Tandem Intramolecular Michael Addition-Aldol Reaction as a Tool for the Construction of the C-Ring of Hexacyclic Acid.

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General Methods

NMR spectra were recorded with Bruker AVS-500, AVS-400 or AM-200 spectrometers. Chemical shifts are reported in parts per million (ppm) relative to tetramethylsilane (0.00 ppm) on δ-scale. Corresponding solvent signal served as an internal standard: for 1H NMR spectra in CDCl$_3$ - the singlet of CHCl$_3$ at δ7.26 ppm, in C$_6$D$_6$ - the singlet of C$_6$D$_5$H at δ7.16 ppm; for $^{13}$C NMR spectra in CDCl$_3$ - the triplet at δ77.00 ppm, in C$_6$D$_6$ - the triplet at δ128.40 ppm. Values of the coupling constant, $J$, are given in hertz (Hz). To clarify the assignments of NMR-signals, the authors have numbered the carbon atoms of the structures. Following abbreviations are used in the experimental section for the description of 1H-NMR spectra: singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), doublet of doublets (dd), doublet of triplet (dt), doublet of quartets (dq), doublet of doublets of doublets (ddd), broad singlet (bs), broad doublet (bd) and broad triplet (bt). The chemical shifts of complex multiplets are given as the range of their occurrence. $^{13}$C-Signals were assigned by means of standard DEPT 135 and DEPT 90 experiments and the following abbreviations are used in the experimental part: quaternary (Cq), methyne (CH), methylene (CH$_2$) and methyl carbon atom (CH$_3$) respectively. Further assignment of NMR-signals was achieved using two-dimensional NMR experiments when appropriate (H,H-COSY, HMQC and HMBC).

Infrared spectra were recorded with Bruker 580 FT-IR photometer. Samples were solved in dichloromethane or applied neat according to the “Golden-Gate” ATR method.

High-resolution electrospray-mass spectra (HRMS-ESI) were recorded with Waters Micromass LCT spectrometer with a Lock-Spray unit.

Analytical gas chromatography (GC) was performed with HP 6890 device using Macherey-Nagel “Optima 5” capillary column (30 m, 5% phenyl - 95% dimethylpolysiloxan) and a flame ionization detector. Nitrogen served as the carrier gas. According to the standard method used, the column temperature was maintained 50 °C for 1 min then rose to 300 °C at a
20 °C/min rate and was maintained at 300 °C till the end of the run. The overall run time was 20 min.
All air- and moisture sensitive reactions were performed under argon in heat gun-dried glassware.
All experiments were monitored by thin layer chromatography (TLC) performed on Merck 60 F-254 (0.2 mm thick) silica gel aluminium supported plates. Spots were visualized by exposure to ultraviolet light (254 nm) or by staining with a “vanillin reagent” (85 mL MeOH, 5 mL H₂SO₄, 10 mL AcOH, 0.5 g vanillin (added last)), “cer reagent” (10 g Ce(SO₄)₂, 25 g phosphomolybdenic acid, 80 mL H₂SO₄, H₂O to 1000 mL), followed by heating or by “permanganate reagent” (3 g KMnO₄, 20 g K₂CO₃, 5 ml 5% aqueous NaOH, 300 mL H₂O).
Tetrahydrofuran (THF) was distilled under argon from sodium/benzophenone.
Dichloromethane was distilled from calcium hydride under argon.
Commercially available reagents were used as supplied.
Flash chromatography was performed with J. T. Baker brand silica gel (40-60 µm, 60Å pores). Eluents used for flash chromatography (usually n-hexane and ethyl acetate) were distilled prior to use.
Trimethyl-(2-(2-(2-methyl-[1,3]dioxolan-2-yl)-ethyl)-cyclohexyldiene-methoxy)-silane (9)

Mg turnings (1.10 g, 46 mmol, 3 eq) were ground in a mortar and transferred immediately to a Schlenk flask fitted with an argon-filled balloon. THF (3 mL) was added. A solution of 2-(2-bromoethyl)-2-methyl-1,3-dioxolane (2.92 g, 15 mmol, 1 eq) and 1,2-dibromoethane (200 mg, 1.3 mmol) in THF (2 mL) was added drop wise over 2 hours to Mg turnings while stirring at 22-24 °C (cooling in a water bath). After the addition was over, the reaction mixture was diluted with THF (15 mL) of and stirred for an hour at rt. The resulting grey solution was separated from the excess of Mg turnings and transferred with a syringe into another clean 100 mL Schlenk flask fitted with an argon-filled balloon. The flask was cooled to -78 °C and the solution of CuBr·Me2S (0.107 g, 0.5 mmol, 3%-mol) in HMPA (3.8 mL, 22 mmol, 1.5 eq) was added. After the resulting mixture was stirred for an hour at -78 °C a mixture of 1-cyclohexene-1-carbaldehyde (929 mg, 8.44 mmol) and TMSCl (2.25 mL, 17 mmol) in THF (10 mL) was added within 8h to the reaction mixture while stirring at -78 °C. The mixture was additionally stirred for 6 hours at -78 °C. After that Et3N (3 mL) was added followed by hexane (30 mL) and H2O (30 mL). Organic layer was separated. Aqueous layer was treated with saturated aqueous NH4Cl solution (10 mL) and extracted with hexane (2×30 mL). Combined hexane extract was washed with water and brine, dried over MgSO4 and concentrated. Flash chromatography on silica gel with hexane-AcOEt-Et3N (100:10:1 v/v/v) gave 9 (2.0 g, 80%) as a colorless oil.

1H-NMR (C6D6, 400 MHz): δ6.19 (s, 1H), 3.57 (s, 4H), 2.60-2.45 (m, 1H), 2.20 (m, 1H), 2.00-1.40 (m, 11H), 1.33 (s, 3H), 0.11 (m, 9H).

13C-NMR (C6D6, 100 MHz): δ131.93 (CH), 125.03 (Cq), 111.02 (Cq), 65.35 (CH2), 65.34 (CH2), 40.35 (CH), 38.66 (CH2), 34.93 (CH3), 28.49 (CH2), 27.13 (CH2), 24.84 (CH3), 24.27 (CH2), 23.77 (CH2), 0.17 (3×CH3).

Elemental Analysis: Anal. C, 63.26%; H, 9.944%; calcd for C16H30O3Si: C, 64.38%; H, 10.13%.
2-[2-(2-methyl-[1,3]dioxolan-2-yl)-ethyl]-cyclohexanecarbaldehyde (10)

\[
\begin{align*}
\text{C}_{13}\text{H}_{22}\text{O}_3 \\
\text{Mol. Wt.: 226.31}
\end{align*}
\]

1.0M TBAF solution in THF (1 mL, 1.0 mmol, 2.3 eq) was added to a solution of of 9 (130 mg, 0.44 mmol) in THF (4 mL). The reaction mixture was stirred at rt for 5 hours. It was then quenched with H\textsubscript{2}O (10 mL), extracted with MTBE (3×10 mL), the combined organic layers were washed with brine, dried over MgSO\textsubscript{4}, filtered and concentrated. Flash chromatography on silica gel with hexane-AcOEt (7:3 v/v) as eluent gave 10 as a colorless oil (53.2 mg, 54%). R\text{f} = 0.3, R\text{f} (silyl enolether) = 0.55.

\( ^1\text{H-NMR (CDCl}_3, 200 \text{ MHz)}: \delta 9.82 \text{ (s), } 9.55 \text{ (d, } J = 3.9 \text{ Hz, 1H), } 3.92 \text{ (m, 4H), } 2.10-0.70 \text{ (complex m, 17H). The signals at 9.82 (s) and 9.55 (d, } J = 3.9 \text{ Hz, 1H) ppm correspond to the absorption of the CHO proton of the cis and the trans isomer respectively. According to the } ^1\text{H NMR spectrum the product was obtained as a 1:7.1 mixture of cis and trans isomers.} \)

\( ^{13}\text{C-NMR (CD}_{6}\text{D}_6, 100 \text{ MHz)}\) for the \textit{cis:trans} mixture: \( \delta 204.62 \text{ (CH), } 204.39 \text{ (CH), } 110.70 \text{ (Cq), } 110.69 \text{ (Cq), } 65.35 \text{ (CH}_2\text{), } 65.32 \text{ (CH}_2\text{), } 56.12 \text{ (CH), } 52.58 \text{ (CH), } 38.35 \text{ (CH}_2\text{), } 38.32 \text{ (CH}_2\text{), } 38.18 \text{ (CH), } 37.14 \text{ (CH), } 37.06 \text{ (CH}_2\text{), } 37.04 \text{ (CH}_2\text{), } 31.04 \text{ (CH}_2\text{), } 30.06 \text{ (CH}_2\text{), } 29.51 \text{ (CH}_2\text{), } 26.67 \text{ (CH}_2\text{), } 26.33 \text{ (CH}_2\text{), } 25.99 \text{ (CH}_2\text{), } 25.60 \text{ (CH}_2\text{), } 25.17 \text{ (CH}_2\text{), } 24.82 \text{ (CH}_2\text{), } 24.68 \text{ (CH}_3\text{), } 24.67 \text{ (CH}_3\text{), } 24.58 \text{ (CH}_2\text{).} \)

\textbf{HRMS ESI } m/z \text{ found: } 227.1640; \text{ calcd for (M+H)}^+: 227.1623.

\textit{Epimerization of 10.}

The solution of aldehyde 10 in hexane-AcOEt (6:1 v/v) was stirred with silica gel (100 mg) for 24h at rt. The reaction mixture was filtered through a plug of cotton and concentrated to give the product. According to \(^1\text{H NMR the cis:trans ratio was 1:8.} \)
(E)-ethyl 3-(2-(2-(2-methyl-1,3-dioxolan-2-yl)ethyl)cyclohexyl)-acrylate

\[
\begin{align*}
\text{Me} & \quad \text{C} \quad \text{OOEt} \\
\text{C}_7\text{H}_{18}\text{O}_4 & \quad \text{Mol. Wt.: 296.4}
\end{align*}
\]

A solution of diethyl ethoxycarbonylmethanephosphonate (688 mg, 3.01 mmol, 1.7 eq) in toluene (3 mL) was added at rt to a suspension of NaH in mineral oil (60%, 106 mg, 2.66 mmol, 1.5 eq) in toluene (4 mL) forming a clear colorless solution which was additionally stirred for 20 min at rt. The solution was cooled to -20 °C and aldehyde 10 (400 mg, 1.77 mmol, 1 eq) was added dropwise over 20 min as a solution in toluene (4 mL). The reaction mixture was stirred for 30 min at -20 °C. When the reaction was complete (TLC hexane-AcOEt (7:3 v/v), product \( R_f = 0.45 \), UV active), the reaction mixture was diluted with MTBE (10 mL) and H\(_2\)O (10 mL). It was extracted with MTBE (3×10 mL) and the combined organic layers were washed with brine, dried over MgSO\(_4\), filtered and concentrated. Silica gel chromatography using hexane-AcOEt (8:2 v/v) as eluent provides the desired product as a colorless oil (240 mg, 46%).

\(^1\)H-NMR (CDCl\(_3\), 400 MHz): \( \delta \) 6.38-6.77 (dd, \( J = 9.5, 15.7 \) Hz, 1H), 5.78 (d, \( J = 15.7 \) Hz 1H), 4.17 (q, \( J = 7.2 \) Hz, 2H), 3.90 (m, 4H), 1.90-0.80 (m). According to the \(^1\)H NMR spectrum the product was obtained as a 1:6.6 mixture of isomers (cis/trans- in respect to the substitution pattern on the cyclohexane ring). Olefinic protons of the minor cis isomer are observed at 7.20-7.07 (dd, \( J = 8.9, 15.7 \) Hz) and 5.82 (d, \( J = 15.7 \) Hz) ppm.

\(^{13}\)C-NMR (CDCl\(_3\), 100 MHz): \( \delta \) 166.68 (O-C=O), 153.53 (CH), 120.62 (CH), 110.07 (Cq), 64.47 (CH\(_2\)), 64.42 (CH\(_2\)), 59.99 (CH\(_2\)), 46.84 (CH), 40.97 (CH), 35.53 (CH\(_2\)), 32.62 (CH\(_2\)), 30.92 (CH\(_2\)), 28.60 (CH\(_2\)), 25.88 (CH\(_2\)), 25.48 (CH\(_2\)), 23.57 (CH\(_3\)), 14.17 (CH\(_3\)).

HRMS ESI \( m/z \) found: 297.2070; calcd for (M+H\(^+\)): 297.2066.

IR (cm\(^{-1}\), neat): 2981 (m), 2924 (s), 2854 (m), 1716 (s), 1650, 1447, 1370, 1323, 1263, 1223, 1174, 1039, 987, 947, 859, 720.
3-[2-(3-oxo-butyl)-cyclohexyl]-acrylic acid ethyl ester (11)

A solution of (E)-ethyl 3-(2-(2-methyl-1,3-dioxolan-2-yl)ethyl)cyclohexyl)-acrylate (253 mg, 0.86 mmol) and pyridinium tosylate (PPTS) (64 mg, 0.256 mmol, 30%-mol) in aqueous acetone (5 mL, 0.5 mL H$_2$O) was refluxed for 4h. When the reaction was complete (TLC hexane-AcOEt (7:3 v/v), product $R_f$ = 0.35, UV active) the excess of the solvent was removed under reduced pressure, MTBE (15 mL) was added and the mixture was washed with saturated aqueous NaHCO$_3$ solution and brine. The organic layer was dried over MgSO$_4$, filtered and concentrated. The crude product was purified with flash chromatography on silica gel with hexane-AcOEt (8:2 v/v) as eluent to give 11 as a colorless oil (199 mg, 92%).

$^1$H-NMR (CDCl$_3$, 400 MHz): δ6.80-6.70 (dd, $J = 9.6, 15.7$ Hz, 1H), 5.81-5.72 (d, $J = 15.6$ Hz, 1H), 4.18 (q, $J = 7.1$ Hz, 2H), 2.51-2.25 (m, 2H), 2.11 (s, 3H), 1.58 (s, 3H), 1.90-1.60 (m, 5H), 1.35-1.15 (m, 8H), 1.00-0.80 (m, 1H). According to the $^1$H NMR spectrum the product was obtained is a 1:6 mixture of isomers (cis/trans- in respect to the substitution pattern on the cyclohexane ring). Olefinic protons of the minor cis isomer are observed at: 7.14-7.08 (dd, $J = 8.8, 15.7$ Hz) and 5.83 (d, $J = 15.7$ Hz) ppm.

$^{13}$C-NMR (CDCl$_3$, 100 MHz): δ208.82 (C=O), 166.55 (O-C=O), 153.00 (CH), 120.94 (CH), 60.04 (CH$_2$), 46.83 (CH), 40.74 (CH$_2$), 40.48 (CH), 32.56 (CH$_2$), 30.80 (CH$_2$), 29.73 (CH$_3$), 28.33 (CH$_2$), 25.74 (CH$_2$), 25.34 (CH$_2$), 14.14 (CH$_3$).

HRMS ESI m/z found: 275.1628; calcd for (M+Na)$^+$: 275.1623.

IR (cm$^{-1}$, neat): 2925 (s), 2854 (m), 1712 (s), 1650 (m), 1447, 1367, 1324, 1266, 1225, 1161, 1133, 1039, 986, 844, 734.

Separation of the cis-trans 1:6 mixture was done on a 250×25 mm “Reprosil-Pur 120 C18 AQ 5 µm” column with a 30×20 mm “Reprosil-Pur 120 C18 AQ 10 µm” forecolumn and CH$_3$CN-H$_2$O (48:52 v/v) as the eluent at 10 ml/min flow rate. Detection with L-7400 “LaChrome” UV detector at 254 nm. The minor diastereomer had a retention time of 57.0 min. The major one: 59.9 min. In a single run 300 µL of the solution of the diastereomeric mixture in CH$_3$CN, containing 60 mg of the substance, was injected.
Preparation of 12a (kinetic product)

To a stirred solution of 11 (83.0 mg, 0.33 mmol, 1 eq) and hexamethyldisilazane (104 µl, 0.49 mmol, 1.5 eq) in 1,2-dichloroethane (3.5 mL) TMSI (58 µl, 0.43 mmol, 1.3 eq) was added dropwise at -30 °C. The mixture was stirred at this temperature for 3h. The reaction mixture was diluted with MTBE (10 mL) and saturated aqueous NH₄Cl solution (10 mL) and the mixture was extracted with MTBE (3×10 mL). Combined organic layers were washed with brine, dried over MgSO₄ and concentrated. The crude product was purified with flash chromatography on silica gel (20×270 mm column) with hexane-Et₂O (50:1 v/v) as eluent to give 12a (56.6 mg, 53%) as a colorless oil. According to the ¹H NMR the product is a 11:1 diastereomeric mixture. Rᵣ = 0.45-0.52 in hexane-AcOEt (10:1 v/v); Rᵣ = 0.17-0.13 in hexane-Et₂O (60:1 v/v).

¹H-NMR (C₆D₆, 400 MHz): δ4.03 (dq, J = 3.8, 7.2 Hz, 1H), 3.98 (dq, J = 3.6, 7.2 Hz, 1H), 3.05-3.02 (d, J = 5.1 Hz, 1H), 2.45-2.31 (m, 2H), 1.98-1.91 (m, 1H), 1.87-1.81 (m, 1H), 1.75-1.62 (m, 4H), 1.43 (s, 3H), 1.14-1.06 (m, 4H), 1.01-0.96 (t, J = 7.2 Hz, 3H), 0.21 (s, 9H).

¹³C-NMR (C₆D₆, 100 MHz): δ172.70 (O-C=O), 74.26 (Cq), 60.12 (CH), 59.99 (CH₂), 55.45 (CH), 50.77 (CH), 49.40 (CH), 37.54 (CH), 32.95 (CH₂), 31.93 (CH₂), 31.92 (CH₂), 27.27 (CH₂), 26.74 (CH₃), 26.62 (CH₂), 14.50 (CH₃), 2.14 (3×CH₃).

HRMS ESI m/z found: 325.2394, 388.2424; calcd for (M+H)⁺ 325.2199, (M+CH₃CN+Na)⁺: 388.2284.
**Preparation of 12b (thermodynamic product)**

![Chemical structure of 12b]

To a stirred solution of 11 (74.3 mg, 0.294 mmol, 1.0 eq) and TMS₂NH (93 µl, 0.442 mmol, 1.5 eq) in 1,2-dichloroethane (3 mL) TMSI (52 µl, 0.383 mmol, 1.3 eq) was added dropwise at 0 °C and the mixture was stirred at this temperature for 24h. The reaction mixture was diluted with MTBE (5 mL), quenched with saturated aqueous NH₄Cl solution (5 mL) and extracted with MTBE (3×10 mL). Combined organic layers were washed with brine, dried over MgSO₄ and concentrated. The crude product was purified with flash chromatography on silica gel (25×400 mm column) with hexane-Et₂O (60:1 v/v) as eluent to give 12b (59 mg, 62%) as a colorless oil. The fractions was judged by GC. Rᵣ = 0.45-0.50 in hexane-AcOEt (10:1 v/v); Rᵣ = 0.15-0.12 in hexane-Et₂O (60:1 v/v).

**¹H-NMR (C₆D₆, 400 MHz):** δ4.15 (dq, J = 10.9, 7.2 Hz, 1H), 4.08 (dq, J = 10.9, 7.2 Hz, 1H), 3.01-2.97 (d, J = 6.8 Hz, 1H), 2.89-2.82 (m, 1H), 2.36-2.31 (t, J = 8.0 Hz, 1H), 2.20-2.13 (dd, J = 12.8, 6.3 Hz, 1H), 1.98-1.91 (m, 1H), 1.71-1.62 (m, 3H), 1.59-1.49 (m, 1H), 1.45 (s, 3H), 1.16-1.12 (m, 5H), 1.02-0.97 (t, J = 7.2 Hz, 3H), 0.97-0.87 (m, 1H), 0.24 (s, 9H).

**¹³C-NMR (C₆D₆, 100 MHz):** δ172.25 (O-C=O), 74.47 (Cq), 59.95 (CH₂), 50.97 (CH), 48.97 (CH), 48.71 (CH), 43.30 (CH), 37.16 (CH), 32.33 (CH₂), 32.32 (CH₂), 27.05 (CH₂), 26.92 (CH₂), 26.90 (CH₃), 26.58 (CH₂), 14.49 (CH₃), 2.14 (3×CH₃).

**HRMS ESI m/z** found: 325.2191, 388.2304; calcld for (M+H)⁺: 325.2199, (M+CH₃CN+Na)⁺: 388.2284.
Preparation of 13a

![Chemical Structure](#)

The solution of silyl ether 12a (69.6 mg, 0.214 mmol) in THF (5 mL) was cooled to -30 °C and 1.0M solution of TBAF in THF (0.214 mmol, 0.214 mL) was added. The reaction mixture was stirred for 30 min at -30 °C, quenched with saturated aqueous NH$_4$Cl solution (5 mL) and extracted with MTBE (3×10 mL). The combined organic layers were washed with brine, dried over MgSO$_4$ and concentrated. The crude product was purified with flash chromatography on silica gel (20×240 mm column) with hexane-AcOEt (20:1 v/v) as eluent to give 13a (43.2 mg, 80%) as a colorless oil.

$^1$H-NMR (CDCl$_3$, 500 MHz): δ 4.07 (q, J = 7.1 Hz, 2H), 3.36 (ddd, J = 8.7, 8.7 and 8.7 Hz, 1H), 2.56 (ddd, J = 16.9, 10.8 Hz, 1H), 2.41 (ddd, J = 16.9, 4.7 Hz, 1H), 2.13 (s, 3H), 2.07 (ddd, J = 8.7, 11.7 and 6.0 Hz, 1H), 1.97 (ddd, J = 20.7, 11.1 and 4.7 Hz, 1H), 1.86-1.80 (m, 1H), 1.79-1.70 (m, 3H), 1.22 (t, J = 7.1 Hz, 3H), 1.27-1.11 (m, 4H), 1.04 (ddd, J = 11.3, 11.2, 11.3, 3.1 Hz, 1H), 1.05-0.96 (m, 1H), 0.90-0.81 (m, 1H).

$^{13}$C-NMR (CDCl$_3$, 100 MHz): δ 213.38 (Cq), 173.91 (Cq), 60.20 (CH$_2$), 50.04 (CH), 49.88 (CH), 45.53 (CH), 43.71 (CH), 36.33 (CH$_2$), 33.40 (CH$_2$), 32.04 (CH$_3$), 31.51 (CH$_2$), 30.09 (CH$_2$), 26.24 (CH$_2$), 25.83 (CH$_2$), 14.18 (CH$_3$).

HRMS ESI m/z found: 275.1636, 316.1883; calcd for (M+Na)$^+$: 275.1623, (M+CH$_3$CN+Na)$^+$: 316,1889.
Preparation of 14a

1.0M solution of TBAF in THF (0.55 mL, 0.55 mmol) was added to the solution of methyl ketone 13a (27.9 mg, 0.111 mmol) in THF (5 mL) at rt. After 3h the reaction mixture was quenched with saturated aqueous NH₄Cl solution and extracted with AcOEt (3×10 mL). The combined organic layers were washed with brine, dried over MgSO₄ and concentrated. The crude product was purified with flash chromatography on silica gel (160×15 mm column) with hexane-AcOEt (10:1 v/v) as eluent to give 14a (15 mg, 54%) as a colorless oil.

**1H-NMR (CDCl₃, 500 MHz):** \(\delta 4.06 \text{ (q, } J = 7.2 \text{ Hz, } 2\text{H}), 2.76 \text{ (ddd, } J = 11.5, 7.6, 3.0 \text{ Hz, } 1\text{H}), 2.49 \text{ (dd, } J = 14.3, 4.3 \text{ Hz, } 1\text{H}), 2.23 \text{ (dddd, } J = 10.9, 7.3, 9.2 \text{ and } 4.2 \text{ Hz, } 1\text{H}), 2.17 \text{ (s, } 3\text{H}), 2.16 \text{ (dd, } J = 14.4, 9.2 \text{ Hz, } 1\text{H}), 1.85-1.75 \text{ (m, } 2\text{H}), 1.75 \text{ (ddd, } J = 12.7, 7.0 \text{ and } 2.9 \text{ Hz, } 1\text{H}), 1.75-1.65 \text{ (m, } 2\text{H}), 1.51 \text{ (ddd, } J = 12.3, 12.1, 12.1 \text{ Hz, } 1\text{H}), 1.29 \text{ (t, } J = 7.2 \text{ Hz, } 3\text{H}), 1.30-1.20 \text{ (m, } 1\text{H}), 1.20-1.10 \text{ (m, } 2\text{H}), 1.10-1.00 \text{ (m, } 1\text{H}), 0.85-0.99 \text{ (m, } 1\text{H}), 0.83 \text{ (dddd, } J = 11.1, 11.1, 11.1 \text{ and } 3.3 \text{ Hz, } 1\text{H}).

**13C-NMR (CDCl₃, 100 MHz):** \(\delta 210.76 \text{ (Cq), 172.94 (Cq), 60.31 (CH₂), 55.40 (CH), 51.72 (CH), 44.52 (CH), 42.95 (CH), 37.87 (CH₂), 34.71 (CH₂), 31.49 (CH₂), 29.86 (CH₂), 29.07 (CH₃), 25.95 (CH₂), 25.92 (CH₂), 14.15 (CH₃)).

**HRMS ESI m/z** found: 253.1742, 275.1669, 316.1901; calcd for (M+H)⁺: 253.1798, (M+Na)⁺: 275.1618, (M+CH₃CN+Na)⁺: 316.1889.
Preparation of 14b

\[
\text{C}_{15}\text{H}_{24}\text{O}_3 \quad \text{Mol. Wt.: 252.3493}
\]

1.0M TBAF solution in THF (0.066 mL, 0.066 mmol, 1.0 eq) was added to the solution of 12b (21.5 mg, 0.066 mmol) in THF (5 mL) at -30 °C. The reaction mixture was stirred at -30 °C for 30 min, then quenched while cold with saturated aqueous NH₄Cl solution (5 mL), MTBE (5 mL) and H₂O (5 mL). The reaction mixture was extracted with MTBE (3×10 mL). Combined extract was washed with brine, dried over MgSO₄, concentrated. After flash chromatographic purification (hexane-AcOEt (8:1 v/v), R_f = 0.17 - 0.20) 13.2 mg (79%) of a colorless oil was obtained. According to 1H NMR the product was a 2.8:1.0 diastereomeric mixture. The signals of the CH₃ group are found at δ1.91 ppm and δ1.93 ppm, respectively (in C₆D₆).

1.0M TBAF solution in THF (0.13 mL, 0.13 mmol, 3 eq) was added to the solution of the above 2.8:1.0 diastereomeric mixture (11.0 mg, 0.044 mmol) in THF (9 mL) at rt. After 3h at rt the reaction mixture was quenched with saturated aqueous NH₄Cl solution (5 mL) and extracted with AcOEt (3×10 mL). Combined extract was washed with brine, dried over MgSO₄ and concentrated. The crude product was purified with flash chromatography on silica gel with hexane-AcOEt (8:1 v/v), R_f = 0.17-0.20 to give 14b (6.7 mg, 61%) as a colorless oil. According to 1H NMR the product is a single diastereomer with the chemical shift of the CH₃ group at δ1.93 ppm (in C₆D₆).

\(^1\)H-NMR (C₆D₆, 500 MHz): δ3.96 (q, J = 7.1, 1H), 3.95 (q, J = 7.1, 1H), 2.88 (dddd, J = 2.9, 5.2, 10.9, 8.2 Hz, 1H), 2.49 (dd, J = 3.2, 8.7, 8.7 Hz, 1H), 2.21 (dd, J = 5.2, 15.2 Hz, 1H), 1.93 (s, 3H), 1.85 (dd, J = 10.9, 15.2 Hz, 1H), 1.73-1.68 (m, 1H), 1.65 (ddd, J = 6.2, 8.5, 12.1 Hz, 1H), 1.61-1.53 (m, 2H), 1.48 - 1.42 (m, 1H), 1.19 (ddd, J = 11.8, 11.8, 9.0 Hz, 1H), 1.20 - 1.13 (m, 1H), 0.98 (t, J = 7.1 Hz, 3H), 0.97 - 0.90 (m, 2H), 0.96 - 0.88 (m, 1H), 0.81 (m, 1H), 0.75 (ddd, J = 2.6, 11.3, 13.0, 12.2 Hz, 1H).

\(^13\)C-NMR (C₆D₆, 125 MHz): δ208.26 (C=O), 173.12 (O-C=O), 60.54 (CH₂), 56.95 (CH), 48.16 (CH), 43.41 (CH), 39.97 (CH), 36.86 (CH₂), 35.93 (CH₂), 32.49 (CH₂), 29.12 (CH₃), 28.05 (CH₂), 26.80 (CH₂), 26.64 (CH₂), 14.64 (CH₃).

HRMS ESI m/z: found: 275.1653, 316.1885; calcd for (M+Na)⁺: 275.1623, (M+CH₃CN+Na)⁺: 316.1889.
10 (cis : trans 1 : 7,1)
cis : trans 1:6,6 - on the cyclohexane ring
cis : trans 1:6,6 - on the cyclohexane ring
C<sub>15</sub>H<sub>24</sub>O<sub>3</sub>  
Mol. Wt.: 252.35  

**11 (HPLC purified)**
11 (HPLC purified)
in C₆D₆, 13C BB, 400 Mhz

12a (kinetic)
12b (thermodynamic)
NOE irradi. at 1.66 ppm in C₆D₆

12b (thermodynamic)
NOE irradiated at 2.46 ppm in C$_6$D$_6$

12b (thermodynamic)
NOE irrad. at 2.97 ppm in C$_6$D$_6$

12b (thermodynamic)
NOE irrad. at 3.10 ppm in C₆D₆

12b (thermodynamic)
\[ \text{Integral} \]

CH$_3$ at 1.96 ppm in C$_6$D$_6$

\[
\begin{array}{c}
\text{C}_{15}\text{H}_{24}\text{O}_3 \\
\text{Mol. Wt.: 252.35}
\end{array}
\]

13a
in C₆D₆

C_{15}H_{24}O_{3}
Mol. Wt.: 252.35

13a
in CDCl₃, 500 Mhz

![NMR spectrum of compound 14a]

Integral: [7.2600, 4.0638, 4.0495, 2.7607, 2.5032, 2.4831, 2.2610, 2.1978, 2.1789, 2.1652, 2.1316, 1.8332, 1.8027, 1.7658, 1.7207, 1.6883, 1.5446, 1.4720, 1.2874, 1.2328, 1.2185, 1.2041, 1.1892, 1.0766, 1.0604, 0.9817, 0.9683, 0.8884, 0.8658, 0.8591, 0.8435, 0.8368, 0.8212, 0.7990, 0.7926]
in CDCl₃, 400 Mhz, 13C BB

![Chemical Structure](image)
CDC\textsubscript{3}, 295K, NOE irradiation at 2.83 ppm

14a
CDCl₃, 295K, NOE irradiation at 2.56 ppm
CH$_3$ at 1.91 ppm in C$_6$D$_6$

\[\text{C}_{16}\text{H}_{24}\text{O}_3\]

Mol. Wt.: 252.35

13b 2.82 : 1.00

CH$_3$ at 1.93 ppm in C$_6$D$_6$

\[\text{C}_{16}\text{H}_{24}\text{O}_3\]

Mol. Wt.: 252.35

14b
CH$_3$ at 1.93 ppm in C$_6$D$_6$

C$_{15}$H$_{24}$O$_3$
Mol. Wt.: 252.35

14b
CH₃ at 1.93 ppm in C₆D₆

C₁₅H₂₄O₃
Mol. Wt.: 252.35

14b
Steimakh ANA42 47mg C6D6/ohne TMS HMQC 21.07.05, Rettstadt
Steimakh ANA44 21.5mg C6D6/ohne TMS H-H-COSY60 13.06.05, Rettstadt
A. Stelmakh, AN 257, CDCl₃, NOESY, t\text{mix}=150 \text{ msec}
Steimakh ANA65 15mg CDCl3/ohne TMS H,H-COSY 14.09.05, Rettstadt

* The coupling constants support H5-H6 anti stereochemistry. The constants are taken from 1H-spectrum of 14a, measured at 500MHz in CDCl3, see S11, S30.
The constants are taken from 1H spectrum of 14b, measured at 500 MHz in CDCl₃, see S12 and S35.