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Synthesis of the Core Structure of Palhinine A

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We present a strategy to the core structure of the alkaloid palhinine A passing through a 2,5-difunctionalized cyclohexenone. This enone was prepared by a domino Michael/aldol condensation sequence. An allylation reaction on the cyclohexenone followed by oxy-Cope rearrangement introduced an allyl group at C3. After the generation of an aldehyde function on the terminus of the C5 substituent, an intramolecular aldol reaction led to a bicyclo[2.2.2]octanone. The five-membered ring of the core structure could be established by an intramolecular nitrile oxide-alkene [3+2]-cycloaddition. Prior to this key transformation, the keto function was converted to an alkene and the allyl group to an oxime.

Introduction

Plants of the genus *Lycopodium* are the source of a wide collection of alkaloids. They are classified into the four main classes phlegmarine (**1**), lycodine (**2**), lycopodine (**3**), and fawcettimine (**4**).[1] Some of the Lycopodium alkaloids show promising biological activities, for example, inhibitory activity on acetylcholinesterase. In 2010, a new *Lycopodium* alkaloid, palhinine A (**5**) was described (Figure 1).[2] It can be considered a derivative of fawcettimine where the hemiaminal has opened to a nine-membered azonane ring, the methyl group at C15 functionalized, the stereochemistry at C15 epimerized, and a new ring formed to C4.[3] This results in an isotwistane core structure. In the meantime, four additional palhinines (B, C, D and isopalhinine A) were isolated (Figure 1). Regarding their bioactivity not much has been reported so far. Nevertheless, due to their novel structures, the palhinines have attracted a lot of interest from organic chemists.

Their key questions are how to prepare the central isotwistane core and when to fashion the nine-membered azacycle. The retrosynthesis of the central isotwistane system itself is fairly obvious (Figure 2). The central six-membered ring is the maximal bridged ring since this ring is bridged at four atoms with another ring. Accordingly, band cuts to these atoms should lead to suitable simplified starting materials.[4]

The challenge is rather the implementation of the synthesis in the laboratory.[5] So far total syntheses of palhinine A were reported by the groups of Fan and Hsieh. In the synthesis of Fan et al.[6] an intramolecular Diels-Alder reaction of triene **10** directly led to the isotwistane **11**. However, due to the transannular strain the formation of the azonane ring by

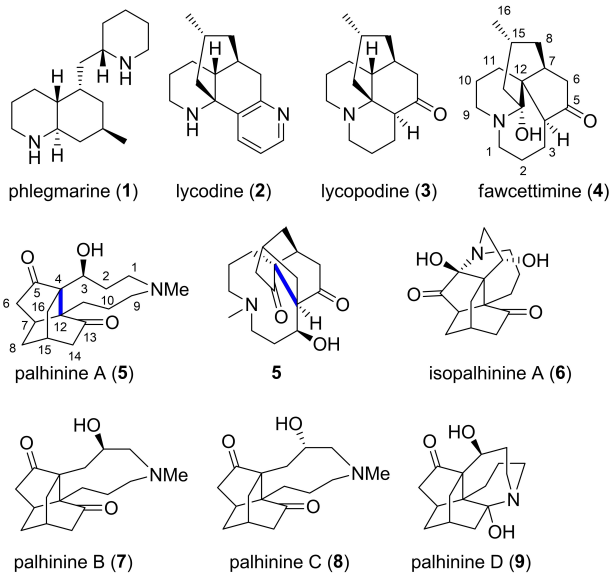

Figure 1. Structures of four main classes of alkaloids that originate from lysine and the fawcettimine derivatives called palhinines. The C4–C12 bond in the depiction of palhinine A (**5**) is highlighted in blue.

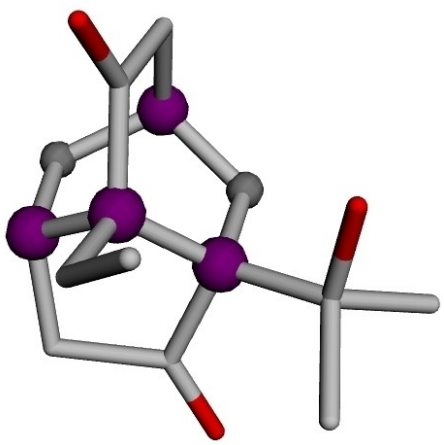

Figure 2. Maximally bridged ring in the isotwistane core of palhinine A (**5**). Violett dots: bridgehead atoms where the six-membered ring is bridged with another ring; grey dots: other atoms of the six-membered (maximally bridged ring).

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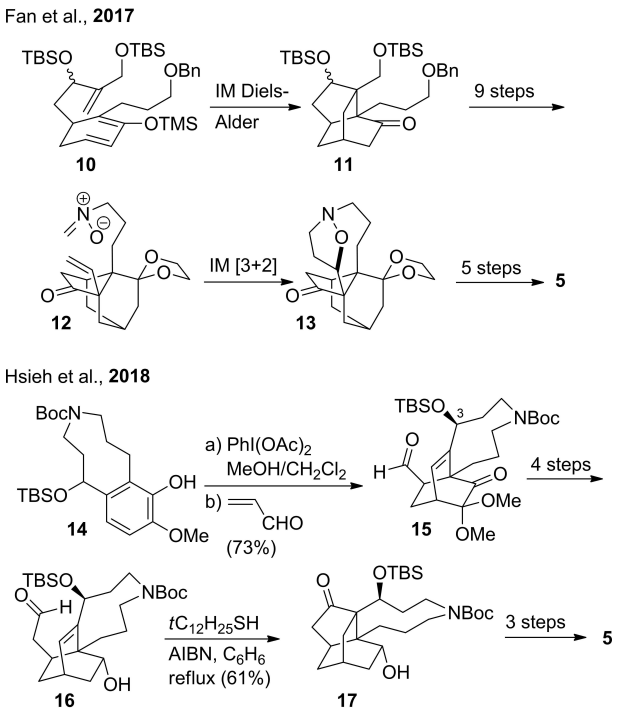
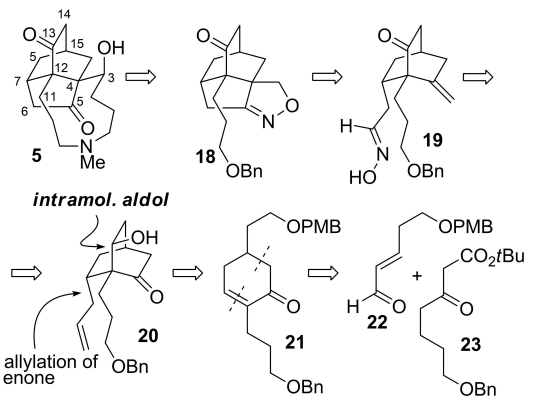
classical ring-closing reactions was not possible. Eventually, an intramolecular nitrone-alkene cycloaddition (**12** to **13**) provided a solution to this problem. In the synthesis of Hsieh et al., a masked *ortho*-benzoquinone, fused to the nine-membered azacycle, was reacted with acrolein to the tricyclic compound **15**.[7] After the conversion of cycloadduct **15** to aldehyde **16** a radical cyclization led to **17**, which was converted to **5** in three steps (Scheme 1).

Various groups, including our own, reported synthetic studies that led to the palhinine A core structure.[5] To fashion the bicyclo[2.2.2]octane skeleton, Diels-Alder reactions of cyclic dienes,[8] radical cyclization,[9] or domino Michael reactions[10] were used. A study by Fan et al. aimed at the construction of the nine-membered azonane ring via an azidoketal fragmentation reaction.[11]



Scheme 1. Key steps in the known total syntheses of palhinine A (**5**).

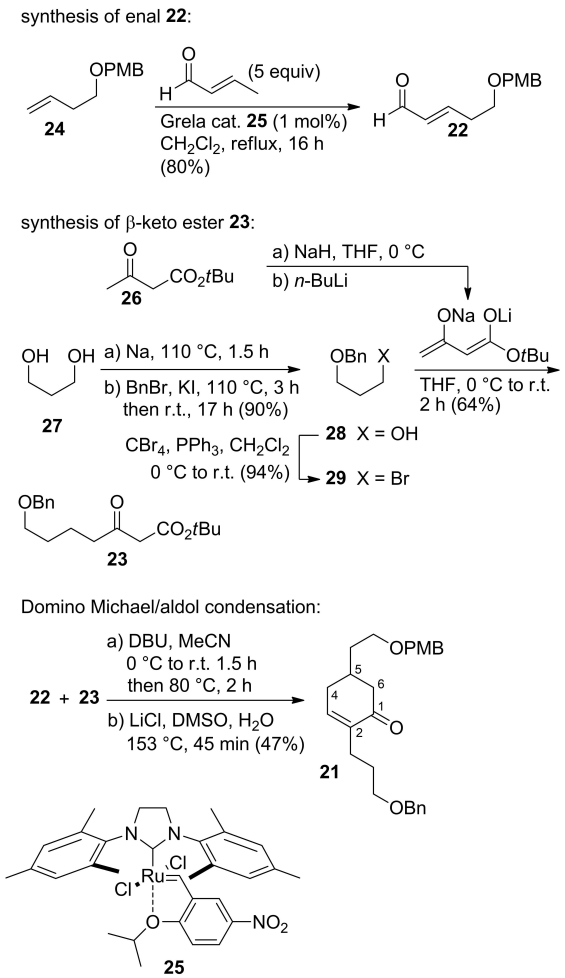


Scheme 2. Plan for the synthesis of the core structure **18** featuring a transannular aldol reaction and an intramolecular [3 + 2] nitrile oxide-alkene cycloaddition.

Results and Discussion

Since in our previous route some functionality on the isotwistane core was lacking, we sought to modify our original plan. Thus, in order to form the five-membered ring an intramolecular nitrile oxide-alkene cycloaddition was envisioned (Scheme 2).[12] This would also introduce a functional group handle at C4. A suitable functionalized bicyclo[2.2.2]octane precursor **20** would be obtained by a transannular aldol reaction. In this paper, we describe the realization of these plans.

We started with the synthesis of cyclohexenone **21**. For this, we required enal **22** and 3-keto ester **23**. Enal **22** was prepared by a cross-metathesis reaction between 3-butenol derivative[13] **24** and crotonaldehyde in presence of the nitro Grela catalyst[14] **25** (1 mol%) (Scheme 3). For the synthesis of keto ester **23** we used a Weiler alkylation[15] of *tert*-butyl 3-oxobutanoate (**26**) with the alkyl bromide[16] **29**, prepared in two steps from 1,3-

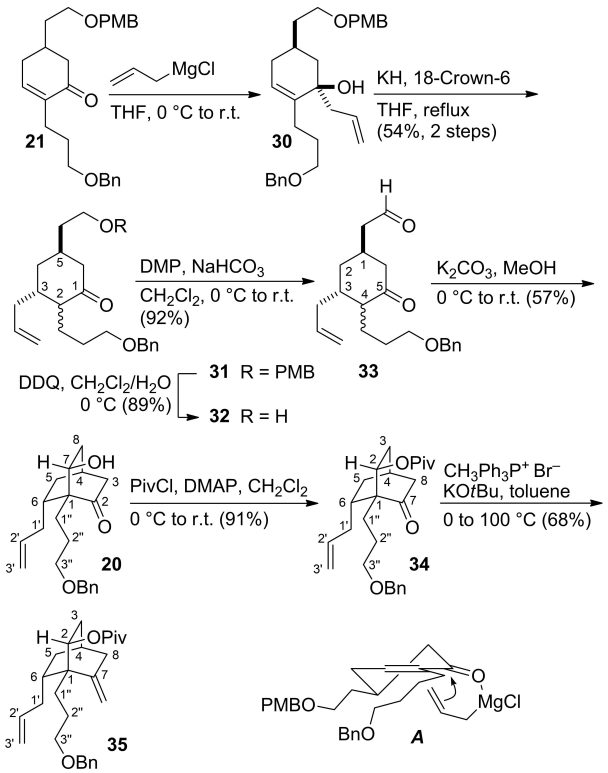


Scheme 3. Synthesis of enal **22**, β-keto ester **23** and their combination to cyclohexanone **21**.

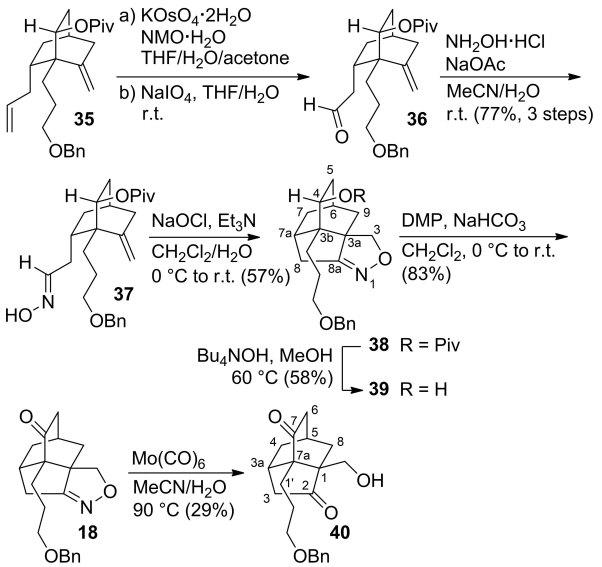
propanediol (**27**). Following a procedure of Carreira et al., we reacted enal **22** with keto ester **23** in a domino Michael/intramolecular aldol condensation using DBU in acetonitrile as base.[17,18] The superfluous carboxylic function was subsequently removed under Krapcho conditions.[19] This way a 47% yield of cyclohexenone **21** was obtained.

We were then faced with the challenge of introducing an allyl group in the 3-position of enone **21**. As it turned out, conjugate addition of allyltrimethylsilane in presence of Lewis acids ($BF_3 \cdot Et_2O$, $TiCl_4$) caused decomposition.[8b,20] The reaction of allylmagnesium chloride with or without CuI only led to 1,2-addition. We assume that the axial attack of the Grignard reagent on half-chair conformer ***A*** leads to tertiary alcohol **30** (Scheme 4). The relative stereochemistry of **30** was assigned based on model **A**, which features an axial attack on the half-chair conformer.[21] Due to signal overlaps in the H,H-NOESY spectrum n the region 1.0–2.5 ppm no unambiguous cross-peaks could be found. However, the later successful formation of the polycycles validated the assignment. A subsequent anionic oxy-Cope rearrangement using KH (1.5 equiv) in presence of 18-crown-6 (1.1 equiv) led to cyclohexanone **31** in 54% yield.[22,23] This compound is epimeric at the 2-position (ratio ~2:1) which is inconsequential. Following the oxidative cleavage of the PMB ether, the resulting alcohol **32** was oxidized to aldehyde **33** using the Dess-Martin periodinane reagent. Upon treatment with potassium carbonate in methanol, keto aldehyde **33** yielded the bicyclic aldol product **20** as a single diastereomer. The subsequent protection of the hydroxyl group was hampered by the formation of diastereomers, for example in the reaction of **20** with TBSOTf or MOMCl. Luckily, protection of the hydroxy function as pivalate **34** using pivaloyl chloride in presence of DMAP proceeded efficiently in 91%. The relative configuration at C2 could be proven by NOESY-spectroscopy. Thus, 2-H shows NOESY correlations to 5- and 6-H. In the ^1H spectrum, these protons appear at $\delta = 1.84–2.00$ ppm and are not overlapping with other peaks. Since we intended to form the third ring by an intramolecular cycloaddition reaction, ketone **34** was converted to exocyclic alkene **35** by a Wittig reaction. Best results were obtained using KO*t*Bu (10 equiv) as a base in toluene.

The terminal mono-substituted double bond of diene **35** was then converted to an aldehyde by a domino sequence consisting of dihydroxylation and periodate cleavage of the intermediate diol.[24] Crude aldehyde **36** was directly converted to oxime **37** (Scheme 5). Oxime **37** formed as a mixture of two isomers. While the isomers could be separated by chromatography, in solution ($CDCl_3$) they isomerized to the original *E*/*Z*-mixture.[25] This is evident from the ^{13}C NMR spectrum where several peaks appear as pairs (for example, C2, 7-CH_2). The intramolecular nitrile oxide-alkene cycloaddition[26] proceeded in 57% using aqueous NaOCl in dichloromethane in presence of Et_3N for the generation of the dipole from oxime.[27] Other conditions for the oxidation of the oxime to the nitrile oxide caused decomposition of substrate **37**.[28] The methylene protons at C3 are diastereotopic and appear at $\delta = 4.27$ (3-*exo*-H) and 3.99 (3-*endo*-H) ppm. Relatively large shift differences are also seen for the protons at C7, C8, C9, and C1′. The imine carbon (C8a) appears at $\delta = 173.9$ ppm. Saponification of the pivalic ester **38** gave tetracyclic alcohol **39**. Inspection of the H,H-NOESY spectrum of **39** allowed assignment of the diastereotopic methylene protons *exo*-3/*endo*-3 and *endo*-8/*exo*-8. For example, *exo*-3-H shows cross-peaks to the 1′-H protons, whereas *endo*-3 shows a correlation with one of the 9-H



Scheme 4. Introduction of an allyl group via oxy-Cope rearrangement and formation of the bicyclic system by transannular aldol reaction.



Scheme 5. Intramolecular nitrile oxide-alkene cycloaddition to form tetracyclic isoxazoline **38** and its conversion to ketones **18** and **40**.

protons. Subsequent oxidation of alcohol **39** delivered ketone **18**. This tetracyclic isoxazoline **18** was obtained quite pure. Similar to the situation in **39**, the H,H-NOESY spectrum of ketone **18** allowed for the assignment of the 3-H and 8-H protons. Finally, it was possible to cleave the isoxazoline ring with molybdenum hexacarbonyl in acetonitrile,[29] albeit in moderate yield and not in high purity. This way, the tricyclic core structure of palhinine A, diketo alcohol **40** was obtained. Even though **40** was not very pure, all hydrogen and carbon atoms could be assigned by 2D-NMR spectroscopy. The two carbonyl groups appear at $\delta = 218.7$ and 213.1 ppm, respectively. There is no indication of hemiacetal formation between the CH_2OH and C7.

Conclusion

We developed a strategy towards the core structure of the alkaloid palhinine A, which features a central isotwistane ring system. In order to create the polycyclic system, two key bond-forming reactions were used. The first one is an intramolecular (transannular) aldol reaction of keto aldehyde **33** to give the bicyclo[2.2.2]octanone derivative **20**. After some functional group manipulations, oxime **37** was obtained. Its conversion to an intermediate nitrile oxide initiated an intramolecular [3 + 2]-cycloaddition to give tetracyclic isoxazoline **38**. This compound could be converted to tricyclic diketone **40**. Future studies might probe a similar strategy where the azonane ring of palhinine A is installed at an earlier stage.

Experimental Section

General. All reactions were performed under nitrogen atmosphere. All solvents used in the reactions were purified before use. The progress of the reactions was followed by TLC (POLYGRAM SIL G/UV254). Flash chromatography was performed on silica gel Silica M, 0.04–0.63 mm, from Machery-Nagel GmbH & Co. KG, Germany. Distilled petroleum ether with a boiling range of 40–60 °C was used. Dry tetrahydrofuran and toluene were distilled from sodium and benzophenone, whereas CH_2Cl_2 and DMSO were distilled from CaH_2. Acetonitrile (CH_3CN) was distilled from P_2O_5. Methanol and Ethanol were used in HPLC grade quality. All commercially available compounds (abcr, Acros, Aldrich, Fluka, Merck, and TCI) were used without purification. ^1H (400.160 MHz) and ^{13}C (100.620 MHz) spectra were recorded on a Bruker Avance 400 III HD spectrometer. Some of the spectra were acquired on a Bruker AMX 600 spectrometer (^1H NMR at 600.139 MHz, ^{13}C NMR at 150.90 MHz). $CDCl_3$ was used as solvent at room temperature. The ^1H NMR spectra were referenced to the residual signal of the non-deuterated solvent component ($CDCl_3$ 7.25 ppm) and the ^{13}C NMR spectra to the signal of the deuterated solvent ($CDCl_3$ 77.0 ppm). Peak assignments were made by NMR spectroscopy (^1H, ^{13}C, DEPT-135, H,H-COSY, HSQC, NOESY, and HMBC). HRMS (ESI-TOF) analysis was performed on Bruker maXis 4G system.

(*E*)-5-((4-Methoxybenzyl)oxy)pent-2-enal[13] (**22**). To a solution of 1-(4-methoxybenzyloxy)-but-3-en[13] (**24**) (10.25 g, 53.31 mmol) in dry, degassed dichloromethane (100 mL, 0.5 M) were added crotonaldehyde (22 mL, 18.7 g, 266 mmol, 5 equiv) and nitro-Grela catalyst **25** (356 mg, 0.53 mmol, 0.01 equiv) all at once at room temperature. The mixture was then refluxed for 16 h. After cooling the mixture to room temperature, the volatile constituents were removed in vacuo. The residue was purified by flash chromatography (petroleum ether/ethyl acetate, 10:1 to 3:1) to give enal **22** (9.42 g, 42.76 mmol, 80 %) as a slightly brownish oil. $R_f = 0.17$ (*n*-hexane/ethyl acetate, 4:1); ^1H NMR (400 MHz, $CDCl_3$): δ [ppm] = 2.63 (ddd, $J = 12.9$, 6.3, 1.5 Hz, 2H, 4-H), 3.62 (t, $J = 6.2$ Hz, 2H, 5-H), 3.81 (s, 3H, OCH_3), 4.47 (s, 2H, $ArCH_2$), 6.14–6.23 (m, 1H, 2-H), 6.84–6.94 (m, 3H, 3-H, H_{Ar}), 7.25–7.30 (m, 2H, H_{Ar}), 9.52 (d, $J = 7.9$ Hz, 1H, 1-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ [ppm] = 32.9 (C-4), 55.1 (OCH_3), 67.4 (C-5), 72.6 ($ArCH_2$), 113.7 (C_{Ar}), 129.2 (C_{Ar}), 129.8 (C_{Ar}), 134.0 (C-2), 155.2 (C-3), 159.2 (C_{Ar}), 193.8 (C-1).

3-(Benzyloxy)propan-1-ol[16] (**28**). Sodium pieces (504 mg, 22 mmol, 1.25 equiv) were added to propanediol (**27**) (7.61 mL, 8.01 g, 105 mmol, 6 equiv) at room temperature. After the reaction had subsided a little, the reaction mixture was stirred for 1.5 h at 110 °C to completely dissolve the sodium. Thereafter, the heating was switched off, KI (30 mg, 0.2 μmol, 0.01 equiv) was added followed by the dropwise addition of benzyl bromide (2.09 mL, 3.00 g, 18 mmol, 1 equiv). The mixture was then stirred vigorously and heated to 110 °C for 3 h and then stirred for 16.5 h at room temperature. After adding water (30 mL), the mixture was extracted with diethyl ether (3 × 30 mL). The combined organic layers were washed with aqueous $Na_2S_2O_3$ solution (10 %, 30 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. After purification by Kugelrohr (bulb to bulb) distillation (8×10^{-2} mbar, 140 °C), benzyl ether **28** (2.64 g, 15.87 mmol, 90 %) was obtained as a colorless oil. $R_f = 0.30$ (*n*-hexane/ethyl acetate, 1:1); ^1H NMR (400 MHz, $CDCl_3$): δ [ppm] = 1.85 (tt, $J = 5.9$, 5.9 Hz, 2H, 2-H), 3.63 (t, $J = 5.9$ Hz, 2H, 1-H), 3.73 (t, $J = 5.8$ Hz, 2H, 3-H), 4.50 (s, 2H, $PhCH_2$), 7.25–7.38 (m, 5H, H_{Ar}); ^{13}C NMR (100 MHz, $CDCl_3$): δ [ppm] = 32.0 (C-2), 61.0 (C-1), 68.7 (C-3), 73.0 ($PhCH_2$), 127.5 (C_{Ar}), 127.5 (C_{Ar}), 128.2 (C_{Ar}), 138.0 (C_{Ar}).

((3-Bromopropoxy)methyl)benzene[16] (**29**). CBr_4 (9.27 g, 27.94 mmol, 1.8 equiv) was added to a solution of benzyl ether **28** (2.58 g, 15.52 mmol) in dry dichloromethane (40 mL) at 0 °C. Subsequently, PPh_3 (5.09 g, 19.40 mmol, 1.25 equiv) was added portionwise, whereupon the solution turned yellow. After 10 min, the cooling bath was removed and a solid precipitated. After 18 h at room temperature, the precipitate was removed by filtration through a frit and the filtrate was concentrated in vacuo. Purification of the brown residue by two bulb to bulb distillations (8×10^{-1} mbar, 1st distillation: 190 °C, 2nd distillation: 130 °C), gave bromide **29** (3.34 g, 14.59 mmol, 94 %) as a slightly yellowish oil. $R_f = 0.50$ (*n*-hexane/ethyl acetate, 5:1); ^1H NMR (400 MHz, $CDCl_3$): δ [ppm] = 2.15 (tt, $J =$ 6.2, 6.3 Hz, 2H, 2-H), 3.55 (t, $J = 6.6$ Hz, 2H, 3-H), 3.62 (t, $J = 5.8$ Hz, 2H, 1-H), 4.54 (s, 2H, $PhCH_2$), 7.27–7.42 (m, 5H, H_{Ar}); ^{13}C NMR (100 MHz, $CDCl_3$): δ [ppm] = 30.6 (C-3), 32.8 (C-2), 67.6 (C-1), 73.0 ($PhCH_2$), 127.6 (C_{Ar}), 127.6 (C_{Ar}), 128.3 (C_{Ar}), 138.2 (C_{Ar}).

tert-Butyl 7-(benzyloxy)-3-oxoheptanoate (**23**). NaH (1.51 g, 62.85 mmol, 3.6 equiv, 2.51 g of a 60 % mineral oil suspension) was washed with dry *n*-hexane (3 × 10 mL), then slurried with dry THF (131 mL, 0.4 M) and cooled to 0 °C. At the same temperature, *tert*-butyl acetoacetate (**26**) (8.69 mL, 8.29 g, 52.38 mmol, 3 equiv) was slowly added dropwise to the NaH suspension, with vigorous evolution of gas. After being stirred for 15 min, *n*-butyllithium (2.5 M in hexane, 20.95 mL, 3.36 g, 52.38 mmol, 3 equiv) was added dropwise at 0 °C. The color changed from colorless to yellow. After 1.5 h at 0 °C, a solution of bromide[16] **29** (4.00 g, 17.46 mmol, 1 equiv) in dry THF (15 mL) was added dropwise at the same temperature. The dropping funnel was rinsed with dry THF (2 × 3 mL). The cooling bath was removed and stirring continued at room temperature. After 2 h, saturated aqueous NH_4Cl solution (200 mL), diethyl ether (100 mL), and water (20 mL) were added. The layers were separated and the aqueous layer was extracted with diethyl ether (3 × 100 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude

product was kept on a rotary evaporator at 60 °C and at 3.7 mbar for 6 h in order to remove as much of the excess *tert*-butyl acetoacetate (**26**) as possible. After purification by flash chromatography (petroleum ether/ethyl acetate, 10:1 to 3:1) β-keto ester **23** (3.45 g, 11.25 mmol, 64%) was obtained as a colorless oil. $R_f = 0.35$ (*n*-hexane/ethyl acetate, 4:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ [ppm] = 1.46 (s, 9H, $C(CH_3)_3$), 1.57–1.75 (m, 4H, 5-H, 6-H), 2.55 (t, J = 7.2 Hz, 2H, 4-H), 3.32 (s, 2H, 2-H), 3.47 (t, J = 6.1 Hz, 2H, 7-H), 4.49 (s, 2 H, $PhCH_2$), 7.25–7.38 (m, 5H, H_{Ar}); ^{13}C NMR (100 MHz, $CDCl_3$): δ [ppm] = 20.2 (C-5), 27.9 ($C(CH_3)_3$), 29.0 (C-6), 42.5 (C-4), 50.6 (C-2), 69.9 (C-7), 72.9 ($PhCH_2$), 81.8 ($C(CH_3)_3$), 127.5 (C_{Ar}), 127.6 (C_{Ar}), 128.3 (C_{Ar}), 138.5 (C_{Ar}), 166.4 (C-1), 203.1 (C-3); HRMS (ESI-TOF): calcd. for $C_{18}H_{26}O_4$ 329.17233 $[M+Na]^+$, found 329.17242.

2-(3-(Benzyloxy)propyl)-5-(2-((4-methoxybenzyl)oxy)ethyl)cyclohex-2-enone (**21**). To a solution of β-keto ester **23** (6.52 g, 21.27 mmol, 1.05 equiv) and enal **22** (4.48 g, 20.34 mmol, 1 equiv) in dry acetonitrile (40 mL) was added at 0 °C DBU (6.07 mL, 6.19 g, 40.68 mmol, 2 equiv). The cooling bath was removed and stirring continued for 1.5 h at room temperature. After the starting materials could no longer be seen in the TLC, the mixture was heated to 80 °C for a further 2 h. The reaction mixture was cooled to room temperature before a saturated aqueous NH_4Cl solution (100 mL) and ethyl acetate (100 mL) were added. The layers were separated and the aqueous layer was extracted with ethyl acetate (3×100 mL). The combined organic layers were washed with saturated aqueous NaCl solution (100 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was used for the decarboxylation step without further purification. $R_f = 0.37$ (*n*-hexane/ethyl acetate, 2:1).

LiCl (8.62 g, 203.42 mmol, 10 equiv) and water (6.8 mL) were added at room temperature to a solution of the crude product from the previous step in dimethyl sulfoxide (68 mL, 0.3 M), followed by refluxing of the mixture. After an internal temperature of 153 °C had been reached, the reaction mixture was held at the same temperature for 45 min. The reaction mixture was then cooled to 0 °C before water (200 ml) and diethyl ether (100 ml) were added. The layers were separated and the aqueous layer was extracted with diethyl ether (3×100 mL). The combined organic layers were washed with saturated aqueous NaCl solution (5×100 mL), dried over $MgSO_4$, filtered and concentrated in vacuo. After purification by repeated flash chromatography (petroleum ether/ethyl acetate, 3:1 to 1:1), cyclohexenone **21** (4.10 g, 10.05 mmol, 47% over 2 steps) was obtained as a slightly brownish oil. $R_f = 0.27$ (*n*-hexane/ethyl acetate, 2:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ [ppm] = 1.61–1.80 (m, 4H, 2′-H, 1′′-H), 2.01–2.16 (m, 2H, 5-H, 6-H), 2.19–2.33 (m, 3H, 4-H, 1′-H), 2.42 (dt, J = 18.2, 4.7 Hz, 1H, 4-H), 2.55 (ddd, J = 15.7, 3.5, 1.3 Hz, 1H, 6-H), 3.44–3.55 (m, 4H, 3′-H, 2′′-H), 3.82 (s, 3H, OCH_3), 4.44 (s, 2H, $PMPCH_2$), 4.51 (s, 2H, $PhCH_2$), 6.64–6.71 (m, 1H, 3-H), 6.87–6.94 (m, 2H, H_{Ar}), 7.25–7.40 (m, 7H, H_{Ar}); ^{13}C NMR (100 MHz, $CDCl_3$): δ [ppm] = 26.1 (C-1′), 28.4 (C-2′), 32.4 (C-4), 32.5 (C-5), 35.4 (C-1′′), 44.6 (C-6), 55.2 (OCH_3), 67.1 (C-2′′), 69.7 (C3′), 72.7 ($PMPCH_2$), 72.8 ($PhCH_2$), 113.8 (C_{Ar}), 127.4 (C_{Ar}), 127.7 (C_{Ar}), 128.3 (C_{Ar}), 129.2 (C_{Ar}), 130.3 (C_{Ar}), 138.5 (C_{Ar}), 139.0 (C-2), 144.5 (C-3), 159.1 (C_{Ar}), 199.3 (C-1); HRMS (ESI-TOF): calcd. for $C_{26}H_{32}O_4$ 431.21928 $[M+Na]^+$, found 431.21944.

rel-(1*R*,5*S*)-1-Allyl-2-(3-(benzyloxy)propyl)-5-(2-((4-methoxybenzyl)oxy)ethyl)cyclohex-2-enol (**30**). Allyl magnesium chloride in THF (8.83 mL, 1.7 M, 15.01 mmol, 1.5 equiv) was added to a solution of enone **21** (4.09 g, 10.00 mmol) in dry THF (100 mL, 0.1 M) at 0 °C. After complete addition, the cooling bath was removed and stirring continued for 45 min at room temperature. Then, saturated aqueous NH_4Cl solution (100 mL) and diethyl ether (50 mL) were added to the mixture. The layers were separated and the aqueous layer was extracted with diethyl ether (3×100 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo to give a colorless oil. The crude product was used for the next reaction step without further purification. $R_f = 0.23$ (*n*-hexane/ethyl acetate, 2:1). For analytical purposes, a sample was purified by flash chromatography (petroleum ether/ethyl acetate, 2:1). The diastereomeric ratio was determined from the integrals of the protons at the 3-position, which yielded a ratio of 5.7:1. ^{1}H NMR (400 MHz, $CDCl_3$): δ [ppm] = 1.09 (t, J = 12.3 Hz, 1H, 6-H), 1.44–1.52 (m, 2H, 1′′′-H), 1.55–1.65 (m, 1H, 4-H), 1.68–1.85 (m, 3H, 5-H, 2′′-H), 1.92 (d, J = 12.4 Hz, 1H, 6-H), 1.97–2.08 (m, 2H, 4-H, 1′′-H), 2.14–2.24 (m, 2H, 1′-H, 1′′-H), 2.28–2.41 (m, 1H, 1-H), 3.36–3.50 (m, 4H, 3′′-H, 2′′′-H), 3.73 (s, 3H, OCH_3), 4.30–4.38 (m, 2H, $PMPCH_2$), 4.42 (s, 2H, $PhCH_2$), 4.96–5.09 (m, 2H, 3′-H), 5.31–5.36 (m, 1H, 3-H), 5.72–5.85 (m, 1H, 2′-H), 6.77–6.84 (m, 2H, H_{Ar}), 7.15–7.30 (m, 7H, H_{Ar}); ^{13}C NMR (100 MHz, $CDCl_3$): δ [ppm] = 25.9 (C-1′′), 28.9 (C-5), 29.1 (C-2′′), 32.4 (C-4), 36.3 (C-1′′′), 42.1 (C-6), 43.3 (C-1′), 55.2 (OCH_3), 67.7 (C-2′′′), 70.1 (C-3′′), 72.6 ($PMPCH_2$), 72.7 ($PhCH_2$), 73.5 (C-1), 113.7 (C_{Ar}), 118.3 (C-3′), 122.5 (C-3), 127.5 (C_{Ar}), 127.6 (C_{Ar}), 128.3 (C_{Ar}), 129.2 (C_{Ar}), 130.5 (C_{Ar}), 133.9 (C-2′), 138.4 (C_{Ar}), 142.0 (C-2), 159.1 (C_{Ar}); HRMS (ESI-TOF): calcd. for $C_{29}H_{38}O_4$ 473.26623 $[M+Na]^+$, found 473.26667.

rel-(3*R*,5*S*)-3-Allyl-2-(3-(benzyloxy)propyl)-5-(2-((4-methoxybenzyl)oxy)ethyl)cyclohexanone (**31**). To a suspension of KH (35% suspension in paraffin oil, 1.72 g, 15.01 mmol, 1.5 equiv) in dry THF (80 mL) was added 18-crown-6 (2.91 g, 11.00 mmol, 1.1 equiv) at room temperature. Then a solution of the crude product **30** from the previous reaction in dry THF (5 mL) was slowly added dropwise at room temperature and the dropping funnel was rinsed with dry THF (3×5 mL). The reaction mixture was refluxed for 2.5 h, then cooled to room temperature before dry methanol (0.5 mL) was added. This was followed by the addition of saturated aqueous NH_4Cl solution (100 mL) and diethyl ether (50 mL). The layers were separated and the aqueous layer was extracted with diethyl ether (3×100 mL). The combined organic layers were washed with saturated aqueous NaCl solution (5×100 mL), dried over $MgSO_4$, filtered and concentrated in vacuo. After purification by flash chromatography (petroleum ether/ethyl acetate, 3:1 to 1:1), cyclohexanone **31** (2.44 g, 5.42 mmol, 54% over 2 steps, epimeric at C-2) was obtained as light yellowish oil. $R_f = 0.59$ (*n*-hexane/ethyl acetate, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ [ppm] = 1.26–2.59 (m, 15H), 3.41–3.54 (m, 4H), 3.79 (s, 3H, OCH_3), 4.39 (s, 2H), 4.46–4.52 (m, 2H), 4.94–5.15 (m, 2H), 5.60–5.89 (m, 1H), 6.85–6.96 (m, 2H, H_{Ar}), 7.23–7.42 (m, 7H, H_{Ar}); ^{13}C NMR (100 MHz, $CDCl_3$): δ [ppm] = 22.9, 26.9, 27.5, 27.6, 31.3, 31.7, 31.7, 31.8, 34.5, 35.7, 36.6, 37.9, 39.2, 39.9, 45.1, 48.3, 53.9, 54.4, 55.2 (OCH_3), 67.3, 67.5, 69.8, 70.3, 72.6, 72.7, 72.8, 72.8, 113.7, 116.3, 116.8, 127.5, 127.6, 127.6, 128.3, 128.3, 129.2, 129.2, 130.4, 136.0, 136.4, 138.5, 138.5, 159.1, 212.1 (CO), 214.1 (CO); HRMS (ESI-TOF): calcd. for $C_{29}H_{38}O_4$ 473.26623 $[M+Na]^+$, found 473.26667.

rel-(3*R*,5*S*)-3-Allyl-2-(3-(benzyloxy)propyl)-5-(2-hydroxyethyl)cyclohexanone (**32**). To a solution of PMB ether **31** (2.33 g, 5.17 mmol) in dry dichloromethane (52 mL, 0.1 M) were added at 0 °C water (2.6 mL) and DDQ (1.41 g, 6.21 mmol, 1.2 equiv). The mixture was stirred at 0 °C for 6 h. The color changed from green to orange-red. Thereafter, saturated aqueous $NaHCO_3$ solution (100 mL) and diethyl ether (100 mL) were added. After vigorous shaking in the separating funnel, the aqueous layer turned to a distinct red color. The layers were separated and the aqueous layer was extracted with diethyl ether (3×100 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo. After purification by flash chromatography (petroleum ether/ethyl acetate, 1:1 to 2:3), alcohol **32** (1.52 g, 4.94 mmol, 89%) was obtained as a C2 epimeric mixture as a yellowish oil. R_f = 0.22 (*n*-hexane/ethyl acetate, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ [ppm] = 1.21–2.55 (m, 16H), 3.40–3.50 (m, 2H), 3.58–3.67 (m, 2H), 4.44–4.49 (m, 2H, $PhCH_2$), 4.94–5.09 (m, 2H, 3′-H), 5.58–5.83 (m, 1H, 2′H), 7.22–7.37 (m, 5H, H_{Ar}); ^{13}C NMR (100 MHz, $CDCl_3$): δ [ppm] =

22.9, 26.8, 27.4, 27.6, 30.9, 31.1, 31.7, 31.8, 34.5, 34.8, 37.9, 38.4, 39.2, 39.3, 39.7, 45.0, 53.9 (C-2), 54.4 (C-2), 60.1, 60.2, 69.8, 70.3, 72.8 ($PhCH_2$), 72.8 ($PhCH_2$), 116.3 (C-3′), 116.9 (C-3′), 127.5 (C_{Ar}), 127.6 (C_{Ar}), 127.6 (C_{Ar}), 128.3 (C_{Ar}), 128.3 (C_{Ar}), 136.0 (C-2′), 136.5 (C-2′), 138.4 (C_{Ar}), 138.5 (C_{Ar}), 212.1 (CO), 214.1 (CO); HRMS (ESI-TOF): calcd. for $C_{21}H_{30}O_3$ 352.20872 $[M+Na]^+$, found 352.20892.

rel-2-((1*S*,3*R*)-3-Allyl-4-(3-(benzyloxy)propyl)-5-oxocyclohexyl) acetaldehyde (**33**). To a solution of alcohol **32** (2.33 g, 5.17 mmol) in dry dichloromethane (52 mL, 0.1 M), $NaHCO_3$ (2.27 g, 27.00 mmol, 6 equiv) and DMP (2.29 g, 5.40 mmol, 1.2 equiv) were added at 0 °C. After 30 min, the cooling bath was removed and the mixture stirred for a further 1.5 h at room temperature. Saturated aqueous $NaHCO_3$ solution (25 mL) and saturated aqueous $Na_2S_2O_3$ solution (25 mL) were then added. The mixture was stirred for 5 min before diethyl ether (50 mL) was added. The layers were separated and the aqueous layer was extracted with diethyl ether (3×50 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo. After purification by flash chromatography (petroleum ether/ethyl acetate, 4:1 to 3:1) aldehyde **33** 1.37 g (4.16 mmol, 92%) was obtained as a C2 epimeric mixture as a slightly yellowish oil. R_f = 0.55 (*n*-hexane/ethyl acetate, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ [ppm] = 1.26–2.67 (m, 15H), 3.39–3.51 (m, 2H, 3″-H), 4.43–4.52 (m, 2H, $PhCH_2$), 4.95–5.10 (m, 2H, 3′-H), 5.59–5.80 (m, 1H, 2′-H), 7.25–7.37 (m, 5H, H_{Ar}), 9.67–9.73 (m, 1H, CHO); ^{13}C NMR (100 MHz, $CDCl_3$): δ [ppm] = 22.9, 26.8, 27.5, 27.6, 28.8, 29.0, 31.6, 31.7, 34.3, 37.8, 39.2, 39.7, 44.7, 47.6, 49.3, 50.1, 53.7 (C-4), 54.2 (C-4), 69.8, 70.2, 72.8, 72.9, 116.7 (C-3′), 117.3 (C-3′), 127.5 (C_{Ar}), 127.5 (C_{Ar}), 127.6 (C_{Ar}), 127.6 (C_{Ar}), 128.3 (C_{Ar}), 128.3 (C_{Ar}), 135.6 (C-2′), 136.1 (C-2′), 138.5 (C_{Ar}), 138.5 (C_{Ar}), 200.5 (CHO), 200.6 (CHO), 210.7 (C-5), 212.8 (C-5); HRMS (ESI-TOF): calcd. for $C_{21}H_{28}O_3$ 383.21928 $[M+Na+CH_3OH]^+$, found 383.21946.

rel-(1*R*,4*S*,6*R*,7*S*)-6-Allyl-1-(3-(benzyloxy)propyl)-7-hydroxybicyclo [2.2.2]octan-2-one (**20**). To a solution of keto aldehyde **33** (1.36 g, 4.14 mmol) in dry methanol (83 mL, 0.05 M), K_2CO_3 (687 mg, 4.97 mmol, 1.2 equiv) was added all at once at 0 °C (ice-water). The reaction was left in the cooling bath overnight so that the temperature slowly reached room temperature. After 20 h, most of the methanol was removed on a rotary evaporator and the residue taken up with aqueous pH 7 phosphate buffer solution (100 mL, pH 7, 3.42 g L^{-1} $NaH_2PO_4 \cdot 2H_2O$, 7.26 g L^{-1} $Na_2HPO_4 \cdot 2H_2O$) and diethyl ether (100 mL). The layers were separated and the aqueous layer was extracted with diethyl ether (3×100 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. After purification by flash chromatography (petroleum ether/ethyl acetate, 5:1), hydroxy ketone **20** (770 mg, 2.34 mmol, 57%) was obtained as a colorless oil. R_f = 0.32 (*n*-hexane/ethyl acetate, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ [ppm] = 1.20–1.29 (m, 1H, 5-H), 1.40–1.62 (m, 4H, 8-H, 1′-H, 2″-H), 1.72–1.85 (m, 4H, 4-H, 5-H, 1″-H), 2.08–2.33 (m, 5H, 3-H, 6-H, 8-H, 1′-H), 2.42 (bs, 1H, OH), 3.41–3.57 (m, 2H, 3″-H), 4.05 (dd, *J* = 2.3, 9.4 Hz, 1H, 7-H), 4.50 (s, 2H, $PhCH_2$), 4.94–5.02 (m, 2H, 3′-H), 5.56–5.69 (m, 1H, 2′-H), 7.26–7.36 (m, 5H, H_{Ar}); ^{13}C NMR (100 MHz, $CDCl_3$): δ [ppm] = 20.5 (C-1″), 21.9 (C-2″), 26.9 (C-4), 32.0 (C-5), 32.9 (C-6), 36.0 (C-8), 36.9 (C-1′), 44.5 (C-3), 54.9 (C-1), 68.6 (C-7), 70.8 (C-3″), 73.3 ($PhCH_2$), 116.8 (C-3′), 127.7 (C_{Ar}), 127.8 (C_{Ar}), 128.4 (C_{Ar}), 135.8 (C-2′), 137.9 (C_{Ar}), 215.1 (C-2); HRMS (ESI-TOF): calcd. for $C_{21}H_{28}O_3$ 351.19307 $[M+Na]^+$, found 351.19307.

rel-(1*R*,2*S*,4*S*,6*R*)-6-Allyl-1-(3-(benzyloxy)propyl)-7-oxobicyclo[2.2.2] octan-2-yl pivalate (**34**). To a solution of hydroxy ketone **20** (424 mg, 1.30 mmol) in dry dichloromethane (13 mL), were added pivaloyl chloride (847 μL, 830 mg, 6.46 mmol, 5 equiv) and DMAP (867 mg, 7.10 mmol, 5.5 equiv) at 0 °C. After the DMAP had completely dissolved, the cooling bath was removed and the mixture stirred at room temperature for 22 h. After adding saturated aqueous NH_4Cl solution (15 mL) and water (5 mL), the mixture was extracted with diethyl ether (3×15 mL). The combined organic layers were successively washed with saturated aqueous $NaHCO_3$ solution (3×10 mL) and saturated aqueous NaCl solution (15 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. After purification by flash chromatography (petroleum ether/ethyl acetate, 10:1), pivalate **34** (487 mg, 1.18 mmol, 91%) was obtained as a colorless oil. R_f = 0.64 (*n*-hexane/ethyl acetate, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ [ppm] = 1.12 (s, 9H, $C(CH_3)_3$), 1.21–1.29 (m, 1H, 5-H), 1.37–1.64 (m, 5H, 3-H, 1′-H, 1″-H, 2″-H), 1.73–2.00 (m, 3H, 6-H, 5-H, 1″-H), 2.20–2.36 (m, 5H, 4-H, 3-H, 8-H, 1′-H), 3.41–3.51 (m, 2H, 3″-H), 4.49 (s, 2H, $PhCH_2$), 4.89–5.08 (m, 2H, 3′-H), 5.15 (d, *J* = 8.6 Hz, 1H, 2-H), 5.59–5.73 (m, 1H, 2′-H), 7.25–7.37 (m, 5H, H_{Ar}); ^{13}C NMR (100 MHz, $CDCl_3$): δ [ppm] = 21.2 (C-1″), 22.5 (C-2″), 26.7 (C-4), 26.8 ($C(CH_3)_3$), 32.2 (C-5), 32.8 (C-6), 34.6 (C-3), 36.4 (C-1′), 38.5 ($C(CH_3)_3$), 44.3 (C-8), 52.4 (C-1), 70.3 (C-2), 70.6 (C-3″), 72.8 ($PhCH_2$), 117.0 (C-3′), 127.3 (C_{Ar}), 127.5 (C_{Ar}), 128.2 (C_{Ar}), 135.5 (C-2′), 138.4 (C_{Ar}), 177.3 ($tBuCO_2$), 213.0 (C-7); HRMS (ESI-TOF): calcd. for $C_{26}H_{36}O_4$ 435.25058 $[M+Na]^+$, found 435.25063.

rel-(1*S*,2*S*,4*R*,6*R*)-6-Allyl-1-(3-(benzyloxy)propyl)-7-methylenebicyclo [2.2.2]octan-2-yl pivalate (**35**). KO*t*Bu (283 mg, 2.52 mmol, 10 equiv) was added all at once to a suspension of methyltriphenylphosphonium bromide (900 mg, 2.52 mmol, 10 equiv) in dry toluene (1 mL) under an argon atmosphere at 0 °C. The ice bath was removed and stirring was continued for 20 min at room temperature, the suspension turning strongly yellow color. A solution of ketone **34** (104 mg, 252 μmol) in dry toluene (0.5 mL) was added dropwise at room temperature. The flask containing the ketone solution was washed with dry toluene (3×0.5 mL), which also was added to the reaction mixture. The reaction was heated to 100 °C in a sealed flask for 18 h. After cooling to room temperature, water (5 mL) and diethyl ether (5 mL) were added to the reaction mixture. The layers were separated and the aqueous layer was extracted with diethyl ether (3×5 mL). The combined organic layers were washed with saturated aqueous NaCl solution (5 mL). Petroleum ether was added up to a mixing ratio of petroleum ether/diethyl ether of 3:1, which made the solution cloudy. Then $MgSO_4$ was added to the mixture. This mixture was filtered through celite and the filtrate was concentrated in vacuo. The residue was taken up in diethyl ether (2 mL) and petroleum ether (6 mL) was added, whereupon the solution became cloudy again. This mixture was filtered again through celite. Silica gel (1 spatula tip) was added and then the volatile constituents are removed in vacuo until the silica gel was free-flowing. After purification by flash chromatography (petroleum ether/ethyl acetate, 15:1), alkene **35** (70 mg, 170 μmol, 68%) was obtained as a slightly brownish oil. R_f = 0.70 (*n*-hexane/ethyl acetate, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ [ppm] = 1.02–1.09 (m, 1H, 5-H), 1.12 (s, 9H, $C(CH_3)_3$), 1.26–1.33 (m, 1H, 3-H), 1.39–1.60 (m, 4H, 1″-H, 2″-H), 1.60–1.71 (m, 3H, 5-H, 6-H, 1′-H), 1.82–1.87 (m, 1H, 4-H), 2.06–2.20 (m, 2H, 3-H, 1′-H), 2.22–2.36 (m, 2H, 8-H), 3.37–3.49 (m, 2H, 3″-H), 4.44–4.52 (m, 2H, $PhCH_2$), 4.80 (bs, 1H, 7-CH_2), 4.92 (dd, *J* = 2.3, 9.1 Hz, 1H, 2-H), 4.93–5.03 (m, 3H, 3′-H, 7-CH_2), 5.65–5.77 (m, 1H, 2′-H), 7.22–7.36 (m, 5H, H_{Ar}); ^{13}C NMR (100 MHz, $CDCl_3$): δ [ppm] = 23.0 (C-1″), 24.6 (C-2″), 25.6 (C-4), 27.0 ($C(CH_3)_3$), 32.4 (C-5), 33.3 (C-6), 35.2 (C-3), 35.5 (C-1′), 36.1 (C-8), 38.6 ($C(CH_3)_3$), 43.1 (C-1), 70.9 (C-3″), 70.9 (C-2), 72.7 ($PhCH_2$), 109.6 (7-CH_2), 115.9 (C-3′), 127.4 (C_{Ar}), 127.5 (C_{Ar}), 128.3 (C_{Ar}), 137.1 (C-2′), 138.6 (C_{Ar}), 147.1 (C-7), 177.8 ($tBuCO_2$); HRMS (ESI-TOF): calcd. for $C_{27}H_{38}O_3$ 433.27132 $[M+Na]^+$, found 433.27164.

rel-(1*S*,2*S*,4*R*,7*S*)-1-(3-(Benzyloxy)propyl)-6-methylene-7-(2-oxoethyl) bicyclo[2.2.2]octan-2-yl pivalate (**36**). To a solution of alkene **35** (70 mg, 170 μmol) in a mixture of THF (2 mL) and water (0.4 mL) were added $K_2OsO_4 \cdot 2H_2O$ (1 mg, 2 μmol, 0.01 equiv) and NMO·H_2O (25 mg, 188 μmol, 1.1 equiv). After 15 min at 0 °C, the cooling bath was removed and the mixture stirred at room temperature. After 1 h, acetone was added (0.2 mL) whereupon the solution changed

from cloudy/colorless to clear/slightly brownish. After 22.5 h at room temperature, solid $NaHSO_3$ (3 spatula tips) was added, and stirring continued for 15 min. Water (5 mL) and chloroform (5 mL) were added. The layers were separated and the aqueous layer was extracted with chloroform (3×5 mL). The combined organic layers were washed with saturated aqueous NaCl solution (5 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography (petroleum ether/ethyl acetate, 1:3) gave crude diol (80 mg, mixture of isomers) as a slightly brownish oil, which was used for the next step without further purification. R_f = 0.12 (*n*-hexane/ethyl acetate, 1:1);

The crude diol from the previous step was dissolved in a solution of THF (4 mL) and water (1 mL). $NaIO_4$ (192 mg, 0.90 mmol, 5.3 equiv) was added all at once at room temperature. After 30 min, saturated aqueous NaCl solution (5 mL) and dichloromethane (5 mL) were added. The layers were separated and the aqueous layer was extracted with dichloromethane (3×5 mL). The combined organic layers were washed with saturated aqueous NaCl solution (5 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. After flash chromatography (*n*-hexane/ethyl acetate 2:1), the crude aldehyde **36** was used for the next step without further purification. R_f = 0.62 (*n*-hexane/ethyl acetate, 1:1).

rel-(1*S*,2*S*,4*R*,6*S*)-1-(3-(Benzyloxy)propyl)-6-(2-(hydroxyimino)ethyl)-7-methylenebicyclo[2.2.2]octan-2-yl pivalate (**37**). To a solution of the crude aldehyde **36** from the previous step in a mixture of acetonitrile (5 mL) and water (1 mL), hydroxylamine hydrochloride (14 mg, 201 μmol, 1.2 equiv) and sodium acetate (19 mg, 234 μmol, 1.4 equiv) were added. After 30 min at room temperature, water (5 mL) and chloroform (5 mL) were added. The layers were separated and the aqueous layer was extracted with chloroform (3×5 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ solution (5 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. After purification by flash chromatography (petroleum ether/ethyl acetate, 5:1 to 3:1), aldoxime **37** (56 mg, 131 μmol, 77% over 3 steps) was obtained. The oxime appears as two isomers which could be separated but after a short time restored the equilibrium: aldoxime **37a** [29 mg, 68 μmol, 40%; R_f = 0.57 (*n*-hexane/ethyl acetate, 1:1)] as a white amorphous solid and aldoxime **37b** [27 mg, 63 μmol, 37%, R_f = 0.47 (*n*-hexane/ethyl acetate, 1:1)] as a white amorphous solid. The NMR spectra show the presence of both isomers. ^{1}H NMR (400 MHz, $CDCl_3$): δ [ppm] = 0.98–1.13 (m, 10H), 1.26–1.35 (m, 1H), 1.39–1.60 (m, 4H), 1.67–1.94 (m, 3H), 2.06–2.39 (m, 4H), 3.35–3.49 (m, 2H, 3′′-H), 4.47 (s, 2H, $PhCH_2$), 4.84 (d, *J* = 11.5 Hz, 1H, 7-CH_2), 4.92 (dt, *J* = 1.9, 9.0 Hz, 1H, 2-H), 4.99 (d, *J* = 9.8 Hz, 7-CH_2), 7.20–7.38 (m, 6H, 2′-H, H_{Ar}); ^{13}C NMR (100 MHz, $CDCl_3$): δ [ppm] = 22.9, 23.0, 24.7, 24.7, 25.4, 25.5, 26.9 ($C(CH_3)_3$), 31.2, 31.4, 31.8, 32.3, 32.7, 35.1, 36.0, 38.6, 42.9, 42.9, 70.6 (C-2), 70.6 (C-2), 70.6 (C-3′′), 70.7 (C-3′′), 72.7 ($PhCH_2$), 72.7 ($PhCH_2$), 110.3 (C-1′′′), 110.5 (7-CH_2), 127.4 (C_{Ar}), 127.4 (C_{Ar}), 127.5 (C_{Ar}), 127.5 (C_{Ar}), 128.3 (C_{Ar}), 138.5 (C_{Ar}), 138.6 (C_{Ar}), 146.2 (C-7), 146.3 (C-7), 151.1 (C-2′), 177.8 (*t*BuCO_2); HRMS (ESI-TOF): calcd. for $C_{26}H_{37}NO_4$ 450.26148 $[M+Na]^+$, found 450.26152.

3b-(3-(Benzyloxy)propyl)-3,3b,4,5,6,7,7a,8-octahydro-3a,6-methanoindeno[2,1-c]isoxazol-4-yl pivalate (**38**). To a solution of aldoxime **37** (23 mg, 54 μmol) in a mixture of dichloromethane (0.5 mL) and triethylamine (8 μL, 59 μmol, 1.1 equiv), water (0.2 mL) was added at 0 °C. To the vigorously stirred mixture, aqueous NaOCl solution (6%, 0.16 mL, 3 equiv) was added at the same temperature, whereupon the solution briefly turned brown and then immediately became colorless again. After 30 min, the cooling bath was removed and stirring was continued for additional 30 min. Thereafter, additional aqueous NaOCl solution (6%, 0.16 mL, 3 equiv) was added. After 1 h and a further hour, additional portions of aqueous NaOCl solution (6%, 0.16 mL, 3 equiv) were added. One hour after the last addition of aqueous NaOCl solution, saturated aqueous $NaHCO_3$ solution (1 mL), solid $NaHSO_3$ (1 spatula tip) and diethyl ether (2 mL) were added. The layers were separated and the aqueous layer was extracted with diethyl ether (3×2 mL). The combined organic layers were washed successively with water (2 mL) and saturated aqueous NaCl solution (2 mL), dried over $MgSO_4$, filtered and concentrated in vacuo. After purification by flash chromatography (*n*-hexane/ethyl acetate, 5:1 to 3:1), isoxazoline **38** (13 mg, 31 μmol, 57%) was obtained as a colorless oil. R_f = 0.48 (*n*-hexane/ethyl acetate, 1:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ [ppm] = 1.12 (s, 9H, $C(CH_3)_3$), 1.27–1.34 (m, 1H, *syn*-5-H), 1.45–1.55 (m, 4H, 7-H, 1′-H, 2′-H), 1.78–1.98 (m, 4H, 6-H, 7-H, 9-H, 1′-H), 2.08–2.25 (m, 3H, *anti*-5-H, 8-H, 9-H), 2.55–2.68 (m, 2H, 7a-H, 8-H), 3.31–3.45 (m, 2H, 3′-H), 3.99 (d, *J* = 8.5 Hz, 1H, *endo*-3-H), 4.27 (d, *J* = 8.5 Hz, 1H, *exo*-3-H), 4.44 (s, 2H, $PhCH_2$), 5.03 (dd, *J* = 2.8, 9.7 Hz, 1H, 4-H), 7.26–7.33 (m, 5H, H_{Ar}); ^{13}C NMR (75 MHz, $CDCl_3$): δ [ppm] = 23.7 (C-6), 24.1 (C-2′), 25.5 (C-1′), 27.1 ($C(CH_3)_3$), 31.3 (C-8), 37.0 (C-7), 37.9 (C-5), 38.6 ($C(CH_3)_3$), 39.3 (C-7a), 40.5 (C-9), 43.4 (*quart* C-3a/3b), 64.3 (*quart* C-3a/3b), 68.2 (C-4), 70.2 (C-3′), 72.9 ($PhCH_2$), 77.8 (C-3), 127.5 (C_{Ar}), 127.6 (C_{Ar}), 128.3 (C_{Ar}), 138.3 (C_{Ar}), 173.9 (C-8a), 177.5 (*t*BuCO_2); HRMS (ESI-TOF): calcd. for $C_{26}H_{35}NO_4$ 448.24583 $[M+Na]^+$, found 448.24595.

3b-(3-(Benzyloxy)propyl)-3,3b,4,5,6,7,7a,8-octahydro-3a,6-methanoindeno[2,1-c]isoxazol-4-ol (**39**). A solution of TBAOH in methanol (1 M, 305 μL, 305 μmol, 10 equiv) was added to a solution of pivalate **38** (13 mg, 31 μmol) in dry methanol (0.3 mL) at room temperature followed by stirring of the mixture for 40 h at 60 °C in a closed flask. After being cooled to room temperature, the mixture was treated with aqueous saturated NH_4Cl solution (2 mL) and extracted with diethyl ether (3×2 mL). The combined organic layers were washed with saturated aqueous NaCl solution, dried over $MgSO_4$, filtered, and concentrated in vacuo. After purification by flash chromatography (*n*-hexane/ethyl acetate, 1:1), alcohol **39** (6 mg, 18 μmol, 58%) was obtained as a slightly yellowish oil. R_f = 0.18 (*n*-hexane/ethyl acetate, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ [ppm] = 1.04–1.13 (m, 1H, 1′-H), 1.38 (dq, *J* = 13.6, 3.1 Hz, 1H, 5-H), 1.47 (dt, *J* = 13.9, 3.4, 3.2 Hz, 1H, 7-H), 1.50–1.74 (m, 4H, 1′-H, 2′-H, OH), 1.78–1.92 (m, 3H, 6, 7-H, 9-H), 1.99–2.14 (m, 2H, 5-H, 9-H), 2.17 (d, *J* = 17.9 Hz, 1H, *endo*-8-H), 2.47 (dd, *J* = 9.1, 6.9 Hz, 1H, 7a-H), 2.60 (dd, *J* = 17.9, 6.6 Hz, 1H, *exo*-8-H), 3.37–3.55 (m, 2H, 3′-H), 3.98 (d, *J* = 8.8 Hz, 1H, *endo*-3-H), 4.05 (dd, *J* = 9.9, 3.3 Hz, 1H, 4-H), 4.21 (d, *J* = 8.7 Hz, 1H, *exo*-3-H), 4.49 (s, 2H, $PhCH_2$), 7.25–7.38 (m, 5H, H_{Ar}); ^{13}C NMR (100 MHz, $CDCl_3$): δ [ppm] = 23.6 (C-2′), 24.1 (C-6), 24.8 (C-1′), 31.2 (C-8), 37.1 (C-7), 39.4 (C-5, 7a), 40.7 (C-9), 45.5 (*quart*-C-3a/3b), 64.0 (*quart*-C-3a/3b), 64.5 (C-4), 70.4 (C-3′), 73.3 ($PhCH_2$), 77.8 (C-3), 127.8 (C_{Ar}), 128.5 (C_{Ar}), 137.9 (C_{Ar}), 174.2 (C-8a); HRMS (ESI-TOF): calcd. for $C_{21}H_{27}NO_3$ 364.18831 $[M+Na]^+$, found 364.18851.

3b-(3-(Benzyloxy)propyl)-3b,5,6,7,7a,8-hexahydro-3a,6-methanoindeno[2,1-c]isoxazol-4(3*H*)-one (**18**). To a solution of alcohol **39** (6 mg, 18 μmol) in dry dichloromethane (0.35 mL) solid $NaHCO_3$ (9 mg, 105 μmol, 6 equiv) and Dess-Martin periodinane (11 mg, 26 μmol, 1.5 equiv) were added. The mixture was kept at 0 °C for 0.5 h, after which it was stirred at room temperature for further 1.5 h. For the work-up, saturated aqueous $NaHCO_3$ solution (2 mL) and dichloromethane (2 mL) were added. After separation of the layers, the aqueous layer was extracted with dichloromethane (3×2 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. After purification by flash chromatography (*n*-hexane/ethyl acetate, 2:1), ketone **18** (5 mg, 15 μmol, 83%) was obtained as a colorless oil. R_f = 0.39 (*n*-hexane/ethyl acetate, 1:2); ^{1}H NMR (400 MHz, $CDCl_3$): δ [ppm] = 1.00–1.09 (m, 1H, 1′-H), 1.40–1.52 (m, 1H, 2′-H), 1.65–1.89 (m, 4H, 7-H, 9-H, 1′-H, 2′-H), 2.08–2.17 (m, 1H, 7-H), 2.18–2.22 (m, 2H, 5-H), 2.22–2.28 (m, 1H, 6-H), 2.33–2.42 (m, 2H, 8-H, 9-H), 2.66 (dd, *J* = 17.9, 6.1 Hz, 1H, *exo*-8-H), 2.90 (dd, *J* = 9.8, 6.6 Hz, 1H, 7a-H), 3.40–3.57 (m, 2H, 3′-H), 3.84 (d, *J* = 8.8 Hz, 1H, *endo*-3-H), 4.09 (d, *J* = 8.7 Hz, 1H, *exo*-3-H), 4.44–

4.52 (m, 2H, $PhCH_2$), 7.26–7.37 (m, 5H, H_{Ar}); ^{13}C NMR (100 MHz, $CDCl_3$): δ [ppm] = 23.7 (C-1′), 25.4 (C-2′), 25.9 (C-6), 30.9 (C-8), 37.1 (C-7), 40.3 (C-9), 40.7 (C-7a), 46.1 (C-5), 54.5 (C-3a), 68.4 (C-3b), 70.4 (C-3′), 72.9 ($PhCH_2$), 76.4 (C-3), 127.5 (C_{Ar}), 127.7 (C_{Ar}), 128.4 (C_{Ar}), 138.4 (C_{Ar}), 172.3 (C-8a), 211.9 (C-4); HRMS (ESI-TOF): calcd. for $C_{21}H_{25}NO_3$ 362.17266 $[M+Na]^+$, found 362.17266.

7a-(3-(Benzyloxy)propyl)-1-(hydroxymethyl)tetrahydro-1*H*-1,5-methanoindene-2,7(3*H*,7a*H*)-dione (**40**). $Mo(CO)_6$ (4.7 mg, 18 μmol, 1.2 equiv) was added at room temperature to a solution of isoxazolinone **18** (5 mg, 15 μmol) in a mixture of acetonitrile (0.5 ml) and water (0.05 ml). The reaction mixture was heated to 90 °C in a closed flask for 2 h. After cooling, the reaction mixture was filtered through celite and the filtrate was extracted with diethyl ether (3×2 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. After purification by flash chromatography (chloroform/methanol, 20:1), diketo alcohol **40** (1.5 mg,4.3 μmol, 29%) was obtained as a slightly greenish oil. R_f = 0.54 (chloroform/methanol, 20:1, only visible under UV-light (254 nm)); ^1H NMR (600 MHz, $CDCl_3$): δ [ppm] = 0.96–1.03 (m, 1H, 1′-H), 1.45–1.51 (m, 1H, 2′-H), 1.63–1.67 (m, 1H, 4-H), 1.71–1.75 (m, 1H, 2′-H), 1.80–1.85 (m, 1H, 8-H), 1.93–1.99 (m, 1H, 1′-H), 2.01–2.08 (m, 2H, 4-H, 8-H), 2.18–2.36 (m, 4H, 1-H, 6-H, 3-*endo*-H), 2.49–2.55 (dd, *J* = 7.3, 18.9 Hz, 1H, 3-*exo*-H), 2.64–2.69 (m, 1H, 3a-H), 3.39–3.49 (m, 2H, 3′-H, CH_2OH), 3.52–3.57 (m, 1H, 3′-H), 3.61–3.68 (m, 1H, CH_2OH), 4.43–4.53 (m, 2H, $PhCH_2$), 7.26–7.37 (m, 5H, H_{Ar}); ^{13}C NMR (150 MHz, $CDCl_3$): δ [ppm] = 24.0 (C-1′), 25.2 (C-2′), 26.7 (C-5), 30.8 (C-3a), 33.6 (C-8), 36.1 (C-4), 44.7 (C-6), 45.5 (C-8), 55.4 (*quart*-C-7a/1), 58.2 (*quart*-C-7a/1), 62.6 (CH_2OH), 70.5 (C-3′), 72.9 ($PhCH_2$), 127.7 (C_{Ar}), 128.4 (C_{Ar}), 138.5 (C_{Ar}), 213.1 (C-7), 218.7 (C-2); HRMS (ESI-TOF): calcd. for $C_{21}H_{26}O_4$ 365.17233 $[M+Na]^+$, found 365.17192.

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Conflict of Interest

The authors declare no conflict of interest.

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