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\(^{1b,2}\) 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.\(^{2b}\) 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).
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 of allylic alcohol 15. 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 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).


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\(_2\)O) as a cooxidant in DCM at 0 °C. 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.$^{2e-g}$

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) ($\text{P}_4\text{O}_{10}$), Et$_2$O (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$_6$D$_6$ solution and are referenced to $^1$H, δ = 7.26; $^{13}$C, δ = 77.16 (CHCl$_3$) and $^1$H, δ = 7.15; $^{13}$C, δ = 128.62 (C$_6$H$_6$) respectively. All $^1$H 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$_2$O and the combined organic layer was washed successively 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$_2$O (60 mL) and the crude ester, dissolved in Et$_2$O (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$_2$O (200 mL) and cooled down to 0 °C. H$_2$O (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$_9$H$_{18}$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 $\nu_{\max}$ 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$_9$H$_{18}$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 \( \text{16} \) (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\(_4\)Cl 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 \textit{in vacuo}, the crude product was purified by column chromatography (hexane/EtOAc = 10:1) to yield \textbf{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\(_3\)): \( \delta \) 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\(_3\)): \( \delta \) 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\(_3\)), 24.2 (CH\(_3\)), 23.3 (CH\(_3\)), 19.5 (CH\(_3\)), 12.6 (CH\(_3\)). IR \( \nu_{\text{max}} \) 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)

\textbf{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\(_2\)O and filtered through Celite\textregistered. The solvent was removed \textit{in vacuo} and the crude product was purified by column chromatography (pentane/Et\(_2\)O = 10:1) to yield \textbf{14a} (5.14 g, 85%) as colorless oil.

M\(_r\) = 228.33, C\(_{13}\)H\(_{24}\)O\(_3\). R\(_f\) = 0.35 (pentane/Et\(_2\)O = 10:1). \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta \) 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\(_3\)): \( \delta \) 213.1 (C), 178.7 (C), 66.6 (CH\(_2\)), 49.7 (C), 39.0 (C), 38.3 (CH), 27.3 (CH\(_3\)), 25.5 (CH\(_3\)), 21.8 (CH\(_3\)), 20.9 (CH\(_3\)), 12.7 (CH\(_3\)). IR \( \nu_{\text{max}} \) 2975, 1729, 1480, 1394, 1366 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\(_{13}\)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)

\textbf{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 \textit{Dean-Stark} trap at 110 °C for 4 h (TLC). After being
cooled down to rt, the reaction mixture was diluted with Et₂O and treated with sat. aq. NaHCO₃ solution. The layers were separated and the aqueous layer was extracted three times with Et₂O. The combined organic layer was washed with brine and dried over MgSO₄. 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, C₁₅H₂₈O₄. R_f = 0.56 (hexane/EtOAc = 5:1). ^1H NMR (400 MHz, C₆D₆): 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). ^13C NMR (101 MHz, C₆D₆): δ 178.4 (C), 114.9 (C), 68.5 (CH₂), 65.4 (CH₂), 64.8 (CH₂), 44.7 (C), 39.4 (C), 39.2 (CH), 28.0 (CH₃, 3C), 22.8 (CH₃), 19.9 (CH₃), 18.8 (CH₃), 13.9 (CH₃). 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 C₁₄H₂₅O₄ (M - CH₃): 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. H₂O 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 MgSO₄ and filtered. The solvent was removed in vacuo to yield alcohol 19 (2.90 g, quant.) as a colorless oil.

M_r = 188.26, C₁₀H₂₀O₃. R_f = 0.17 (Hex/EE = 5:1). ^1H NMR (400 MHz, C₆D₆): 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). ^13C NMR (101 MHz, C₆D₆): δ 114.5 (C), 65.9 (CH₂), 65.1 (CH₂), 64.3 (CH₂), 44.4 (C), 42.3 (CH), 24.1 (CH₃), 19.9 (CH₃), 17.2 (CH₃), 14.2 (CH₃). 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 C₉H₁₇O₃ (M - CH₃): 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 NaHCO₃ (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). Et₂O was added and the suspension was treated with sat. aq. NaHCO₃ and sat. aq. Na₂S₂O₃ solution. After being vigorously stirred for 30 min at rt, the layers were separated and the aqueous layer was extracted three times with Et₂O. The combined organic layer was washed successively with sat. aq. NaHCO₃ solution, water and brine, dried over MgSO₄, filtered and concentrated in vacuo. The crude material was purified by column
chromatography (pentane/Et$_2$O = 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$_6$D$_6$): 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$_6$D$_6$): 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 $\nu$$_{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$_4$Cl 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 $\nu$$_{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$_2$O 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$_2$Si. 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 (CH₃, 3C), 25.4 (CH₃), 22.4 (CH₃), 20.4 (CH₃), 19.3 (C), 12.4 (CH₃). IR \( \nu_{\text{max}} \) 3049, 2962, 1704, 1589, 1471, 1427, 1187, 1111, 741, 702 cm\(^{-1}\). MS (EI, 70 eV, 30 °C): \( m/z \): 323, 280, 241, 223, 211, 170, 158, 147, 142, 111, 74, 70 cm\(^{-1}\). HRMS (70 eV, 30 °C): \( m/z \) calcd for C\(_{20}\)H\(_{25}\)O\(_2\)Si (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\(_4\)Cl. The mixture was allowed to warm up and diluted with Et\(_2\)O. Water was added and the layers were separated. The aqueous layer was extracted three times with Et\(_2\)O 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\(_5\)Si. R\(_f\) = 0.40 (hexane/EtOAc = 5:1). d.e. ~ 5:4 (determined by \(^1\)H NMR)

**major diastereomer:**

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta \) 7.65 (m, 4H), 7.39 (m, 6H), 4.65 (m, 1H), 3.92 (m, 4H), 3.54 (dd, 1H, \( J = 10.2, 5.4 \text{ Hz} \)), 3.41 (m, 1H), 2.95 (d, 1H, \( J = 3.7 \text{ Hz} \)), 2.72 (dd, 1H, \( J = 19.3, 8.5 \text{ Hz} \)), 2.38 (dd, 1H, \( J = 17.3, 4.3 \text{ Hz} \)), 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\(_3\)): \( \delta \) 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 :**

\(^1\)H NMR (400 MHz, C\(_6\)D\(_6\)): \( \delta \) 7.65 (m, 4H), 7.39 (m, 6H), 4.65 (m, 1H), 3.92 (m, 4H), 3.60 (dd, 1H, \( J = 10.1, 5.2 \text{ Hz} \)), 3.41 (m, 1H), 3.03 (d, 1H, \( J = 3.5 \text{ Hz} \)), 2.76 (dd, 1H, \( J = 17.2, 8.7 \text{ Hz} \)), 2.26 (dd, 1H, \( J = 17.2, 3.7 \text{ Hz} \)), 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\(_3\)): \( \delta \) 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 \( \nu_{\text{max}} \) 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\(_5\)Si (M –
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 Et₂O (50 mL). The organic layer was washed successively with sat. aq. NH₄Cl solution, water, and brine, dried over MgSO₄, 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·H₂O (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 Et₂O, filtration over SiO₂ (pretreated with NEt₃) yielded 23 (18.0 mg, 55%) as a colorless oil.

Mr = 324.41, C十八H₂₈O₅. Rf = 0.40 (hexane/EtOAc = 2:1). Mixture of diastereomers, due to overlap of signals, the ratio could not be determined by NMR. ¹H NMR (400 MHz, CDCl₃): 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), 1.15 (s, 3H), 1.10 (m, 3H), 1.03 (s, 3H), 1.01 (s, 3H). ¹³C NMR (101 MHz, CDCl₃): δ 202.4 (C), 175.0 (C), 166.1 (C), 114.3 (C), 104.5 (CH), 64.9 (CH₂), 64.6 (CH₂), 48.3 (CH), 45.5 (C), 44.2 (CH), 43.7 (C), 25.3 (CH₃), 23.7 (CH₃), 21.2 (CH₃), 20.3 (CH₃), 19.4 (CH₃), 13.6 (CH₃), 9.1 (CH₃). IR νmax 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十八H₂₈O₅: 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 NH₃ (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.

Mr = 323.43, C十八H₂₉NO₄. Rf = 0.46 (hexane/EtOAc = 2:1). Mixture of diastereomers, due to overlap of signals, the ratio could not be determined by NMR. ¹H NMR (400 MHz, CDCl₃): 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 Hz), 1.06 (bs, 3H), 1.01 (bs, 3H). ¹³C NMR (101 MHz, CDCl₃): δ 205.1 (C), 179.2 (C), 165.5 (C), 114.3 (C), 97.8
(CH), 64.7 (CH₂), 64.4 (CH₂), 50.0 (CH), 45.8 (CH), 45.2 (C), 42.7 (C), 26.9 (CH₃), 24.6 (CH₃), 20.9 (CH₃), 20.7 (CH₃), 19.4 (CH₃), 14.0 (CH₃), 9.9 (CH₃). **IR** νₘₐₓ 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 C₁₈H₂₉NO₄: 323.2097, found: 323.2088.

**Synthesis of 3,4,4-trimethyl-1-[3,3,4-trimethyl-5-oxopyrrolidin-(2Z)-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 H₂O (0.50 mL) and heated at 110 °C for 2 h. After being cooled down to rt, sat. aq. NaHCO₃ 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 H₂O and brine, dried over MgSO₄, 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, C₁₆H₂₅N₂O₃. R_f = 0.40 (hexane/EtOAc = 2:1). Mixture of diastereomers, due to overlap of signals, the ratio could not be determined by NMR. **¹H NMR** (400 MHz, CDCl₃): 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). **¹³C NMR** (101 MHz, CDCl₃): 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 (CH₃), 25.8 (CH₃), 24.5 (CH₃), 24.2 (CH₃), 23.3 (CH₃), 21.3 (CH₃), 9.7 (CH₃). **IR** νₘₐₓ 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 C₁₆H₂₅N₂O₃: 279.1834, found: 279.1841.

**Synthesis of 3,4,4-trimethyl-5-[1-(3,4,4,5-tetramethyl-3,4-dihydro-2H-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 NH₃ (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 **¹H NMR** spectra were recorded. After 96 h, 60% conversion of the starting material was achieved according to the **¹H NMR** spectra. M_r = 260.37, C₁₆H₂₄N₂O. R_f = 0.20 (hexane/EtOAc = 2:1). Mixture of diastereomers, due to overlap of signals, the ratio could not be determined by NMR. **¹H NMR** (400 MHz, CDCl₃): 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). **¹³C NMR** (101 MHz, CDCl₃): 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 (CH₃), 24.5 (CH₃), 21.2 (CH₃), 21.1 (CH₃), 15.4 (CH₃), 10.1 (CH₃), 8.9 (CH₃). **IR** νₘₐₓ 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 C₁₆H₂₄N₂O: 260.1889, found: 260.1881.
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