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A Biomimetic Approach Towards Enterocin and Deoxyenterocin

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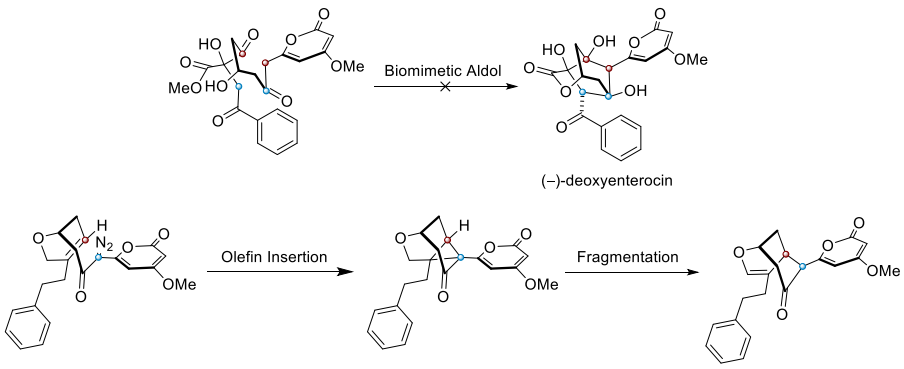


Abstract: Enterocin (vulgamycin) is a structurally remarkable natural product with significant antibiotic activity. The synthesis of a linear polyketide resembling a biosynthetic precursor was achieved using an unusual acyloin reaction. A diazo group was introduced as a protecting group for an enolizable ketone. We were unable to bring about the envisioned biomimetic aldol addition cascade and gained insights into the feasibility of this process by DFT calculations. As an alternative approach to enterocin, we developed a Cu-catalyzed intramolecular cyclopropanation followed by a MgI_2-induced fragmentation to install the 2-oxabicyclo[3.3.1]nonane core of the natural product.

Introduction

The sheer challenge of synthesizing highly oxygenated natural products has long inspired and motivated synthetic chemists to push the boundaries of organic synthesis. To this day, they still represent a strong impetus for the development of effective synthetic strategies and enabling methodologies. In this regard, (–)-enterocin (**1**) stands as an unsolved synthetic problem. In the late 1970s, the Miyairi[1a] and Seto[1b] groups independently reported the isolation of a new polyketide natural product from terrestrial strains of *Streptomyces* which they respectively named enterocin (**1**) and vulgamycin (**Figure 1**). The relative configuration of **1** was elucidated by NMR analysis,[1b] and the absolute configuration was unequivocally determined by X-ray crystallographic analysis of a benzoylated derivative (**3**).[1c] In 1991,[1d] a third isolation of **1** from a different strain of *Steptomyces* was reported. Shortly thereafter, Fenical[1e] reisolated the molecule from a marine ascidian of the genus *Didemnum* together with its biosynethetic precursor (–)-deoxyenterocin (**2**) and minor amounts of enterocin-5-behenate (**5**) and enterocin-5-arachidate (**6**), suggesting their origin from endophytic microorganisms. Moreover, both **1** and **2** present marked bioactivities as enterocin is a bacteriostatic antibiotic[1a,b] and deoxyenterocin exhibits inhibitory activity against the H1N1 influenza virus.[1g]

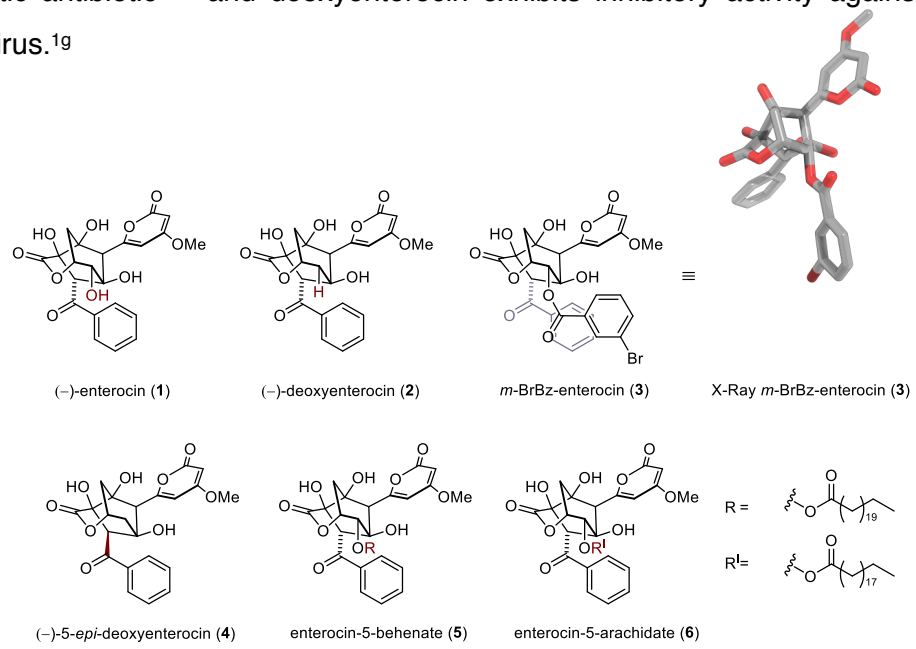


Figure 1. Enterocin polyketides; X-ray of derivatized enterocin.[1c]

Structurally, enterocin (**1**) provides a daunting challenge for synthesis, featuring a rigid oxa-protoadamantane[2] core adorned with a complicated oxygenation pattern. (**Figure 2**). This rare skeleton is found only in a handful of biosynthetically unrelated compounds such as the trixanolides (**7**),[3a] anisatinic acid (**8**),[3b] and a few from the annotinolides series (**9** and **10**),[3c] none of which have been prepared by total synthesis. Enterocin's seven contiguous

stereocenters are situated on the core. Four of them bear a hydroxy group while the other two are attached to a benzoyl and an α-pyronyl residue, respectively.

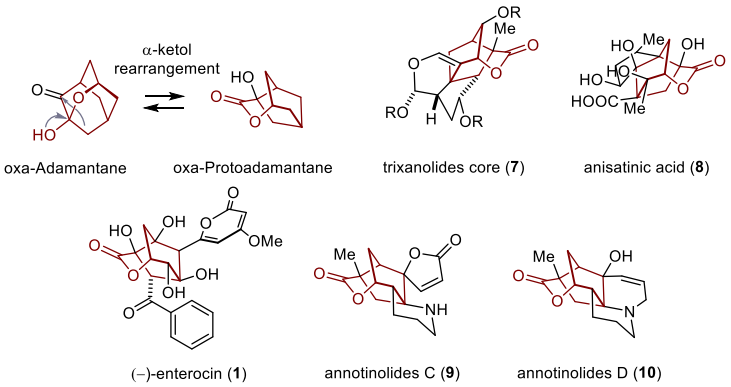


Figure 2. Oxa-protoadamantane and natural products containing the protoadamantane core.

Despite the considerable challenge provided by **1**, only three synthetic studies have been published to date. In 1986 Khuong-Huu[4a] demonstrated that the 2-oxabicyclo[3.3.1]nonane core (**11**) could be derived from (–)-quinic acid (**Figure 3**), and in 2017 Bach reported a convergent strategy to **12** utilizing a Mukaiyama aldol reaction.[4b,c] More recently, we have disclosed an ongoing study based on the late-stage functionalization of a bicyclic scaffold prepared by an intramolecular Cu-mediated Barbier cyclization (**13**).[4d] Herein, we wish to report our initial biomimetic studies towards enterocin, which failed to provide the target molecule, showed the limits of biomimetic cascade reactions and resulted in pyrone building blocks[4e-g] and protecting group strategies that should be useful to the synthetic community.

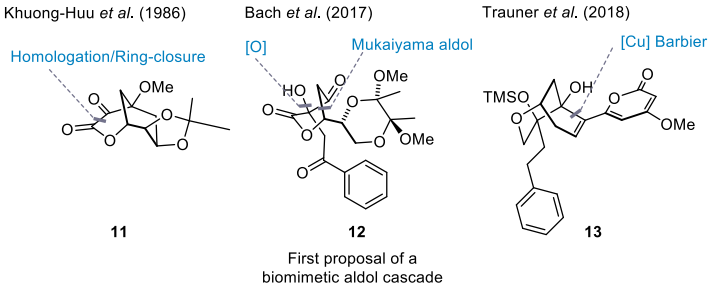
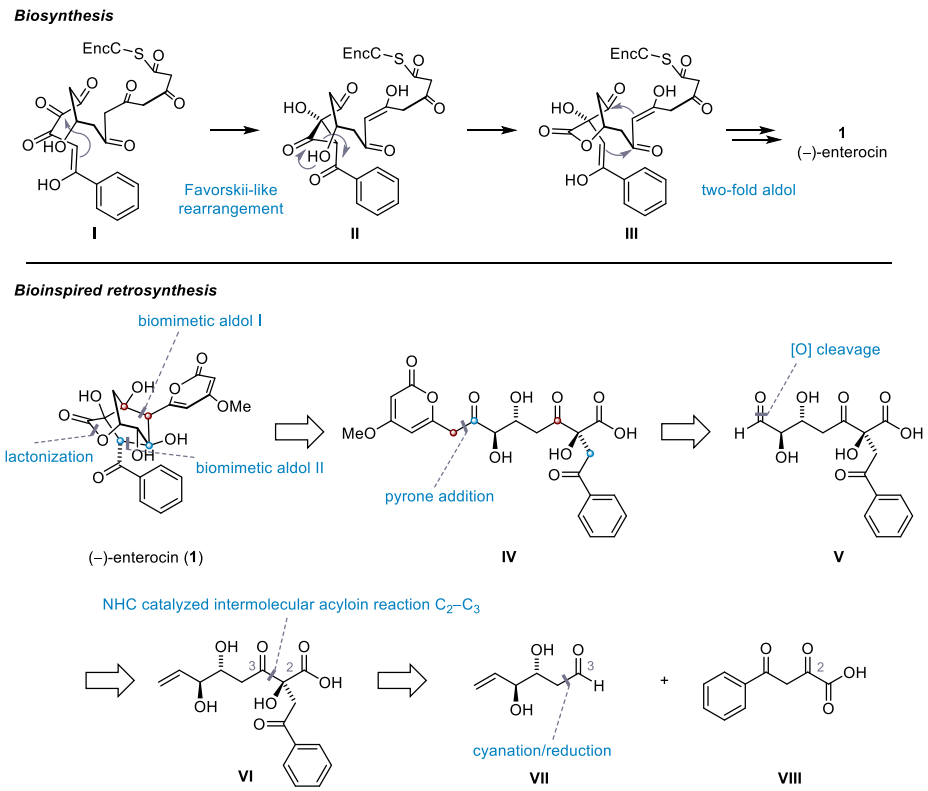


Figure 3. Synthetic approaches to enterocin (**1**).

As established by Moore,[5] the biosynthetic pathway toward enterocin proceeds via a Favorskii-like oxidative rearrangement of linear polyketide **I** and lactonization to **II** (**Scheme 1**). The tricyclic core is then formed by a two-fold aldol reaction (**III**). Inspired by this

biosythetic proposal, we developed a retrosynthesis of enterocin that relied on two aldol closures to assemble its bicyclo[3.2.1]octane core. These aldol disconnections were previously proposed in the synthetic study by Bach *et al.*[4b] However, the precursor could not be obtained, highlighting that, besides the final cyclization, a major challenge lies in the efficient preparation of a polyhydroxylated substrate with several enolizable carbons. Indeed, disconnection of the aforementioned bonds unraveled linear, fully functionalized, polyketide-like intermediate **IV**. We sought to assemble this biomimetic precursor by the addition of a pyrone segment onto an aldehyde (**V**), which in turn could arise from the oxidative cleavage of a terminal olefin (**VI**). The resulting chiral triketide fragment was envisioned to be constructed using an unusual intermolecular acyloin reaction which, to the best of our knowledge, is unreported in the setting of complex natural product synthesis. Such disconnection at $C_2 - C_3$ greatly simplified the preparation of this linear precursor to known compounds.

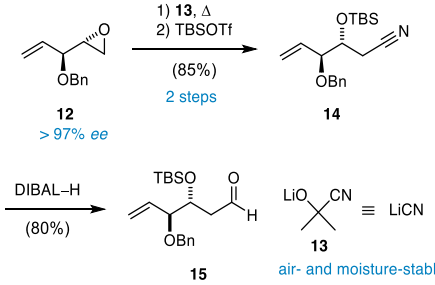


Scheme 1. Retrosynthetic analysis consisting of two biomimetic aldol reactions and an intramolecular acyloin reaction.

Results and Discussion

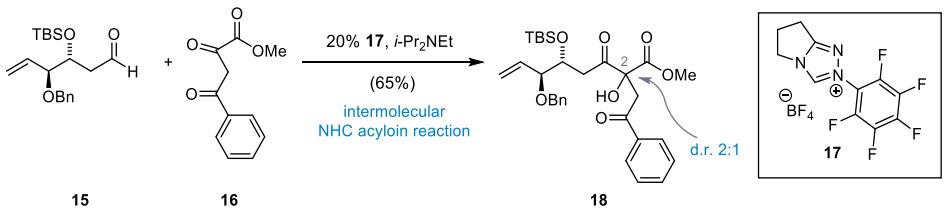
The synthesis commenced with Sharpless asymmetric epoxidation of divinyl carbinol followed by benzyl protection providing epoxide **12** on a multigram scale with excellent *ee* (**Scheme 2**).[6a] We were then faced with a seemingly straightforward cyanation of **12**, but

soon found that reported methods were cumbersome on larger scales, requiring excess amounts of KCN, long reaction times, and providing only moderate regioselectivities. Therefore, we employed lithium cyanohydrin **13** as an air stable LiCN source.[6b] This reagent delivered the cyanide with perfect regioselectivity and allowed for the direct silylation of the crude mixture to afford nitrile **14**, which was then reduced to aldehyde **15** using DIBAL–H.



Scheme 2. Construction of the central aldehyde **15** with $LiOC(Me)_2CN$ (**13**).

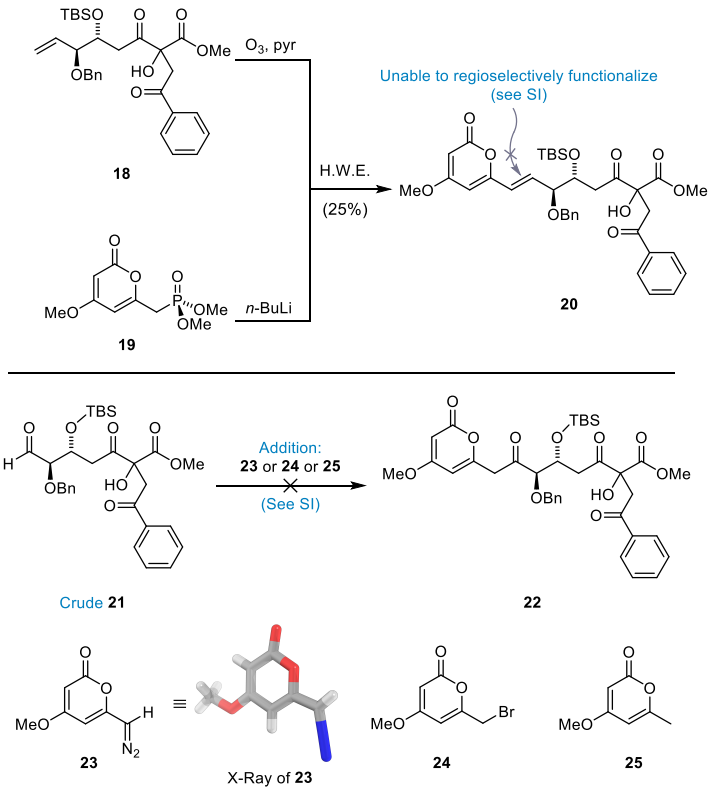
With **15** in hand, we explored the intermolecular acyloin fragment coupling (**Scheme 3**).[7a-c] Using precatalyst **17**, hydroxy β-keto ester **18** could indeed be obtained, albeit in low yield. The mass balance was attributed to dimerization of **15**. After adjusting the reaction stoichiometry, we were able to isolate **18** as a 2:1 mixture of diastereomers at C_2 in good yield. Interestingly, the TMS-protected analogue could be obtained in comparable yield with an improved 4:1 diastereomeric ratio (see Experimental section and S.I., compound **S4**). Although the assignment of the C_2 configuration was not possible, these results suggest that stereocontrol may be imparted by either a chiral catalyst or by introduction of a chiral auxiliary into ester **16**. Such studies were postponed in order to first confirm the feasibility of the full route.



Scheme 3. Execution of the key NHC mediated acyloin coupling.

After coupling of the first two fragments, we proceeded to treat phosphonate **19**[8] with *n*-BuLi and directly added the ozonolysis product of **18** to the resulting stabilized phosphorus ylide (**Scheme 4**).[9] This one-pot protocol yielded the expected vinyl pyrone **20** in moderate amounts and with complete (*E*)-selectivity. This was the first time we reached the full carbon

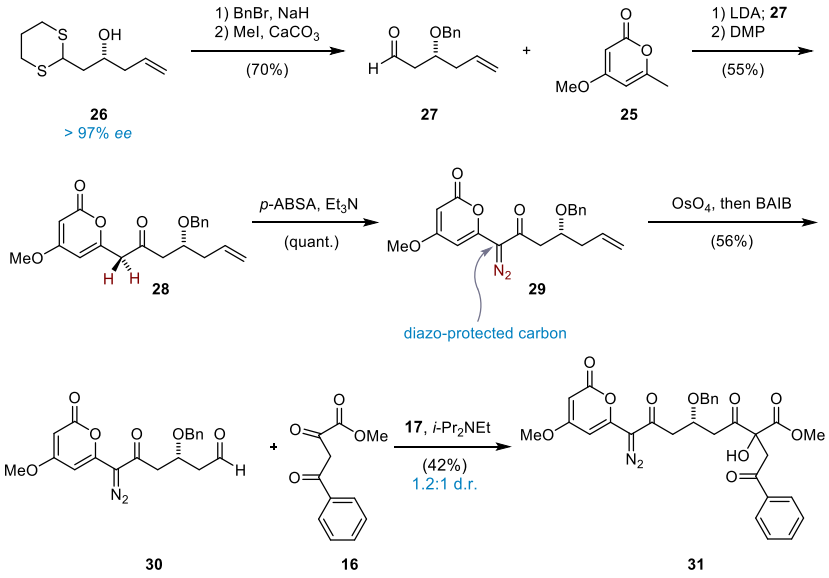
count of enterocin (**1**), but any attempts to functionalize olefin **20**, such as hydration, dihydroxylation or epoxidation, to yield β-keto pyrone **22** were unsuccessful (see Supporting Information, **Table S1**). Additionally, all attempts to add a pyrone fragment to aldehyde **21**, via Roskamp reaction[10] of diazo-pyrone **23** or by metalation of pyrones **24** or **25**, failed (see Supporting Information, **Table S2**). Though, compound **23** (X-Ray shown in **Scheme 4**) could be a useful building block for a variety of α-pyrone natural products**.**



Scheme 4. Attempted fragment coupling to linear precursor **22**.

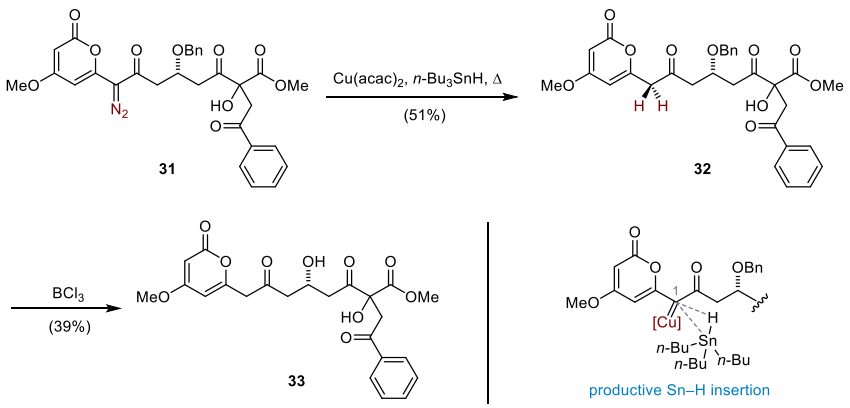
In view of these unsuccessful attempts, we decided to assemble the linear precursor through an inverted order of events wherein the pyrone was first added to a less functionalized central fragment followed by acyloin coupling, which was deemed chemoselective enough to avoid unwanted side-reactions. In order to rapidly test the feasibility of this strategy, we first pursued the synthesis of a linear precursor that corresponded to (–)-deoxyenterocin (**2**), which lacks the C_5 hydroxyl (**Figure 1**). Elaboration of known dithiane **26** (≥ 97% *ee*)[11] delivered multigram quantities of enantioenriched **27** for coupling with pyrone **25** (**Scheme 5**)**.** Despite the challenges encountered in regioselective deprotonations of pyrones,[12] metalation with LDA in Et_2O followed by addition of **27** and Dess-Martin oxidation delivered ketone **28** in moderate, yet reliable yields. Surprisingly, the oxidative cleavage of the terminal

alkene of **28** proved problematic. Moreover, a variety of dihydroxylation conditions resulted in complex mixtures and degradation. We presumed that the high acidity of the β-ketopyrone protons[13] interfered with the desired reaction outcome. After experimentation with enol ethers, acetals and reduced analogues, we devised an unusual protecting group strategy by diazotization of compound **28**.



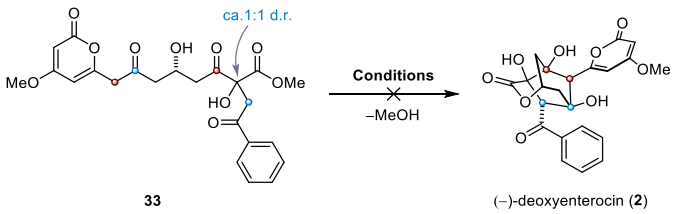
Scheme 5. Second generation approach to the construction of a biomimetic precursor.

Pyrone **28** underwent smooth diazotransfer using *p*-ABSA to yield **29** in quantitative yield. Following this protection, it was indeed possible to mildly oxidize the terminal alkene of **29** by OsO_4/BAIB to the corresponding aldehyde **30**. Thereafter, the chemoselective coupling of α-ketoester **16** with **30** yielded complete carbon chain precursor **31** as an inseparable mixture of diastereomers, with each carbon at the correct oxidation state. As we described above in the case of compounds **18** and **S4** (**Scheme 3**), the diastereomeric ratio at the newly formed stereocenter is dependent on the protecting group present on the β-hydroxyl to the aldehyde. The lower yield in comparison to **18** was attributed to the more facile dimerization of the aldehyde. Removal of the diazo protecting group could then be achieved using *n*-Bu_3SnH with either irradiation (Rayonet 420 nm)[14] or heating with $Cu(acac)_2$ to cleanly deliver **32** (**Scheme 6**).[15] The final debenzylation could be accomplished with BCl_3, albeit in moderate yield. Thus, we have established a diazo group as a methylene protecting group in this particular context.



Scheme 6. Mild and orthogonal removal of the masking diazo-group and debenzylation.

With ample material to screen the biomimetic two-fold aldol/lactonization, pyrone **33** was subjected to a variety of amine bases and organocatalysts (**Table 1**, entry 1-4). No productive reaction occurred under these conditions.

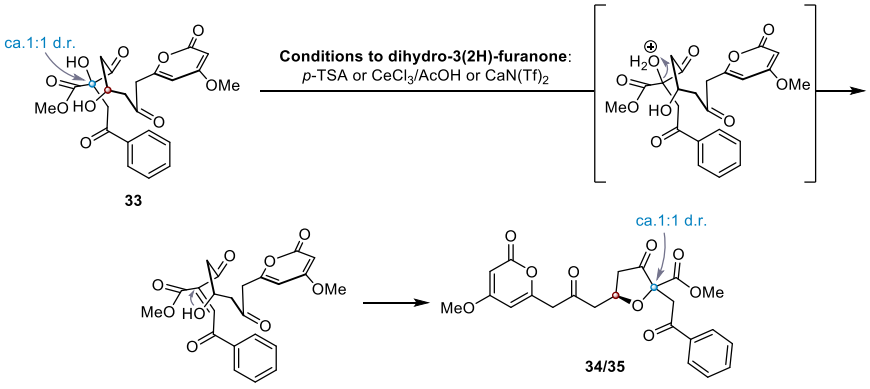


Entry	Conditions	Result
1	L-Proline	S.M.
2	Cat. *i*-Pr_2NH	S.M. + Decomp.
3	Schreiner's thiourea	S.M.
4	Takemoto's catalyst	S.M. + Decomp.
5	LiCl, DBU	Decomp.
6	*t*-BuOK	S.M. + Decomp.
7	LDA	Decomp.
8	$Zn(OTf)_2$	S.M.
9	10% $HCl_{(aq.)}$, Δ	S.M. + Decomp.
10	$TiCl_4$, *n*-Bu_3N	S.M.
11	$Hg(ClO_4)_2$•$3H_2O$	S.M.
12	*p*-TSA, toluene, Δ	**34** / **35**
13	$CeCl_3$, AcOH, Δ	**34** / **35**
14	$CaN(Tf)_2$, Δ	**34** / **35**

Table 1. Representative conditions screened for the bioinspired aldol cascade. For a complete list see Supporting Information, **Table S3**.

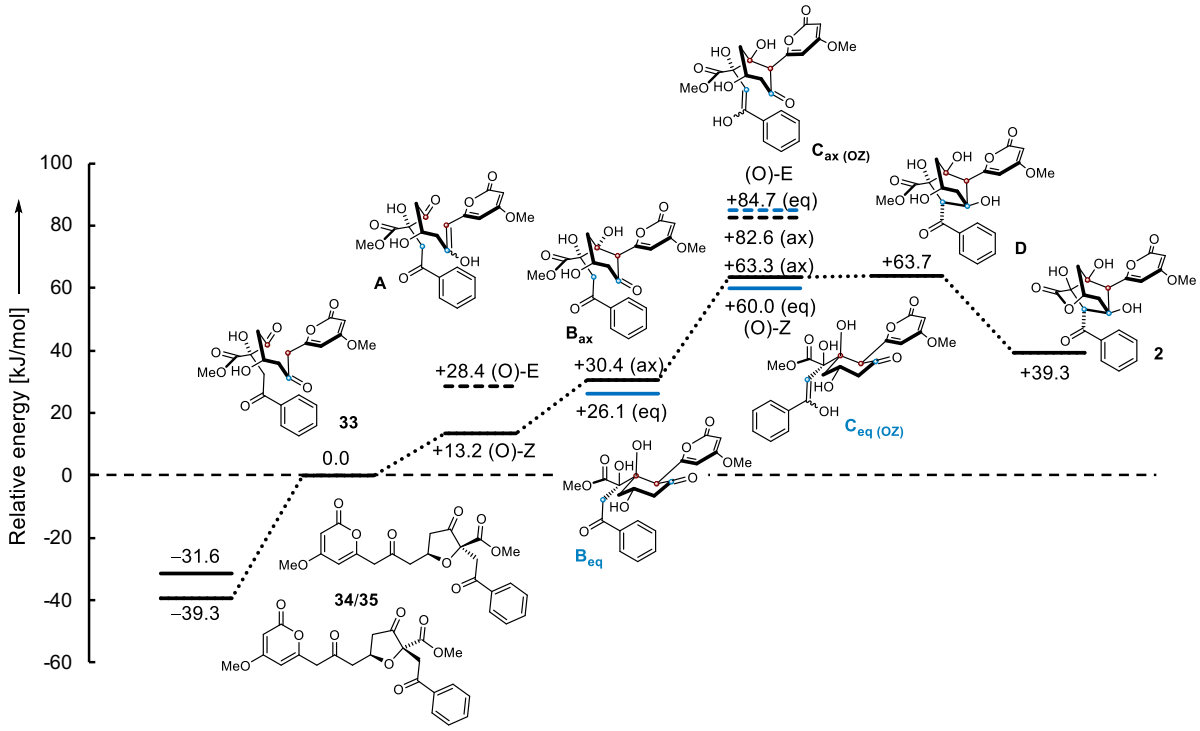
Stronger bases such as *t*-BuOK, DBU or LDA led to complete degradation of **33** (entry 5-7). Use of Lewis acids was also fruitless,[16a-d] although under the influence of $CeCl_3$, $CaN(Tf)_2$ or

p-TSA, the formation of traces of two diastereomeric dihydro-3(2*H*)-furanone adducts (**34** / **35**) was observed (entry 12-14).[16a,b] These products presumably arise from the elimination of the tertiary hydroxyl group and subsequent intramolecular oxa-Michael addition (**Scheme 7**).



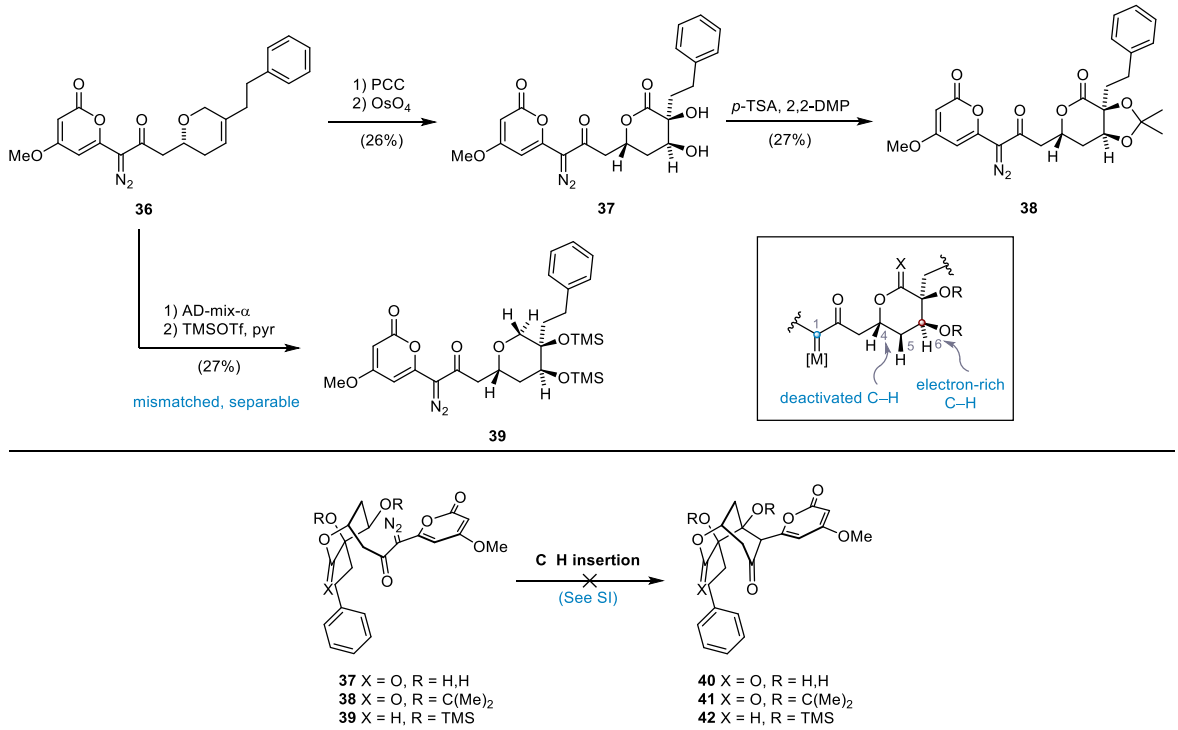
Scheme 7. Efforts to enact the biomimetic ring-closure led to the isolation of traces of dihydro-3(2*H*)-furanones **34** / **35**.

We have also studied the proposed cyclization of **33** to **2** *in silico* (**Scheme 8**) employing DFT calculations at the B3LYP-D3/6-311++G(3df,2pd) // B3LYP-D3/6-31G(d,p) level of theory in aqueous solution.[17] These calculations revealed that cyclization of **33** to deoxyenterocin (**2**) is energetically disfavored by +39 kJ/mol, with the final transesterification to the natural product being the only energetically favorable step in the entire process. In agreement with our experimental results, the cyclization to dihydro-3(2*H*)-furanones **34** and **35** was found to be significantly exergonic (–32 and –39 kJ/mol) and therefore constitutes the thermodynamic minimum of the whole sequence. While these calculations do not provide information on the kinetic preference of formation of **34** and **35** vs **2**, they do provide a rational for the absence of formation of **2**. Due to the level of endergonicity (+39.3 kJ/mol) of its formation, one would require the latter to be an irreversible process, leading to a rate-determining step over 120 kJ/mol - an infeasible process under the reaction conditions.



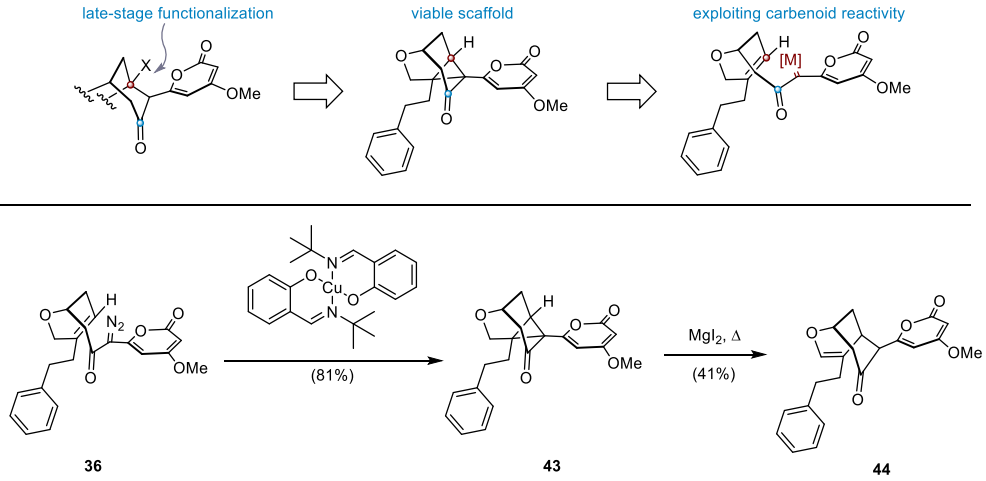
Scheme 8. Gibbs energy profile for cyclization to **2** and furanones **34** and **35** from linear precursor **33** as calculated at the B3LYP-D3/6-311++G(3df,2pd) // B3LYP-D3/6-31G(d,p) level of theory in aqueous solution.

Due to the inability to effect the biomimetic cascade, we began to explore the diazo group in C–H insertions. As the deprotection with tin hydride is a controlled insertion into a Sn–H bond, we surmised that the diazo group might also undergo a productive C–H insertion with an appropriate catalyst. Although challenging, an analysis of the scaffold's electronics suggested that such a closure may be possible (**Scheme 9**). The formation of a four-membered ring was deemed unlikely due to lactone deactivation, whereas the lower electron density of C_5 over C_6 could disfavor closure to a cyclopentane. Therefore, proceeding from compound **36**,[4d] we selectively executed an allylic oxidation of the ether bridge in the presence of the α-diazo group using PCC.[18] Notably, oxidation attempts on an unprotected substrate were ineffective. Subsequent dihydroxylation[19] stereoselectively delivered diol **37** and, after treatment with 2,2-DMP, acetonide **38** was isolated. We speculated that use of acetonide **38** may suppress undesired retro-aldol reactivity. This sequence advanced us to two possible substrates to enact the carbenoid insertion. Additionally, we prepared desoxo **39** to serve as a stereoelectronically differentiated substrate. Notably, the unoptimized yields of this sequence demonstrate that in principle the diazo group is stable under certain acidic and oxidative conditions.



Scheme 9. Construction of diazo compounds for intramolecular C–H insertion.

Several commercially available Rh- and Cu-based catalysts were subjected to the diazo substrates by reverse addition, but in all cases decomposition ensued (**Scheme 9**, see Supporting Information for a complete list of the screened catalysts, **Table S4**). This recalcitrance toward bicycle construction by C–H insertion led us to explore a more reactive partner for the diazo group. As olefins show high rates for carbenoid addition[20] we decided to use compound **36** as a platform to explore this possibility and, after cyclization, implement a late-stage functionalization strategy (**Scheme 10**).



Scheme 10. Design considerations for 2-oxabicyclo[3.3.1]nonane synthesis by cyclopropanation and its execution and fragmentation.

Thus, compound **36** was subjected to Rh- and Cu-based catalysts to induce an intramolecular cyclopropanation to compound **43**. Eventually, only $Cu(TBS)_2$,[21] as popularized by Corey,[22] proved capable of cleanly delivering the tricyclic adduct in good yield, forging the 2-oxabicyclo[3.3.1]nonane scaffold for the first time. After considerable optimization (see Supporting Information, Table S5), freshly prepared MgI_2 was found to afford enol ether **44** in moderate yield.[23] This compound proved to be stable enough to be isolated, but decomposed under a variety of conditions. Attempts to dihydroxylate, epoxidize or ring-open the enol ether were met with failure, possibly due to the juxtaposition of the acidic α-pyrone proton and the endocyclic enol ether.

In conclusion, we report two synthetic approaches to (–)-enterocin (**1**) and (–)-deoxyenterocin (**2**). The first bioinspired strategy comprised the synthesis of a linear precursor which upon double aldol cyclization would form the congested framework of the enterocins. This work introduced the diazo group as a useful protecting group for acidic methylene protons and proved the viability of an intermolecular acyloin reaction. The final cyclization cascade could not be realized under a variety of conditions. We provided a rationalization of such result by performing DFT calculations that support the endergonic nature of this process.

In a second approach, we elected to use the diazo protecting group as part of a metal carbenoid insertion strategy to bypass the elusive aldol reactivity. Although a C-H insertion could not be executed, a Cu-catalyzed intramolecular cyclopropanation proved capable of constructing the 2-oxabicyclo[3.3.1]nonane bicyclic structure of enterocin. The results presented herein motivate, and perhaps necessitate, a late-stage functionalization strategy to reach enterocin.

Experimental Section

Magnetic stirring was applied to all the reactions. If air or moisture sensitive, the reactions were carried out under nitrogen atmosphere using standard Schlenk techniques in oven-dried glassware (150 °C oven temperature) and then further dried under vacuum with a heat-gun at 500 °C. All reaction temperatures were recorded using an external thermometer placed into the baths. Reactions under cryogenic conditions were carried out in a Dewar vessel filled with acetone/dry ice (–78 °C to –10 °C) or distilled water/ice (0 °C). High temperature reactions were conducted using a heated silicon oil bath in reaction vessels equipped with a reflux condenser or in a pressure tube. Tetrahydrofuran (THF) and diethyl

ether (Et_2O) were distilled over sodium and benzophenone prior to use. Dichloromethane (CH_2Cl_2), triethylamine (Et_3N) and diisopropylethylamine (DIPEA) were distilled over calcium hydride under a nitrogen atmosphere. All other solvents were purchased from Acros Organics as 'extra dry' reagents. All other reagents with a purity > 95% were obtained from commercial sources (Sigma Aldrich, Acros, TCI, Chempur, Alfa Aesar) and used without further purification. **Flash column chromatography** was performed with Merck silica gel 60 (0.040-0.063 mm). For thin layer chromatography (TLC) Merck silica gel 60 F254 glassbacked plates were used. Visualization was done under UV light at 254 nm. Ceric ammonium molybdate (CAM), *p*-anisaldehyde (PAA) and potassium permanganate ($KMnO_4$) solutions were used as stains and subsequent heating was used to visualize the result. **High resolution mass spectra** (HRMS) were recorded using a Finnigan MAT 95 instrument by electron impact ([EI] double-focusing magnetic sector mass spectrometer) or a Thermo Finnigan LTQ FT Ultra Fourier Transform Ion Cyclotron Resonance spectrometer using electrospray ionization (ESI). **Infrared spectra (IR)** were recorded from 4000 cm^{-1} to 600 cm^{-1} on a PERKIN ELMER Spectrum BX II, FT-IR instrument. Detection: SMITHS DETECTION DuraSamplIR II Diamond ATR sensor. The frequencies of absorption (cm^{-1}) data are reported. **NMR spectra** (^1H NMR, $^{13}C\{1H\}$ NMR and $^{31}P\{1H\}$ NMR) were recorded in deuterated chloroform ($CDCl_3$), benzene (C_6D_6) or methanol (CD_3OD) on a Bruker Avance III HD 400 MHz spectrometer, a Varian VXR400 S spectrometer, a Varian 600 spectrometer or a Bruker Avance III HD 800 MHz spectrometer. ^1H NMR spectra are reported as follows: δ (chemical shift) in ppm (multiplicity, coupling constant *J* in Hz, number of protons). ^{13}C NMR spectra are reported as follows: δ (chemical shift) in ppm. Multiplicities abbreviations are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, br = broad, m = multiplet, or combinations thereof. For internal reference the residual solvent peaks of $CDCl_3$ (δ_H = 7.26 ppm, δ_C = 77.16 ppm), C_6D_6 (δ_H = 7.16 ppm, δ_C = 128.06 ppm) and CD_3OD (δ_H = 4.87 ppm, δ_C = 49.00 ppm) were used. Two dimensional NMR data (COSY, HMBC, HSQC and NOESY experiments) were used for assignment. **Optical rotation** values were recorded on an Anton Paar MCP 200 polarimeter. Specific rotation: $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20\,^{\circ}C}}$ = (α × 100) / (c × d). Wavelength (λ) is reported in nm. Temperature (T) is reported in °C. Recorded optical rotation is α. Concentration c is in 1 g/100 mL and length of the cuvette (d) is in dm. Specific rotation: 10^{-1}·deg·cm^2·g^{-1}. Sodium D line (λ = 589 nm) is indicated by D. **X-ray diffraction analysis** was carried out by Dr. Peter Mayer (Ludwig-Maximilians-Universität München). The data collections were done on a Bruker D8 Venture using Mo Kα-radiation (λ = 0.71073 Å, graphite monochromator). For all systems, geometry optimizations and frequency calculations were performed at the B3LYP/6-31G(d,p) level of theory with the IEFPCM

solvation model for water and Grimme's D3 dispersion correction with the Gaussian set of codes (for details and references see the SI). Enthalpy corrections obtained with B3LYP/6-31G(d,p) were subsequently combined with single point energies of the optimized structures at the B3LYP-D3/6-311++G(3df,2pd) (IEFPCM=water) level. A free energy correction +1.89 kcal/mol was applied to all free energies to consider the conversion from gas phase (1 atm) to liquid phase (1 M).

Epoxide (**S1**). A flame dried flask under argon was charged with oven dried 4 Å MS (4.5 g) and dry CH_2Cl_2 (124 mL). Then, the reaction vessel was cooled to –20 °C and (+)-DIPT (2.25 mL, 10.7 mmol, 0.18 eq.) and freshly distilled Ti(*i*-PrO)$_4$ (2.80 mL, 9.50 mmol, 0.16 eq.) were added to the mixture. Subsequently, TBHP (21.6 mL, 118.8 mmol, 2.0 eq., 5.5 M in decane over 4 Å MS) was added dropwise and the reaction was stirred for 15 minutes. Then, neat divinylcarbinol (5.00 g, 59.4 mmol, 1.0 eq.) was added and a sudden color change to orange was observed. The reaction was placed in a –25 °C freezer for 7 days. Subsequently, the reaction was diluted with a mixture of acetone (100 mL), H_2O (10 mL) and citric acid monohydrate (1.26 g). The reaction was stirred at RT for 1 h. Afterwards, the solution was filtered over celite, the filtrate was extracted three times with Et_2O, the combined organic fractions were washed with brine, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude product was purified by FCC (Et_2O/pent 1:2) to afford epoxide **S1** (4.36 g, 43.6 mmol, 73%) as a colorless oil.

R_f: 0.3, EtOAc/*i*-hex 4:6, CAM, no UV. $[\alpha]_D^{20\,°C}$: +63.0 (c = 1.5, $CHCl_3$). Literature: $[\alpha]_D^{20\,°C}$: +57.3 (c = 0.96, $CHCl_3$).[24c] **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 5.85 (ddd, *J* = 17.0, 10.5, 6.3 Hz, 1H), 5.41 (dt, *J* = 17.2, 1.3 Hz, 1H), 5.28 (dt, *J* = 10.4, 1.2 Hz, 1H), 4.38 – 4.35 (m, 1H), 3.12 – 3.10 (m, 1H), 2.82 (dd, *J* = 5.0, 2.8 Hz, 1H), 2.77 (dd, *J* = 5.0, 4.0 Hz, 1H). **^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ** = 135.5, 117.9, 70.2, 54.0, 43.6. **IR (ATR, neat)**: ν_{max} = 3398 (b), 3082 (w), 2992 (w), 2875 (w), 1645 (w), 1427 (m), 1251 (s) 1026 (m), 993 (m), 930 (s), 885 (s), 833 (m) cm^{-1}. **HRMS-EI (m/z)**: calc. for $C_5H_7O_2$ $[M–H]^{\bullet+}$: 99.0441; found: 99.0440.

Benzyl ether (**12**). A flame dried flask under argon was sequentially charged with **S1** (3.43 g, 34.3 mmol, 1.0 eq.), dry THF (80 mL), BnBr (4.89 mL, 41.1 mmol, 1.2 eq.) and TBAI (1.26 g, 3.43 mmol, 0.1 eq.). The reaction vessel was cooled to –20 °C. Then, NaH (1.5 g, 37.5 mmol, 1.1 eq., 60% dispersion in mineral oil) was added to the suspension and the reaction was stirred for 10 minutes. Afterwards, the cooling bath was removed and the reaction was monitored by TLC until completion (ca. 5 h). Then, the reaction was quenched

by addition of sat. $NH_4Cl_{(aq.)}$. The aqueous phase was extracted three times with Et_2O, the combined organic fractions were washed with brine, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude product was purified by FCC (Et_2O/pent 5:95) to afford benzylether **12** (5.87 g, 30.9 mmol, 90%) as a colorless oil.

R_f: 0.8, Et_2O/pent 1:2, CAM, no UV. $[\alpha]_D^{20\,°C}$: +35.9 (c = 0.9, $CHCl_3$). Literature: $[\alpha]_D^{20\,°C}$+35.3 (c = 0.93, $CHCl_3$).[24c] **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 7.37 – 7.27 (m, 5H), 5.87 – 5.79 (m, 1H), 5.38 – 5.33 (m, 2H), 4.64 (d, *J* = 11.9 Hz, 1H), 4.47 (d, *J* = 11.9 Hz, 1H), 3.81 (ddt, *J* = 7.4, 4.2, 1.0 Hz, 1H), 3.09 (td, *J* = 4.1, 2.6 Hz, 1H), 2.78 (dd, *J* = 5.2, 4.0 Hz, 1H), 2.69 (dd, *J* = 5.2, 2.6 Hz, 1H). **^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ** = 138.2, 134.6, 128.5, 127.8, 127.8, 119.8, 79.5, 70.8, 53.4, 45.0. **IR (ATR, neat)**: ν_{max} = 3064 (w), 2990 (w), 2863 (w), 1644 (w), 1606 (w), 1496 (w), 1454 (m), 1251 (w), 1065 (s), 932 (m), 882 (m), 735 (s), 697 (s) cm^{-1}. **HRMS-EI (m/z)**: calc. for $C_{10}H_{11}$ $[M–C_2H_3O_2]^{\bullet+}$: 131.0855; found: 131.0855.

Nitrile (**14**). A flame dried flask under argon, equipped with a reflux condenser, was charged sequentially with **12** (1.00 g, 5.26 mmol, 1.0 eq.), dry THF (60 mL), Li-cyanohydrin **13** (1.05 g, 11.5 mmol, 2.2 eq.) and the reaction vessel was heated to 60 °C. The reaction was monitored by TLC until completion (ca. 1.5 h). Then, the reaction was cooled to RT, the solvent was removed under reduced pressure and the residue partitioned between H_2O and Et_2O. The aqueous phase was extracted three times with Et_2O, the combined organic fractions were washed with brine, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude alcohol was used in the next step without further purification. **R_f**: 0.2, *i*-hex:EtOAc 8:2, CAM, UV.

A flame dried flask under argon was charged sequentially with the crude alcohol, dry CH_2Cl_2 (60 mL), 2,6-lutidine (1.60 mL, 13.8 mmol, 2.6 eq.) and the reaction vessel was cooled to 0 °C. Neat TBSOTf (1.44 mL, 6.27 mmol, 1.2 eq.) was added dropwise and the reaction was stirred for 10 minutes at the same temperature. Then, the cooling bath was removed and the reaction was monitored by TLC until completion (ca. 3 h). Afterwards, the reaction was quenched by addition of sat. $NaHCO_{3(aq)}$. The aqueous phase was extracted three times with EtOAc, the combined organic fractions were washed with brine, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude product was purified by FCC (EtOAc/*i*-hex 1:9) to afford **14** (1.57 g, 4.75 mmol, 90%) as a yellow oil.

R_f: 0.7, *i*-hex:EtOAc 8:2, CAM, PAA (yellow), UV. $[\alpha]_D^{20\,°C}$: +15.7 (c = 0.7, $CHCl_3$). **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 7.37 – 7.28 (m, 5H), 5.75 (ddd, *J* = 17.6, 10.5, 7.5 Hz, 1H), 5.42 – 5.36 (m, 2H), 4.61 (d, *J* = 11.5 Hz, 1H), 4.40 (d, *J* = 11.5 Hz, 1H), 3.90 (q, *J* = 5.4 Hz, 1H), 3.80 (t,

J = 6.7 Hz, 1H), 2.72 (dd, *J* = 16.7, 5.5 Hz, 1H), 2.51 (dd, *J* = 16.7, 4.4 Hz, 1H), 0.89 (s, 9H), 0.11 (s, 3H), 0.05 (s, 3H). **$^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ** = 138.0, 135.1, 128.6, 128.1, 127.9, 120.8, 118.0, 82.7, 71.1, 70.8, 25.9, 23.2, 18.1, –4.2, –4.6. **IR (ATR, neat)**: ν_{max} = 3067 (w), 3032 (w), 2929 (w), 2857 (w), 1471 (w), 1414 (w), 1252 (s), 1108 (s), 994 (m), 924 (m), 836 (s), 777 (s), 697 (m) cm^{-1}. **HRMS-ESI (m/z)**: calc. for $C_{19}H_{33}N_2O_2Si$ $[M+NH_4]^+$: 349.2306; found: 349.2306.

Aldehyde (**15**). A flame dried flask under argon charged with nitrile **14** (2.07 g, 6.24 mmol, 1.0 eq.) and dry toluene (65 mL) was cooled to –50 °C. A solution of DIBAL-H (9.39 mL, 9.39 mmol, 1.5 eq., 1 M in toluene) was added in a single aliquot and the reaction was monitored by TLC until completion (ca. 3 h). Afterwards, the reaction was quenched by addition of EtOH, allowed to warm to RT, a sat. solution of Rochelle's salt was added under vigorous stirring and the mixture stirred for 30 minutes. Then, the aqueous phase was extracted three times with Et_2O, the combined organic fractions were washed with brine, dried with $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude product was purified by FCC (EtOAc/*i*-hex 5:95) to afford aldehyde **15** (1.67 g, 4.99 mmol, 80%) as a yellow oil.

R_f: 0.5, *i*-hex:EtOAc 8:2, CAM, PAA (blue), UV. $[\alpha]_D^{20\,°C}$: +20.0 (c = 0.1, $CHCl_3$). **^1H NMR (400 MHz, $CDCl_3$) δ** = 9.78 (t, *J* = 2.5 Hz, 1H), 7.36 – 7.27 (m, 5H), 5.76 (ddd, *J* = 17.6, 10.4, 7.5 Hz, 1H), 5.37 – 5.28 (m, 2H), 4.59 (d, *J* = 11.8 Hz, 1H), 4.39 (d, *J* = 11.7 Hz, 1H), 4.21 (q, *J* = 5.5 Hz, 1H), 3.73 (dd, *J* = 7.5, 5.1 Hz, 1H), 2.65 (ddd, *J* = 15.9, 5.7, 2.5 Hz, 1H), 2.53 (ddd, *J* = 15.9, 5.6, 2.4 Hz, 1H), 0.85 (s, 9H), 0.05 (d, *J* = 2.4 Hz, 6H). **$^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ** = 201.6, 138.2, 135.6, 128.5, 128.0, 127.7, 120.0, 83.8, 71.0, 70.8, 48.2, 25.9, 18.2, –4.1, –4.6. **IR (ATR, neat)**: ν_{max} = 2928 (m), 2856 (m), 1724 (s), 1472 (w), 1252 (s), 1103 (s), 836 (s), 777 (s), 698 (m) cm^{-1}. **HRMS-ESI (m/z)**: calc. for $C_{19}H_{34}NO_3Si$ $[M+NH_4]^+$: 352.2302; found: 352.2303.

Acyloin (**18**). A flame dried flask under argon was charged with oven dried 4 Å MS (0.2 g), α-ketoester **16** (0.74 g, 3.60 mmol, 6.0 eq.) and pre-catalyst **17** (0.02 g, 0.06 mmol, 0.2 eq.).Then, a solution of aldehyde **15** (0.2 g, 0.60 mmol, 1.0 eq.) in dry CH_2Cl_2 (5 mL + 1 mL to rinse) was added and the mixture was stirred for 5 minutes. Subsequently, dry DIPEA (0.11 mL, 0.65 mmol, 1.0 eq.) was added and the solution turned yellow. The reaction was monitored by TLC until completion (ca. 4 h). The reaction mixture was eluted directly with EtOAc over a silica pad and the solvent removed under reduced pressure. The crude product was purified by FCC (EtOAc/*i*-hex 8:2, long column) to afford acyloin **18** (0.2 g, 0.37 mmol, 61%, 1.9:1 d.r.) as an amorphous yellow solid.

R_f: 0.6, *i*-hex:EtOAc 8:2, CAM, PAA (blue), UV. **^{1}H NMR (400 MHz, $CDCl_3$, * denotes minor diastereomer) δ** = 7.90 – 7.85 (m, 2H+2H*), 7.61 – 7.57 (m, 1H+1H*), 7.45 (t, *J* = 7.7 Hz, 2H+2H*), 7.32 (d, *J* = 4.2 Hz, 5H+5H*), 5.80 (dddd, *J* = 17.8, 10.3, 7.6, 2.3 Hz, 1H+1H*), 5.40 – 5.16 (m, 2H+2H*), 4.58 (dd, *J* = 11.8, 5.2 Hz, 1H+1H*), 4.43 – 4.37 (m, 2H+2H*), 3.88 (dd, *J* = 18.0, 7.8 Hz, 1H+1H*), 3.75 (d, *J* = 4.4 Hz, 3H+3H*), 3.70 (dd, *J* = 7.8, 4.0 Hz, 1H+1H*), 3.56 (dd, *J* = 18.0, 3.3 Hz, 1H+1H*), 3.13 (dd, *J* = 18.1, 6.6 Hz, 1H), 3.05 (dd, *J* = 18.6, 4.4 Hz, 1H*), 2.84 (dd, *J* = 18.6, 6.9 Hz, 1H*), 2.75 (dd, *J* = 18.1, 5.0 Hz, 1H), 0.83 (d, *J* = 9.3 Hz, 9H+9H*), 0.07 – 0.03 (m, 6H+6H*). **^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ** = 204.3, 197.7, 197.5, 170.8, 138.6, 136.18, 136.15, 135.4, 134.0, 128.8, 128.39, 128.37, 127.90, 127.86, 127.53, 127.50, 119.9, 119.7, 84.2, 83.9, 82.6, 82.5, 70.5, 70.2, 70.0, 53.8, 53.7, 44.3, 44.0, 42.1, 42.0, 26.1, 26.0, 18.3, 18.3, –4.2, –4.2, –4.7, –4.8. **IR (ATR, neat)**: ν_{max} = 3490 (bw), 3066 (w), 2928 (w), 2855 (w), 1746 (m), 1724 (s), 1686 (m), 1358 (m), 1249 (m), 1216 (s), 1091 (s), 832 (s), 777 (s), 688 (m) cm^{-1}. **HRMS-ESI (m/z)**: calc. for $C_{30}H_{44}NO_7Si$ $[M+NH_4]^+$: 558.2882; Found: 558.2885.

Nitrile (**S2**). A flame dried flask under argon, equipped with a reflux condenser, was charged sequentially with **12** (1.00 g, 5.26 mmol, 1.0 eq.), dry THF (60 mL), Li-cyanohydrin **13** (1.05 g, 11.5 mmol, 2.2 eq.) and the reaction vessel was heated to 60 °C. The reaction was monitored by TLC until completion (ca. 1.5 h). Then, the reaction was cooled to RT, the solvent was removed under reduced pressure and the residue partitioned between H_2O and Et_2O. The aqueous phase was extracted three times with Et_2O, the combined organic fractions were washed with brine, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude alcohol was used in the next step without further purification. **R_f**: 0.2, *i*-hex:EtOAc 8:2, CAM, UV.

A flame dried flask under argon was charged sequentially with the crude alcohol, dry CH_2Cl_2 (60 mL), 2,6-lutidine (1.60 mL, 13.8 mmol, 2.6 eq.) and the reaction vessel was cooled to 0 °C. Neat TMSOTf (1.14 mL, 6.30 mmol, 1.2 eq.) was added dropwise and the reaction was stirred for 10 minutes at the same temperature. Then, the cooling bath was removed and the reaction was monitored by TLC until completion (ca. 3 h). Afterwards, the reaction was quenched by addition of sat. $NaHCO_{3(aq)}$. The aqueous phase was extracted three times with EtOAc, the combined organic fractions were washed with brine, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude product was purified by FCC (EtOAc/*i*-hex 5:95) to afford **S2** (1.37 g, 4.73 mmol, 90%) as a yellow oil.

R_f: 0.7, *i*-hex:EtOAc 8:2, CAM, PAA (yellow), UV. $[\alpha]_D^{20\,°C}$: +30.8 (c = 0.5, $CHCl_3$). **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 7.37 – 7.28 (m, 5H), 5.73 (ddd, *J* = 17.5, 10.4, 7.4 Hz, 1H), 5.42 – 5.35

(m, 2H), 4.62 (d, *J* = 11.6 Hz, 1H), 4.38 (d, *J* = 11.6 Hz, 1H), 3.91 (td, *J* = 6.2, 4.7 Hz, 1H), 3.72 (t, *J* = 6.9 Hz, 1H), 2.65 – 2.56 (m, 2H), 0.12 (s, 9H). **^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ** = 137.9, 135.1, 128.6, 128.1, 128.0, 120.8, 118.3, 82.6, 71.0, 70.9, 23.4, 0.5. **IR (ATR, neat)**: ν_{max} = 3066 (w), 3032 (w), 2957 (w), 2897 (w), 1454 (w), 1415 (w), 1250 (s), 1107 (s), 994 (w), 925 (m), 839 (s), 749 (m), 697 (m) cm^{-1}. **HRMS-EI (m/z)**: calc. for $C_{16}H_{23}NO_2Si$ $[M]^{+\cdot}$: 289.1493; found: 289.1495.

Aldehyde (**S3**). A flame dried flask under argon charged with **S2** (1.37 g, 4.73 mmol, 1.0 eq.) dry toluene (40 mL) was cooled to –50 °C. A solution of DIBAL-H (6.65 mL, 6.65 mmol, 1.4 eq., 1 M in toluene) was added in a single aliquot and the reaction was monitored by TLC until completion (ca. 3 h). Afterwards, the reaction was quenched by addition of EtOH, allowed to warm to RT, a sat. solution of Rochelle's salt was added under vigorous stirring and the mixture stirred for 30 minutes. Then, the aqueous phase was extracted three times with Et_2O, the combined organic fractions were washed with brine, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude product was purified by FCC (EtOAc/*i*-hex 5:95) to afford aldehyde **S3** (0.94 g, 3.21 mmol, 68%) as a yellow oil.

R_f: 0.7, *i*-hex:EtOAc 8:2, CAM, PAA (blue), UV. $[\alpha]_D^{20\,°C}$: +39.8 (c = 1.0, $CHCl_3$). **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 9.76 (t, *J* = 2.3 Hz, 1H), 7.36 – 7.28 (m, 5H), 5.76 (ddd, *J* = 17.6, 10.4, 7.6 Hz, 1H), 5.39 – 5.28 (m, 2H), 4.61 (d, *J* = 11.8 Hz, 1H), 4.37 (d, *J* = 11.8 Hz, 1H), 4.22 (q, *J* = 5.9 Hz, 1H), 3.68 (dd, *J* = 7.5, 5.5 Hz, 1H), 2.67 – 2.55 (m, 2H), 0.09 (s, 6H). **^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ** = 201.5, 138.1, 135.6, 128.5, 128.1, 127.8, 120.1, 83.5, 70.6, 70.6, 48.2, 0.5. **IR (ATR, neat)**: ν_{max} = 3066 (w), 2956 (w), 2724 (w), 1724 (s), 1454 (w), 1249 (s), 1091 (bs), 995 (m), 838 (s), 748 (s), 697 (s) cm^{-1}. **HRMS-EI (m/z)**: calc. for $C_{15}H_{21}O_3Si$ $[M–CH_3]^{+\cdot}$: 277.1254; found: 277.1264.

Acyloin (**S4**). A flame dried flask under argon was charged with oven dried 4 Å MS (0.3 g), α-ketoester **16** (0.63 g, 3.06 mmol, 3.0 eq.) and pre-catalyst **17** (0.04 g, 0.1 mmol, 0.1 eq.). Then, a solution of aldehyde **S3** (0.3 g, 1.03 mmol, 1 eq.) in dry CH_2Cl_2 (18 mL + 2 ml to rinse) was added and the mixture stirred for 5 minutes. Subsequently, dry DIPEA (0.18 mL, 1.06 mmol, 1.0 eq.) was added and the solution turned yellow. The reaction was monitored by TLC until completion (ca. 6 h). The reaction mixture was eluted directly with EtOAc over a silica pad and the solvent was removed under reduced pressure. The crude product was purified by FCC (EtOAc/*i*-hex 8:2, long column) to afford acyloin **S4** (0.27 g, 0.54 mmol, 54%, 4:1 d.r.) as colorless oil.

R_f: 0.7, *i*-hex:EtOAc 7:3, CAM, UV. **^{1}H NMR (400 MHz, $CDCl_3$, *** denotes minor diastereomer**) δ** = 7.92 – 7.88 (m, 2H+2H*), 7.59 (t, *J* = 7.4 Hz, 1H+1H*), 7.46 (t, *J* = 7.6 Hz, 2H+2H*), 7.32 (d, *J* = 4.1 Hz, 5H+5H*), 5.78 (ddd, *J* = 17.7, 10.4, 7.7 Hz, 1H+1H*), 5.37 – 5.25 (m, 2H+2H*), 4.62 – 4.52 (m, 2H+2H*), 4.40 – 4.30 (m, 2H+2H*), 3.89 (dd, *J* = 17.9, 13.5 Hz, 1H+1H*), 3.77 (d, *J* = 2.5 Hz, 3H+3H*), 3.66 (dd, *J* = 7.7, 5.1 Hz, 1H+1H*), 3.60 (d, *J* = 17.8 Hz, 1H+1H*), 3.19 – 3.11 (m, 1H), 3.04 (dd, *J* = 18.3, 3.4 Hz, 1H*), 2.90 (dd, *J* = 18.2, 8.3 Hz, 1H*), 2.77 (dd, *J* = 17.7, 3.6 Hz, 1H), 0.09 (s, 9H), 0.07 (s, 9H*). **^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ** = 204.6, 204.5, 197.5, 197.3, 171.3, 170.73, 170.67, 138.5, 136.2, 135.6, 135.5, 133.98, 133.95, 128.9, 128.43, 128.37, 127.9, 127.6, 120.0, 119.9, 83.6, 83.5, 82.6, 82.5, 77.4, 70.5, 60.6, 53.8, 53.7, 44.2, 43.8, 42.1, 41.8, 21.2, 14.4, 0.6, 0.5. **IR (ATR, neat)**: ν_{max} = 3485 (bw), 3066 (w), 2955 (w), 2903 (w), 1745 (m), 1723 (s), 1685 (m), 1597 (w), 1449 (m), 1354 (m), 1247 (s), 1216 (s), 1089 (s), 1070 (s), 1001 (m), 929 (m), 839 (s), 753 (s), 688 (s) cm^{-1}. **HRMS-ESI (m/z)**: calc. for $C_{27}H_{38}NO_7Si$ $[M+NH_4]^+$: 516.2412; found: 516.2409.

Bromo-pyrone (**24**). A flask was charged with 4-hydroxy-6-methyl-2-pyrone (1.00 g, 7.93 mmol, 1.0 eq.), CCl_4 (165 mL), NBS (1.39 g, 7.90 mmol, 1.0 eq.), AIBN (0.12 g, 0.73 mmol, 0.1 eq.). The mixture was stirred at 80 °C and illuminated with a 160 W floodlamp. The mixture was monitored by TLC until completion (ca. 1 h). Afterwards, the solvent was distilled under reduced pressure and the crude product was purified by FCC (EtOAc/*i*-hex 4:6) to afford **24** (0.92 g, 4.20 mmol, 53%) as a yellow solid.[25]

R_f: 0.4, *i*-hex:EtOAc 1:1, CAM, UV. **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 6.09 (s, 1H), 5.49 (s, 1H), 4.11 (s, 2H), 3.82 (s, 3H).**^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ** = 170.5, 163.6, 158.7, 102.4, 89.7, 56.3, 26.7. **IR (ATR, neat)**: ν_{max} = 3032 (w), 1703 (s), 1649 (s), 1565 (s), 1459 (m), 1411 (m), 1333 (w), 1254 (s), 1149 (m), 942 (m), 815 (s) cm^{-1}. **HRMS-ESI (m/z)**: calc. for $C_7H_8BrO_3$ $[M+H]^+$: 218.9651; found: 218.9651.

Phosphonate (**19**). A flask equipped with a reflux condenser was charged with **24** (0.20 g, 0.91 mmol, 1.0 eq.) and $P(OMe)_3$ (0.2 mL, 1.70 mmol, 1.9 eq.) at RT. Then, the reaction was heated to 60 °C and was monitored by TLC until completion (ca. 5 h). Afterwards, the reaction was directly purified by FCC (EtOAc/*i*-hex 2:1 then MeOH/EtOAc 4:96) to afford phosphonate **19** (0.26 g, 0.92 mmol, quant.) as a white solid.[26]

R_f: 0.3, MeOH:EtOAc 4:96, $KMnO_4$, UV. **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 6.01 (t, *J* = 2.9 Hz, 1H), 5.45 (d, *J* = 2.1 Hz, 1H), 3.82 (s, 3H), 3.80 (d, *J* = 3.2 Hz, 6H), 3.04 (d, *J* = 22.0 Hz, 2H). **^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ** = 171.0, 164.1, 155.8, 102.9, 88.5, 56.1, 53.4, 32.2, 30.8. **^{31}P NMR (162 MHz, $CDCl_3$) δ** = 23.42. **IR (ATR, neat)**: ν_{max} = 3085 (w), 2957 (w), 2916 (w),

1721 (s), 1650 (s), 1565 (s), 1414 (m), 1242 (s), 1183 (m), 1022 (s), 938 (m), 843 (s), 792 (s), 693 (m) cm^{-1}. **HRMS-EI (m/z)**: calc. for $C_9H_{13}O_6P$ $[M]^{+\cdot}$: 248.0444; found: 248.0445.

Alkene (**20**). A flame dried flask under argon was charged with acyloin **18** (0.020 g, 0.037 mmol, 1.0 eq.), pyridine (12 μL, 0.15 mmol, 4.0 eq.) and dry CH_2Cl_2 (0.55 mL). Then the mixture was cooled to –78 °C. A stream of ozone was passed through the reaction for 160 seconds and then the solution was purged with a N_2 stream. The reaction was monitored by TLC for completion. The solution was cannulated directly into the following reaction. $\mathbf{R_f}$: 0.7, *i*-hex:EtOAc 7:3, CAM, UV.

A flame dried flask under argon was charged with phosphonate **19** (0.01 g, 0.04 mmol, 1.1 eq.), dry THF (0.40 mL) and cooled to –78 °C. A solution of *n*-BuLi (0.04 mL, 0.04 mmol, 1.15 eq, 1 M in hexanes) was added and the reaction was stirred for 30 minutes. Then, the solution of ozonolyzed **18** was cannulated into the mixture, stirred at the same temperature for 1 h and then the cooling bath was removed. The reaction was monitored by TLC until completion (ca. 2 h). Afterwards, the reaction was quenched by addition of sat. $NH_4Cl_{(aq.)}$, the aqueous phase was extracted three times with EtOAc, the combined organic fractions were washed with brine, dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The crude product was purified by FCC (EtOAc/*i*-hex 4:6) to afford alkene **20** (6.30 mg, 0.0095 mmol, 26%) as a yellow oil.

$\mathbf{R_f}$: 0.6, *i*-hex:EtOAc 1:1, CAM, UV. **^{1}H NMR (400 MHz, $CDCl_3$, *** denotes minor diastereomer**) δ** = 7.89 – 7.84 (m, 2H+2H*), 7.59 (t, *J* = 7.0 Hz, 1H+1H*), 7.45 (t, *J* = 7.6 Hz, 2H+2H*), 7.34 – 7.32 (m, 5H+5H*), 6.61 (ddd, *J* = 15.7, 6.4, 4.0 Hz, 1H+1H*), 6.19 (dd, *J* = 15.7, 11.0 Hz, 1H+1H*), 5.85 (dd, *J* = 9.0, 2.1 Hz, 1H+1H*), 5.48 (d, *J* = 2.6 Hz, 1H+1H*), 4.58 (q, *J* = 5.3 Hz, 2H+2H*), 4.54 – 4.46 (m, 1H+1H*), 4.46 – 4.36 (m, 1H+1H*), 4.04 – 3.96 (m, 1H+1H*), 3.88 (dd, *J* = 18.0, 13.0 Hz, 1H+1H*), 3.81 (s, 3H+3H*), 3.75 (d, *J* = 6.5 Hz, 3H+3H*), 3.55 (d, *J* = 17.9 Hz, 1H+1H*), 3.19 (dd, *J* = 18.0, 6.5 Hz, 1H), 3.08 (dd, *J* = 18.5, 4.4 Hz, 1H*), 2.89 (dd, *J* = 18.5, 6.8 Hz, 1H*), 2.75 (dd, *J* = 18.0, 4.8 Hz, 1H), 0.84 (s, 9H), 0.82 (s, 9H*), 0.06 (s, 6H+6H*). **^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ** = 204.1, 197.5, 171.1, 170.7, 164.0, 157.7, 138.1, 136.1, 135.6, 134.0, 128.9, 128.5, 128.5, 128.4, 128.0, 127.9, 127.8, 127.8, 124.4, 124.3, 101.5, 101.5, 89.3, 82.6, 71.7, 70.3, 67.3, 56.1, 53.8, 52.9, 44.3, 44.0, 42.0, 41.7, 29.9, 26.0, 24.0, 18.2, -4.3, -4.8. **IR (ATR, neat)**: ν_{max} = 3460 (bw), 3064 (w), 2953 (w), 2928 (w), 2856 (w), 1721 (s), 1690 (m), 1559 (s), 1451 (m), 1248 (s), 1218 (s), 1095 (m), 1036 (m), 832 (s), 777 (s), 732 (m), 689 (m) cm^{-1}. **HRMS-ESI (m/z)**: calc. for $C_{36}H_{48}NO_{10}Si$ $[M+NH_4]^+$: 682.3042; found: 682.3049.

Aldehyde (**21**). A flame dried flask under argon was charged with acyloin **18** (0.020 g, 0.037 mmol, 1.0 eq.), pyridine (12 μL, 0.15 mmol, 4.0 eq.) and dry CH_2Cl_2 (0.55 mL). Then it was cooled to −78 °C. A stream of ozone was passed through the reaction for 1.4 minutes and then the solution was purged with a N_2 stream. The reaction was monitored by TLC for completion. The solution was passed through a pad of silica gel (EtOAc) to afford crude **21**. **R_f**: 0.7, *i*-hex:EtOAc 7:3, CAM, UV. **HRMS-ESI (m/z)**: calc. for $C_{29}H_{42}NO_8Si$ $[M+NH_4]^+$: 560.2674; found: 560.2680. The crude ^{1}H NMR spectrum is available in the Supporting Information.

Azido-pyrone (**S5**). A flask was charged with **24** (0.20 g, 0.91 mmol, 1.0 eq.), dry DMF (165 mL) and NaN_3 (0.11 g, 1.69 mmol, 1.9 eq.). The heterogeneous orange mixture was stirred at RT and monitored by TLC until completion (ca. 1 h). Afterwards, the reaction was partitioned between H_2O and EtOAc, the aqueous phase was extracted three times with EtOAc, the combined organic fractions were washed with brine, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude product was purified by FCC (EtOAc/*i*-hex 1:1) to afford **S5** (0.17 g, 0.94 mmol, quant.) as a white solid.

R_f: 0.4, *i*-hex:EtOAc 1:1, CAM, UV. **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 6.04 – 6.03 (m, 1H), 5.48 (t, *J* = 1.6 Hz, 1H), 4.13 (s, 2H), 3.83 (d, *J* = 1.0 Hz, 3H). **^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ** = 170.7, 163.6, 158.7, 101.0, 89.1, 56.3, 51.0. **IR (ATR, neat)**: ν_{max} = 3082 (w), 2107 (s), 1731 (s), 1707 (s), 1652 (s), 1569 (s), 1453 (m), 1415 (m), 1249 (w), 1137 (s), 914 (m), 829 (s) cm^{-1}. **HRMS-ESI (m/z)**: calc. for $C_7H_8N_3O_3$ $[M+H]^+$: 182.0560; found: 182.0561.

Diazo-pyrone (**23**). A flask was charged with **S5** (0.10 g, 0.55 mmol, 1.0 eq.), THF (1.0 mL), H_2O (0.15 mL) and perfluorophenyl-3-(diphenylphosphanyl)propanoate (0.25 g, 0.60 mmol, 1.1 eq.). The heterogeneous yellow mixture was stirred at RT and monitored by TLC until completion (ca. 1 h). Afterwards, a solution of sat. $NaHCO_{3(aq.)}$ (1 mL) was added (gas evolution!). The heterogeneous orange mixture was monitored by TLC until completion (ca. 2 h). Then, the reaction was partitioned between H_2O and CH_2Cl_2, the aqueous phase was extracted three times with CH_2Cl_2, the combined organic fractions were washed with brine, dried with Na_2SO_4, filtered and the solvent was removed under reduced pressure. The crude product was purified by FCC (EtOAc/*i*-hex 2:8) to afford diazo-pyrone **23** (0.05 g, 0.30 mmol, 55%) as an orange solid.

R_f: 0.4, *i*-hex:EtOAc 1:1, CAM, UV. **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 5.56 (t, *J* = 1.5 Hz, 1H), 5.24 (t, *J* = 1.5 Hz, 1H), 4.94 (d, *J* = 1.0 Hz, 1H), 3.79 (d, *J* = 1.0 Hz, 3H). **^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ** = 171.8, 163.6, 155.5, 91.8, 84.3, 55.9, 48.5. **IR (ATR, neat)**: ν_{max} = 3288 (b), 3064 (m), 2148 (w), 2077 (s), 1714 (s), 1616 (m), 1545 (m), 1407 (m), 1243 (m), 1171 (m),

1042 (m), 946 (w), 807 (m) cm^{-1}. **HRMS-ESI (m/z)**: calc. for $C_7H_7N_2O_3$ $[M+H]^+$: 167.0451; found: 167.0451.

Ether (**S6**). A flame dried flask under argon was charged with alcohol **26**[4d] (3.00 g, 14.7 mmol, 1.0 eq.) and dry THF (36 mL). The solution was cooled to –20 °C. To this were added sequentially BnBr (2.30 mL, 19.4 mmol, 1.3 eq.), TBAI (0.54 g, 1.46 mmol, 0.1 eq.) and NaH (60% dispersion in mineral oil, 0.77 g, 19.3 mmol, 1.3 eq.). The reaction mixture was allowed to warm to RT and was monitored by TLC until completion (ca. 10 h). Afterwards, the reaction was quenched by addition of $NH_4Cl_{(aq.)}$, the aqueous phase was extracted three times with Et_2O, the combined organic fractions were washed with brine, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude product was purified by FCC (EtOAc/*i*-hex 5:95) to afford ether **S6** (3.80 g, 12.9 mmol, 88%) as a yellow oil.

R_f: 0.6, *i*-hex:EtOAc 9:1, CAM, UV. $[\alpha]_D^{20\,°C}$: –38.3 (c = 1.0, $CHCl_3$). **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 7.38 – 7.27 (m, 5H), 5.88 – 5.77 (m, 1H), 5.14 – 5.07 (m, 2H), 4.65 – 4.62 (d, 1H), 4.52 – 4.49 (d, 1H), 4.20 – 4.16 (m, 1H), 3.83 – 3.77 (m, 1H), 2.91 – 2.74 (m, 4H), 2.42 – 2.30 (m, 2H), 2.14 – 1.82 (m, 4H). **^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ** = 138.8, 134.2, 128.5, 128.0, 127.7, 117.9, 75.2, 71.7, 44.1, 40.2, 38.6, 30.5, 30.1, 26.2. **IR (ATR, neat)**: ν_{max} = 2898 (w), 1640 (w), 1496 (w), 1453 (w), 1422 (w), 1347 (w),n1275 (w), 1243 (w), 1206 (w), 1179 (w), 1088 (m), 1068 (s), 1027 (m), 992 (m), 908 (m), 734 (s), 695 (s), 663 (w) cm^{-1}. **HRMS-EI (m/z)**: calc. for $C_{16}H_{22}OS_2$ $[M]^{+\cdot}$: 294.1112; found: 294.1104.

Aldehyde (**27**). A flask was charged sequentially with ether **S6** (3.80 g, 12.9 mmol, 1.0 eq.), MeCN/H_2O (9/1, 165 mL), MeI (8.05 mL, 129 mmol, 10.0 eq.) and $CaCO_3$ (6.45 g, 64.5 mmol, 5.0 eq.). The reaction mixture was heated to 45 °C and it was monitored by TLC until completion (ca. 8 h). Afterwards, the solvent was removed and the residue was partitioned between EtOAc and H_2O, the aqueous phase was extracted three times with EtOAc, the combined organic fractions were washed with brine, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude product was purified by FCC (EtOAc/*i*-hex 1:9) to afford aldehyde **27** (2.07 g, 10.1 mmol, 78%) as a colorless oil.

R_f: 0.4, *i*-hex:EtOAc 9:1, CAM, UV. $[\alpha]_D^{20\,°C}$: –43.3 (c = 1.0, $CHCl_3$). **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 9.71 (s, 1H), 7.30 – 7.18 (m, 5H), 5.80 – 5.70 (m, 1H), 5.09 – 5.05 (m, 2H), 4.57 – 4.54 (d, 1H), 4.47 – 4.44 (d, 1H), 4.00 – 3.94 (m, 1H), 2.65 – 2.58 (m, 1H), 2.53 – 2.47 (m, 1H), 2.42 – 2.28 (m, 2H). **^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ** = 201.4, 138.1, 133.6, 128.5, 127.8, 118.4, 73.7, 71.3, 48.0, 38.3. **IR (ATR, neat)**: ν_{max} = 3066 (w), 2863 (w), 2729 (w),

1722 (s), 1641 (w), 1496 (w), 1454 (w), 1346 (m), 1206 (w), 1090 (m), 1069 (mw), 1027 (m), 995 (m), 916 (m), 735 (s), 696 (s) cm^{-1}. **HRMS-EI (m/z)**: calc. for $C_{13}H_{16}O_2$ $[M]^{+\cdot}$: 204.1145; found: 204.1143.

Ketone (**28**). A flame dried flask under argon was charged with pyrone **25** (1.85 g, 13.2 mmol, 1.3 eq.), HMPA (2.65 mL, 15.2 mmol, 1.5 eq.) and dry Et_2O (70 mL). This solution was cooled to –78 °C and a freshly prepared solution of LDA (12.7 mL, 12.9 mmol, 1.3 eq., 1.02 M in THF) was added slowly. The reaction was stirred at the same temperature for 40 minutes. Then, a solution of aldehyde **27** (2.07 g, 10.1 mmol, 1.0 eq.) in dry Et_2O (30.0 mL) was added dropwise and the reaction mixture was stirred for 1.5 h. Afterwards, the reaction was quenched by addition of Na_2SO_4•10 H_2O (2 eq.) and was allowed to warm to RT. The precipitate was filtered, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude product was passed through a silica pad (EtOAc/*i*-hex 4:6 to 6:4) to afford the crude alcohol as a yellow oil that was carried through to the next step without further purification. $\mathbf{R_f}$: 0.7, *i*-hex:EtOAc 2:3, CAM, UV. **HRMS-EI (m/z)**: calc. for $C_{20}H_{24}O_5$ $[M]^{+\cdot}$: 344.1618. Found: 344.1634.

A flame dried flask under argon was charged with the crude alcohol, dry CH_2Cl_2 (75 mL) and it was cooled to 0 °C. To this solution was added DMP (3.80 g, 8.96 mmol, 0.9 eq.) and it was stirred at the same temperature for 5 minutes. Then, the cooling bath was removed and the reaction was monitored by TLC until completion (ca. 3 h). Afterwards, the reaction was quenched by addition of a mixture of sat. $Na_2S_2O_{3(aq.)}$ and sat. $NaHCO_{3(aq.)}$ (1:1). The aqueous phase was extracted three times with EtOAc, the combined organic fractions were washed with brine, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude product was purified by FCC (EtOAc/*i*-hex 3:7 to 4:6) to afford ketone **28** (1.90 g, 5.55 mmol, 55% over two steps) as a colorless solid.

$\mathbf{R_f}$: 0.6, *i*-hex:EtOAc 2:8, CAM, UV. $[\alpha]_D^{20\,°C}$: –36.4 (c = 0.3, $CHCl_3$). **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 7.29 – 7.21 (m, 5H), 5.78 – 5.70 (m, 2H), 5.37 (d, *J* = 2.2 Hz, 1H), 5.08 – 5.03 (m, 2H), 4.54 (d, *J* = 11.3 Hz, 1H), 4.40 (d, *J* = 11.2 Hz, 1H), 3.96 (ddt, *J* = 8.2, 6.6, 4.7 Hz, 1H), 3.72 (s, 3H), 3.45 (s, 2H), 2.72 (dd, *J* = 16.1, 8.2 Hz, 1H), 2.54 (dd, *J* = 16.1, 4.3 Hz, 1H), 2.34 – 2.27 (m, 2H). **^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ** = 202.5, 170.9, 164.4, 157.7, 138.2, 133.7, 128.6, 128.0, 127.9, 118.5, 103.1, 88.6, 75.0, 71.9, 56.1, 48.2, 47.5, 38.3. **IR (ATR, neat)**: ν_{max} = 3080 (w), 2918 (m), 1712 (s), 1645 (m), 1565 (s), 1454 (m), 1420 (m), 1394 (m), 1318 (m), 1256 (m), 1129 (m), 1063 (m), 1031 (m), 997 (m), 940 (m), 909 (m), 852 (m), 742 (m), 698 (m) cm^{-1}. **HRMS-ESI (m/z)**: calc. for $C_{20}H_{23}O_5$ $[M+H]^+$: 343.1540; found: 343.1541.

Diazo (**29**). A flame dried flask under argon was charged with ketone **28** (0.92 g, 2.69 mmol, 1.0 eq.), dry MeCN (19 mL) and *p*-ABSA (0.77 g, 3.21 mmol, 1.2 equiv). To this solution Et_3N (0.58 mL, 4.18 mmol, 1.5 eq.) was added dropwise. The orange suspension was monitored by TLC until completion (ca. 10 h). Afterwards, it was concentrated to the volume of ca. 3 mL and purified by FCC (EtOAc/*i*-hex 3:7) to afford diazo **29** (0.99 g, 2.69 mmol, quant.) as an orange oil.

R_f: 0.5, *i*-hex:EtOAc 1:1, CAM, UV. $[\alpha]_D^{20\,°C}$: –37.3 (c = 0.5, $CHCl_3$). **^{1}H NMR (800 MHz, $CDCl_3$) δ** = 7.31 – 7.29 (m, 2H), 7.27 – 7.25 (m, 3H), 6.89 (s, 1H), 5.84 – 5.79 (m, 1H), 5.36 (d, *J* = 2.3 Hz, 1H), 5.15 – 5.13 (m, 2H), 4.63 (d, *J* = 11.5 Hz, 1H), 4.45 (d, *J* = 11.4 Hz, 1H), 4.06 – 4.01 (m, 1H), 3.82 (s, 3H), 2.83 – 2.80 (m, 1H), 2.61 – 2.59 (m, 1H), 2.44 – 2.37 (m, 2H). **^{13}C{^{1}H} NMR (201 MHz, $CDCl_3$) δ** = 188.8, 171.8, 162.4, 148.9, 138.0, 133.4, 128.6, 128.0, 127.9, 118.7, 98.7, 86.8, 76.1, 75.2, 72.1, 56.1, 44.3, 38.5. **IR (ATR, neat)**: ν_{max} = 3107 (vw), 3077 (vw), 3029 (vw), 2978 (vw), 2942 (vw), 2908 (vw), 2361 (vw), 2340 (vw), 2099 (s), 1725 (vs), 1651 (s), 1618 (s), 1545 (vs), 1496 (w), 1454 (m), 1408 (s), 1377 (s), 1282 (w), 1228 (vs), 1185 (m), 1086 (m), 1065 (s), 1025 (m), 987 (s), 960 (s), 917 (m), 874 (m), 829 (s), 800 (s), 737 (m), 697 (s) cm^{-1}. **HRMS-ESI (m/z)**: calc. for $C_{19}H_{21}O_4$ $[M–N_2–CO+H]^+$: 313.1434; found: 313.1449.

Aldehyde (**30**). A flask was charged sequentially with diazo **29** (1.00 g, 2.71 mmol, 1.0 eq.), acetone/H_2O (10/1, 20 mL), NMO (0.38 g, 3.24 mmol, 1.2 eq.) and 2,6-lutidine (0.62 mL, 5.34 mmol, 2.0 eq.). Then, OsO_4 (0.30 mL, 0.05 mmol, 0.02 eq., 4% in H_2O) was added and the reaction was monitored by TLC until completion (ca. 8 h). Upon completion, BAIB (1.04 g, 3.23 mmol, 1.2 eq.) was added and the reaction was monitored by TLC until completion (ca. 4 h). Afterwards, the reaction was quenched by addition of sat. $Na_2S_2O_{3(aq.)}$. The aqueous phase was extracted three times with EtOAc, the combined organic fractions were washed with sat. $CuSO_{4(aq.)}$, brine, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude product was purified by FCC (EtOAc/*i*-hex 1:1) to afford aldehyde **30** (0.56 g, 1.51 mmol, 56%) as a yellow oil.

$R_{f\ diol}$: 0.14, *i*-hex:EtOAc 2:8, CAM, UV. **R_f**: 0.5, *i*-hex:EtOAc 2:8, CAM, UV. $[\alpha]_D^{20\,°C}$: +17.5 (c = 0.05, $CHCl_3$). **^{1}H NMR (800 MHz, $CDCl_3$) δ** = 9.79 (s, 1H), 7.33 – 7.26 (m, 6H), 5.36 (d, *J* = 2.3 Hz, 1H), 4.60 (d, *J* = 11.4 Hz, 1H), 4.52 (d, *J* = 11.4 Hz, 1H), 4.50 – 4.47 (m, 1H), 3.83 (s, 3H), 2.91 (dd, *J* = 15.1, 7.1 Hz, 1H), 2.82 – 2.75 (m, 3H). **^{13}C{^{1}H} NMR (201 MHz, $CDCl_3$) δ** = 200.0, 187.7, 171.8, 162.3, 148.4, 137.5, 128.7, 128.3, 128.1, 98.9, 87.0, 75.1, 72.7, 71.3, 56.2, 48.3, 44.3. **IR (ATR, neat)**: ν_{max} = 2952 (vs), 2917 (vs), 2838 (m), 2395 (w), 1725 (s, b),

1647 (w), 1567 (m), 1455 (vs), 1408 (w), 1377 (vs), 1253 (m), 1166 (m), 998 (w), 974 (w), 810 (w), 760 (s) cm^{-1}. **HRMS-ESI (m/z)**: calc. for $C_{19}H_{17}N_2O_6$ $[M-H]^-$: 369.1092; found: 369.1099.

Acyloin (**31**). A flame dried flask under argon was charged with oven dried 4 Å MS (0.60 g), α-ketoester **16** (3.00 g, 14.5 mmol, 10.0 eq.) and pre-catalyst **17** (0.05 g, 0.15 mmol, 0.1 eq.). Then, a solution of aldehyde **30** (0.56 g, 1.51 mmol, 1.0 eq.) in dry CH_2Cl_2 (20 mL + 10 mL to rinse) was added and the mixture stirred for 5 minutes. Subsequently, dry DIPEA (0.26 mL, 1.53 mmol, 1.0 eq.) was added and the solution turned yellow. The reaction was monitored by TLC until completion (ca. 4 h). The reaction mixture was eluted directly with EtOAc over a silica pad and the solvent was removed under reduced pressure. The crude product was purified by FCC (EtOAc/*i*-hex 1:1 to 8:2, long column) to afford acyloin **31** (0.37 g, 0.64 mmol, 42%, 1.3:1 d.r.) as an amorphous yellow solid.

R_f: 0.4, *i*-hex:EtOAc 4:6, CAM, UV. **^{1}H NMR (800 MHz, $CHCl_3$, *** denotes minor diastereomer**) δ** = 7.92 (tt, 2H+2H*), 7.60 (tt, *J* = 7.3, 1.3 Hz, 1H+1H*), 7.47 (tt, 2H+2H*), 7.31 – 7.27 (m, 3H+3H*), 7.26 – 7.23 (m, 2H+2H*), 6.87 (s, 1H+1H*), 5.35 (d, *J* = 2.3 Hz, 1H+1H*), 4.63 – 4.58 (m, 2H+2H*), 4.49 – 4.45 (m, 2H+2H*), 3.87 (d, *J* = 17.8 Hz, 1H+1H*), 3.82 (d, *J* = 1.7 Hz, 3H+3H*), 3.78 (s, 3H), 3.74 (s, 3H*), 3.73 – 3.71 (m, 1H+1H*), 3.28 (dd, *J* = 17.7, 5.5 Hz, 1H), 3.15 (dd, *J* = 17.7, 6.2 Hz, 1H*), 3.07 (dd, *J* = 17.7, 6.0 Hz, 1H*), 2.97 (dd, *J* = 17.7, 6.6 Hz, 1H), 2.91 (dd, *J* = 15.0, 7.4 Hz, 1H*), 2.86 (dd, *J* = 14.9, 7.1 Hz, 1H), 2.81 (ddd, *J* = 15.0, 9.1, 4.7 Hz, 1H+1H*). **^{13}C{^{1}H} NMR (201 MHz, $CDCl_3$) δ** = 204.62, 204.59, 197.5, 197.4, 187.97, 187.95, 171.8, 170.48, 170.45, 162.4, 148.7, 137.73, 137.70, 136.1, 134.2, 128.9, 128.59, 128.56, 128.4, 128.1, 128.0, 98.82, 98.79, 86.9, 82.62, 82.58, 75.1, 72.8, 72.7, 72.41, 72.37, 56.1, 54.0, 53.9, 44.32, 44.25, 44.24, 44.1, 41.6, 41.3. **IR (ATR, neat)**: ν_{max} = 3458 (b), 3108 (vw), 3088 (vw), 3064 (vw), 3030 (vw), 2950 (vw), 2920 (vw), 2361 (vw), 2341 (vw), 2250 (vw), 2102 (m), 1720 (vs), 1687 (m), 1651 (s), 1618 (m), 1597 (m), 1580 (w), 1546 (s), 1496 (vw), 1453 (m), 1410 (m), 1382 (m), 1357 (m), 1282 (m), 1230 (vs), 1185 (m), 1087 (m), 1069 (m), 1025 (m), 1001 (m), 988 (m), 960 (m), 911 (m), 878 (m), 822 (m), 803 (m), 753 (m), 729 (s), 689 (s) cm^{-1}. **HRMS-ESI (m/z)**: calc. for $C_{30}H_{32}N_3O_{10}$ $[M+NH_4]^+$: 594. 2082; found: 594.2088.

Ketone (**32**). A flame dried flask under argon was charged with acyloin **31** (0.25 g, 0.43 mmol, 1.0 eq.), *n*-Bu_3SnH (1.14 mL, 4.31 mmol, 10.0 eq.), $Cu(acac)_2$ (1 mg, 0.004 mmol, 0.01 eq.) and dry benzene (17 mL, degassed by sparging with argon for 20 minutes). Then, the solution was immersed in a preheated 80 °C oil bath. The reaction was monitored by TLC until completion (ca. 1 h). Afterwards, the reaction mixture was cooled to RT and directly

charged on a silica column (EtOAc/*i*-hex 4:6 to 7:3) to afford ketone **32** (0.12 g, 0.22 mmol, 51%) as an amorphous yellow solid.

R_f: 0.7, *i*-hex:EtOAc 2:8, CAM, UV. **^{1}H NMR (800 MHz, $CHCl_3$, *** denotes minor diastereomer**) δ** = 7.92 (ddd, *J* = 8.5, 6.4, 1.3 Hz, 2H+2H*), 7.60 (tt, *J* = 7.4, 1.3 Hz, 1H+1H*), 7.47 (tt, *J* = 7.5, 1.1 Hz, 2H+2H*), 7.34 – 7.27 (m, 5H+5H*), 5.87 (t, *J* = 2.2 Hz, 1H+1H*), 5.44 (dd, *J* = 2.3, 0.8 Hz, 1H+1H*), 4.62 – 4.54 (m, 2H+2H*), 4.51 (dd, *J* = 11.2, 5.1 Hz, 1H+1H*), 4.47 – 4.43 (m, 1H+1H*), 3.87 (dd, *J* = 17.8, 12.4 Hz, 1H+1H*), 3.79 (d, *J* = 2.5 Hz, 3H+3H*), 3.74 (d, *J* = 29.3 Hz, 3H+3H*), 3.70 (dd, *J* = 17.8, 3.3 Hz, 1H+1H*), 3.52 (d, *J* = 3.7 Hz, 2H+2H*), 3.27 (dd, *J* = 17.4, 5.8 Hz, 1H*), 3.09 – 3.03 (m, 1H+1H*), 2.90 – 2.87 (m, 1H+1H*), 2.83 (dd, *J* = 16.4, 6.8 Hz, 1H), 2.78 (ddd, *J* = 16.4, 5.2, 2.1 Hz, 1H+1H*). **^{13}C{^{1}H} NMR (201 MHz, $CDCl_3$) δ** = 204.6, 204.5, 201.74, 201.72, 197.53, 197.45, 170.9, 170.53, 170.46, 157.52, 157.49, 138.01, 137.98, 136.1, 134.10, 134.10, 128.9, 128.58, 128.55, 128.4, 128.11, 128.09, 127.97, 127.95, 103.21, 103.20, 88.63, 88.62, 82.62, 82.56, 72.5, 71.66, 71.64, 56.1, 53.92, 53.90, 48.0, 47.6, 47.5, 44.2, 44.1, 41.7, 41.5. **IR (ATR, neat)**: ν_{max} = 3443 (b), 3089 (vw), 3063 (vw), 3031 (vw), 2951 (vw), 2924 (vw), 2851 (vw), 2106 (vw), 1720 (vs), 1650 (m), 1597 (w), 1567 (s), 1496 (w), 1453 (m), 1413 (m), 1356 (m), 1250 (s), 1219 (m), 1182 (m), 1143 (m), 1089 (m), 1070 (m), 1030 (m), 1001 (w), 943 (w), 819 (w), 755 (w), 738 (w), 691 (w) cm^{-1}. **HRMS-ESI (m/z)**: calc. for $C_{30}H_{34}NO_{10}$ $[M+NH_4]^+$: 568.2177; found: 568.2186.

Alcohol (**33**). A flame dried flask under argon was charged with ketone **32** (20.0 mg, 0.036 mmol, 1.0 eq.), pentamethylbenzene (31.0 mg, 0.21 mmol, 5.8 eq.) and dry CH_2Cl_2 (0.2 mL). The solution was cooled to –78 °C. Then, BCl_3 (0.1 mL, 0.10 mmol, 3.0 eq., 1 M in CH_2Cl_2) was added dropwise and the color changed to yellow. The reaction was monitored by TLC until completion (ca. 1 h) and then it was quenched by addition of MeOH. The cooling bath was removed, the mixture was allowed to reach RT and then the solvent was removed under reduced pressure. The crude product was purified by FCC (EtOAc/*i*-hex 9:1 to 1:0) to afford alcohol **33** (6.2 mg, 14 *μ*mol, 39%) as a yellow oil.

R_f: 0.2, *i*-hex:EtOAc 2:8, CAM, UV. **^{1}H NMR (800 MHz, $CHCl_3$, *** denotes minor diastereomer**) δ** = 7.94 (ddd, *J* = 8.3, 2.1, 1.2 Hz, 2H+2H*), 7.61 (ddt, *J* = 7.4, 6.4, 1.1 Hz, 1H+1H*), 7.50 – 7.46 (m, 2H+2H*), 5.93 (d, *J* = 2.1 Hz, 1H+1H*), 5.46 (d, *J* = 2.2 Hz, 1H+1H*), 4.63 (s, 1H+1H*), 4.63 – 4.57 (m, 2H+2H*), 3.89 (dd, *J* = 17.8, 10.7 Hz, 1H+1H*), 3.83 (d, *J* = 1.3 Hz, 3H+3H*), 3.80 (s, 3H+3H*), 3.76 (dd, *J* = 17.8, 5.4 Hz, 1H+1H*), 3.60 (d, *J* = 3.2 Hz, 2H+2H*), 3.18 – 3.05 (m, 1H+1H*), 3.06 (dd, *J* = 17.7, 4.1 Hz, 1H*), 2.89 (dd, *J* = 17.7, 8.1 Hz, 1H*), 2.85 (dd, *J* = 17.6, 4.1 Hz, 1H), 2.80 (ddd, *J* = 17.1, 8.0, 2.1 Hz, 1H+1H*), 2.75 (ddd, *J* = 17.1, 4.2, 1.6 Hz, 1H+1H*). **^{13}C{^{1}H} NMR (201 MHz, CDCl3) δ** = 207.0, 206.0,

202.9, 170.7, 170.3, 164.1, 157.1, 135.9, 134.1, 128.8, 128.3, 103.2, 88.5, 82.3, 64.1, 56.0, 53.9, 48.4, 47.7, 44.2, 43.1, 31.0, 29.7. **IR (ATR, neat)**: ν_{max} = 3440 (b), 2948 (vw), 2849 (vw), 1717 (vs), 1647 (m), 1566 (vs), 1450 (s), 1411 (s), 1247 (s), 1220 (m), 1143 (m), 1037 (m), 942 (m), 815 (w), 755 (w), 738 (w), 689 (s) cm^{-1}. **HRMS-ESI (m/z)**: calc. for $C_{23}H_{28}NO_{10}$ $[M+NH_4]^+$: 478.1708; found: 478.1714.

Crude data for **34** / **35**. **HRMS-ESI (m/z)**: calc. for $C_{23}H_{23}O_9$ $[M+H]^+$: 443.1337; found: 443.1341. The stereochemistry at C_2 is not assigned. Crude ^1H NMR and HSQC data are available in the Supporting Information.

Diol (**37**). A flame dried flask under argon was charged with 4 Å MS (1.0 g), diazo **36**[4d] (0.49 g, 1.24 mmol, 1.0 eq.), pyridine (0.6 mL, 7.43 mmol, 6.0 eq.), PCC (1.07 g, 4.96 mmol, 4.0 eq.) and dry CH_2Cl_2 (12.5 mL). The mixture was heated at 40 °C and it was monitored by TLC until completion (ca. 20 h, after 12 h additional 2.8 eq. of PCC were added). Afterwards, the reaction was cooled to RT and celite was added. This mixture was poured into a pad of celite impregnated with EtOAc, filtered and the cake washed with more EtOAc. The solvent was removed under reduced pressure and the residue passed through a silica pad (EtOAc/*i*-hex 6:3) to afford the crude lactone (0.24 g) which was used in the next step without further purification. $\mathbf{R_f}$: 0.4, *i*-hex:EtOAc 1:1, CAM, UV.

A flask was charged sequentially with the crude lactone, THF/H_2O (5/1, 5.0 mL) and NMO (0.14 g, 1.19 mmol, 1.0 eq.). Then, OsO_4 (0.08 mL, 12.5 μmol, 0.01 eq., 4% in H_2O) was added and the reaction was monitored by TLC until completion (ca. 2 h). Upon complete conversion, the reaction was quenched by adding a solution of sat. $Na_2S_2O_{3(aq.)}$. The aqueous phase was extracted three times with EtOAc, the combined organic fractions were washed with brine, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude product was purified by FCC (MeOH/Acetone/CH_2Cl_2 2:8:90) to afford diol **37** (0.14 g, 0.32 mmol, 26%) as a yellow solid.

$\mathbf{R_f}$: 0.2, *i*-hex:EtOAc 2:8, CAM, UV. $[\alpha]_D^{20\,°C}$: –11.7 (c = 3.2, $CHCl_3$). **^{1}H NMR (800 MHz, $CDCl_3$) δ** = 7.29 – 7.27 (m, 2H), 7.21 – 7.19 (m, 1H), 7.17 – 7.16 (m, 2H), 6.92 – 6.81 (m, 1H), 5.37 (d, *J* = 2.3 Hz, 1H), 5.32 – 5.29 (m, 1H), 4.13 (dd, *J* = 3.5, 2.4 Hz, 1H), 3.82 (s, 3H), 2.97 – 2.91 (m, 2H), 2.76 – 2.73 (m, 1H), 2.64 (ddd, *J* = 13.6, 11.5, 5.3 Hz, 1H), 2.28 – 2.26 (m, 2H), 2.02 – 1.96 (m, 2H). **^{13}C{^{1}H} NMR (201 MHz, $CDCl_3$) δ** = 185.6, 175.9, 171.7, 162.2, 140.7, 128.8, 128.5, 126.4, 99.2, 87.1, 76.1, 75.0, 69.8, 56.2, 43.6, 42.9, 39.4, 32.0, 29.9, 29.3. **IR (ATR, neat)**: ν_{max} = 2919 (w), 2850 (w), 2106 (m), 1641 (s), 1453 (m), 1407 (m),

1232 (m), 1124 (w), 1016 (m), 810 (m), 699 (m) cm^{-1}. **HRMS-ESI (m/z)**: calc. for $C_{22}H_{26}O_8N_3$ $[M+NH_4]^+$: 460.1714; found: 460.1717.

Acetonide (**38**). A flask was charged sequentially with **37** (57.0 mg, 0.13 mmol, 1.0 eq.), dry CH_2Cl_2 (1.3 mL), 2,2-DMP (25 μL, 0.20 mmol, 1.6 eq.) and *p*-TSA (3.0 mg, 17 μmol, 0.1 eq.). The reaction was monitored by TLC until completion (ca. 2 h). Upon full conversion, the reaction was quenched by addition of a solution of sat. $NaHCO_{3(aq.)}$. The aqueous phase was extracted three times with EtOAc, the combined organic fractions were washed with brine, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude product was purified by FCC (EtOAc/*i*-hex 6:4) to afford **38** (17 mg, 35 μmol, 27%) as a yellow solid.

R_f: 0.7, *i*-hex:EtOAc 2:8, CAM, UV. $[\alpha]_D^{20\,°C}$: +2.1 (c = 0.5, $CHCl_3$). **^{1}H NMR (800 MHz, $CDCl_3$) δ** = 7.28 (t, *J* = 7.6 Hz, 2H), 7.21 – 7.17 (m, 3H), 6.85 (s, 1H), 5.36 (d, *J* = 2.2 Hz, 1H), 5.24 (dddd, *J* = 11.9, 7.2, 5.2, 2.5 Hz, 1H), 4.38 (dd, *J* = 3.6, 2.1 Hz, 1H), 3.81 (s, 3H), 3.01 (dd, *J* = 15.6, 6.7 Hz, 1H), 2.85 (dd, *J* = 15.7, 5.1 Hz, 1H), 2.77 (td, *J* = 12.9, 5.2 Hz, 1H), 2.64 (td, *J* = 12.9, 4.9 Hz, 1H), 2.38 (ddd, *J* = 15.0, 3.6, 2.6 Hz, 1H), 2.24 (ddd, *J* = 14.0, 12.3, 4.9 Hz, 1H), 2.17 – 2.13 (m, 1H), 2.04 – 1.98 (m, 1H), 1.46 (d, *J* = 17.3 Hz, 6H). **^{13}C{^{1}H} NMR (201 MHz, $CDCl_3$) δ** = 185.7, 171.7, 162.2, 148.0, 140.6, 128.7, 128.4, 126.5, 110.4, 99.2, 87.1, 80.6, 75.5, 75.2, 71.8, 56.2, 43.9, 37.6, 31.1, 30.0, 27.3, 26.8. **IR (ATR, neat)**: ν_{max} = 2925 (w), 2853 (w), 2104 (vw), 1723 (s), 1568 (s), 1256 (m), 1176 (m), 1089 (m), 1024 (m), 813 (m), 699 (m) cm^{-1}. **HRMS-ESI (m/z)**: calc. for $C_{25}H_{30}O_8N_3$ $[M+NH_4]^+$: 500.2027; found: 500.2031.

TMS diol (**39**). A flask under air was charged with AD-mix-α (0.60 g) and *t*-BuOH/H_2O (1.8 mL, 1/1). The flask was closed with a stopper and stirred at RT for 30 min. Diazo **36** (0.14 g, 0.35 mmol, 1.0 eq.) and $MeSO_2NH_2$ (0.07 g, 0.74 mmol, 2.0 eq.) were added to the mixture. The reaction was monitored by TLC analysis until completion (ca. 20 h). Afterwards, the reaction was quenched with solid $Na_2S_2O_3$ (0.8 g), stirred for 15 minutes and then partitioned between H_2O/EtOAc. The aqueous phase was extracted three times with EtOAc, the combined organic phases were dried with Na_2SO_4, filtered and the solvent was removed under reduced pressure. The crude oil (crude ^{1}H NMR 1.6:1 d.r.) was purified by FCC (MeOH/Acetone/CH_2Cl_2 2.5:2.5:95) to afford the separated diols. Both were contaminated with inseparable $MeSO_2NH_2$ and were therefore used in the next step without further purification. **R_f diol**: 0.4, *i*-hex:EtOAc 2:8, CAM, UV. **R_f diol'**: 0.2, *i*-hex:EtOAc 2:8, CAM, UV.

A flame dried flask under argon was charged sequentially with one crude alcohol, dry CH_2Cl_2 (2 mL), 2,6-lutidine (0.14 mL, 1.2 mmol) and the reaction vessel was cooled to 0 °C. Neat

TMSOTf (0.1 mL, 0.55 mmol) was added dropwise and the reaction was stirred for 10 minutes at the same temperature. Then, the cooling bath was removed and the reaction was monitored by TLC until completion (ca. 2 h). Afterwards, the reaction was quenched by addition of sat. $NaHCO_{3(aq)}$. The aqueous phase was extracted three times with EtOAc, the combined organic fractions were washed with brine, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude product was purified by FCC (EtOAc/*i*-hex 3:7) to afford **39** (56.0 mg, 0.1 mmol, 27% over 2 steps) as a yellow oil. Structural determination was performed by analysis of the 2D NMR data (NOESY) of both diasteromers.

R_f : 0.6, *i*-hex:EtOAc 6:4, CAM, UV. $[\alpha]_D^{20\,°C}$: +12.8 (c = 0.9, $CHCl_3$). **^{1}H NMR (800 MHz, C_6D_6)** **δ** = 7.23 – 7.19 (m, 4H), 7.12 – 7.07 (m, 1H), 5.08 (t, *J* = 2.3 Hz, 1H), 4.23 (td, *J* = 7.4, 3.8 Hz, 1H), 3.86 (d, *J* = 10.4 Hz, 1H), 3.78 – 3.77 (m, 1H), 3.43 (dd, *J* = 10.4, 1.4 Hz, 1H), 2.87 (dd, *J* = 5.9, 4.4 Hz, 3H), 2.74 (td, *J* = 12.8, 4.5 Hz, 1H), 2.62 (td, *J* = 12.8, 5.5 Hz, 1H), 2.21 – 2.17 (m, 1H), 2.07 – 2.03 (m, 2H), 1.88 – 1.84 (m, 2H), 1.49 (dddd, *J* = 23.3, 14.2, 11.5, 2.8 Hz, 2H), 0.16 (s, 9H), 0.12 (s, 9H). **^{13}C{^{1}H} NMR (201 MHz, C_6D_6) δ** = 187.8, 171.3, 161.1, 149.3, 142.9, 128.9, 128.7, 128.4, 128.3, 126.3, 98.3, 86.8, 75.0, 70.7, 69.7, 69.5, 55.1, 44.9, 39.3, 37.7, 32.2, 29.7, 3.1, 0.6. **IR (ATR, neat)**: ν_{max} = 3026 (vw), 2955 (w), 2103 (s), 1731 (s), 1656 (m), 1549 (s), 1409 (m), 1230 (s), 1124 (m), 1077 (m), 834 (s), 698 (m) cm^{-1}. **HRMS-ESI (m/z)**: calc. for $C_{28}H_{44}O_7N_3Si_2$ $[M+NH_4]^+$: 590.2712; found: 590.2723.

TMS diol (**39'**). **^{1}H NMR (800 MHz, C_6D_6) δ** = 7.18 – 7.14 (m, 5H), 7.06 (tt, *J* = 7.1, 1.4 Hz, 1H), 5.09 (d, *J* = 2.3 Hz, 1H), 3.79 (d, *J* = 11.9 Hz, 1H), 3.66 (dddd, *J* = 11.7, 7.7, 4.1, 2.1 Hz, 1H), 3.32 (dd, *J* = 11.3, 4.7 Hz, 1H), 2.88 (s, 3H), 2.86 (d, *J* = 11.9 Hz, 1H), 2.65 (ddd, *J* = 13.8, 12.5, 4.5 Hz, 1H), 2.48 – 2.36 (m, 2H), 2.14 (ddd, *J* = 13.9, 12.9, 4.5 Hz, 1H), 2.05 (dd, *J* = 14.7, 4.1 Hz, 1H), 1.84 (q, *J* = 11.7 Hz, 1H), 1.46 (ddd, *J* = 12.3, 4.7, 2.1 Hz, 1H), 1.38 (ddd, *J* = 14.0, 12.5, 5.3 Hz, 1H), 0.32 (s, 9H), 0.05 (s, 9H). **^{13}C{^{1}H} NMR (201 MHz, C_6D_6) δ** = 187.6, 171.3, 161.0, 149.4, 142.6, 128.9, 128.5, 128.4, 128.3, 126.3, 125.5, 98.2, 75.7, 75.2, 74.2, 73.9, 73.2, 55.1, 45.2, 37.5, 36.8, 29.7, 3.3, 0.5.

Enol (**44**). A flame dried flask under argon was sequentially charged with Mg turnings (0.81 g, 33.3 mmol, 1.25 eq.) and dry Et_2O (100 mL). Under vigorous stirring, I_2 (7.00 g, 27.6 mmol, 1.0 eq.), was added and the reaction vessel was placed in a 40 °C preheated oil bath. The reaction mixture turned from dark brown to milky white. Then the solids were filtered under argon, washed three times with dry Et_2O and dried under high vacuum. This material was used without further purification in the following reaction.

A flame dried flask under argon was charged with freshly prepared MgI_2 (0.07 g, 0.25 mmol, 2.0 eq.) and a solution of **43**[4d] (46.0 mg, 0.13 mmol, 1.0 eq.) in dry toluene (1.2 mL). The reaction vessel was placed in an 80 °C preheated oil bath. The resulting mixture was monitored by TLC until completion (1 h). The reaction was allowed to cool to RT and then it was quenched by addition of sat. $NaHCO_{3(aq.)}$, the aqueous phase was extracted three times with EtOAc, dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. The crude product was purified by FCC (EtOAc/*i*-hex 35:65) to afford **44** (18.0 mg, 0.05 mmol, 41%) as a slightly yellow oil.

R_f: 0.5, EtOAc/*i*-hex 7:3, CAM, UV. **^{1}H NMR (800 MHz, $CDCl_3$) δ** = 7.28 (t, *J* = 7.6 Hz, 2H), 7.20 – 7.18 (m, 1H), 7.15 – 7.14 (m, 2H), 6.13 (d, *J* = 1.2 Hz, 1H), 5.70 (dd, *J* = 2.2, 1.1 Hz, 1H), 5.45 (d, *J* = 2.2 Hz, 1H), 4.69 (dd, *J* = 4.0, 2.1 Hz, 1H), 3.80 (s, 3H), 3.57 (s, 1H), 2.84 (dt, *J* = 3.9, 2.2 Hz, 1H), 2.80 – 2.72 (m, 3H), 2.64 (dt, *J* = 13.7, 8.1 Hz, 1H), 2.33 (dt, *J* = 13.9, 2.2 Hz, 1H), 2.21 (ddd, *J* = 8.3, 6.8, 1.3 Hz, 2H), 2.05 – 2.03 (m, 1H). **^{13}C{^{1}H} NMR (201 MHz, $CDCl_3$) δ** = 204.1, 170.8, 163.8, 160.8, 141.4, 139.4, 128.6, 128.5, 126.2, 112.3, 101.5, 88.5, 70.2, 56.9, 56.2, 47.5, 34.6, 33.1, 32.5, 24.7. **HRMS-ESI (m/z)**: calc. for $C_{22}H_{23}O_5$ $[M+H]^+$: 367.1540; found: 367.1543.

Associated Content

Supporting Information

^{1}H and ^{13}C spectra for all new compounds, procedures for the computational part and geometries of the optimized structures. This material is available free of charge via the Internet at http://pubs.acs.org.

X-ray data for compound **23** (CIF)

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Notes

The authors declare no competing financial interest

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