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STUDY TOWARD AN ASYMMETRIC AND CATALYTIC SYNTHESIS OF KOUMINE

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Abstract – A synthetic study of koumine, a natural product with a densely functionalized and inspiring heterocyclic skeleton, was conducted by exploring a strategy of desymmetrization of 1,3-cyclohexanedione by an intramolecular vinylation reaction of an enolate under palladium catalysis to give a strained bridgehead 1,3-cyclohexanedione scaffold. In the course of the study, a domino ring expansion was discovered and developed.

Koumine (**1**) is a natural product isolated from the *Gelsemium elegans*, a flowering plant with applications in traditional Chinese medicine against chronic pain and skin ulcer (Figure 1). Among other alkaloids found in the plant, gelsemine (**2**), gelsenicine (**3**), gelsevirine (**4**) and gelsemoxonine (**5**) are noteworthy for their fascinating structures that contain an oxindole moiety.[1] Deprived of this structural feature, koumine shares elements of structure with the above-mentioned natural products such as tetrahydropyrane and azacycle intertwined scaffolds. The molecule has attracted attention due to its low toxicity and to some biological investigations according to which an interesting activity was unveiled against rheumatoid arthritis and for other applications.[2] Even if amount of the molecule can be extracted by preparative separation,[3] establishing a synthetic route toward such a complex structure and its analogues offers a formidable challenge to the creativity of synthetic chemists. Since its isolation and structure identification, only few total syntheses, formal synthesis and hemisynthesis of koumine were devised.[4] Pioneering studies from Magnus led to the first diastereoselective synthesis starting from (*S*)-tryptophan.[5] From the same starting material, a formal synthesis of the target was described by Bailey.[6] Years later, Takayama reported a diastereoselective route to prepare molecules of this family including koumine thanks to an innovative access to chiral starting materials.[7] And recently Kerr devised a new strategy to reach the racemic target and structurally related molecules.[8]

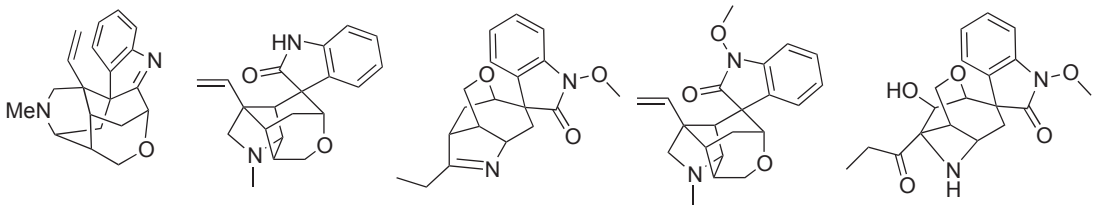
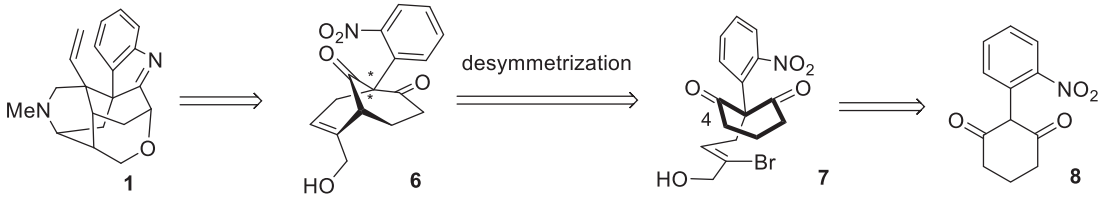


Figure 1. Koumine (**1**) and related alkaloids

Exploitation of hidden symmetry in alkaloids allowed the design of simplified synthetic routes.[9] A similar approach was explored with koumine in which a hidden symmetry was tentatively exploited. Hence it was anticipated that desymmetrization of 2-nitrophenyl-1,3-cyclohexanedione **7** by intramolecular C-C bond formation in position 4 with an appendage would give an intermediate **6** en route to **1** (Scheme 1). From compound **6**, most of the stereocenters of the target would have been installed and the remaining tasks would have encompassed the construction of the piperidine and tetrahydropyrane rings which was envisaged to occur stereoselectively thanks to the setting of the two stereocenters during the desymmetrization step.

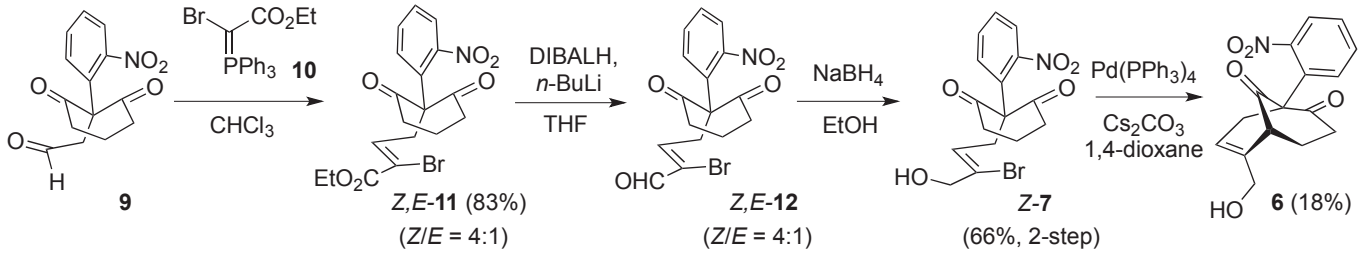


Scheme 1. Retrosynthetic analysis of koumine (**1**)

A further advantage of such an approach would rely on the availability of large quantity of 2-nitrophenyl-1,3-cyclohexanedione (**8**) that results from the metal-free arylation of 1,3-cyclohexanedione described by Bonjoch and Bosch.[10]

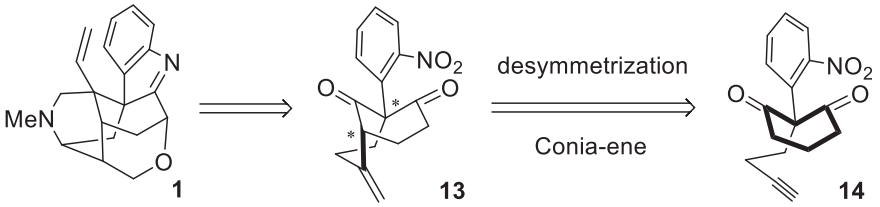
The study began with the construction of vinyl bromide **7** by Wittig reaction from the known aldehyde **9** prepared in 2 steps from **8** (Scheme 2). The coupling of ylide **10** with **9** gave the functionalized 1,3-cyclohexanedione **11** in good yield (83%) and with the required selectivity (*Z*/*E* =4:1) to harness the C-Br bond in palladium-catalysed vinylation reactions of ketone enolate.[11] But first, the acrylate was converted into alcohol **7** in two steps: i) treatment with DIBALH/*n*-BuLi and ii) exposure of the resulting α-bromoenal **12** to $NaBH_4$. In the course of the process, only *Z*-**7** was isolated in 66% yield (2-steps) which amounted to the chemoselective reduction of the acrylate ester versus the electron-deficient ketones. Attempts to perform the cyclization $Pd(PPh_3)_4$, Cs_2CO_3, 1,4-dioxane, 100 °C, 2 h) of this product gave the desired compound **6**, albeit in a modest yield of 18%. Alas the efficiency of this step remained low despite

several experiments involving various bases and solvent or catalyst, this being possibly due to the low stability of the allylic alcohol of **7** with palladium species.



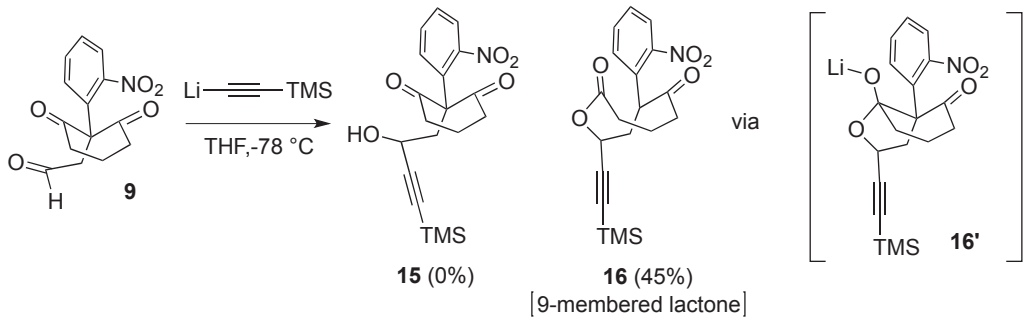
Scheme 2. Desymmetrization of *Z*-**7**

These observations called for a new strategy in which the desymmetrization step could proceed by a Conia-ene reaction of alkyne **14** which would unveil the alkene **13** with two new stereocenters (Scheme 3).[12]



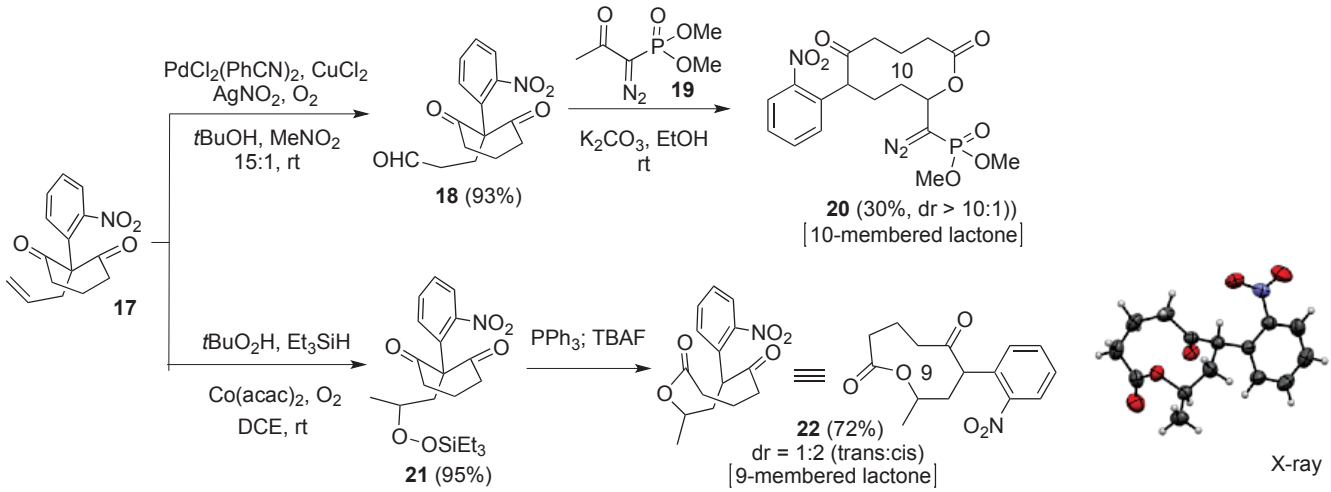
Scheme 3. Updated retrosynthesis of koumine (**1**)

Embarked in the synthesis of alkyne **14**, the aldehyde **9** was treated with alkynyllithium with the intent to perform the Conia-ene cyclisation upon the alcohol **15** (Scheme 4). As it happened, the alcohol **15** was not observed, the lactone **16** was instead directly obtained (45% yield) after a domino sequence of reactions involving the transient formation of the alcoholate of **15**, then lactolate **16'** which was followed by a spontaneous anionic fragmentation. While this sequence was further examined in details in a spin-off study and put in perspective,[13] this result indicated that anionic species had to be avoided within the 2-nitrophenyl-1,3-cyclohexanedione scaffold and an alternative route to alkyne **14** was needed.



Scheme 4. 9-Membered lactone formation from **9**

Accordingly, we sought to prepare **14** by a reaction of alkynylation using less basic reagents such as the Ohira-Bestmann reagent. In order to explore this route, the required aldehyde **18** was obtained by Wacker-type oxidation[14] of the olefin **17** in 93% yield and was then treated with reagent **19** (Scheme 5). Instead of alkyne **14**, the 10-membered lactone **20** incorporating the nucleophilic part of the Ohira-Bestmann reagent was recovered in 30% yield as a single isomer. The mechanism explaining the formation of **20** is thought to be similar to the previous example with the 9-membered lactone **16**. The formation of the hydroxylate provoked the fragmentation of the 2-nitrophenyl-1,3-cyclohexanedione. While frustrated by this undesired outcome, we were also intrigued by this result as it represents an expedient and protecting-group free synthesis of a 10-membered lactone containing a diazophosphonate appendage. Furthermore, it was found that Mukaiyama olefinic oxidation of olefin **17** using Inoue method[15] led to the 9-membered lactone **22** after a sequence encompassing regioselective peroxidation into **21** (95% yield), subsequent reduction with PPh_3 and fragmentation upon TBAF exposure (45%, 2-steps).



Scheme 5. Formation of 9- and 10-membered lactones by anionic fragmentation

As it turned out, oxidation of olefin **17** paved the way to the synthesis of strained and functionalized 9- or 10-lactones upon addition of an internal or external nucleophiles, even mild, which impeded our initial plan to prepare koumine from **8**. In conclusion, our synthetic study toward koumine led to the discovery of a series of ring expansion by anionic fragmentation leading to strained and functionalized lactones **16**, **20** and **22** from the 2-nitroaryl-1,3-cyclohexanedione scaffold. The fact that olefin **17** can be efficiently oxidized with Markovnikov or anti-Markovnikov selectivity suggests that new molecular spaces may be explored from 9- and 10-membered lactones that would have been difficult to access otherwise. To reach our initial goal, a new strategy is being currently devised while the exploitation of the ring expansion methodology for the synthesis of other natural products is ongoing.

EXPERIMENTAL

All reagents were purchased from Alfa Aesar, Sigma Aldrich, or TCI Europe and were used without further purification. Unless mentioned otherwise, solvents were used without further purification. ^{1}H and ^{13}C NMR spectra were recorded in deuterated chloroform on a Bruker DRX 300 MHz spectrometer and were referenced to residual chloroform (7.26 ppm, ^{1}H; 77.36 ppm, ^{13}C). The chemical shifts (δ) are expressed in parts per million (ppm), and coupling constants are indicated in hertz (Hz). Abbreviations for signal coupling are as follows: s = singlet; d = doublet; dd = doublet of doublets; t = triplet; q = quartet; quin = quintet; m = multiplet; br = broad signal. High-resolution mass spectra (HRMS) were performed on Q-TOF Micro WATERS by electrospray ionisation (ESI). Infrared (IR) spectra were recorded with a Perkin Elmer 16 PC FT-IR ATR spectrometer, using the pure product (oil or solid). Melting points were determined using a Kopfler hot stage apparatus and are uncorrected. Flash column chromatography (FCC) was performed on silica gel column (Merck silica gel, 40–63 μm) using air pressure. Compounds **8**, **9** and **17** are known.[10] CCDC 1867334 (**22**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data request/cif.

Methyl 2-bromo-4-(1-(2-nitrophenyl)-2,6-dioxocyclohexyl)but-2-enoate (11)

Distilled $CHCl_3$ (over P_2O_5) was used after sparging the solvent with dried argon for 1 h. N-Bromosuccinimide (3.88 g, 21.82 mmol) was added portionwise (6 portions over 1 h) under argon to a solution of methyl (triphenylphosphoranylidene)acetate (6.07 g, 18.18 mmol) and K_2CO_3 (6.27 g, 45.45 mmol) in $CHCl_3$ (60 mL) cooled to –20 °C. The solution was stirred for 20 more min at –20 °C and then added to a solution of aldehyde **9** (2.00 g, 7.27 mmol) in $CHCl_3$ (100 mL) at 0 °C through a fritted glass filter. After stirring for 14 h at 0 °C, the solvent was evaporated under reduced pressure and the residue purified by FCC (PE/AcOEt, 7:3). Bromoolefin **11** was obtained as a yellowish powder in 83% yield (2.47 g, 6.03 mmol) and *E*/*Z* ratio of 1:4; R_f = 0.27 (PE/AcOEt, 7:3); ^{1}H NMR (300 MHz, $CDCl_3$) major/*minor*: δ = 8.13 (dd, J_1 = 8.1, J_2 = 1.4 Hz, 1H), 8.12 (dd, J_1 = 8.1, J_2 = 1.4 Hz, 1H), 7.70 (m, 1H, 1H), 7.53 (m, 1H, 1H), 7.39 (dd, J_1 = 7.9, J_2 = 1.2 Hz, 1H), 7.31 (dd, J_1 = 7.9, J_2 = 1.2 Hz, 1H), 6.98 (t, J = 6.0 Hz, 1H), 6.42 (t, J = 6.3 Hz, 1H), 3.87 (s, 3H), 3.76 (s, 3H), 3.61 (d, J = 6.3 Hz, 2H), 3.28 (d, J = 6.0 Hz, 2H), 2.99 – 2.72 (m, 4H, 4H), 2.39 (m, 1H, 1H), 2.21 (m, 1H, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) major/*minor*: δ = 205.1 (2C), 205.0 (2C), 162.9, 161.65, 147.6, 147.4, 141.1, 137.9, 134.1, 133.95, 131.8, 131.65, 131.1, 131.0, 129.0, 128.9, 126.1, 126.1, 119.7, 113.5, 71.55, 71.3, 53.55, 53.3, 36.7 (2C), 36.7 (2C), 36.0, 34.3, 17.0, 16.9 ppm; IR (neat) ν: 1693, 1522, 1342, 1251, 1049, 790, 730, 570 cm^{-1}; HRMS (TOF MS CI^+) *m/z* calcd for $[M+H]^+$ (^{79}Br): 410.0239, and $[M+H]^+$ (^{81}Br): 412.0224, found: (^{79}Br) 410.0201 and (^{81}Br) 412.0221.

(*Z*)-2-(3-Bromo-4-hydroxybut-2-en-1-yl)-2-(2-nitrophenyl)cyclohexane-1,3-dione (*Z*-7)

To a stirred solution of DIBAL-H (894 μL, 1.073 mmol, 2.2 equiv) in dry THF (6 mL) at –78 °C was added

nBuLi (409 μL, 1.024 mmol, 2.1 equiv). After 15 min, the mixture was added dropwise to a solution of **11** (200 mg, 0.487 mmol, 1 equiv) in dry THF (18 mL) at –78 °C. After 1 h 15 min of reaction, MeOH and a 10% aqueous solution of citric acid were sequentially added at –78 °C. Water was introduced and the solution was extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude was solubilized in EtOH (10 mL) and cooled to –78 °C, $NaBH_4$ (26 mg, 0.683 mmol, 1.4 equiv) was added and the reaction mixture was stirred for 5 h. Then 10% citric acid aqueous solution was added to the mixture and allowed to warm to rt. Water was added and the solution was extracted with CH_2Cl_2, the combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by FCC (CH_2Cl_2/MeOH 95:5) and allylic alcohol ***Z*-7** was obtained in 66% yield (123 mg, 0.321 mmol) as a yellow foam; R_f = 0.55 (CH_2Cl_2/MeOH, 95:5); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.11 (dd, J_1 = 8.1, J_2 = 1.4 Hz, 1H), 7.68 (td, J_1 = 7.7, J_2 = 1.4 Hz, 1H), 7.50 (m, 1H), 7.41 (dd, J_1 = 8.0, J_2 = 1.2 Hz, 1H), 5.77 (m, 1H), 4.13 (s, 2H), 3.23 – 3.13 (m, 2H), 2.98 – 2.71 (m, 4H), 2.5 (br, 1H), 2.37 (m, 1H), 2.23 (m, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 205.6 (2C), 147.7, 134.0, 132.2, 131.4, 131.1, 129.0, 126.2, 122.0, 71.95, 67.9, 36.9 (2C), 35.0, 17.2 ppm; IR (neat) ν: 2922, 2853, 1693, 1522, 1461, 1344, 1174, 1086, 1019, 907, 787, 731, 569 cm^{-1} ; HRMS (TOF MS ESI$^+$) *m/z* calcd for $[M+NH_4]^+$ $C_{16}H_{20}N_2O_5{}^{79}Br$: 399.0556, found: 399.0549. *m/z* calcd for $[M+NH_4]^+$ $C_{16}H_{20}N_2O_5{}^{81}Br$: 401.0535, found: 401.0538.

6-(Hydroxymethyl)-1-(2-nitrophenyl)bicyclo[3.3.1]non-6-ene-2,9-dione (6)

Anhydrous 1,4-dioxane was degassed for 3 h under a continuous dried argon sparging. To a solution of alcohol ***Z*-7** (20 mg, 0.052 mmol, 1 equiv) in 1,4-dioxane (2.6 mL) were sequentially added Cs_2CO_3 (26 mg, 0.078 mmol, 1.5 equiv) and $Pd(PPh_3)_4$ (9 mg, 7.8 μmol, 0.15 equiv). The mixture was stirred at reflux under argon for 2 h. The reaction was quenched with a 0.1 M buffer solution KH_2PO_4/$KHPO_4$ (pH = 6.97) and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The crude was purified by FCC (CH_2Cl_2/MeOH, 99:1) and cyclic alcohol **6** was obtained in 18% yield (3 mg, 0.01 mmol) as a yellow foam; R_f = 0.17 (CH_2Cl_2/MeOH, 99:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.14 (dd, J_1 = 8.1, J_2 = 1.3 Hz, 1H), 7.70 (td, J_1 = 7.7, J_2 = 1.4 Hz, 1H), 7.56 – 7.45 (m, 2H), 5.97 (m, 1H), 4.26 – 4.15 (m, 2H), 3.36 (t, J = 3.0 Hz, 1H), 3.25 – 3.06 (m, 2H), 2.92 (dd, J_1 = 18.6, J_2 = 5.7 Hz, 1H), 2.69 (m, 1H), 2.40 (m, 1H), 2.22 (m, 1H), 1.60 (broad, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 207.2, 205.45, 147.6, 134.1, 133.3, 132.2, 130.1, 128.6, 125.4, 124.8, 68.2, 60.6, 51.4, 41.2, 18.9, 14.3 ppm; IR (neat) ν: 3418, 2920, 1694, 1521, 1345, 1174, 1046, 908, 728, 569 cm^{-1}

3-(1-(2-Nitrophenyl)-2,6-dioxocyclohexyl)propanal (18)

A mixture of $PdCl_2(PhCN)_2$ (38 mg, 0.088 mmol, 0.12 equiv), $CuCl_2$ (12 mg, 0.088 mmol, 0.12 equiv) and $AgNO_2$ (7 mg, 0.044 mmol, 0.06 equiv) in *t*BuOH/$MeNO_2$ (15 mL, 15:1) was bubbled with O_2 for 3 min, then olefin **17** was added (200 mg, 0.73 mmol, 1 equiv) and the mixture was stirred at 23 °C for 18 h. Water

was added and the resulting mixture was extracted with CH_2Cl_2. The organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude was filtered through a short pad of silica gel and washed with AcOEt. Aldehyde **18** was obtained in 93% yield (196 mg, 0.678 mmol) as a light brown solid; R_f = 0.28 (PE/AcOEt, 1:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.65 (s, 1H), 8.08 (dd, J_1 = 8.1, J_2 = 1.4 Hz, 1H), 7.68 (m, 1H), 7.50 (m, 1H), 7.35 (dd, J_1 = 7.9, J_2 = 1.0 Hz, 1H), 2.97 – 2.84 (m, 2H), 2.81 – 2.70 (m, 2H), 2.68 – 2.61 (m, 2H), 2.56 – 2.49 (m, 2H), 2.43 – 2.20 (m, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 206.1 (2C), 199.1, 148.05, 133.7, 131.9, 130.9, 128.85, 126.2, 71.8, 39.1, 36.9 (2C), 24.5, 17.1 ppm; IR (neat) ν: 2854, 1716, 1691, 1529, 1348, 855, 789, 740, 571, 421 cm^{-1}; HRMS (TOF MS ESI$^+$) *m/z* calcd for $[M+H]^+$ $C_{15}H_{16}NO_5$: 290.1028, found: 290.1028. *m/z* calcd for $[M+NH_4]^+$ $C_{15}H_{19}N_2O_5$: 307.1294, found: 307.1283.

Dimethyl (diazo(5-(2-nitrophenyl)-6,10-dioxooxecan-2-yl)methyl)phosphonate (20)

In a dry flask, **19** (19 µL, 0.12 mmol, 1.2 equiv) and K_2CO_3 (28 mg, 0.2 mmol, 2 equiv) were stirred in EtOH (1 mL) at rt for 5 min. Then aldehyde **18** (30 mg, 0.1 mmol, 1 equiv) was added and the mixture was stirred at rt for 18 h. The reaction was quenched with a sat. aq. $NaHCO_3$ solution and the mixture was extracted with AcOEt. The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude was purified by FCC (PE/AcOEt, 1:2) and compound **20** was obtained in 30% yield (13 mg, 0.031 mmol); R_f = 0.22 (PE/AcOEt, 1:2); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.81 (dd, J_1 = 8.1, J_2 = 1.4 Hz, 1H), 7.51 (td, J_1 = 7.7, J_2 = 1.4 Hz, 1H), 7.38 (ddd, J_1 = 8.1, J_2 = 7.5, J_3 = 1.4 Hz, 1H), 7.30 (dd, J_1 = 7.9, J_2 = 1.4 Hz, 1H), 5.02 (ddd, J_1 = 15.6, J_2 = 11.6, J_3 = 1.6 Hz, 1H), 4.52 (d, J = 10.0 Hz, 1H), 3.77 (d, J = 1.2 Hz, 3H), 3.73 (d, J = 1.2 Hz, 3H), 2.80 – 2.58 (m, 2H), 2.44 – 2.36 (m, 2H), 2.27 – 2.15 (m, 3H), 2.07 (m, 1H), 1.96 (m, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 208.8, 171.9, 149.5, 133.5, 133.3, 129.2, 128.3, 124.7, 73.2 (d, J = 10 Hz), 53.3 – 53.1 (m, 2C), 51.8, 42.5, 34.9, 33.6 (d, J = 0.8 Hz), 31.3, 21.5 ppm. (C-N_2 not observed); IR (neat) ν: 2955, 2098, 1732, 1525, 1351, 1183, 1018, 787, 730, 557 cm^{-1}; HRMS (TOF MS ESI$^+$) *m/z* calcd fr $[M+NH_4]^+$ $C_{18}H_{26}N_4O_8P$: 457.1488, found: 457.1487.

2-(2-Nitrophenyl)-2-(2-((triethylsilyl)peroxy)propyl)cyclohexane-1,3-dione (21)

Et_3SiH (292 µL, 1.83 mmol, 2.5 equiv) and *t*BuO_2H (5.5 M in hexanes, 6.6 µL, 36.6 µmol, 0.05 equiv) were successively added to a solution of olefin **17** (200 mg, 0.73 mmol, 1 equiv) and $Co(acac)_2$ (56.5 mg, 0.219 mmol, 0.3 equiv) in 1,2-dichloroethane (7 mL) which was sparged with O_2 for 1 h beforehand. The reaction mixture was stirred under O_2 atmosphere for 18 h at rt. After being diluted with PE (10 mL), the mixture was filtered through a short pad of silica gel and eluted with PE/AcOEt (8:2) to afford peroxide **21** (301 mg, 0.71 mmol) in >95% yield as a yellow solid; R_f = 0.7 (PE/AcOEt, 8:2); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.08 (dd, J_1 = 8.0, J_2 = 1.4 Hz, 1H), 7.65 (ddd, J_1 = 8.0, J_2 = 7.3, J_3 = 1.5 Hz, 1H), 7.54 – 7.44 (m, 2H), 4.06 (m, 1H), 3.11 – 2.65 (m, 5H), 2.38 – 2.18 (m, 3H), 1.31 (d, J_1 = 6.3 Hz, 3H), 0.96 (m, 9H), 0.67 (m, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 206.1, 204.8, 148.0, 133.5, 132.9, 130.9, 128.55, 126.05, 77.5, 71.9, 37.6, 37.1, 36.9, 19.5, 17.0, 6.7, 3.75 ppm; IR (neat) ν: 2962, 2876, 1724, 1697, 1523, 1348, 1175, 1037,

843, 801, 735, 568 cm^{-1}; HRMS (TOF MS ESI^+) *m/z* calcd for $[M+Na]^+$ $C_{21}H_{31}NO_6NaSi$: 444.1818, found: 444.1820; Mp 86 °C (AcOEt).

9-Methyl-7-(2-nitrophenyl)oxonane-2,6-dione (22)

To a stirred solution of **21** (120 mg, 0.28 mmol, 1 equiv) in anhydrous THF (2.5 mL) was added PPh_3 (82 mg, 0.31 mmol, 1.1 equiv). The reaction was stirred at rt for 14 h, then the solvent was removed under vacuum. The crude was purified by FCC (PE/AcOEt, 8:2) to afford silyl ether (89 mg, 0.219 mmol) in 78% yield as a yellow solid; R_f = 0.38 (PE/AcOEt, 8:2); ^1H NMR (300 MHz, $CDCl_3$): δ = 8.09 (dd, J_1 = 8.1, J_2 = 1.4 Hz, 1H), 7.66 (td, J_1 = 7.65, J_2 = 1.4 Hz, 1H), 7.48 (m, 1H), 7.34, (dd, J_1 = 8.0, J_2 = 1.0 Hz, 1H), 3.96 (m, 1H), 3.06 (ddd, J_1 = 16.2, J_2 = 11.1, J_3 = 6.6 Hz, 1H), 2.99 – 2.73 (m, 2H), 2.65 (dtd, J_1 = 16.2, J_2 = 5.0, J_3 = 1.0 Hz, 1H), 2.54 (dd, J_1 = 15.6, J_2 = 7.4 Hz, 1H), 2.41 – 2.12 (m, 3H), 1.28 (d, J_1 = 6.2 Hz, 3H), 0.86 (m, 9H), 0.50 (m, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 206.2, 204.9, 148.2, 133.3, 133.1, 130.7, 128.4, 126.0, 72.5, 65.6, 44.6, 37.8, 36.6, 25.0, 17.2, 6.85, 4.95 ppm; IR (neat) ν: 2950, 2871, 1696, 1524, 1350, 1133, 1076, 1041, 1004, 954, 854, 727, 569 cm^{-1}; HRMS (TOF MS ESI^+) *m/z* calcd for $[M+Na]^+$ $C_{21}H_{31}NO_5NaSi$: 428.1869, found: 428.1870; Mp 122 °C (CH_2Cl_2).

To a stirred solution of silyl ether (30 mg, 0.074 mmol, 1 equiv) in anhydrous THF (1 mL) was added TBAF (77 µL, 0.077 mmol, 1.05 equiv). The reaction was stirred at rt for 15 min, and then water was added (2 mL). The mixture was extracted with CH_2Cl_2, the combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude was purified by FCC (PE/AcOEt, 7:3) to afford lactone **22** in 93% yield (20 mg, 0.068 mmol) with a dr = 1:2 (*trans/cis*). Crystals from ***trans*-22** for X ray analysis were obtained from a solution of the mixture in MeOH; ***trans*-22** (minor), colorless crystals; R_f = 0.56 (PE/AcOEt, 7:3); Lactone ***trans*-22** (X-ray); ^1H NMR (300 MHz, $CDCl_3$): δ = 7.78 (dd, J_1 = 8.1, J_2 = 1.3 Hz, 1H), 7.68 (dd, J_1 = 8.0, J_2 = 1.4 Hz, 1H), 7.57 (ddd, J_1 = 8.0, J_2 = 7.2, J_3 = 1.4 Hz, 1H), 7.37 (ddd, J_1 = 8.1, J_2 = 7.2, J_3 = 1.5 Hz, 1H), 5.12 (qd, J_1 = 6.7, J_2 = 2.8 Hz, 1H), 4.62 (dd, J_1 = 10.6, J_2 = 2.8 Hz, 1H), 3.08 (m, 1H), 2.91 (m, 1H), 2.50 (m, 1H), 2.38 – 2.16 (m, 3H), 2.00 (m, 1H), 1.83 (dd, J_1 = 13.7, J_2 = 2.8, 1H), 1.34 (d, J_1 = 6.7 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 211.0, 171.4, 149.3, 133.1, 133.0, 130.3, 127.8, 123.8, 67.2, 47.4, 42.6, 41.5, 33.8, 22.3, 20.3 ppm; IR (neat) ν: 1732, 1521, 1352, 1260, 1202, 1130, 1045, 784, 745, 714, 437, 405 cm^{-1}; HRMS (TOF MS ESI^+) *m/z* calcd for $[M+NH_4]^+$ $C_{15}H_{21}N_2O_5$: 309.1450, found: 309.1448; Mp 146 °C (MeOH); ***cis*-22**, yellow powder; R_f = 0.56 (PE/AcOEt, 7:3); ^1H NMR (300 MHz, $CDCl_3$): δ = 7.81 – 7.72 (m, 2H), 7.58 (m, 1H), 7.37 (m, 1H), 5.06 (m, 1H), 4.23 (dd, J_1 = 11.7, J_2 = 1.6 Hz, 1H), 2.80 – 2.61 (m, 2H), 2.61 – 2.39 (m, 3H), 2.21 (m, 1H), 2.00 (m, 1H), 1.91 (m, 1H), 1.32 (d, J_1 = 6.2 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 210.9, 172.6, 149.2, 133.0, 132.9, 130.1, 127.8, 123.9, 71.5, 50.3, 43.9, 43.0, 34.1, 22.2, 20.3 ppm; IR (neat) ν: 1732, 1521, 1352, 1260, 1202, 1130, 1045, 784, 745, 714, 437, 405 cm^{-1}; HRMS (TOF MS ESI^+) *m/z* calcd for $[M+NH_4]^+$ $C_{15}H_{21}N_2O_5$: 309.1450, found: 309.1447; Mp 88 °C (MeOH).

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