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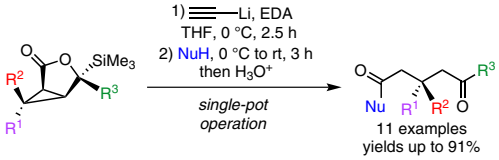
Formation of Carbon Quaternary Stereogenic Center in Acyclic Systems via a Sequence of Carbometalation–Intramolecular Cyclization–Silicon Activation

Maya Preshel-Zlatsin
Fa-Guang Zhang
Guillaume Eppe
Ilan Marek*

The Mallat Family Laboratory of Organic Chemistry, Schulich Faculty of Chemistry and The Lise Meitner-Minerva Center for Computational Quantum Chemistry, Technion-Israel Institute of Technology, Technion City, Haifa 32000, Israel
chilanm@tx.technion.ac.il



Dedicated to the memory of Jean Normant, a wonderful teacher and truly inspirational colleague

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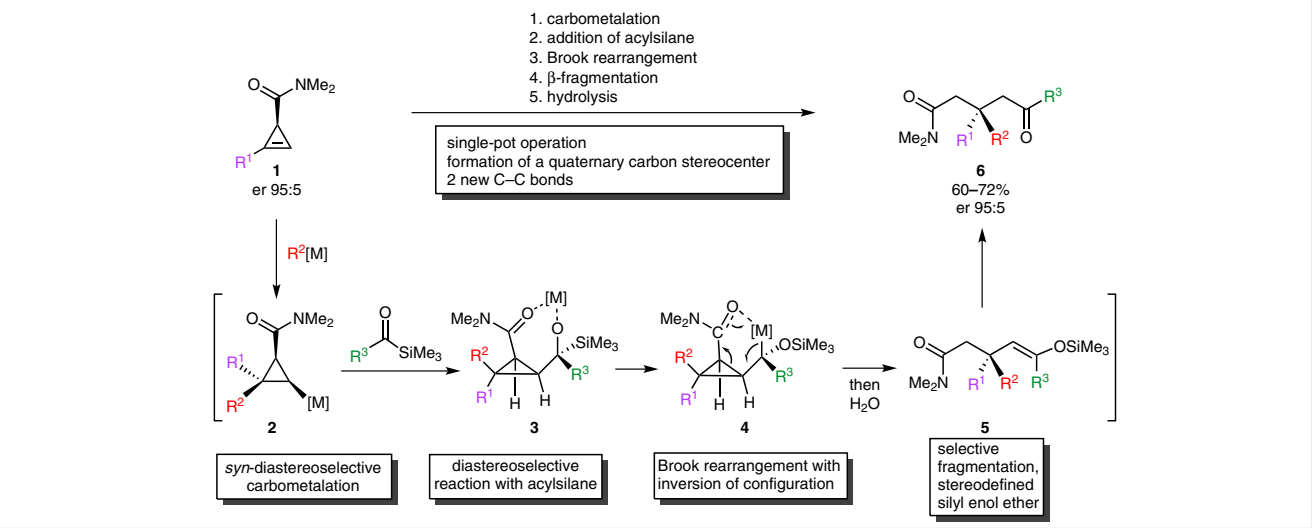
Abstract The diastereoselective carbometalation reaction of cyclopropenyl esters followed by reaction with acylsilanes provides γ-silylated lactones that undergo a 'sila-Grob' fragmentation to give pyrone enolates as a new source of acyclic δ-diketones, δ-keto acid, and δ-keto ester derivatives possessing a quaternary stereocenter.

Key words quaternary carbon stereocenters, carbometalation, cyclopropenes, silicon activation, fragmentation

In the last few decades, we have witnessed remarkable accomplishments for the efficient creation of new carbon–carbon bonds in acyclic systems *en route* to complex molecular frameworks.[1] In this context, single-pot operations combining several steps that collectively provide the same increase of complexity as multistep processes are of high value.[2] Particularly interesting would be the development of one-pot strategies leading to the formation of enantiomerically enriched quaternary carbon stereocenters in acyclic systems.[3] If one wants to reach these goals in a single-pot operation with the creation of several C–C bonds,[4] polyfunctional intermediates such as bismetalated,[5] carbenoids,[6] and oxenoids[7] species may be used, but perfect control of the reactivity and selectivity of those species is needed.[8] One additional bifunctional intermediate that could provide quaternary stereocenters with the same increase of complexity as multistep processes was found in the anionic migration of a silyl group from a carbon to an oxygen, namely the Brook rearrangement,[9] as described in Scheme 1.[10] This one-pot procedure for the transformation of enantiomerically enriched cyclopropenyl amide[11] **1** into acyclic δ-keto amide **6** proceeds through a sequence of: (i) regio- and diastereoselective copper-catalyzed carbomagnesiation reaction of cyclopropenyl amide leading to the formation of diastereoisomerically pure cyclopropyl magnesium species **2**;[12] (ii) addition of acylsilane giving the corresponding α-trimethylsilyl metal alkoxide **3** as a single diastereoisomer that undergoes, by simple addition of THF, (iii) Zn Brook rearrangement[13] with inversion of configuration at the benzylic carbon center;[14] (iv) followed by a selective ring cleavage[15] of organometallic species **4** into the corresponding silyl enol ether **5** as a single geometrical isomer after addition of water. Acidic hydrolysis provided, in a single-pot operation from **1**, the formation of δ-keto amide **6** possessing the quaternary carbon stereocenter in high enantiomeric ratio.[10]

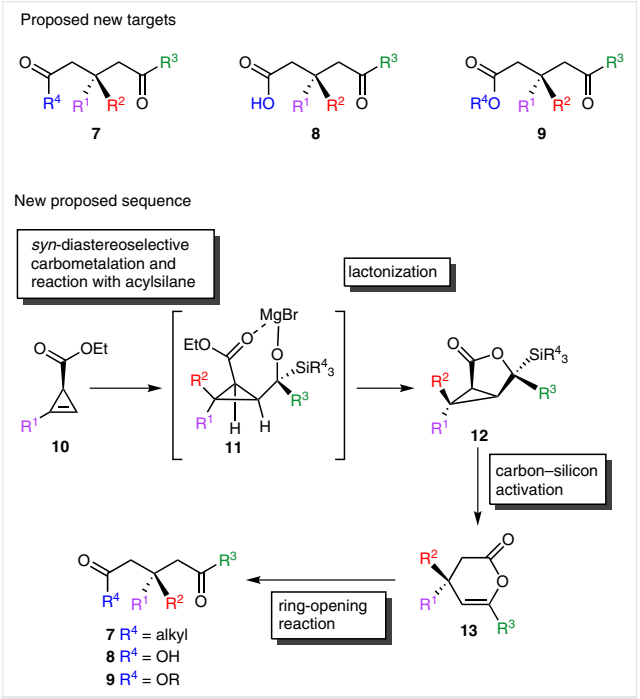
Although the described sequence of Scheme 1 is very efficient, we soon realized that any subsequent chemical transformations of the amide function in the presence of the ketone functional group (R^3 = aryl, alkyl) would be challenging. To solve this potential issue of chemoselectivity, we have then decided to develop an alternative approach that should give an easy access to either δ-diketo **7**, δ-keto acid **8**, and δ-keto ester **9** derivatives (Scheme 2). This new sequence would also start from the easily accessible cyclopropenyl ester **10**, easily accessible in enantiomerically enriched form,[11] that would undergo the known diastereoselective carbometalation reaction as described in Scheme 2.[12] However, upon addition of acylsilane, the diastereoisomerically pure α-silyl carbinol intermediate **11** would undergo cyclization by intramolecular nucleophilic attack of the alkoxide on the ester moiety providing bicyclic lactone **12**. If, indeed, this reaction were to happen, one would then need to trigger a fragmentation of the lactone **12** by activation of the C–Si bond into α-pyrone derivatives **13** that



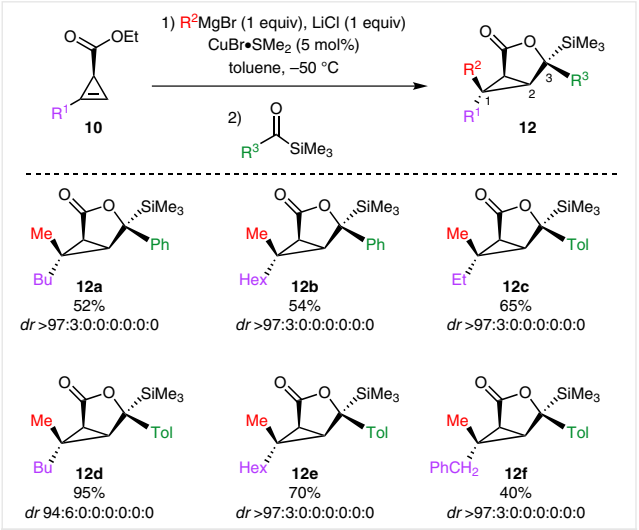
Scheme 1 Brook rearrangement as a trigger for the ring opening of strained carbocycle

would then be able to react with a large range of nucleophiles to provide the corresponding δ-keto acid **7**, δ-keto ester **8**, and δ-diketo **9** derivatives as described in Scheme 2.

We were pleased to observe that the best experimental conditions described for the diastereoselective carbometalation reaction of cyclopropenyl amide[10] could be similarly applied to cyclopropenyl ester **10** and subsequent addition of various acylsilanes directly gave the lactone **12a–f** in good overall yield as unique diastereoisomers as described in Scheme 3. The formation of a unique diastereoisomer for **12** results from the diastereoselectivity of the carbometalation reaction (control of the stereochemistry in C_1–C_2) and reaction with acylsilane (control of the stereochemistry in C_3). The stereochemistry of **12** has been deduced from X-ray crystal structure analysis of a structurally related compound and the diastereoisomeric ratio by ^{1}H NMR.[10]



Scheme 2 Proposed targets and synthetic plan

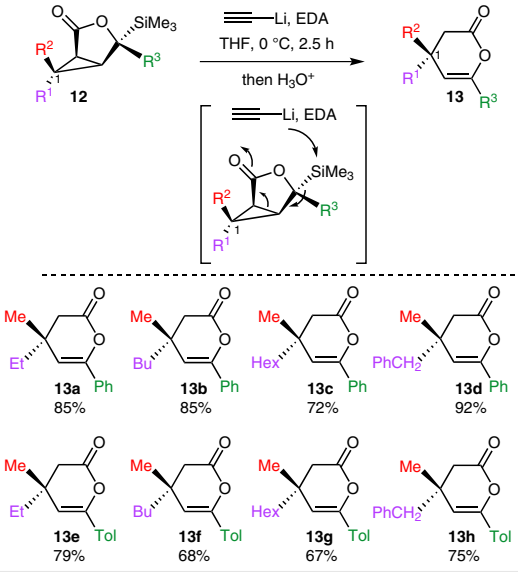


Scheme 3 Formation of lactone **12** via the carbometalation of cyclopropenyl ester followed by addition of acylsilane

Having in hand the diastereoenriched lactones **12a–f**, the next step towards the formation of the acyclic fragments **7–9** possessing the quaternary carbon stereocenters was the transformation of **12** into the α-pyrone **13** via the addition of a nucleophile (Scheme 2). One obvious potential pitfall would be the reaction of the nucleophile on the carbonyl group of the lactone to provide back the cyclopropyl

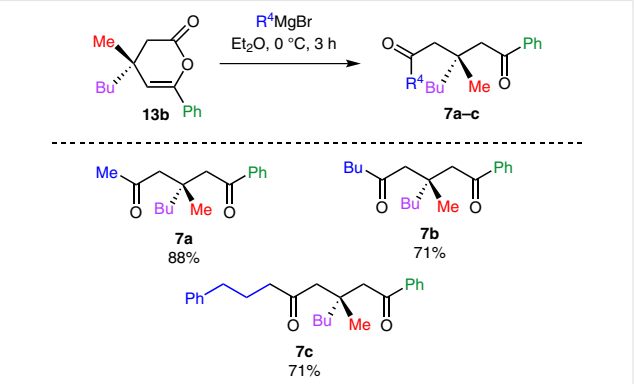
ring derivative **11**. However, we were confident that reactions on the carbonyl group would be difficult as both diastereotopic faces of the carbonyl group were shielded by substituents of the quaternary stereocenter on one hand and by the substituents of the original acylsilane on the other.

We were indeed pleased to observe that the addition of commercially available lithium acetylide, ethylenediamine complex (EDA) trigger selectively the 'sila-Grob'-type fragmentation reaction,[16] leading to α-pyrones **13** as described in Scheme 4. It should be emphasized that α-pyrones are well-known secondary metabolites from microorganisms such as streptomycetes, having a role in spore germination, pseudomonads, fungi, and as bacterial signaling molecules.[17]



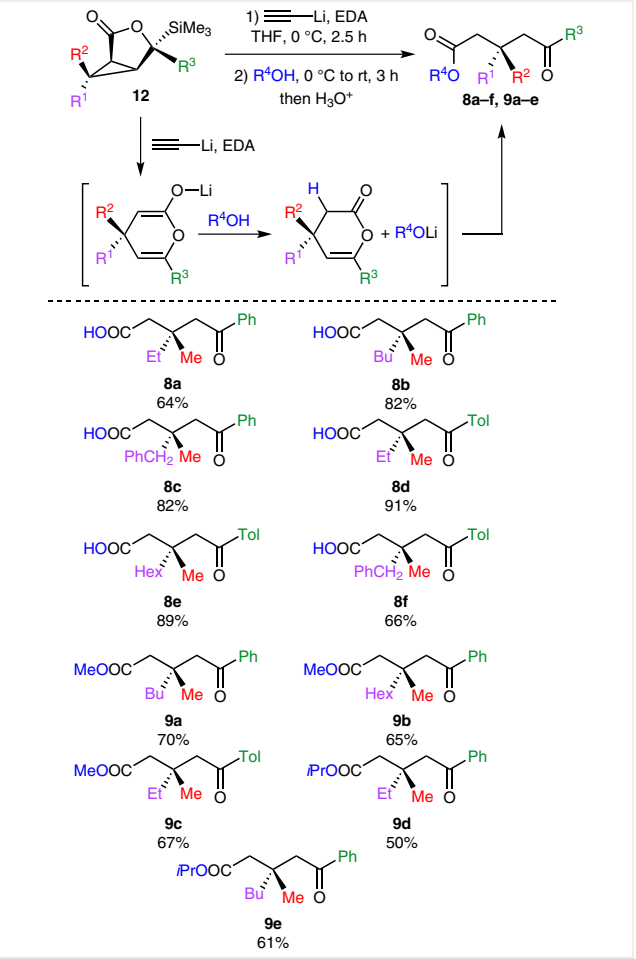
Scheme 4 Synthesis of α-pyrones **13**

In all cases, the α-pyrones were obtained in excellent yields. Interestingly, other alkyllithiums species such as *n*-BuLi, MeLi, or alkylmagnesium bromides, such as MeMgBr, as well as various sources of fluoride anion (CsF, Bu_4NF, KF) in different conditions and solvents provided only traces of α-pyrones, underlining again not only the difficulty for a nucleophile to reach the carbonyl group of the lactone but also to activate the silicon. Only non-bulky and reactive organolithium species, such as alkynyllithium, could promote this 'sila-Grob' fragmentation. It was then obvious that the addition of a nucleophile to the carbonyl group of the α-pyrones **13** should be an easy process and indeed addition of alkylmagnesium bromides to **13b** gave the corresponding acyclic δ-diketones **7a–c** possessing a quaternary carbon stereocenter in very good yields (Scheme 5).



Scheme 5 Ring opening of α-pyrones *en route* to acyclic δ-diketo products **7**

To further improve efficiency, we then decided to prepare the desired acyclic δ-keto acids **8** as well as δ-keto esters **9** in a single-pot operation directly from the bicyclic lactone **12**. To reach this goal, two rings need to be opened



Scheme 6 One-pot conversion of lactone **12** into acyclic δ-keto acid **8** and δ-keto ester **9**

consecutively. Treatment of the initial lactone **12** with alkynyllithium species promotes the first ring opening of the cyclopropyl ring to afford the pyrone lithium enolate intermediate. Then, the success of this strategy resides in the introduction of a second reagent that would not only protonate the pyrone enolate but also generates in situ a nucleophile that would subsequently react with the carbonyl of the pyrone to promote the second ring opening. Pleasingly, the addition of water or alcohol could fulfill these two requirements and provide the formation of either acyclic carboxylic acids **8** or esters **9** in excellent overall yields (Scheme 6).

In conclusion, the diastereoselective carbometalation reaction of cyclopropenyl ester followed by reaction with acylsilane provides a lactone that undergo a 'sila-Grob' fragmentation to give pyrone enolate as a new source of δ-diketones **7**, δ-keto acids **8**, and δ-keto esters **9** possessing an acyclic quaternary stereocenter.

All reactions involving organometallic compounds were carried out in flame-dried glassware under positive pressure of argon in dry solvents under anhydrous conditions using standard Schlenk techniques, unless otherwise stated. Progress of the reactions was monitored by analytical TLC using Merck pre-coated silica gel glass plates with F_{254} indicator. Visualization of spots was accomplished by using UV light (254 nm), *p*-anisaldehyde, phosphomolybdic acid (PMA), or $KMnO_4$ stain. All organometallic compounds, dry solvents, and reagents were transferred using plastic single-use syringes and oven-dried stainless steel needles. The purification of crude mixtures was accomplished either by Celite 535 filter aid (Aldrich) or by preparative flash column chromatography on silica gel 60 Å (Aldrich) using gradient mixtures of either Et_2O/*n*-pentane or *n*-hexane. Yields refer to chromatography and spectroscopically pure compounds, unless otherwise indicated. ^1H and ^{13}C NMR spectra were measured in $CDCl_3$ solution at r.t. on a Bruker Avance AVII400 (400 MHz ^1H, 100 MHz ^{13}C) spectrometer. THF and Et_2O were purified and dried immediately prior to use by an Innovative Technology Pure-Solv PS-MD-2 solvent purifier (alumina columns) and kept under positive pressure of N_2 (99.9999% purity grade). CH_2Cl_2, toluene, and Et_3N were freshly distilled from CaH_2, Na/benzophenone, and $CaSO_4$, respectively, prior to use. *n*-BuLi (2.5 M in hexanes), *t*-BuLi (1.7 M in pentane), MeLi (1.6 M in Et_2O), MeMgBr (3.0 M in Et_2O), lithium acetylide, ethylenediamine complex, $Rh_2(OAc)_4$, CuI, and CuBr·SMe_2, were purchased from Aldrich without further purification. Other chemical compounds were purchased from commercial suppliers and were purified if needed according to suitable procedures. The cyclopropenyl esters[18] and acylsilanes[19] were synthesized according to known procedures.

Bicyclic Lactones 12; General Procedure

LiCl (1.2 mmol) was added to a 3-neck flask prior to flame-drying. CuBr·SMe_2 (5 mol%) was added and diluted in dry toluene (4 mL). Then, the mixture was cooled to –50 °C, MeMgBr (1.2 mmol) was added dropwise, and the mixture was stirred for 15 min at this temperature. The appropriate cyclopropenyl ester **10** (1.5 mmol) diluted in toluene (1 mL) was added dropwise and the mixture was allowed to warm to –35 °C. Then, the appropriate acylsilane (1.0 mmol) was added dropwise and the mixture was stirred for 2.5 h while warming to –25 °C. The reaction was quenched with aq NH_4Cl–NH_4OH solution. The aqueous layer was washed with Et_2O (3 × 5 mL) and the combined organic layers were dried (Na_2SO_4).

(1*S**,4*S**,5*R**,6*R**)-6-Butyl-6-methyl-4-phenyl-4-(trimethylsilyl)-3-oxabicyclo[3.1.0]hexan-2-one (12a)

White solid; yield: 164 mg (0.59 mmol, 52%); R_f = 0.3 (hexane/Et_2O, 4:1); mp 65 °C.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.26–7.21 (m, 2 H), 7.15–7.11 (m, 3 H), 2.27 (d, *J* = 6.4 Hz, 1 H), 2.01 (d, *J* = 6.4 Hz, 1 H), 1.33–1.27 (m, 3 H), 1.26–1.21 (m, 2 H), 1.17–1.13 (m, 1 H), 0.85 (t, *J* = 7.1 Hz, 3 H), 0.61 (s, 3 H), –0.00 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.20, 140.97, 127.86, 125.94, 84.97, 39.98, 33.95, 32.80, 28.53, 28.16, 22.79, 14.39, 14.00, –4.83.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{28}O_2Si$ + H: 317.1931; found: 316.8995.

(1*S**,4*S**,5*R**,6*R**)-6-Hexyl-6-methyl-4-phenyl-4-(trimethylsilyl)-3-oxabicyclo[3.1.0]hexan-2-one (12b)

White solid; yield: 186 mg (0.54 mmol, 54%); R_f = 0.3 (hexane/Et_2O, 4:1); mp 80 °C.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.26–7.21 (m, 3 H), 7.15–7.12 (m, 2 H), 2.22 (d, *J* = 6.4 Hz, 1 H), 2.01 (d, *J* = 6.4 Hz, 1 H), 1.32–1.31 (m, 3 H), 1.28–1.27 (m, 1 H), 1.27–1.24 (m, 4 H), 1.22–1.20 (m, 2 H), 0.82 (t, *J* = 6.8 Hz, 3 H), 0.61 (s, 3 H), –0.00 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.43, 141.15, 128.04, 126.12, 125.45, 85.17, 40.48, 34.17, 32.97, 31.94, 29.57, 28.39, 26.55, 22.81, 14.57, 14.26, –4.64.

HRMS (APCI): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{32}O_2Si$ + H: 345.2244; found: 345.2258.

(1*S**,4*S**,5*R**,6*R**)-6-Ethyl-6-methyl-4-(*p*-tolyl)-4-(trimethylsilyl)-3-oxabicyclo[3.1.0]hexan-2-one (12c)

White solid; yield: 196 mg (0.65 mmol, 65%); R_f = 0.3 (hexane/Et_2O, 4:1); mp 67 °C.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.10–7.09 (m, 4 H), 2.32 (s, 3 H), 2.24 (d, *J* = 6.4 Hz, 1 H), 2.05 (d, *J* = 6.4 Hz, 1 H), 1.43–1.41 (m, 1 H), 1.25–1.22 (m, 1 H), 0.97 (t, *J* = 7.4 Hz, 3 H), 0.67 (s, 3 H), 0.04 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.53, 137.98, 135.62, 128.72, 124.99, 85.15, 33.98, 33.17, 32.82, 29.12, 21.19, 14.04, 10.82, –4.66.

HRMS (APCI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{26}O_2Si$ + H: 303.1775; found: 303.1804.

(1*S**,4*S**,5*R**,6*R**)-6-Butyl-6-methyl-4-(*p*-tolyl)-4-(trimethylsilyl)-3-oxabicyclo[3.1.0]hexan-2-one (12d)

White solid; yield: 313 mg (1.31 mmol, 95%); R_f = 0.3 (hexane/Et_2O, 4:1); mp 70 °C.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.15–7.07 (m, 4 H), 2.33 (s, 3 H), 2.24 (d, *J* = 6.4 Hz, 1 H), 2.05 (d, *J* = 6.4 Hz, 1 H), 1.39–1.23 (m, 6 H), 0.90 (t, *J* = 7.1 Hz, 3 H), 0.67 (s, 3 H), 0.04 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.61, 137.96, 135.63, 128.74, 85.27, 40.20, 34.11, 33.00, 28.72, 28.30, 22.99, 21.21, 14.60, 14.19, –4.64.

(1*S**,4*S**,5*R**,6*R**)-6-Hexyl-6-methyl-4-(*p*-tolyl)-4-(trimethylsilyl)-3-oxabicyclo[3.1.0]hexan-2-one (12e)

White solid; yield: 250 mg (0.70 mmol, 70%); R_f = 0.3 (hexane/Et_2O, 4:1); mp 75 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.10–7.08 (m, 4 H), 2.33 (s, 3 H), 2.24 (d, *J* = 6.4 Hz, 1 H), 2.05 (d, *J* = 6.4 Hz, 1 H), 1.37–1.32 (m, 4 H), 1.29–1.26 (m, 6 H), 0.89 (t, *J* = 6.7 Hz, 3 H), 0.67 (s, 3 H), 0.05 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.55, 137.99, 135.63, 128.74, 125.73, 85.23, 40.51, 34.14, 32.98, 31.95, 29.58, 28.32, 26.55, 22.81, 21.22, 14.60, 14.26, –4.63.

HRMS (APCI): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{34}O_2Si$ + H: 359.2401; found: 359.2414.

(1*S,4*S**,5*R**,6*R**)-6-Benzyl-6-methyl-4-(*p*-tolyl)-4-(trimethylsilyl)-3-oxabicyclo[3.1.0]hexan-2-one (12f)**

White solid; yield: 146 mg (0.40 mmol, 40%); R_f = 0.3 (hexane/Et_2O, 4:1); mp 122 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31–7.27 (m, 2 H), 7.25–7.21 (m, 2 H), 7.14–7.12 (m, 2 H), 6.94–6.88 (m, 3 H), 2.70 (d, *J* = 13.9 Hz, 1 H), 2.54 (d, *J* = 13.9 Hz, 1 H), 2.41 (d, *J* = 6.5 Hz, 1 H), 2.25 (d, *J* = 6.5 Hz, 1 H), 2.24 (s, 3 H), 0.63 (s, 3 H), –0.00 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.00, 137.72, 137.21, 135.33, 129.19, 128.30, 126.65, 85.00, 45.26, 32.90, 32.14, 28.26, 20.83, 14.87, –4.99.

HRMS (APCI): *m*/*z* [M + H]$^+$ calcd for $C_{23}H_{28}O_2Si$ + H: 365.1931; found: 365.1943.

α-Pyrones 13; General Procedure from Bicyclic Lactones 12

Lithium acetylide ethylenediamine complex (approx. 2 mmol) was added to a weighed flask and the flask was weighed again. THF was added (15 mL) and the solution was cooled using an ice bath. The appropriate bicyclic lactone **12** (0.5 mmol, 1/3 equiv from the lithium acetylide, EDA complex weighed) diluted in THF (2 mL) was added dropwise and the mixture was stirred at this temperature following the reaction by TLC (full consumption of starting material after 2.5 h). The reaction was quenched with aq NH_4Cl solution. The aqueous layer was washed with Et_2O (3 × 15 mL), and the combined organic layers were dried (Na_2SO_4).

4-Ethyl-4-methyl-6-phenyl-3,4-dihydro-2*H*-pyran-2-one (13a)

Yellow oil; yield: 92 mg (0.42 mmol, 85%); R_f = 0.3 (hexane/Et_2O, 4:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.62 (dd, *J* = 8.0, 1.4 Hz, 2 H), 7.39–7.33 (m, 3 H), 5.65 (s, 1 H), 2.59 (d, *J* = 15.6 Hz, 1 H), 2.47 (d, *J* = 15.6 Hz, 1 H), 1.55–1.49 (m, 2 H), 1.17 (s, 3 H), 0.94 (t, *J* = 7.5 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.87, 148.65, 132.26, 128.75, 128.32, 124.40, 109.83, 40.82, 34.70, 33.70, 25.69, 8.46.

HRMS (APCI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{16}O_2$ + H: 217.1223; found: 217.1225.

4-Butyl-4-methyl-6-phenyl-3,4-dihydro-2*H*-pyran-2-one (13b)

Yellow oil; yield: 104 mg (0.42 mmol, 85%); R_f = 0.3 (hexane/Et_2O, 4:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.57 (dd, *J* = 8.1, 1.5 Hz, 2 H), 7.32–7.28 (m, 3 H), 5.61 (s, 1 H), 2.54 (d, *J* = 15.6 Hz, 1 H), 2.41 (d, *J* = 15.6 Hz, 1 H), 1.45–1.36 (m, 2 H), 1.28–1.25 (m, 4 H), 1.13 (s, 3 H), 0.86 (t, *J* = 6.8 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.02, 148.68, 132.50, 128.95, 128.53, 124.61, 110.39, 41.49, 41.18, 34.64, 26.50, 26.44, 23.25, 14.04.

HRMS (APCI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{20}O_2$ + H: 245.1536; found: 245.1559.

4-Hexyl-4-methyl-6-phenyl-3,4-dihydro-2*H*-pyran-2-one (13c)

Yellow oil; yield: 98 mg (0.36 mmol, 72%); R_f = 0.3 (hexane/Et_2O, 4:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.62 (d, *J* = 6.6 Hz, 2 H), 7.37–7.35 (m, 3 H), 5.66 (s, 1 H), 2.60 (d, *J* = 15.6 Hz, 1 H), 2.47 (d, *J* = 15.6 Hz, 1 H), 1.47–1.43 (m, 2 H), 1.35–1.33 (m, 8 H), 1.28 (s, 3 H), 0.87 (t, *J* = 6.0 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.17, 148.80, 132.60, 129.05, 128.63, 124.72, 110.51, 41.61, 41.58, 34.79, 31.87, 29.93, 26.54, 24.41, 22.77, 14.21.

HRMS (APCI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{24}O_2$ + H: 273.1849; found: 273.2020.

4-Benzyl-4-methyl-6-phenyl-3,4-dihydro-2*H*-pyran-2-one (13d)

Yellow oil; yield: 127 mg (0.46 mmol, 92%); R_f = 0.3 (hexane/Et_2O, 4:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.57 (dd, *J* = 7.8, 1.6 Hz, 2 H), 7.36–7.34 (m, 3 H), 7.29–7.25 (m, 3 H), 7.14 (dd, *J* = 6.4 Hz, 2 H), 5.64 (s, 1 H), 2.74 (s, 2 H), 2.65 (d, *J* = 15.6 Hz, 1 H), 2.45 (d, *J* = 15.6 Hz, 1 H), 1.24 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.63, 149.02, 136.65, 132.53, 130.63, 129.20, 128.68, 128.40, 127.07, 124.81, 109.99, 47.10, 41.41, 35.92, 26.38.

HRMS (APCI): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{18}O_2$ + H: 279.1380; found: 279.1389.

4-Ethyl-4-methyl-6-(*p*-tolyl)-3,4-dihydro-2*H*-pyran-2-one (13e)

Yellow oil; yield: 91 mg (0.39 mmol, 79%); R_f = 0.3 (hexane/Et_2O, 4:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.51 (d, *J* = 8.2 Hz, 2 H), 7.17 (d, *J* = 8.1 Hz, 2 H), 5.59 (s, 1 H), 2.57 (d, *J* = 15.6 Hz, 1 H), 2.45 (d, *J* = 15.6 Hz, 1 H), 2.36 (s, 3 H), 1.52–1.49 (m, 2 H), 1.16 (s, 3 H), 0.93 (t, *J* = 7.5 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.33, 149.02, 139.06, 129.79, 129.30, 124.62, 109.21, 41.19, 34.94, 34.04, 26.04, 21.38, 8.76.

HRMS (APCI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{18}O_2$ + H: 231.1380; found: 231.1385.

4-Butyl-4-methyl-6-(*p*-tolyl)-3,4-dihydro-2*H*-pyran-2-one (13f)

Yellow oil; yield: 88 mg (0.34 mmol, 68%); R_f = 0.3 (hexane/Et_2O, 4:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.50 (d, *J* = 8.2 Hz, 2 H), 7.17 (d, *J* = 8.1 Hz, 2 H), 5.60 (s, 1 H), 2.59 (d, *J* = 15.6 Hz, 1 H), 2.46 (d, *J* = 15.6 Hz, 1 H), 2.36 (s, 3 H), 1.57–1.44 (m, 2 H), 1.32–1.28 (m, 4 H), 1.17 (s, 3 H), 0.90 (t, *J* = 6.7 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.38, 148.86, 139.09, 129.82, 129.33, 124.64, 109.60, 41.69, 41.36, 34.71, 26.63, 23.38, 21.42, 14.17.

HRMS (APCI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{22}O_2$ + H: 259.1693; found: 259.1904.

4-Hexyl-4-methyl-6-(*p*-tolyl)-3,4-dihydro-2*H*-pyran-2-one (13g)

Yellow oil; yield: 96 mg (0.33 mmol, 67%); R_f = 0.3 (hexane/Et_2O, 4:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.50 (d, *J* = 8.2 Hz, 2 H), 7.17 (d, *J* = 10.8 Hz, 2 H), 5.59 (s, 1 H), 2.58 (d, *J* = 15.6 Hz, 1 H), 2.45 (d, *J* = 15.6 Hz, 1 H), 2.36 (s, 3 H), 1.47–1.43 (m, 2 H), 1.28–1.26 (m, 8 H), 1.17 (s, 3 H), 0.87 (t, *J* = 6.4 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.39, 148.86, 139.09, 129.83, 129.34, 124.64, 109.62, 41.64, 34.75, 31.89, 29.98, 26.61, 24.43, 22.79, 21.43, 14.24.

HRMS (APCI): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{26}O_2$ + H: 287.2006; found: 287.2218.

4-Benzyl-4-methyl-6-(*p*-tolyl)-3,4-dihydro-2*H*-pyran-2-one (13h)

Yellow oil; yield: 109 mg (0.37 mmol, 75%); R_f = 0.3 (hexane/Et_2O, 4:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40 (d, *J* = 8.1 Hz, 2 H), 7.21 (t, *J* = 6.8 Hz, 3 H), 7.11–7.07 (m, 4 H), 5.52 (s, 1 H), 2.66 (s, 2 H), 2.58 (d, *J* = 15.6 Hz, 1 H), 2.38 (d, *J* = 15.6 Hz, 1 H), 2.29 (s, 3 H), 1.15 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.79, 149.07, 139.23, 136.73, 130.63, 129.74, 129.37, 128.37, 127.02, 124.73, 109.08, 47.14, 41.47, 35.86, 26.42, 21.42.

HRMS (APCI): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{20}O_2$ + H: 293.1536; found: 293.1545.

Acyclic Diketones 7; General Procedure from α-Pyrone 13b

The α-pyrone **13b** (98 mg, 0.4 mmol, 1.0 equiv) was charged in dried flask with dry Et_2O (8 mL). Then Grignard reagent (0.48 mmol, 1.2 equiv) was added dropwise at 0 °C under argon and the mixture was stirred at this temperature for 3 h. The reaction was quenched with 1 M HCl and extracted with Et_2O. The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. The crude product was purified by chromatography (silica gel, hexane/Et_2O).

3-Butyl-3-methyl-1-phenylhexane-1,5-dione (7a)

Colorless oil; yield: 92 mg (0.35 mmol, 88%); R_f = 0.4 (hexane/Et_2O, 6:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.95–7.81 (m, 2 H), 7.48 (t, *J* = 7.3 Hz, 1 H), 7.39 (t, *J* = 7.5 Hz, 2 H), 3.18 (d, *J* = 16.6 Hz, 1 H), 3.10 (d, *J* = 16.6 Hz, 1 H), 2.74 (d, *J* = 17.3 Hz, 1 H), 2.65 (d, *J* = 17.3 Hz, 1 H), 2.04 (s, 3 H), 1.51–1.42 (m, 2 H), 1.24–1.13 (m, 4 H), 1.06 (s, 3 H), 0.83 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 208.99, 200.59, 138.43, 132.79, 128.53, 128.01, 50.45, 44.86, 40.55, 35.61, 31.88, 25.99, 25.80, 23.37, 14.16.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{24}O_2$ + H: 261.1849; found: 261.1851.

3-Butyl-3-methyl-1-phenylnonane-1,5-dione (7b)

Colorless oil; yield: 85 mg (0.28 mmol, 71%); R_f = 0.5 (hexane/Et_2O, 6:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.85 (d, *J* = 7.2 Hz, 2 H), 7.45 (t, *J* = 7.3 Hz, 1 H), 7.35 (t, *J* = 7.5 Hz, 2 H), 3.16 (d, *J* = 16.6 Hz, 1 H), 3.07 (d, *J* = 16.6 Hz, 1 H), 2.66 (d, *J* = 17.2 Hz, 1 H), 2.58 (d, *J* = 17.2 Hz, 1 H), 2.27 (t, *J* = 7.4 Hz, 2 H), 1.42 (dd, *J* = 15.1, 7.3 Hz, 4 H), 1.17 (dt, *J* = 14.4, 8.8 Hz, 6 H), 1.02 (s, 3 H), 0.79 (t, *J* = 7.3 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 211.46, 200.68, 138.51, 132.79, 128.56, 128.06, 77.48, 77.16, 76.84, 49.72, 45.01, 44.29, 40.64, 35.71, 26.06, 25.93, 25.90, 23.42, 22.39, 14.21, 13.96.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{30}O_2$ + H: 303.2319; found: 303.2332.

3-Butyl-3-methyl-1,8-diphenyloctane-1,5-dione (7c)

Colorless oil; yield: 103 mg (0.28 mmol, 71%); R_f = 0.4 (hexane/Et_2O, 6:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.84 (d, *J* = 7.3 Hz, 2 H), 7.42 (t, *J* = 7.3 Hz, 1 H), 7.33 (t, *J* = 7.5 Hz, 2 H), 7.17 (t, *J* = 7.4 Hz, 2 H), 7.07 (dd, *J* = 13.6, 7.2 Hz, 3 H), 3.14 (d, *J* = 16.6 Hz, 1 H), 3.06 (d, *J* = 16.6 Hz, 1 H), 2.63 (d, *J* = 17.2 Hz, 1 H), 2.55 (d, *J* = 17.2 Hz, 1 H), 2.48 (t, *J* = 7.6 Hz, 2 H), 2.27 (t, *J* = 7.3 Hz, 2 H), 1.81–1.70 (m, 2 H), 1.45–1.36 (m, 2 H), 1.19–1.08 (m, 4 H), 1.00 (s, 3 H), 0.78 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 210.86, 200.61, 141.79, 138.45, 132.79, 128.54, 128.53, 128.40, 128.04, 125.94, 77.48, 77.16, 76.84, 49.77, 44.95, 43.57, 40.64, 35.67, 35.14, 26.03, 25.89, 25.21, 23.39, 14.20.

HRMS (APCI): *m*/*z* [M + H]$^+$ calcd for $C_{25}H_{32}O_2$ + H: 365.2475; found: 365.2498.

Acyclic Acids 8; General Procedure from Bicyclic Lactones 12

Lithium acetylide, ethylenediamine complex (approx. 1 mmol) was added to a weighed flask and the flask was weighed again. THF (1 mL) was added and the solution was cooled to 0 °C using an ice bath. The appropriate bicyclic lactone **12** (0.5 mmol, 1/3 equiv from the lithium acetylide, EDA complex weighed) diluted in THF (1 mL) was added dropwise and stirred at this temperature following the reaction by TLC (full consumption of the starting material after 2.5 h). Then, sat. aq KOH solution was added and the mixture was stirred for an additional hour. The aqueous layer was washed with EtOAc (5 × 3 mL). The aqueous layers were combined and few drops of concd HCl were added (pH 1), the aqueous layer was then washed with CH_2Cl_2 (5 × 3 mL). The combined organic layers were dried (Na_2SO_4).

3-Ethyl-3-methyl-5-oxo-5-phenylpentanoic Acid (8a)

Colorless oil; yield: 0.08 mmol, 64%); R_f = 0.2 (hexane/Et_2O, 1:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.69 (bs), 7.95 (d, *J* = 7.4 Hz, 2 H), 7.54 (t, *J* = 7.3 Hz, 1 H), 7.45 (t, *J* = 7.6 Hz, 2 H), 3.12–3.10 (m, 2 H), 2.61 (d, *J* = 14.4 Hz, 1 H), 2.55 (d, *J* = 14.4 Hz, 1 H), 1.52–1.48 (m, 2 H), 1.10 (s, 3 H), 0.87 (t, *J* = 7.4 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.10, 138.22, 133.34, 128.77, 128.35, 44.79, 42.93, 36.33, 33.27, 25.19, 8.29.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{18}O_3$ + H: 235.1329; found: 235.2642.

3-Methyl-3-(2-oxo-2-phenylethyl)heptanoic Acid (8b)

Colorless oil; yield: 159 mg (0.70 mmol, 82%); R_f = 0.2 (hexane/Et_2O, 1:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.62 (bs), 7.94–7.92 (m, 2 H), 7.56–7.52 (t, *J* = 7.4 Hz, 1 H), 7.42 (t, *J* = 7.6 Hz, 2 H), 3.17–3.08 (m, 2 H), 2.65 (d, *J* = 14.6 Hz, 1 H), 2.58 (d, *J* = 14.6 Hz, 1 H), 1.55–1.47 (m, 2 H), 1.22–1.20 (m, 4 H), 1.13 (s, 3 H), 0.87 (t, *J* = 6.7 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 200.20, 177.96, 137.95, 132.81, 128.36, 127.86, 44.76, 42.78, 40.09, 35.54, 25.70, 25.32, 23.04, 13.85.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{22}O_3$ + H: 263.1642; found: 263.1640.

3-Benzyl-3-methyl-5-oxo-5-phenylpentanoic Acid (8c)

Colorless oil; yield: 29 mg (0.10 mmol, 82%); R_f = 0.2 (hexane/Et_2O, 1:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.83 (d, *J* = 7.3 Hz, 2 H), 7.47 (t, *J* = 7.4 Hz, 1 H), 7.36 (t, *J* = 7.7 Hz, 2 H), 7.20–7.18 (m, 3 H), 7.08 (d, *J* = 6.5 Hz, 2 H), 3.08–2.97 (m, 2 H), 2.90 (d, *J* = 13.2 Hz, 1 H), 2.81 (d, *J* = 13.2 Hz, 1 H), 2.69 (d, *J* = 14.9 Hz, 1 H), 2.49 (d, *J* = 14.9 Hz, 1 H), 1.06 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 200.92, 177.72, 138.45, 137.94, 133.61, 131.30, 129.08, 128.55, 128.53, 126.95, 46.32, 44.86, 43.00, 37.11, 25.92.

HRMS (APCI): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{20}O_3$ + H: 297.1485; found: 297.1497.

3-Ethyl-3-methyl-5-oxo-5-(*p*-tolyl)pentanoic Acid (8d)

Colorless oil; yield: 21 mg (0.08 mmol, 91%); R_f = 0.2 (hexane/Et_2O, 1:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.62 (bs), 7.79 (d, *J* = 8.1 Hz, 2 H), 7.25 (d, *J* = 8.3 Hz, 2 H), 3.00 (s, 2 H), 2.48 (d, *J* = 14.2 Hz, 1 H), 2.42 (d, *J* = 14.2 Hz, 1 H), 2.34 (s, 3 H), 1.49–1.45 (m, 2 H), 1.02 (s, 3 H), 0.80 (t, *J* = 7.4 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.47, 176.77, 144.71, 135.99, 129.81, 128.94, 44.98, 43.49, 36.86, 33.71, 25.57, 22.13, 8.62.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{20}O_3$ + H: 249.1485; found: 249.1736.

3-Methyl-3-[2-oxo-2-(*p*-tolyl)ethyl]nonanoic Acid (8e)

Colorless oil; yield: 48 mg (0.16 mmol, 89%); R_f = 0.2 (hexane/Et_2O, 1:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.14 (d, *J* = 8.2 Hz, 2 H), 7.53 (d, *J* = 8.1 Hz, 2 H), 3.36 (m, 2 H), 2.87 (d, *J* = 14.3 Hz, 1 H), 2.74 (d, *J* = 14.3 Hz, 1 H), 2.69 (s, 3 H), 1.78–1.71 (m, 2 H), 1.53–1.51 (m, 8 H), 1.39 (s, 3 H), 1.13 (t, *J* = 6.7 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.26, 177.42, 144.63, 136.00, 129.78, 128.88, 43.74, 42.41, 36.63, 32.23, 30.29, 26.13, 23.08, 22.11, 14.54.

3-Benzyl-3-methyl-5-oxo-5-(*p*-tolyl)pentanoic Acid (8f)

Colorless oil; yield: 41 mg (0.13 mmol, 66%); R_f = 0.2 (hexane/Et_2O, 1:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.10 (d, *J* = 8.1 Hz, 2 H), 7.55–7.49 (m, 5 H), 7.43 (d, *J* = 6.6 Hz, 2 H), 3.39 (d, *J* = 16.6 Hz, 1 H), 3.30 (d, *J* = 16.6 Hz, 1 H), 3.22 (d, *J* = 28.3, 13.2 Hz, 1 H), 3.16 (d, *J* = 28.3, 13.2 Hz, 1 H), 3.00 (d, *J* = 14.7 Hz, 1 H), 2.82 (d, *J* = 14.7 Hz, 1 H), 2.68 (s, 3 H), 1.38 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 200.66, 176.74, 144.35, 137.59, 135.59, 131.02, 129.49, 128.49, 128.22, 126.62, 46.14, 44.44, 37.01, 25.66, 21.81.

HRMS (APCI): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{22}O_3$ + H: 311.1642; found: 311.1644.

Acyclic Esters 9; General Procedure from Bicyclic Lactones 12

Lithium acetylide, ethylenediamine complex (approx. 1 mmol) was added to a weighed flask and the flask was weighed again. THF (1 mL) was added and the solution was cooled to 0 °C using an ice bath. The appropriate bicyclic lactone **12** (0.5 mmol, 1/3 equiv from the lithium acetylide, EDA complex weighed) diluted in THF (1 mL) was added dropwise and stirred at this temperature following the reaction by TLC (full consumption of the starting material after 2.5 h). Then, either aq *i*-PrOH or 3 M NaOMe in MeOH was added and the mixture was stirred for 1.5 h. The aqueous layer was washed with Et_2O (3 × 5 mL) and the combined organic layers were dried (Na_2SO_4).

Methyl 3-Methyl-3-(2-oxo-2-phenylethyl)heptanoate (9a)

Colorless oil; yield: 79 mg (0.29 mmol, 70%); R_f = 0.3 (hexane/Et_2O, 7:3).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.94 (d, *J* = 7.4 Hz, 2 H), 7.52 (t, *J* = 7.3 Hz, 1 H), 7.43 (t, *J* = 7.6 Hz, 2 H), 3.59 (s, 3 H), 3.16 (d, *J* = 14.7 Hz, 1 H), 3.08 (d, *J* = 16.8 Hz, 1 H), 2.61 (d, *J* = 14.7 Hz, 1 H), 2.55 (d, *J* = 14.7 Hz, 1 H), 1.55–1.49 (m, 2 H), 1.27–1.25 (m, 4 H), 1.13 (s, 3 H), 0.87 (t, *J* = 6.8 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.66, 172.72, 138.21, 138.21, 132.59, 128.34, 127.77, 50.96, 44.90, 42.60, 40.03, 35.48, 25.79, 25.35, 23.13, 13.92.

HRMS (APCI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{24}O_3$ + H: 277.1798; found: 277.1864.

Methyl 3-Methyl-3-(2-oxo-2-phenylethyl)nonanoate (9b)

Colorless oil; yield: 53 mg (0.17 mmol, 65%); R_f = 0.3 (hexane/Et_2O, 7:3).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.94 (d, *J* = 7.3 Hz, 2 H), 7.54 (t, *J* = 7.3 Hz, 1 H), 7.44 (t, *J* = 7.6 Hz, 2 H), 3.60 (s, 3 H), 3.16 (d, *J* = 16.8 Hz, 1 H), 3.08 (d, *J* = 16.8 Hz, 1 H), 2.61 (d, *J* = 14.7 Hz, 1 H), 2.54 (d, *J* = 14.7 Hz, 1 H), 1.56–1.49 (m, 2 H), 1.29–1.24 (m, 8 H), 1.13 (s, 3 H), 0.86 (t, *J* = 6.4 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.69, 172.73, 138.23, 132.59, 128.35, 127.78, 50.98, 44.92, 42.62, 40.34, 35.54, 31.65, 29.74, 25.36, 23.54, 22.48, 13.92.

HRMS (APCI): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{28}O_3$ + H: 305.2111; found: 305.2145.

Methyl 3-Ethyl-3-methyl-5-oxo-5-(*p*-tolyl)pentanoate (9c)

Colorless oil; yield: 50 mg (0.19 mmol, 67%); R_f = 0.3 (hexane/Et_2O, 7:3).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.78 (d, *J* = 8.2 Hz, 2 H), 7.18 (t, *J* = 7.4 Hz, 2 H), 3.52 (s, 3 H), 3.04 (d, *J* = 16.5 Hz, 1 H), 2.97 (d, *J* = 16.5 Hz, 1 H), 2.53 (d, *J* = 14.7 Hz, 1 H), 2.46 (d, *J* = 14.7 Hz, 1 H), 2.33 (s, 3 H), 1.53–1.49 (m, 2 H), 1.04 (s, 3 H), 0.86 (t, *J* = 7.5 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.35, 172.76, 143.34, 135.75, 129.03, 127.96, 50.99, 44.35, 42.25, 35.70, 32.66, 24.78, 21.44, 8.00.

HRMS (APCI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{22}O_3$ + H: 263.1642; found: 263.2108.

Isopropyl 3-Ethyl-3-methyl-5-oxo-5-phenylpentanoate (9d)

Colorless oil; yield: 17 mg (0.06 mmol, 50%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.94 (d, *J* = 7.2 Hz, 2 H), 7.53 (t, *J* = 7.3 Hz, 1 H), 7.44 (t, *J* = 7.5 Hz, 2 H), 4.96 (dt, *J* = 12.5, 6.3 Hz, 1 H), 3.15 (d, *J* = 16.7 Hz, 1 H), 3.07 (d, *J* = 16.7 Hz, 1 H), 2.54 (d, *J* = 14.3 Hz, 1 H), 2.48 (d, *J* = 14.3 Hz, 1 H), 1.59–1.55 (m, 2 H), 1.16 (dd, *J* = 6.3, 0.6 Hz, 6 H), 1.11 (s, 3 H), 0.87 (t, *J* = 7.5 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 200.28, 172.45, 138.88, 133.23, 128.99, 128.43, 67.72, 45.33, 43.41, 36.40, 33.29, 25.41, 22.34, 22.32, 8.65.

Isopropyl 3-Methyl-3-(2-oxo-2-phenylethyl)heptanoate (9e)

Colorless oil; yield: 30 mg (0.10 mmol, 61%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.94 (d, *J* = 7.2 Hz, 2 H), 7.53 (t, *J* = 7.3 Hz, 1 H), 7.44 (t, *J* = 7.5 Hz, 2 H), 4.96 (dt, *J* = 12.5, 6.3 Hz, 1 H), 3.16 (d, *J* = 16.8 Hz, 1 H), 3.07 (d, *J* = 16.8 Hz, 1 H), 2.55 (d, *J* = 14.3 Hz, 1 H), 2.49 (d, *J* = 14.3 Hz, 1 H), 1.53–1.49 (m, 2 H), 1.26–1.25 (m, 4 H), 1.16 (d, *J* = 6.2 Hz, 6 H), 1.13 (s, 3 H), 0.87 (t, *J* = 6.7 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.91, 172.09, 138.55, 132.87, 128.64, 128.08, 67.36, 45.44, 43.50, 40.35, 35.88, 26.11, 25.66, 23.47, 22.00, 14.27.

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References

(1) Carreira, E. M.; Kvaerno, L. *Classics in Stereoselective Synthesis*; Wiley-VCH: Weinheim, **2009**.

(2) For reviews published in 2014, see: (a) Volla, C. M. R.; Atodiresei, I.; Rueping, M. *Chem. Rev.* **2014**, *114*, 2390. (b) Rotstein, B. H.; Zaretsky, S.; Rai, V.; Yudin, A. K. *Chem. Rev.* **2014**, *114*, 8323. (c) Cioc, R. C.; Ruijter, E.; Orru, R. V. A. *Green Chem.* **2014**, *16*, 2958. (d) Cho, H. Y.; Morken, J. P. *Chem. Soc. Rev.* **2014**, *43*, 4368.

(3) For reviews of quaternary carbon stereocenters, see: (a) Quasdorf, K. W.; Overman, L. E. *Nature (London)* **2014**, *516*, 181. (b) Hong, A. Y.; Stoltz, B. M. *Eur. J. Org. Chem.* **2013**, 2745. (c) Hawner, C.; Alexakis, A. *Chem. Commun.* **2010**, *46*, 7295. (d) Bella, M.; Casperi, T. *Synthesis* **2009**, 1583. (e) Cozzi, P. G.; Hilgraf, R.; Zimmermann, N. *Eur. J. Org. Chem.* **2007**, 5969. (f) Trost, B. M.; Jiang, C. *Synthesis* **2006**, 369. (g) Denissova, I.; Barriault, L. *Tetrahedron* **2003**, *59*, 10105. (h) Christoffers, J.; Mann, A. *Angew. Chem. Int. Ed.* **2001**, *40*, 4591. (i) Corey, E. J.; Guzman-Perez, A. *Angew. Chem. Int. Ed.* **1998**, *37*, 388.

(4) For reviews, see: (a) Eppe, G.; Didier, D.; Marek, I. *Chem. Rev.* **2015**, *115*, 9175. (b) Das, J. P.; Marek, I. *Chem. Commun.* **2011**, *47*, 4593. (c) Marek, I.; Sklute, G. *Chem. Commun.* **2007**, 1683.

(5) (a) Vasseur, A.; Perrin, L.; Eisenstein, O.; Marek, I. *Chem. Sci.* **2015**, *6*, 2770. (b) Masarwa, A.; Didier, D.; Zabrodski, T.; Schinkel, M.; Ackermann, L.; Marek, I. *Nature (London)* **2014**, *505*, 199.

(6) (a) Vabre, R.; Island, B.; Diehl, C. J.; Schreiner, P. R.; Marek, I. *Angew. Chem. Int. Ed.* **2015**, *54*, 9996. (b) Pasco, M.; Gilboa, N.; Mejuch, T.; Marek, I. *Organometallics* **2013**, *32*, 942. (c) Mejuch, T.; Gilboa, N.; Gayon, E.; Wang, H.; Houk, K. N.; Marek, I. *Acc. Chem. Res.* **2013**, *46*, 1659. (d) Mejuch, T.; Dutta, B.; Botoshansky, M.; Marek, I. *Org. Biomol. Chem.* **2012**, *10*, 5803. (e) Mejuch, T.; Botoshansky, M.; Marek, I. *Org. Lett.* **2011**, *13*, 3604. (f) Gilboa, N.; Wang, H.; Houk, K. N.; Marek, I. *Chem. Eur. J.* **2011**, *17*, 8000. (g) Dutta, B.; Gilboa, N.; Marek, I. *J. Am. Chem. Soc.* **2010**, *132*, 5588. (h) Kolodney, G.; Sklute, G.; Perrone, S.; Knochel, P.; Marek, I. *Angew. Chem. Int. Ed.* **2007**, *46*, 9291. (i) Das, J. P.; Chechik, H.; Marek, I. *Nat. Chem.* **2009**, *1*, 128. (j) Sklute, G.; Marek, I. *J. Am. Chem. Soc.* **2006**, *128*, 4642. (k) Marek, I. *Tetrahedron* **2002**, *58*, 9463.

(7) (a) Nairoukh, Z.; Marek, I. *Angew. Chem. Int. Ed.* **2015**, *54*, 14393. (b) Simaan, M.; Delaye, P.-O.; Shi, M.; Marek, I. *Angew. Chem. Int. Ed.* **2015**, *54*, 12345. (c) Minko, Y.; Marek, I. *Org. Biomol. Chem.* **2014**, *12*, 1535. (d) Minko, Y.; Pasco, M.; Lercher, L.; Marek, I. *Nat. Protoc.* **2013**, *8*, 749. (e) Minko, Y.; Pasco, M.; Botoshansky, M.; Marek, I. *Nature (London)* **2012**, *490*, 522. (f) Delaye, P.-O.; Didier, D.; Marek, I. *Angew. Chem. Int. Ed.* **2013**, *52*, 5333.

(8) Marek, I.; Masarwa, A.; Delaye, P.-O.; Leibeling, M. *Angew. Chem. Int. Ed.* **2015**, *54*, 414.

(9) Brook, A. G. *Acc. Chem. Res.* **1974**, *7*, 77.

(10) Zhang, F.-G.; Eppe, G.; Marek, I. *Angew. Chem. Int. Ed.* **2016**, *55*, 714.

(11) For the enantioselective cyclopropenylation of alkynes, see: (a) Briones, J. F.; Davies, H. M. L. *J. Am. Chem. Soc.* **2012**, *134*, 11916. (b) Uehara, M.; Suematsu, H.; Yasutomi, Y.; Katsuki, T. *J. Am. Chem. Soc.* **2011**, *133*, 170. (c) Cui, X.; Xu, X.; Lu, H.; Zhu, S.; Wojtas, L.; Zhang, X. P. *J. Am. Chem. Soc.* **2011**, *133*, 3304. (d) Goto, K.; Takeda, K.; Shiamda, N.; Nambu, H.; Anada, M.; Shiro, M.; Ando, K.; Hashimoto, S. *Angew. Chem. Int. Ed.* **2011**, *50*, 6803. (e) Briones, J. F.; Davies, H. M. L. *Tetrahedron* **2011**, *67*, 4313. (f) Briones, J. F.; Hansen, J. H.; Hardcastle, K. I.; Autschbach, J.; Davies, H. M. L. *J. Am. Chem. Soc.* **2010**, *132*, 17211. (g) Lou, Y.; Horikawa, M.; Kloster, R. A.; Hawryluk, N. A.; Corey, E. J. *J. Am. Chem. Soc.* **2004**, *126*, 8916.

(12) (a) Müller, D.; Marek, I. *Chem. Soc. Rev.* **2016**, in press; DOI: 10.1039/C5CS00897B. (b) Didier, D.; Delaye, P.-O.; Simaan, M.; Island, B.; Eppe, G.; Eijsberg, H.; Kleiner, A.; Knochel, P.; Marek, I. *Chem. Eur. J.* **2014**, *20*, 1038. (c) Nakamura, M.; Isobe, H.; Nakamura, E. *Chem. Rev.* **2003**, *103*, 1295. (d) Fox, J. M.; Yan, N. *Curr. Org. Chem.* **2005**, *9*, 719. (e) Rubin, M.; Rubina, M.; Gevorgyan, V. *Synthesis* **2006**, 1221. (f) Rubin, M.; Rubina, M.; Gevorgyan, V. *Chem. Rev.* **2007**, *107*, 3117. (g) Zhu, Z.-B.; Wei, Y.; Shi, M. *Chem. Soc. Rev.* **2011**, *40*, 5534.

(13) (a) Smirnov, P.; Katan, E.; Mathew, J.; Kostenko, A.; Karni, M.; Nijs, A.; Bolm, C.; Marek, I. *J. Org. Chem.* **2014**, *79*, 12122. (b) Smirnov, P.; Mathew, J.; Nijs, A.; Katan, E.; Karni, M.; Bolm, C.; Marek, I. *Angew. Chem. Int. Ed.* **2013**, *52*, 13717. (c) Unger, R.; Cohen, T.; Marek, I. *Tetrahedron* **2010**, *66*, 4874. (d) Unger, R.; Cohen, T.; Marek, I. *Eur. J. Org. Chem.* **2009**, 1749. (e) Unger, R.; Weisser, F.; Chinkov, N.; Stanger, A.; Cohen, T.; Marek, I. *Org. Lett.* **2009**, *11*, 1853.

(14) (a) Brook, A. G.; Pascoe, J. D. *J. Am. Chem. Soc.* **1971**, *93*, 6224. (b) Biernbaum, M. S.; Mosher, H. S. *J. Am. Chem. Soc.* **1971**, *93*, 6221.

(15) For recent reviews on C–C cleavage, see: (a) Souillart, L.; Cramer, N. *Chem. Rev.* **2015**, *115*, 9410. (b) Souillart, L.; Parker, E.; Cramer, N. *Top. Curr. Chem.* **2014**, *346*, 163. (c) Ruhland, K. *Eur. J. Org. Chem.* **2012**, 2683. (d) Aïssa, C. *Synthesis* **2011**, 3389. (e) Murakami, M.; Matsuda, T. *Chem. Commun.* **2011**, *47*, 1100. (f) Masarwa, A.; Marek, I. *Chem. Eur. J.* **2010**, *16*, 9712.

(16) (a) Grob, C. A.; Baumann, W. *Helv. Chim. Acta* **1955**, *38*, 594. (b) Drahl, M. A.; Manpadi, M.; Williams, L. J. *Angew. Chem. Int. Ed.* **2013**, *52*, 2.

(17) (a) Chemler, J. A.; Buchloz, T. J.; Geders, T. W.; Akey, D. L.; Rath, C. M.; Chlipala, G. E.; Smith, J. L.; Sherman, D. H. *J. Am. Chem. Soc.* **2012**, *134*, 7359. (b) Aoki, Y.; Matsumoto, D.; Kawaide, H.; Natsume, M. *J. Antibiot. (Tokyo)* **2011**, *64*, 607. (c) Chu, M.; Mierzwa, R.; Xu, L.; He, L.; Terracciano, J.; Patel, M.; Zhao, W.; Black, T. A.; Chan, T. M. *J. Antibiot. (Tokyo)* **2002**, *55*, 215. (d) Kong, F.; Singh, M. P.; Carter, G. T. *J. Nat. Prod.* **2005**, *68*, 920. (e) Brachmann, A. O.; Brameyer, S.; Kresovic, D.; Hitkova, I.; Kopp, Y.; Manske, C.; Schubert, K.; Bode, H. B.; Heerman, R. *Nat. Chem. Biol.* **2013**, *9*, 573.

(18) Liao, L.-A.; Zhang, F.; Yan, N.; Golen, J. A.; Fox, J. M. *Tetrahedron* **2004**, *60*, 1803.

(19) Danheiser, R. L.; Fink, D. M.; Okano, K.; Tsai, Y. M.; Szczepanski, S. W. *J. Org. Chem.* **1985**, *50*, 5393.