EtOAc = 5:1). **^{1}H NMR** (400 MHz, C_6D_6): δ 9.61 (d, 1H, *J* = 4.8 Hz), 3.43 (m, 4H), 2.34 (dq, 1H, *J* = 7.3, 4.8 Hz), 1.05 (s, 3H), 0.91 (s, 3H), 0.85 (s, 3H), 0.81 (d, 3H, *J* = 7.3 Hz). **^{13}C NMR** (101 MHz, C_6D_6): δ 201.9 (CH), 114.6 (C), 65.6 (CH_2), 64.4 (CH_2), 51.2 (CH), 45.7 (C), 23.6 (CH_3), 19.9 (CH_3), 18.9 (CH_3), 10.7 (CH_3). **IR** ν_{max} 2973, 1770, 1461, 1384, 1097 cm^{-1}.

Synthesis of *tert*-butyldiphenyl(2,3,3,4-tetramethylpent-4-enyloxy)silane (17b)

To a solution of alcohol **16** (2.00 g, 14.1 mmol, 1.00 eq) in DCM (50 mL) were added NEt_3 (5.10 mL, 36.6 mmol, 2.60 eq), TBDPSCl (4.80 mL, 18.3 mmol, 1.30 eq) and DMAP (cat.) at rt. The resulting suspension was stirred for 18 h (TLC). Sat. aq. NH_4Cl solution was added and the layers were separated. The aqueous layer was extracted two times with DCM and the combined organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (hexane/EtOAc = 10:1) to yield **17b** (5.10 g, 96%) as a colorless oil.

M_r = 380.64, $C_{25}H_{36}OSi$. R_f = 0.82 (hexane/ EtOAc = 5:1). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.67 (m, 4H), 7.39 (m, 6H), 4.65(m, 2H), 3.69 (m, 1H), 3.37 (m,1H), 1.79 (m, 1H), 1.61 (s, 3H), 1.06 (s, 9H), 0.96 (d, 3H, *J* = 6.8 Hz), 0.93 (s, 3H), 0.91 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 152.8 (C), 135.8 (CH, 4C), 134.3 (C, 2C), 129.6 (CH, 2C), 127.7 (CH, 4C), 109.6 (CH_2), 65.9 (CH_2), 41.4 (CH), 40.7 (C), 27.1 (CH_3, 3C), 24.2 (CH_3), 23.6 (CH_3), 19.4 (C), 19.4 (CH_3), 12.9 (CH_3). **IR** ν_{max} 3071, 3050, 2965, 2858, 1635, 1589, 1472, 1390, 1376, 1159, 1111, 739, 700 cm^{-1}. **MS** (EI, 70 eV, 30 °C): *m/z*: 323, 280, 241, 223, 183, 141, 84. **HRMS** (70 eV, 30 °C): *m/z* calcd for $C_{21}H_{27}OSi$ (M – *t*-Bu): 323.1831, found: 323.1829.

Synthesis of 5-(*tert*-butyldiphenylsilanyloxy)-3,3,4-trimethylpentan-2-one (14b)

17b (5.10 g, 13.4 mmol, 1.00 eq) was dissolved in a mixture of CCl_4 (20 mL), MeCN (20 mL) and water (30 mL) and cooled to 0°C. $NaIO_4$ (11.5 g, 53.6 mmol, 4.00 eq) and $RuCl_3$ (278 mg, 1.34 mmol, 0.10 eq) were added with stirring and the resulting mixture was stirred at rt until completion (TLC). After dilution with DCM and water, the layers were separated and the aqueous layer was extracted three times with DCM. After drying the organic layer over $MgSO_4$, filtration and concentration under a reduced pressure, the residue was taken up in Et_2O and filtered through Celite®. The solvent was removed *in vacuo* and the crude product was purified by column chromatography (hexane/EtOAc = 10:1) to yield **14b** (3.60 g, 70%) as a colorless oil.

M_r = 382.61, $C_{24}H_{34}O_2Si$. R_f = 0.42 (hexane/EtOAc = 10:1). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.66 (m, 4H), 7.40 (m, 6H), 3.53 (dd, 1H, *J* = 10.2, 5.8 Hz), 3.41 (dd, 1H, *J* = 10.2, 7.3 Hz), 2.14 (m, 1H), 2.05 (s, 3H), 1.05 (s, 9H), 1.01 (s, 3H), 0.99 (s, 3H), 0.89 (d, 3H, *J* = 6.9 Hz). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 213.8 (C), 135.9 (CH, 4C), 133.9 (C, 2C), 130.3 (CH, 2C), 128.0 (CH, 4C), 66.4 (CH_2), 49.7 (C), 42.0

(CH), 27.1 (CH_3, 3C), 25.4 (CH_3), 22.4 (CH_3), 20.4 (CH_3), 19.3 (C), 12.4 (CH_3). **IR** ν_{max} 3049, 2962, 1704, 1589, 1471, 1427, 1187, 1111, 741, 702 cm^{-1}. **MS** (EI, 70 eV, 30 °C): *m/z*: 323, 280, 241, 223, 183, 141, 84. **HRMS** (70 eV, 30 °C): *m/z* calcd for $C_{20}H_{25}O_2Si$ (M – *t*-Bu) : 325.1624, found: 325.1631.

Synthesis of 1-(*tert*-butyldiphenylsilanyloxy)-6-hydroxy-2,3,3,7,8-pentamethyl-8-(2-methyl-1,3-dioxolan-2-yl)nonan-4-one (20)

To a solution of freshly prepared LDA (0.39 M, 10.0 mL, 3.92 mmol, 1.50 eq) in THF (8 mL) was added slowly ketone (**14b**) (1.00 g, 2.61 mmol, 1.00 eq) in THF (8 mL) with stirring at -78 °C. Stirring of the slightly yellow solution was continued for additional 30 min. Then aldehyde **13** (730 mg, 3.92 mmol, 1.50 eq) in THF (6 mL) was added at once. The solution was kept at -78 °C for 2 ½ h (TLC) and then quenched by the addition of MeOH and solid NH_4Cl. The mixture was allowed to warm up and diluted with Et_2O. Water was added and the layers were separated. The aqueous layer was extracted three times with Et_2O and the combined organic layer was washed with water and brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (hexane/EtOAc = 10:1) to yield **20** (1.04 g, 70%) as a colorless oil.

M_r = 568.86, $C_{34}H_{52}O_5Si$. R_f = 0.40 (hexane/EtOAc = 5:1). d.e. ~ 5:4 (determined by ^1H NMR)

major diastereomer:

^1H NMR (400 MHz, $CDCl_3$): δ 7.65 (m, 4H), 7.39 (m, 6H), 4.65 (m, 1H), 3.92 (m, 4H), 3.54 (dd, 1H, *J* = 10.2, 5.4 Hz), 3.41 (m, 1H), 2.95 (d, 1H, *J* = 3.7 Hz), 2.72 (dd, 1H, *J* = 19.3, 8.5 Hz), 2.38 (dd, 1H, *J* = 17.3, 4.3 Hz), 2.13 (m, 1H), 1.43 (m, 1H), 1.04 (s, 9H), 1.00 (m, 18H), 0.89 (m, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 215.1 (C), 135.8 (CH, 4C), 133.7 (C, 2C), 129.8 (CH, 2C), 127.8 (CH, 4C), 114.8 (C), 67.4 (CH), 66.0 (CH_2), 64.9 (CH_2), 64.5 (CH_2), 49.7 (C), 45.1 (C), 43.9 (CH), 43.1 (CH_2), 41.2 (CH), 27.0 (CH_3, 3C), 23.6 (CH_3), 21.6 (CH_3), 21.1 (CH_3), 20.7 (CH_3), 20.1 (CH_3), 19.3 (C), 12.5 (CH_3), 9.1 (CH_3).

minor diastereomer :

^1H NMR (400 MHz, C_6D_6): δ 7.65 (m, 4H), 7.39 (m, 6H), 4.65 (m, 1H), 3.92 (m, 4H), 3.60 (dd, 1H, *J* = 10.1, 5.2 Hz), 3.41 (m, 1H), 3.03 (d, 1H, *J* = 3.5 Hz), 2.76 (dd, 1H, *J* = 17.2, 8.7 Hz), 2.26 (dd, 1H, *J* = 17.2, 3.7 Hz), 2.13 (m, 1H), 1.43 (m, 1H), 1.04 (s, 9H), 1.00 (m, 18H), 0.89 (m, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 215.8 (C), 135.7 (CH, 4C), 133.7 (C, 2C), 129.8 (CH, 2C), 127.8 (CH, 4C), 114.8 (C), 67.6 (CH), 65.9 (CH_2), 64.9 (CH_2), 64.5 (CH_2), 49.8 (C), 45.1 (C), 43.6 (CH), 43.1 (CH_2), 41.2 (CH), 27.0 (CH_3, 3C), 23.4 (CH_3), 21.3 (CH_3), 21.1 (CH_3), 20.6 (CH_3), 20.1 (CH_3), 19.3 (C), 12.7 (CH_3), 9.0 (CH_3).

IR ν_{max} 3518, 3071, 2973, 2884, 1698, 1589, 1471, 1427, 1112, 741, 703 cm^{-1}. **MS** (EI, 70 eV, 30 °C): *m/z*: 553, 511, 449, 325, 239, 199, 125, 87, 55. **HRMS** (70 eV, 30 °C): *m/z* calcd for $C_{33}H_{49}O_5Si$ (M –

CH_3): 553.3349, found: 553.3338.

Synthesis of 5-[3,4-dimethyl-4-(2-methyl-1,3-dioxolan-2-yl)-2-oxopent-(*Z*)-ylidene]-3,4,4-trimethyl-dihydrofuran-2-one (23)

To a solution of **20** (1.00 g, 1.76 mmol, 1.00 eq) in THF (21 mL) was added TBAF (1 M in THF, 2.64 mL, 2.64 mmol, 1.50 eq) at rt. The resulting yellow solution was stirred for 1 h (TLC) and then diluted with Et_2O (50 mL). The organic layer was washed successively with sat. aq. NH_4Cl solution. water and brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (hexane/EtOAc = 4:1) to yield **21** (491 mg, 85%) as a colorless oil. A solution of **21** (34.0 mg, 0.10 mmol, 1.00 eq) in DCM (1.5 mL) was cooled with stirring to 0 °C. Then, TPAP (4.00 mg, 0.01 mmol, 0.10 eq) and $NMO \cdot H_2O$ (270 mg, 2.00 mmol, 20.0 eq) were added, the resulting green mixture was stirred for 30 min at 0 °C and additionally for 30 min at rt (TLC). After dilution with Et_2O, filtration over SiO_2 (pretreated with NEt_3) yielded **23** (18.0 mg, 55%) as a colorless oil.

M_r = 324.41, $C_{18}H_{28}O_5$. R_f = 0.40 (hexane/EtOAc = 2:1). Mixture of diastereomers, due to overlap of signals, the ratio could not be determined by NMR. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.38 (m, 1H), 3.89 (m, 4H), 3.22 (m, 1H), 2.52 (m, 1H), 1.31 (s, 3H), 1.27 (m, 3H), 1.20 (m, 3H), 1.15 (s, 3H), 1.10 (m, 3H), 1.03 (s, 3H), 1.01 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 202.4 (C), 175.0 (C), 166.1 (C), 114.3 (C), 104.5 (CH), 64.9 (CH_2), 64.6 (CH_2), 48.3 (CH), 45.5 (C), 44.2 (CH), 43.7 (C), 25.3 (CH_3), 23.7 (CH_3), 21.2 (CH_3), 20.3 (CH_3), 19.4 (CH_3), 13.6 (CH_3), 9.1 (CH_3). **IR** ν_{max} 2978, 2882, 1817, 1679, 1652, 1468, 1374, 1159 cm^{-1}. **MS** (EI, 70 eV, 30 °C): *m/z*: 324, 309, 249, 167, 87, 69, 55. **HRMS** (70 eV, 30 °C): *m/z* calcd for $C_{18}H_{28}O_5$: 324.1937, found: 324.1926.

Synthesis of 5-[3,4-dimethyl-4-(2-methyl-1,3-dioxolan-2-yl)-2-oxopent-(*Z*)-ylidene]-3,4,4-trimethyl-pyrrolidin-2-one (25)

23 (10.0 mg, 0.03 mmol, 1.00 eq) was dissolved in DCM (1.00 mL) and treated with NH_3 (2M in EtOH, 0.30 mmol, 0.15 mL, 10.0 eq) and stirred at rt overnight. After evaporation of the solvent *in vacuo*, the residue was dissolved in toluene (5 mL). A micro distillation apparatus was attached and the toluene was distilled off under heating at 140 °C. Drying under a reduced pressure yielded **25** (8.70 mg, 90%) as a yellow oil.

M_r = 323.43, $C_{18}H_{29}NO_4$. R_f = 0.46 (hexane/EtOAc = 2:1). Mixture of diastereomers, due to overlap of signals, the ratio could not be determined by NMR. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 10.65 (bs, 1H), 5.39 (bs, 1H), 3.89 (m, 4H), 2.75 (dq, 1H, *J* = 7.1, 2.2 Hz), 2.35 (dq, 1H, *J* = 7.5, 1.7 Hz), 1.28 (d, 3H, *J* = 1.7 Hz), 1.27 (bs, 3H), 1.15 (d, 3H, *J* = 7.5 Hz), 1.13 (d, 3H, *J* = 2.2 Hz), 1.10 (d, 3H, *J* = 7.1 Hz), 1.06 (bs, 3H), 1.01 (bs, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 205.1 (C), 179.2 (C), 165.5 (C), 114.3 (C), 97.8

(CH), 64.7 (CH_2), 64.4 (CH_2), 50.0 (CH), 45.8 (CH), 45.2 (C), 42.7 (C), 26.9 (CH_3), 24.6 (CH_3), 20.9 (CH_3), 20.7 (CH_3), 19.4 (CH_3), 14.0 (CH_3), 9.9 (CH_3). **IR** ν_{max} 3294, 2974, 1745, 1660, 1586, 1456, 1375, 1333, 1160 cm^{-1}. **MS** (EI, 70 eV, 30 °C): *m/z*: 323, 280, 261, 246, 220, 205, 195, 185, 166. **HRMS** (70 eV, 30 °C): *m/z* calcd for $C_{18}H_{29}NO_4$: 323.2097, found: 323.2088.

Synthesis of 3,4,4-trimethyl-1-[3,3,4-trimethyl-5-oxopyrrolidin-(2*Z*)-ylidene]hexane-2,5-dione (26)

23 (32 mg, 0.10 mmol, 1.00 eq) was added to a suspension of ammonium acetate (154 mg, 2.00 mmol, 20.0 eq) in AcOH (2.00 mL) and H_2O (0.50 mL) and heated at 110 °C for 2 h. After being cooled down to rt, sat. aq. $NaHCO_3$ solution was added cautiously under stirring at 0 °C. Ethyl acetate was added and the layers were separated. The aqueous layer was extracted three times with ethyl acetate, the combined organic layer was washed with H_2O and brine, dried over $MgSO_4$, filtered and concentrated *in vacuo.* Purification by column chromatography (hexane/EtOAc = 2:1) yielded **26** (21 mg, 75%) as a yellow oil.

M_r = 279.37, $C_{16}H_{25}NO_3$. R_f = 0.40 (hexane/EtOAc = 2:1). Mixture of diastereomers, due to overlap of signals, the ratio could not be determined by NMR. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 10.59 (bs, 1H), 5.46 (s, 1H), 3.04 (dq, 1H, *J* = 7.4, 2.3 Hz), 2.28 (d, 1H, *J* = 7.4 Hz), 2.19 (s, 3H), 1.29 (s, 3H), 1.21 (s, 3H), 1.16 (s, 3H), 1.14 (s, 3H), 1.11 (s, 3H), 1.10 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 213.2 (C), 202.9 (C), 179.0 (C), 166.9 (C), 96.3 (CH), 51.9 (C), 49.0 (CH), 45.7 (CH), 42.5 (C), 26.8 (CH_3), 25.8 (CH_3), 24.5 (CH_3), 24.2 (CH_3), 23.3 (CH_3), 21.3 (CH_3), 9.7 (CH_3). **IR** ν_{max} 3294, 2925, 1727, 1664, 1581, 1465, 1380 cm^{-1}. **MS** (EI, 70 eV, 30 °C): *m/z*: 279, 230, 187, 122. **HRMS** (70 eV, 30 °C): *m/z* calcd for $C_{16}H_{25}NO_3$: 279.1834, found: 279.1841.

Synthesis of 3,4,4-trimethyl-5-[1-(3,4,4,5-tetramethyl-3,4-dihydro-2*H*-pyrrol-2-yl)meth-(*Z*)-ylidene]-pyrrolidin-2-one (27)

26 (5 mg, 0.02 mmol, 1.00 eq) was dissolved in EtOH (0.4 mL), treated with NH_3 (2M in EtOH, 0.20 mmol, 0.10 mL, 10 eq) and stirred at rt. For monitoring of the reaction, the solvent was evaporated, the residue was dried under a reduced pressure and a ^{1}H NMR spectra were recorded. After 96 h, 60% conversion of the starting material was achieved according to the ^{1}H NMR spectra.

M_r = 260.37, $C_{16}H_{24}N_2O$. R_f = 0.20 (hexane/EtOAc = 2:1). Mixture of diastereomers, due to overlap of signals, the ratio could not be determined by NMR. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 10.36 (bs, 1H), 5.18 (s, 1H), 2.35 (d, 1H, *J* = 7.5 Hz), 2.12 (s, 3H), 1.79 (s, 3H), 1.31 (s, 3H), 1.16 (s, 3H), 1.14 (s, 3H), 1.03 (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 185.7 (C), 177.9 (C), 149.5 (C), 143.3 (C), 133.0 (C), 90.6 (CH), 56.1 (C), 47.1 (CH), 42.1 (C), 27.3 (CH_3), 24.5 (CH_3), 21.2 (CH_3), 21.1 (CH_3), 15.4 (CH_3), 10.1 (CH_3), 8.9 (CH_3). **IR** ν_{max} 3295, 2926, 1730, 1660, 1458 cm^{-1}. **MS** (EI, 70 eV, 30 °C): *m/z*: 260, 245, 166, 147, 97, 70. **HRMS** (70 eV, 30 °C): *m/z* calcd for $C_{16}H_{24}N_2O$: 260.1889, found: 260.1881.

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