Synthesis of the Tricyclic Core of the Marine Natural Product Labiatin A

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Dedicated to Professor Steven V. Ley, FRS, on the occasion of his 60th birthday

Abstract: A synthetic route to a model of the tricyclic core of labiatin A is described. Two catalytic metal carbenoid reactions, C–H insertion and oxonium ylide generation with subsequent [2,3]-sigmatropic rearrangement, have been used to assemble the tricyclic system in an efficient and stereoselective manner.

Key words: carbenoid, ylide, rearrangement, stereoselective synthesis, natural product

Labiatin A, a highly oxygenated natural product belonging to the eunicellin (cladiellin) family of diterpenoids, was isolated from a sample of the gorgonian coral *Eunicella labiata* collected off the coast of Senegal (Figure 1).[1] Four other eunicellin diterpenoids (labiatins B and C, and labiatamides A and B) were later isolated from the same coral and were found to possess the C-2–C-9 ether linkage which is characteristic of this class of natural product (e.g. labiatins B and C, Figure 1).[2] In contrast, labiatin A has an unusual C-2–C-6 ether bridge and is structurally unique with regard to marine natural products.

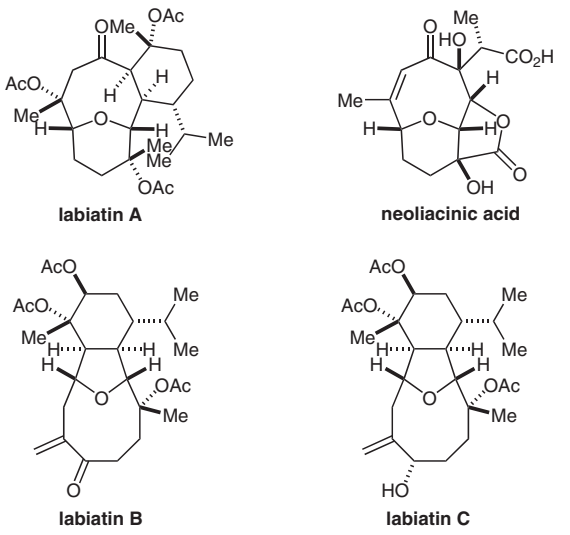
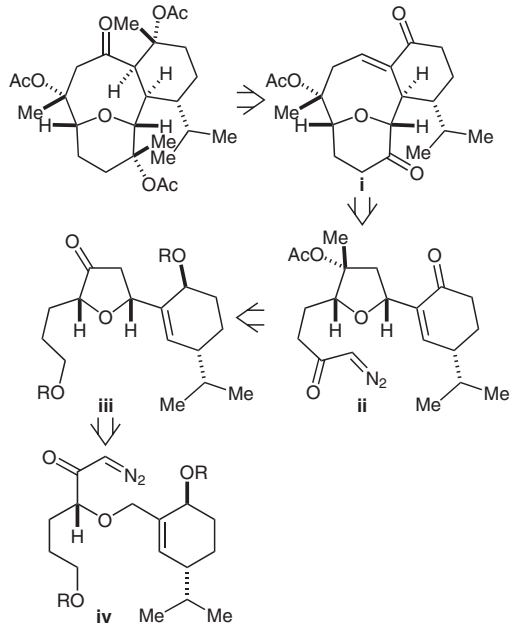


Figure 1 The labiatin family of marine natural products and neoliacinic acid

The unusual tricyclic framework of labiatin A coupled with the dense array of oxygen-containing functionality and multiple stereogenic centres make it an attractive but challenging synthetic target. In other work, we have developed a powerful strategy for the synthesis of the bridged ether core of the structurally related terrestrial natural product neoliacinic acid (Figure 1), by sequential use of a carbenoid C–H insertion reaction and tandem oxonium ylide generation and rearrangement.[3] The retrosynthetic analysis of labiatin A incorporating this strategy is shown in Scheme 1. Simple functional group interconversion and dehydration leads to the diketone **i**. Disconnection via a retrosynthetic ylide formation and rearrangement sequence gives the diazo ketone **ii**, and further simplification produces the dihydro-3(2*H*)-furanone **iii**. A retrosynthetic carbenoid C–H insertion reaction then reveals the diazo ketone **iv**.



Scheme 1 Retrosynthetic analysis of labiatin A

In order to test the viability of the synthetic strategy implied by the retrosynthetic analysis shown above, we prepared the diazo ketone **5** (Scheme 2). The synthesis commenced with the alcohol **1**, which we have prepared previously[3] by chelation-controlled addition of an organocopper reagent to the chiral pool derived compound (*R*)-isopropylideneglyceraldehyde (Scheme 2).[4] The alcohol

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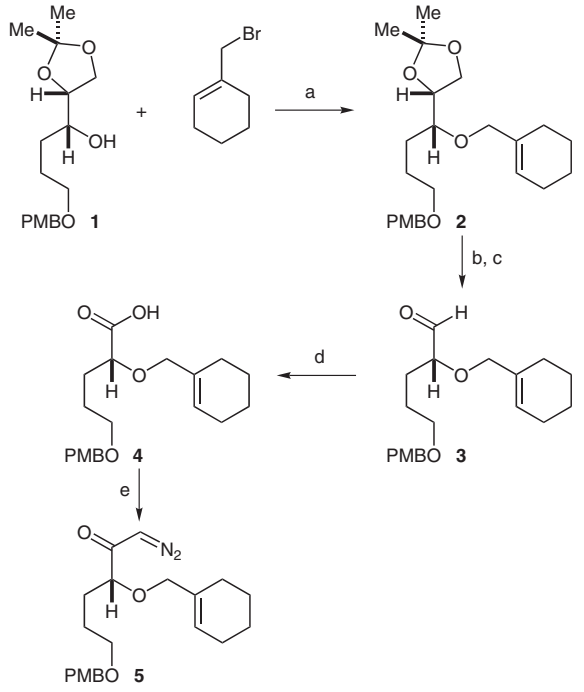
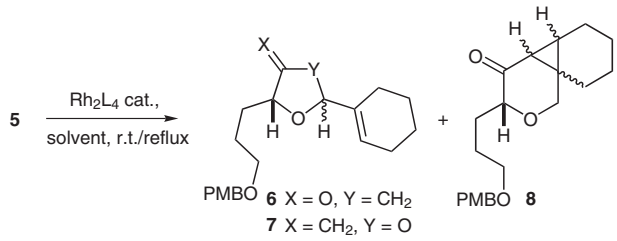
1 was converted into the ether **2** by standard Williamson coupling with 1-(bromomethyl)cyclohexene (prepared from a commercially available ester in two steps).[5] Removal of the acetonide protecting group afforded the corresponding 1,2-diol and treatment of the diol with sodium periodate delivered the aldehyde **3**. Subsequent chlorite oxidation[6] provided the carboxylic acid **4** and this was then converted into the diazo ketone **5** by reaction with isobutylchloroformate and treatment of the resulting mixed anhydride with a large excess of ethereal diazomethane.



Scheme 2 Preparation of the diazo ketone **5**, the precursor required for the carbenoid C–H insertion reaction. *Reagents and conditions*: (a) NaH, THF, r.t. → reflux, then 1-(bromomethyl)cyclohexene, THF, r.t. → reflux, 91% (based on recovered starting material); (b) PPTS (0.2 equiv), $HO(CH_2)_2OH$–THF–CH_2Cl_2 (2:1:1), reflux; (c) $NaIO_4$ (4 equiv), THF–H_2O, r.t., 96% over 2 steps; (d) $NaClO_2$ (7.5 equiv), NaH_2PO_4 (6.5 equiv), 2-methyl-2-butene (8.1 equiv), *t*-BuOH, H_2O, r.t.; (e) *i*-BuOCOCl (1 equiv), Et_3N, Et_2O, r.t. then CH_2N_2, Et_2O, 0 °C → r.t., 76% over 2 steps.

Reaction of the diazo ketone **5** with rhodium(II) trifluoroacetamide[7] in THF at reflux resulted in rhodium carbenoid formation and subsequent intramolecular C–H insertion to give the required dihydro-3(2*H*)-furanone **6** as an inseparable mixture of diastereoisomers (ca. 2:1, *cis*:*trans*) in 60% yield (Scheme 3 and Table 1, entry 1). Diastereoisomeric mixtures of the acetal **7**, arising from anomalous C–H insertion,[8] and the intramolecular cyclopropanation product **8** were also isolated. The inseparable 2:1 mixture of diastereoisomers of dihydro-3(2*H*)-furanone **6** was used in the next step of the synthesis (Scheme 4).



Scheme 3

In subsequent studies, the carbenoid C–H insertion reaction was explored in detail and several rhodium catalysts and reaction conditions were investigated (Scheme 3, Table 1). The catalysts were selected based on data obtained during our work concerning the synthesis of neoliacinic acid.[3] The results obtained using rhodium(II) trifluoroacetamide dimer as catalyst under various reaction conditions are shown (Table 1, entries 1–4). CH_2Cl_2 proved to be an unsuitable solvent because it tended to promote alkene cyclopropanation at the expense of C–H insertion. Lowering the reaction temperature from reflux to ambient temperature resulted in an improvement in the ratio of *cis*:*trans* isomers (2:1 → 6:1) of the (2*H*)-furanone **6** without altering the yield. The use of rhodium(II) acetate dimer as the catalyst (Table 1, entries 5 and 6) resulted in a decrease in the yield of the required C–H insertion product **6**. In studies concerning the synthesis of neoliacinic acid, the bulky catalyst rhodium(II) triphenylacetate

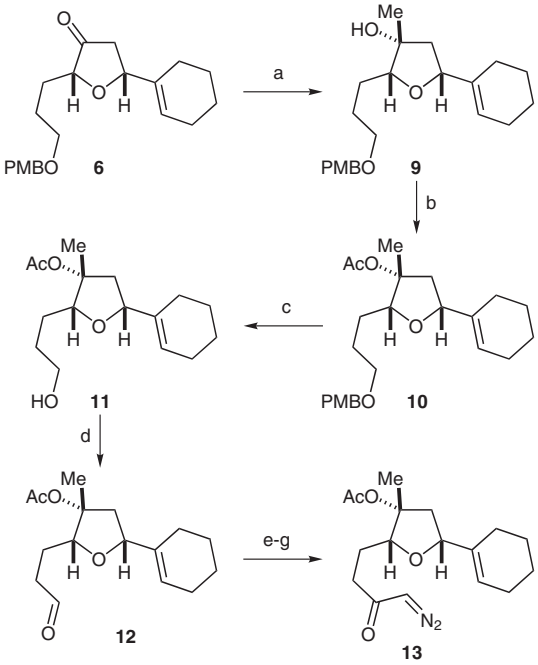
Table 1 The Influence of Catalyst and Conditions on the Reaction of the Diazo Ketone **5** (Scheme 3)

Entry	L	Solvent	Temp	Yield of **6** (%) (*cis*:*trans*)[a]	Yield of **7**, **8** (%)
1	$HNCOCF_3$	THF	reflux	60 (2:1)	**7** (13), **8** (16)
2	$HNCOCF_3$	THF	r.t.	59 (6:1)	**8** (13)
3	$HNCOCF_3$	CH_2Cl_2	reflux	21 (2:1)	**8** (35)
4	$HNCOCF_3$	CH_2Cl_2	r.t.	33 (3:1)	**8** (27)
5	O_2CCH_3	THF	reflux	26 (7:1)	**7** (2), **8** (36)
6	O_2CCH_3	THF	r.t.	16 (4:1)	**8** (21)
7	O_2CCPh_3	CH_2Cl_2	r.t.	32 (2:3)	**7** (7), **8** (16)

[a] Diastereomeric ratio determined by NMR.

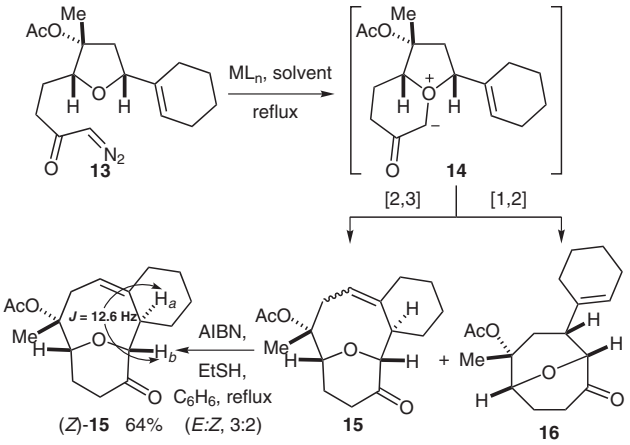
dimer had given good results,[3a] but low yields were obtained when this catalyst was employed, and in one case only starting material was isolated. The unstable acetal **7**, arising by anomalous C–H insertion, was also isolated in low yield from several of the reactions (entries 1, 5 and 7).[8]

Conversion of the (2*H*)-furanone **6** into the key cyclisation precursor **13** was accomplished using the route shown in Scheme 4. The methyl group was installed by treatment of the ketone **6** with methyllithium. At this stage, ^{1}H NMR NOE experiments performed on the tertiary alcohol **9** confirmed that the required *cis* relationship had been established upon carbenoid C–H insertion, and that nucleophilic addition of methyllithium had given the expected diastereoisomer. Acetylation of the tertiary alcohol to give the ester **10** was achieved using standard techniques and removal of the *p*-methoxybenzyl protecting group using CAN[9] gave the alcohol **11**. Oxidation of the free hydroxyl group to give the aldehyde **12** was performed using Dess–Martin periodinane, and subsequent chlorite oxidation delivered the corresponding carboxylic acid.[6] The diazo ketone **13** was then obtained by conversion of the carboxylic acid into the corresponding acid chloride followed by treatment with diazomethane.



Scheme 4 Preparation of the diazo ketone **13**, the precursor required for the tandem oxonium ylide formation and rearrangement. *Reagents and conditions*: (a) MeLi (2 equiv), PhMe, –78 °C → r.t., 60%; (b) Ac_2O (5 equiv), DMAP (3 equiv), Et_3N, Et_2O, r.t., 77%; (c) CAN (2 equiv), MeCN–H_2O (9:1), r.t., 86%; (d) Dess–Martin periodinane (1.5 equiv), CH_2Cl_2, 0 °C → r.t., 83%; (e) $NaClO_2$ (7.5 equiv), NaH_2PO_4 (6.5 equiv), 2-methyl-2-butene (8 equiv), *t*-BuOH, H_2O, r.t.; (f) NaOMe (1 equiv), MeOH, r.t.; (g) $(COCl)_2$ (5 equiv), C_6H_6, r.t. then CH_2N_2, Et_2O, 0 °C, 77% over 3 steps.

It was now possible to explore the pivotal model reaction that would deliver the fused tricyclic framework found in labiatin A (Scheme 5). Several reaction conditions were investigated, but the optimum conditions were those used during our work concerning the synthesis of the core of neoliacinic acid (Table 2, entry 1).[3] Treatment of the α-diazo ketone **13** with copper(II) hexafluoroacetylacetonate [$Cu(hfacac)_2$] in CH_2Cl_2 at reflux afforded the ether-bridged compounds **15** and **16** in a combined yield of 83% with the required [2,3]-rearrangement product **15** (3:2, *E*:*Z* isomer mixture) predominating. It proved difficult to separate the oxabicyclo[3.3.1]nonane **16**, arising from a [1,2]-shift of the oxonium ylide intermediate, from the required [2,3]-rearrangement product **15** and so the mixture was subjected to isomerisation,[10] giving the thermodynamically favoured (*Z*)-**15** (Scheme 5).



Scheme 5 Construction of the tricyclic core of labiatin A

Table 2 The Influence of Catalyst and Conditions on the Reaction of Diazo Ketone **13** (Scheme 5)

Entry	ML_n	Solvent	Yield **15** + **16** (%), Ratio[a] **15**:**16**	Ratio[a] **15** (*E*:*Z*)
1	$Cu(hfacac)_2$	CH_2Cl_2	83, 2:1	3:2
2	$Cu(hfacac)_2$	C_6H_6	52, 6:1	4:1
3	$Cu(acac)_2$	CH_2Cl_2	35, 2:1	1:1
4	$Rh_2(O_2CCH_3)_4$	CH_2Cl_2[b]	22, 3:1	1:6

[a] Product and diastereomeric ratio determined by NMR.
[b] Reaction performed at r.t.

It was important to establish that the relative configuration of the stereogenic centre in the cyclohexyl ring of the tricyclic product (*Z*)-**15** corresponded to that in labiatin A. The ^{1}H NMR data for compound (*Z*)-**15** proved to be conclusive: the signal for the proton H_b is a doublet with J = 12.6 Hz as a consequence of the coupling between H_a and H_b. The magnitude of the coupling constant is indicative of a large dihedral angle and that the relationship between H_a and H_b is *anti*. The ^{1}H NMR NOE data also provided strong evidence that the relative configurations of the stereogenic centres in the tricyclic compound (*Z*)-**15** are the same as the corresponding stereogenic centres in labiatin A.

In summary, we have assembled the core of labiatin A in an efficient manner using metal carbenoid transformations. Intramolecular C–H insertion was used to construct a dihydro-3(2*H*)-furanone and subsequent elaboration by a sequence involving tandem oxonium ylide formation and [2,3]-rearrangement delivered the complete tricyclic system.

We are currently exploiting carbenoid methodology to synthesise labiatin A. Results of this work will be reported in due course.

Solvents were distilled prior to use: THF by distillation from sodium and benzophenone, Et_2O by distillation from sodium and benzophenone, CH_2Cl_2 by distillation from CaH_2. Reagents were used as supplied unless otherwise stated. Petroleum ether (PE) used had the boiling point in the range 40–60 °C. TLC was performed using Merck Kiesegel 60 F_{254} plates and visualisation was by UV light and staining with ethanolic anisaldehyde or ceric ammonium molybdate with heat. Flash column chromatography was performed using Merck Kiesegel silica gel. ^{1}H NMR spectra were recorded on a Bruker DRX 500 or Bruker AV 400 FT spectrometer at ambient temperature. Data are reported as chemical shifts in ppm relative to residual $CHCl_3$ or TMS on the δ scale, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, or combinations thereof), coupling constant (*J*), integration, and assignment. ^{13}C NMR spectra were recorded on a Bruker DRX 500 (125 MHz) or a Bruker AV 400 (100 MHz) FT spectrometer at ambient temperature. Data are reported as chemical shifts in ppm relative to residual $CHCl_3$ on the δ scale and assignment. Assignments were made using DEPT 135 and DEPT 90 pulse experiments and HMQC experiments. IR spectra were recorded in the range 600–4000 cm^{-1} on a Perkin–Elmer 1600 FT-IR instrument at ambient temperature. HRMS data were obtained using chemical ionisation on a Fisons VG autospec instrument. Elemental analyses were carried out on an Exeter Analytical Inc. CE-440 elemental analyser. Optical rotations were obtained using a Jasco DIP 370 digital polarimeter.

4-*O*-(Cyclohex-1-en-1-ylmethyl)-2,3-dideoxy-1-*O*-(4-methoxybenzyl)-5,6-*O*-(1-methylethylidene)-D-*threo*-hexitol (2)

A solution of the alcohol **1** (5.80 g, 18.7 mmol) in anhyd THF (31 mL) was added to a stirred suspension of NaH (539 mg, 24.3 mmol) in anhyd THF (196 mL) at r.t. under N_2. The mixture was heated at reflux for 1 h under N_2, then a solution of 1-(bromomethyl)cyclohexene (4.26 g, 22.4 mmol) in anhyd THF (78 mL) was added by cannula under N_2. The reaction was heated at reflux for 24 h and then allowed to cool to r.t. The reaction was quenched by the addition of sat. NH_4Cl solution (50 mL) and water (200 mL). The reaction mixture was then extracted with Et_2O (3 × 150 mL). The Et_2O extracts were combined and washed with water (200 mL) and brine (100 mL), then dried ($MgSO_4$) and concentrated in vacuo to give a brown oil. Flash column chromatography on silica gel (PE–EtOAc, 19:1 → 1:1) gave the ether **2** (5.92 g, 78%) as a clear oil; $[\alpha]_D^{22}$ +20.5 (*c* = 1.9, $CHCl_3$).

IR ($CHCl_3$): 2934, 2860, 2838, 1681, 1612, 999, 861, 840 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.25 (d, *J* = 8.6 Hz, 2 H, ArH), 6.87 (d, *J* = 8.6 Hz, 2 H, ArH), 5.67 (br, 1 H, C=CH), 4.42 (s, 2 H, OCH_2Ar), 4.16 (ddd, *J* = 6.3, 6.6, 7.4 Hz, 1 H, OCH_2CHO), 4.02 (d, *J* = 11.3 Hz, 1 H, OCH_2C=CH), 3.96 (dd, *J* = 6.6, 8.2 Hz, 1 H, OCH_2CHO), 3.88 (d, *J* = 11.3 Hz, 1 H, OCH_2C=CH), 3.79 (s, 3 H, OCH_3), 3.68 (dd, *J* = 7.4, 8.2 Hz, 1 H, OCH_2CHO), 3.40–3.48 (m, 2 H, CH_2OPMB), 3.33 (ddd, *J* = 3.6, 6.3, 8.7 Hz, 1 H, $OCHCHO$), 1.98–2.05 (m, 4 H, CH_2C=$CHCH_2$), 1.85–1.75 (m, 1 H, $OCHCH_2CH_2$), 1.71–1.49 (m, 6 H, $OCHCH_2CH_2$, $CH_2CH_2CH_2CH_2$, $OCHCH_2CH_2$), 1.37–1.48 (m, 1 H, $OCHCH_2CH_2$), 1.41 [s, 3 H, $C(CH_3)_2$], 1.35 [s, 3 H, $C(CH_3)_2$].

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.1 (C), 135.3 (C), 130.7 (C), 129.2 (CH), 125.1 (CH), 113.7 (CH), 109.2 (C), 78.9 (CH), 78.0 (CH), 75.8 (CH_2), 72.5 (CH_2), 69.9 (CH_2), 65.8 (CH_2), 55.2 (CH_3), 27.1 (CH_2), 26.5 (CH_3), 26.1 (CH_2), 25.9 (CH_2), 25.4 (CH_3), 25.0 (CH_2), 22.5 (CH_2), 22.4 (CH_2).

HRMS (CI; CH_4): *m*/*z* [M^+ + H] calcd for $C_{24}H_{37}O_5$: 405.2641; found: 405.2624.

Anal. Calcd for $C_{24}H_{36}O_5$ (404.55): C, 71.26; H, 8.97. Found: C, 71.26; H, 9.02.

(2*R*)-5-(Benzyloxy)-2-(cyclohex-1-en-1-ylmethoxy)pentanal (3)

Pyridinium *p*-toluene sulfonate (656 mg, 2.61 mmol) was added to a solution of **2** (5.28 g, 13.1 mmol) in ethylene glycol (184 mL), THF (92 mL) and CH_2Cl_2 (92 mL) and heated at reflux for 20 h. The reaction was allowed to cool to r.t. and was neutralised with concd NH_3 solution (ca. 2 mL). The mixture was diluted with water (200 mL) and extracted with CH_2Cl_2 (3 × 100 mL). The organic extracts were combined and washed with water (150 mL) and brine (100 mL), dried ($MgSO_4$) and concentrated in vacuo to give a yellow oil. The crude diol was dissolved in THF (153 mL) and then water (61 mL) and sodium periodate (11.17 g, 52.22 mmol) were added at r.t. over 10 min. The mixture was allowed to stir for 90 min, quenched with water (150 mL), and then extracted with Et_2O (3 × 100 mL). The Et_2O extracts were combined and washed with water (150 mL) and brine (100 mL), then dried ($MgSO_4$) and concentrated in vacuo to give a yellow oil. Flash column chromatography on silica gel (PE–EtOAc, 9:1 → 4:1) gave the aldehyde **3** (4.15 g, 96%) as a colourless oil; $[\alpha]_D^{23}$ +4.6 (*c* = 0.82, $CHCl_3$).

IR ($CHCl_3$): 2936, 2861, 2838, 1722, 1612, 995, 908, 835 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.61 (d, *J* = 2.2 Hz, 1 H, CHO), 7.24 (d, *J* = 8.7 Hz, 2 H, ArH), 6.87 (d, *J* = 8.7 Hz, 2 H, ArH), 5.67 (br, 1 H, C=CH), 4.41 (s, 2 H, OCH_2Ar), 3.95 (d, *J* = 11.1 Hz, 1 H, OCH_2C=CH), 3.84 (d, *J* = 11.1 Hz, 1 H, OCH_2C=CH), 3.79 (s, 3 H, OCH_3), 3.64–3.68 (m, 1 H, $OCHCH_2CH_2$), 3.40–3.48 (m, 2 H, CH_2OPMB), 2.00–2.03 (m, 4 H, CH_2C=$CHCH_2$), 1.53–1.80 (m, 8 H, $OCHCH_2CH_2$, $CH_2CH_2CH_2CH_2$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 204.2 (CH), 159.2 (C), 134.2 (C), 130.5 (C), 129.3 (CH), 126.6 (CH), 113.8 (CH), 82.7 (CH), 75.6 (CH_2), 72.6 (CH_2), 69.4 (CH_2), 55.3 (CH_3), 26.9 (CH_2), 26.1 (CH_2), 25.1 (CH_2), 25.0 (CH_2), 22.4 (CH_2), 22.3 (CH_2).

HRMS (CI; CH_4): *m*/*z* [M^+] calcd for $C_{20}H_{28}O_4$: 332.1988; found: 332.1985.

(3*R*)-3-(Cyclohex-1-en-1-ylmethoxy)-1-diazo-6-[(4-methoxybenzyl)oxy]hexan-2-one (5)

A solution of sodium chlorite (80%, 8.73 g, 96.6 mmol) and sodium dihydrogenorthophosphate dihydrate (13.04 g, 83.60 mmol) in water (129 mL) was added dropwise over 10 min at r.t. to a solution of the aldehyde **3** (4.15 g, 12.9 mmol) and 2-methyl-2-butene (11.0 mL of 90% solution, 104 mmol) in *t*-BuOH (65 mL). The mixture was left to stir for 90 min at r.t., then the volatile compounds were removed in vacuo and the mixture was extracted with Et_2O (3 × 100 mL). The Et_2O extracts were combined and washed with water (100 mL) and brine (80 mL), dried ($MgSO_4$) and concentrated in vacuo.

The unpurified acid was dissolved in anhyd Et_2O (84 mL), stirred at r.t. under Ar and Et_3N (1.97 mL, 14.2 mmol) and isobutylchloroformate (1.84 mL, 14.2 mmol) were added sequentially. The mixture was stirred for 3 h, then filtered and added dropwise over 20 min to a solution of diazomethane (ca. 129 mmol in 161 mL of Et_2O) at 0 °C. The resulting solution was stirred overnight and the excess diazomethane was then quenched with AcOH (3 mL). After 30 min the solution was diluted with Et_2O (100 mL) and washed with sat.

$NaHCO_3$ solution (100 mL) and brine (80 mL). The ethereal solution was then dried ($MgSO_4$) and concentrated in vacuo. The resulting yellow oil was purified by flash column chromatography on silica gel (PE–EtOAc, 10:1 → 7:1) to afford the diazo ketone **5** (3.67 g, 76%) as a yellow oil; $[\alpha]_D^{21}$ +49.8 (*c* = 1.28, $CHCl_3$).

IR ($CHCl_3$): 2934, 2860, 2838, 2109, 1634, 1000, 878, 835 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.25 (d, *J* = 8.6 Hz, 2 H, ArH), 6.87 (d, *J* = 8.6 Hz, 2 H, ArH), 5.72 (s, 1 H, CHN_2), 5.67 (br, 1 H, C=CH), 4.41 (s, 2 H, OCH_2Ar), 3.91 (d, *J* = 11.4 Hz, 1 H, OCH_2C=CH), 3.80 (s, 3 H, OCH_3), 3.74 (d, *J* = 11.4 Hz, 1 H, OCH_2C=CH), 3.72–3.78 (m, 1 H, $OCHCH_2CH_2$), 3.44 (t, *J* = 5.6 Hz, 2 H, CH_2OPMB), 1.96–2.04 (m, 4 H, CH_2C=$CHCH_2$), 1.53–1.80 (m, 8 H, $OCHCH_2CH_2$, $CH_2CH_2CH_2CH_2$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.9 (C), 159.2 (C), 134.1 (C), 130.7 (C), 129.3 (CH), 126.1 (CH), 113.8 (CH), 83.0 (CH), 75.4 (CH_2), 72.6 (CH_2), 69.7 (CH_2), 55.3 (CH_3), 52.3 (CH), 30.1 (CH_2), 26.2 (CH_2), 25.5 (CH_2), 25.0 (CH_2), 22.5 (CH_2), 22.3 (CH_2).

HRMS (CI, CH_4): *m*/*z* [M^+ + H] calcd for $C_{21}H_{29}N_2O_4$: 373.2127; found: 373.2143.

Anal. Calcd for $C_{21}H_{28}O_4N_2$ (372.47): C, 67.72; H, 7.58; N, 7.52. Found: C, 67.52; H, 7.57; N, 7.52.

(2*R*,5*R*)-5-Cyclohex-1-en-1-yl-2-{3-[(4-methoxybenzyl)oxy]propyl}dihydrofuran-3(2*H*)-one (6), (2*R*,4*R*)-2-Cyclohex-1-en-1-yl-4-{3-[(4-methoxybenzyl)oxy]propyl}-5-methylene-1,3-dioxolane (7) and (3*R*)-3-{3-[(4-Methoxybenzyl)oxy]propyl}hexahydrobenzo[1,3]cyclopropa[1,2-*c*]pyran-4(3*H*)-one (8)

A solution of diazo ketone **5** (130 mg, 0.349 mmol) in anhyd THF (15 mL) was added dropwise over 40 min to a solution of rhodium(II) trifluoroacetamide dimer (2 mg) in anhyd THF (2 mL) under N_2 at reflux. The reaction was stirred at reflux for a further 10 min, allowed to cool to r.t. and concentrated in vacuo. Flash column chromatography on silica gel (hexane–EtOAc, 9:1 → 4:1) gave the dihydro-3(2*H*)-furanone **6** (67.5 mg, 60%, 2:1 mixture of diastereoisomers), the enol ether acetal **7** (16 mg, 13%, 4:1 mixture of diastereoisomers) and the cyclopropane **8** (18.5 mg, 16%, 2:1 mixture of diastereoisomers) as colourless oils.

Compound **6**

Mixture of isomers (2:1).

IR ($CHCl_3$): 2934, 2860, 2838, 1754, 1613, 894, 838 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.25 (d, *J* = 8.6 Hz, 2 H, ArH), 6.87 (d, *J* = 8.6 Hz, 2 H, ArH), 5.83 [s, 1 H, C=C*H* (*cis*)], 5.74 [s, 1 H, C=CH (*trans*)], 4.66 [t, *J* = 7.2 Hz, 1 H, OC*H*C=CH (*trans*)], 4.45 [dd, *J* = 5.8, 10.8 Hz, 1 H, OC*H*C=CH (*cis*)], 4.42 (s, 2 H, OCH_2Ar), 3.96 [dd, *J* = 3.8, 8.0 Hz, 1 H, $OCHCH_2CH_2$ (*trans*)], 3.75–3.85 [m, 1 H, $OCHCH_2CH_2$ (*cis*)], 3.80 (s, 3 H, OCH_3), 3.43–3.48 (m, 2 H, CH_2OCH_2Ar), 2.54 [dd, *J* = 7.2, 18.0 Hz, 1 H, CH_2C=O (*trans*)], 2.48 [dd, *J* = 5.7, 18.0 Hz, 1 H, CH_2C=O (*cis*)], 2.45 [dd, *J* = 7.2, 18.0 Hz, 1 H, CH_2C=O (*trans*)], 2.34 [dd, *J* = 10.8, 18.0 Hz, 1 H, CH_2C=O (*cis*)], 2.11–1.96 (m, 4 H, CH_2C=$CHCH_2$), 1.53–1.92 (m, 8 H, $OCHCH_2CH_2$, $OCHCH_2CH_2$, $CH_2CH_2CH_2CH_2$).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 216.7 (C), 216.4 (C), 159.1 (C), 136.2 (C), 135.6 (C), 130.6 (C), 129.3 (CH), 125.6 (CH), 124.6 (CH), 113.8 (CH), 81.1 (CH), 79.4 (CH), 79.3 (CH), 78.6 (CH), 72.5 (CH_2), 69.7 (CH_2), 69.5 (CH_2), 55.3 (CH_3), 41.5 (CH_2), 40.6 (CH_2), 27.8 (CH_2), 27.7 (CH_2), 25.7 (CH_2), 25.4 (CH_2), 25.0 (CH_2), 25.0 (CH_2), 24.0 (CH_2), 23.5 (CH_2), 22.4 (CH_2), 22.4 (CH_2).

HRMS (CI, NH_3): *m*/*z* [M^+] calcd for $C_{21}H_{28}O_4$: 344.1988; found: 344.1984.

Anal. Calcd for $C_{21}H_{28}O_4$ (344.45): C, 73.23; H, 8.19. Found: C, 72.84; H, 8.36.

Compound **7**

Mixture of isomers (4:1).

IR ($CHCl_3$): 2928, 2862, 1684, 1614, 983, 899 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.26 (d, *J* = 8.7 Hz, 2 H, ArH), 6.88 (d, *J* = 8.7 Hz, 2 H, ArH), 5.97–5.99 [m, 1 H, C=CH (minor)], 5.91–5.94 [m, 1 H, C=CH (major)], 5.51 [s, 1 H, OCHO (major)], 5.37 [s, 1 H, OCHO (minor)], 4.62–4.65 [m, 1 H, $OCHCH_2$ (major)], 4.48–4.53 [m, 1 H, $OCHCH_2$ (minor)], 4.44 (s, 2 H, OCH_2Ar), 4.31 [t, *J* = 2.0 Hz, 1 H, CH_2=C (major)], 4.29 [t, *J* = 2.2 Hz, 1 H, CH_2=C (minor)], 3.83 [dd, *J* = 1.3, 2.2 Hz, 1 H, CH_2=C (major)], 3.80–3.81 [m, 1 H, CH_2=C (minor)], 3.81 (s, 3 H, OCH_3), 3.45–3.54 (m, 2 H, CH_2OCH_2Ar), 1.98–2.09 (m, 4 H, CH_2C=$CHCH_2$), 1.71–1.85 (m, 4 H, $OCHCH_2CH_2CH_2O$), 1.58–1.68 (m, 4 H, $CH_2CH_2CH_2CH_2$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.2 (C), 160.0 (C), 159.2 (C), 134.6 (C), 133.9 (C), 130.7 (C), 130.6 (CH), 129.4 (CH), 129.3 (CH), 113.9 (CH), 107.3 (CH), 107.1 (CH), 78.1 (CH), 78.1 (CH_2), 77.8 (CH_2), 72.7 (CH_2), 72.6 (CH_2), 69.6 (CH_2), 69.4 (CH_2), 55.4 (CH_3), 32.0 (CH_2), 31.1 (CH_2), 26.6 (CH_2), 25.8 (CH_2), 25.2 (CH_2), 25.0 (CH_2), 22.3 (CH_2), 22.0 (CH_2), 21.5 (CH_2), 21.4 (CH_2).

HRMS (CI, NH_3): *m*/*z* [M^+] calcd for $C_{21}H_{28}O_4$: 344.1988; found: 344.1992.

Compound **8**

Mixture of isomers (2:1).

IR ($CHCl_3$): 2935, 2859, 1679, 1613, 999, 867 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.23–7.26 (m, 2 H, ArH), 6.84–6.88 (m, 2 H, ArH), 4.42 [s, 2 H, OCH_2Ar (minor)], 4.41 [s, 2 H, OCH_2Ar (major)], 3.87–3.91 (m, 1 H, $OCHCH_2$), 3.85 [d, *J* = 11.3 Hz, 1 H, OCH_2 (major)], 3.79 (s, 3 H, OCH_3), 3.68 [d, *J* = 11.6 Hz, 1 H, OCH_2 (minor)], 3.58–3.61 (m, 1 H, $OCHCH_2$), 3.59 (d, *J* = 11.6 Hz, 1 H, OCH_2), 3.54 (d, *J* = 11.3 Hz, 1 H, CH_2), 3.40–3.47 (m, 2 H, CH_2OCH_2Ar), 2.35 (m, 1 H, O=CCHC*H*), 1.84–1.97 (m, 2 H, $CH_2CH_2CH_2CH_2$, $OCHCH_2CH_2$), 1.55–1.78 (m, 7 H, $OCHCH_2CH_2$, $OCHCH_2CH_2$, $CH_2CH_2CH_2CH_2$, $CH_2CH_2CH_2CH_2$, O=CC*H*CH), 1.25–1.38 (m, 4 H, $CH_2CH_2CH_2CH_2$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 207.8 (C), 207.4 (C), 159.1 (C), 130.7 (C), 129.2 (CH), 113.7 (CH), 82.1 (CH), 78.7 (CH), 72.5 (CH_2), 72.4 (CH_2), 69.7 (CH_2), 69.4 (CH_2), 67.8 (CH_2), 62.1 (CH_2), 55.3 (CH_3), 39.0 (CH), 37.9 (CH), 29.0 (CH_2), 28.7 (C), 28.6 (CH_2), 25.9 (CH_2), 25.7 (CH_2), 25.5 (CH_2), 24.6 (CH), 24.3 (CH_2), 23.2 (CH), 23.1 (CH_2), 21.1 (CH_2), 20.4 (CH_2).

HRMS (CI, CH_4): *m*/*z* [M^+] calcd for $C_{21}H_{28}O_4$: 344.1988; found: 344.1985.

(2*R*,5*R*)-2-[3-(Benzyloxy)propyl]-5-cyclohex-1-en-1-yl-3-methyltetrahydrofuran-3-ol (9)

Methyllithium (1.60 M solution in Et_2O, 345 μL, 0.552 mmol) was added dropwise over 5 min to a solution of the ketone **6** (95 mg, 0.28 mmol, 2:1 mixture of diastereoisomers) in anhyd toluene (4 mL) at –78 °C under Ar. The reaction was stirred for 16 h, being allowed to warm to r.t. during this period. The reaction was quenched with water (5 mL) at 0 °C and the mixture was extracted with Et_2O (3 × 10 mL). The combined Et_2O extracts were washed with water (10 mL) and brine (8 mL), and then dried ($MgSO_4$) and concentrated in vacuo to give an oil. Flash column chromatography on silica gel (hexane–EtOAc, 9:1 → 1:1) gave the alcohol **9** (59 mg, 60%, ca. 90% based on isomer composition of ketone **6**) as a colourless oil; $[\alpha]_D^{21}$ +10.5 (*c* = 1.0, $CHCl_3$).

IR ($CHCl_3$): 2936, 2860, 2838, 1612, 996, 914 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.26 (d, *J* = 8.6 Hz, 2 H, ArH), 6.87 (d, *J* = 8.6 Hz, 2 H, ArH), 5.82 (br, 1 H, C=CH), 4.44 (s, 2 H, OCH_2Ar), 4.17–4.20 (m, 1 H, OC*H*C=CH), 3.80 (s, 3 H, OCH_3),

3.44–3.56 (m, 2 H, CH_2OPMB), 3.41 (dd, J = 3.7, 8.8 Hz, 1 H, OC*H*CH_2CH_2), 2.10 (dd, J = 9.0, 13.4 Hz, 1 H, CH_2CHC=CH), 2.01–2.04 (m, 2 H, C=CHCH_2), 1.87–1.96 (m, 2 H, CH_2C=CH), 1.89 (dd, J = 5.6, 13.4 Hz, 1 H, CH_2CHC=CH), 1.82 (br, 1 H, OH), 1.53–1.75 (m, 8 H, OCHCH_2CH_2, CH_2CH_2CH_2C$H_2$$CH_2$), 1.26 (s, 3 H, CCH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.1 (C), 138.7 (C), 130.8 (C), 129.3 (CH), 121.8 (CH), 113.8 (CH), 86.4 (CH), 79.5 (CH), 78.5 (C), 72.6 (CH_2), 70.1 (CH_2), 55.3 (CH_3), 46.0 (CH_2), 27.1 (CH_2), 25.1 (CH_2), 24.9 (CH_2), 24.6 (CH_2), 23.1 (CH_3), 22.6 (CH_2), 22.5 (CH_2).

HRMS (CI, CH_4): m/z [M^+] calcd for $C_{22}H_{32}O_4$: 360.2301; found: 360.2315.

Anal. Calcd for $C_{22}H_{32}O_4$ (360.49): C, 73.30; H, 8.95. Found: C, 73.15; H, 8.87.

(2*R*,3*S*,5*R*)-5-Cyclohex-1-en-1-yl-2-[3-(4-methoxybenzyl)oxypropyl]-3-methyltetrahydrofuran-3-yl Acetate (10)

Ac_2O (864 μL, 9.15 mmol) was added to a solution of the alcohol **9** (660 mg, 1.83 mmol), DMAP (671 mg, 5.49 mmol) and Et_3N (2.04 mL, 14.6 mmol) in anhyd Et_2O (24 mL) at r.t. under Ar and the resulting solution was stirred for 20 h. Water (30 mL) was added and the mixture was extracted with Et_2O (3 × 50 mL). The Et_2O extracts were combined and washed with water (50 mL) and brine (30 mL), then dried ($MgSO_4$) and concentrated in vacuo to give an oil. Flash column chromatography on silica gel (PE–EtOAc, 19:1 → 4:1) gave the acetate **10** (570 mg, 77%) as a colourless oil; $[\alpha]_D^{21}$ –9.7 (c = 1.01, $CHCl_3$).

IR ($CHCl_3$): 2935, 2860, 2839, 1727, 1612, 997, 950, 909 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.26 (d, J = 8.7 Hz, 2 H, ArH), 6.87 (d, J = 8.7 Hz, 2 H, ArH), 5.72 (br, 1 H, C=CH), 4.46 (d, J = 11.6 Hz, 1 H, OCH_2Ar), 4.43 (d, J = 11.6 Hz, 1 H, OCH_2Ar), 4.14 (t, J = 7.7 Hz, 1 H, OC*H*C=CH), 3.80 (s, 3 H, OCH_3), 3.45–3.56 (m, 2 H, CH_2OPMB), 3.42 (dd, J = 4.5, 6.1 Hz, 1 H, OC*H*CH_2CH_2), 2.36 (dd, J = 7.9, 14.2 Hz, 1 H, CH_2CHC=CH), 2.23 (dd, J = 7.6, 14.2 Hz, 1 H, CH_2CHC=CH), 1.93–2.03 (m, 3 H, C=CHCH_2, CH_2C=CH), 1.98 (s, 3 H, CH_3C=O), 1.80–1.92 (m, 2 H, OCHCH_2CH_2, OCHCH_2CH_2), 1.48–1.76 (m, 7 H, OCHCH_2CH_2, OCHCH_2CH_2, CH_2C=CH, CH_2CH_2C$H_2$$CH_2$), 1.52 (s, 3 H, CCH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.6 (C), 159.1 (C), 137.0 (C), 130.8 (C), 129.2 (CH), 123.3 (CH), 113.8 (CH), 87.2 (CH), 86.5 (C), 80.7 (CH), 72.5 (CH_2), 70.0 (CH_2), 55.3 (CH_3), 42.7 (CH_2), 27.0 (CH_2), 25.7 (CH_2), 25.0 (CH_2), 23.8 (CH_2), 22.5 (CH_2), 22.5 (CH_2), 22.1 (CH_3), 21.8 (CH_3).

HRMS (CI, CH_4): m/z [M^+] calcd for $C_{24}H_{34}O_5$: 402.2406; found: 402.2388.

Anal. Calcd for $C_{24}H_{34}O_5$ (402.53): C, 71.61; H, 8.51. Found: C, 71.55; H, 8.43.

(2*R*,3*S*,5*R*)-5-Cyclohex-1-en-1-yl-2-(3-hydroxypropyl)-3-methyltetrahydrofuran-3-yl Acetate (11)

CAN (1.55 g, 2.83 mmol) was added to a solution of the PMB ether **10** (570 mg, 1.42 mmol) in MeCN (29 mL) and water (3.2 mL) at r.t. The resulting mixture was stirred at r.t. for 30 min, then diluted with water (30 mL) and EtOAc (30 mL). The aqueous layer was separated and extracted with EtOAc (3 × 50 mL). The EtOAc extracts were combined and washed with water (20 mL) and brine (20 mL), then dried ($MgSO_4$) and concentrated in vacuo to give an oil. Flash column chromatography on silica gel (PE–EtOAc, 3:1 → 2:1) gave the alcohol **11** (342 mg, 86%) as a colourless oil; $[\alpha]_D^{21}$ –10.3 (c = 0.68, $CHCl_3$).

IR ($CHCl_3$): 3425, 2933, 2860, 2839, 1728, 1000, 871 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.70 (br, 1 H, C=CH), 4.18 (dd, J = 7.7, 7.8 Hz, 1 H, OC*H*C=CH), 3.64–3.72 (m, 2 H, CH_2OH), 3.41–3.45 (m, 1 H, OC*H*CH_2CH_2), 2.54 (br, 1 H, OH), 2.40 (dd, J = 7.8, 14.3 Hz, 1 H, CH_2CHC=CH), 2.23 (dd, J = 7.7, 14.3 Hz, 1 H, CH_2CHC=CH), 1.94–1.99 (m, 2 H, C=CHCH_2), 1.97 (s, 3 H, CH_3C=O), 1.80–1.94 (m, 2 H, CH_2C=CH), 1.71–1.77 (m, 4 H, OCHCH_2CH_2), 1.50–1.65 (m, 4 H, CH_2CH_2C$H_2$$CH_2$), 1.52 (s, 3 H, CCH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.6 (C), 136.6 (C), 123.5 (CH), 87.7 (CH), 86.5 (C), 80.9 (CH), 63.0 (CH_2), 42.5 (CH_2), 30.5 (CH_2), 26.0 (CH_2), 25.0 (CH_2), 23.9 (CH_2), 22.5 (CH_2), 22.5 (CH_2), 22.1 (CH_3), 21.6 (CH_3).

HRMS (CI, NH_3): m/z [M^+ + H] calcd for $C_{16}H_{27}O_4$: 283.1909; found: 283.1901.

3-[(2*R*,3*S*,5*R*)-3-(Acetyloxy)-5-cyclohex-1-en-1-yl-3-methyltetrahydrofuran-2-yl]propanal (12)

Dess–Martin periodinane (771 mg, 1.82 mmol) was added in 3 portions at 30 min intervals to a solution of the alcohol **11** (342 mg, 1.21 mmol) in anhyd CH_2Cl_2 (17 mL) at 0 °C under Ar. The mixture was stirred for a further 1 h at r.t. and then quenched by the addition of sat. sodium thiosulfate solution (10 mL). The mixture was extracted with CH_2Cl_2 (3 × 30 mL) and the combined extracts were washed with sat. $NaHCO_3$ solution (20 mL), water (20 mL) and brine (20 mL). The extracts were dried ($MgSO_4$) and concentrated in vacuo to give a cloudy oil. Flash column chromatography on silica gel (PE–EtOAc, 9:1 → 4:1) gave the aldehyde **12** (282 mg, 83%) as a colourless oil; $[\alpha]_D^{21}$ –9.6 (c = 1.08, $CHCl_3$).

IR ($CHCl_3$): 2933, 2860, 2838, 1725, 996, 950, 892 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.83 (t, J = 1.3 Hz, 1 H, CHO), 5.71 (br, 1 H, C=CH), 4.16 (dd, J = 7.6, 8.0 Hz, 1 H, OC*H*C=CH), 3.47 (dd, J = 4.4, 8.3 Hz, 1 H, OC*H*CH_2CH_2), 2.73 (dddd, J = 1.3, 6.5, 7.8, 18.1 Hz, 1 H, $OCHCH_2CH_2$), 2.61 (dddd, J = 1.3, 7.2, 7.7, 18.1 Hz, 1 H, $OCHCH_2CH_2$), 2.37 (dd, J = 8.0, 14.2 Hz, 1 H, CH_2CHC=CH), 2.26 (dd, J = 7.6, 14.2 Hz, 1 H, CH_2CHC=CH), 1.90–2.04 (m, 5 H, OCHCH_2CH_2, CH_2C=CH, C=CHCH_2), 2.00 (s, 3 H, CH_3C=O), 1.81–1.88 (m, 1 H, CH_2C=CH), 1.50–1.66 (m, 4 H, $CH_2CH_2CH_2CH_2$), 1.55 (s, 3 H, CCH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 202.3 (CH), 170.4 (C), 136.7 (C), 123.4 (CH), 86.3 (CH), 86.2 (C), 80.8 (CH), 42.5 (CH_2), 41.1 (CH_2), 24.9 (CH_2), 23.7 (CH_2), 22.5 (CH_2), 22.5 (CH_2), 22.0 (CH_3), 21.7 (CH_3), 21.6 (CH_2).

HRMS (CI, CH_4): m/z [M^+] calcd for $C_{16}H_{24}O_4$: 280.1675; found: 280.1675.

(2*R*,3*S*,5*R*)-5-Cyclohex-1-en-1-yl-2-(4-diazo-3-oxo-butyl)-3-methyltetrahydrofuran-3-yl Acetate (13)

A solution of sodium chlorite (80%, 380 mg, 4.20 mmol) and sodium dihydrogenorthophosphate dihydrate (567 mg, 3.63 mmol) in water (5.6 mL) was added dropwise over 10 min to a solution of the aldehyde **12** (157 mg, 0.560 mmol) and 2-methyl-2-butene (475 μL, 4.48 mmol) in *t*-BuOH (2.8 mL). The reaction was stirred at r.t. for 90 min and then the volatile compounds were removed in vacuo. The mixture was diluted with water (10 mL) and the mixture was extracted with Et_2O (3 × 20 mL). The Et_2O extracts were combined and washed with water (20 mL) and brine (20 mL), and then dried ($MgSO_4$) and concentrated in vacuo to give the carboxylic acid as an oil.

The crude acid was dissolved in anhyd MeOH (6.5 mL) under Ar and MeONa (32 mg, 0.59 mmol) was added in one portion. The mixture was stirred for 15 min, concentrated in vacuo and dried for 1 h under high vacuum. The white solid was dissolved in anhyd benzene (6.5 mL) and oxalyl chloride (244 μL, 2.80 mmol) was added dropwise over 10 min at r.t. under Ar. The mixture was stirred for 2 h, concentrated in vacuo and diluted with CH_2Cl_2 (50 mL). The so-

lution was then added dropwise over 30 min to an ethereal solution of diazomethane (ca. 2.8 mmol in 16 mL of Et_2O) at 0 °C. The resulting mixture was stirred for 2 h and the excess diazomethane was then quenched with AcOH (2 mL). After 30 min the reaction mixture was diluted with Et_2O (50 mL) and washed with sat. $NaHCO_3$ solution (80 mL). The aqueous washings were extracted with Et_2O (2×10 mL) and the Et_2O extracts were combined and washed with water (80 mL) and brine (50 mL). The Et_2O extracts were dried ($MgSO_4$) and concentrated in vacuo to give an oil. Flash column chromatography (PE–EtOAc, 9:1 → 4:1) gave the diazo ketone **13** (138 mg, 77%) as a yellow oil; $[\alpha]_D^{21}$ –12.4 (c = 1.0, $CHCl_3$).

IR ($CHCl_3$): 2936, 2860, 2108, 1729, 1640, 1000, 952, 877 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 5.73 (br, 1 H, C=CH), 5.28 (br, 1 H, CHN_2), 4.17 (dd, J = 7.7, 7.9 Hz, 1 H, OC*H*C=CH), 3.45 (dd, J = 3.1, 9.6 Hz, 1 H, OC*H*CH_2CH_2), 2.52–2.63 (m, 1 H, OCHCH_2C*H*$_2$), 2.48–2.52 (m, 1 H, OCHCH_2C*H*$_2$), 2.38 (dd, J = 7.9, 14.2 Hz, 1 H, C*H*$_2$CHC=CH), 2.25 (dd, J = 7.7, 14.2 Hz, 1 H, C*H*$_2$CHC=CH), 1.91–2.06 (m, 5 H, OCHC*H*$_2$CH$_2$, C*H*$_2$C=CH, C=CHC*H*$_2$), 1.99 (s, 3 H, CH_3C=O), 1.90–1.82 (m, 1 H, C*H*$_2$C=CH), 1.65–1.52 (m, 4 H, CH_2C*H*$_2$C*H*$_2$CH$_2$), 1.55 (s, 3 H, CCH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 194.9 (C), 170.5 (C), 136.9 (C), 123.6 (CH), 86.4 (CH), 86.3 (C), 80.9 (CH), 54.5 (CH), 42.5 (CH_2), 37.8 (CH_2), 25.0 (CH_2), 24.3 (CH_2), 23.8 (CH_2), 22.6 (CH_2), 22.6 (CH_2), 22.1 (CH_3), 21.7 (CH_3).

HRMS (CI, CH_4): m/z [M^+ + H] calcd for $C_{17}H_{25}N_2O_4$: 321.1814; found: 321.1827.

(4a*R*,5*R*,9*R*,10*R*,12*Z*)-10-Methyl-6-oxo-1,2,3,4,4a,5,6,7,8,9,10,11-dodecahydro-5,9-epoxybenzo[10]annulen-10-yl Acetate [(*Z*)-15] and (1*R*,2*R*,4*R*,5*R*)-4-Cyclohex-1-en-1-yl-2-methyl-6-oxo-9-oxabicyclo[3.3.1]non-2-yl Acetate (16)

A solution of diazo ketone **13** (20 mg, 0.062 mmol) in anhyd CH_2Cl_2 (4 mL) was added dropwise over 5 min to a solution of copper(II) hexafluoroacetylacetonate (1.5 mg, 0.0031 mmol, 5.0 mol%) in anhyd CH_2Cl_2 (1 mL) at reflux under N_2. The reaction was stirred at reflux for 30 min, cooled to r.t. and concentrated in vacuo to give an oil. Flash column chromatography on silica gel (hexane–EtOAc, 4:1) gave the [1,2]-shift product **16** and the [2,3]-rearrangement product **15** (3:2, *E*:*Z* isomers) as an inseparable mixture of **15** and **16** (3:1, overall yield 15 mg, 83%).

AIBN (4.5 mg, 0.027 mmol) was added in 4 portions, over 4 h, to a solution of the alkene **15** (15 mg, 0.055 mmol) and ethanethiol (0.2 mL) in anhyd benzene (3 mL) at reflux under Ar. After this time the solution was cooled and concentrated in vacuo to give an oil. Flash column chromatography on silica gel (hexane–EtOAc, 4:1) gave a mixture of the [1,2]-shift product **16** (4 mg) and the fused tricyclic compound (*Z*)-**15** (7 mg, 64%). The products (oils) were separable by column chromatography (10% $AgNO_3$ absorbed on silica).

Compound (*Z*)-**15**

$[\alpha]_D^{20}$ +21.3 (c = 0.60, $CHCl_3$).

IR ($CHCl_3$): 2935, 1722, 1601, 874 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 5.49 (ddd, J = 2.3, 8.2, 8.4 Hz, 1 H, CH=C), 4.36 (dd, J = 6.9, 11.9 Hz, 1 H, OC*H*CH_2CH_2), 3.90 (d, J = 12.6 Hz, 1 H, OCHC=O), 2.72 (dd, J = 3.3, 12.6 Hz, 1 H, OCHC*H*), 2.54–2.65 (m, 3 H, C*H*$_2$CH=C, C*H*$_2$C=O), 2.46 (ddd, J = 6.3, 13.5, 17.7 Hz, 1 H, C*H*$_2$C=O), 1.90–2.26 (m, 5 H, OCHC*H*$_2$CH$_2$, CH=CC*H*$_2$, OCHCHC*H*$_2$), 1.97 (s, 3 H, CH_3C=O), 1.72–1.74 (m, 1 H, CH=CCH$_2$C*H*$_2$), 1.71 (s, 3 H, CCH_3), 1.55–1.58 (m, 1 H, OCHCHCH$_2$C*H*$_2$), 1.40–1.48 (m, 2 H, OCHCHC*H*$_2$, OCHCHCH$_2$C*H*$_2$), 1.26–1.32 (m, 1 H, CH=CCH$_2$C*H*$_2$).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 210.5 (C), 170.0 (C), 139.5 (C), 121.7 (CH), 87.4 (C), 79.8 (CH), 77.8 (CH), 39.9 (CH), 34.6 (CH_2), 31.8 (CH_2), 30.7 (CH_2), 25.9 (CH_2), 24.4 (CH_2), 22.6 (CH_3), 22.3 (CH_3), 21.1 (CH_2), 19.7 (CH_2).

HRMS (CI, NH_3): m/z [M^+ + H] calcd for $C_{17}H_{25}O_4$: 293.1753; found: 293.1743.

Compound **16**

$[\alpha]_D^{20}$ –23.2 (c = 0.65, $CHCl_3$).

IR ($CHCl_3$): 2934, 1728, 1602, 876 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 5.33–5.37 (m, 1 H, C=CH), 4.47–4.50 (m, 1 H, OC*H*CH_2CH_2), 4.21 (d, J = 5.9 Hz, 1 H, OCHC=O), 2.55–2.65 (m, 2 H, OCHC*H*, C*H*$_2$C=O), 1.95–2.33 (m, 7 H, C*H*$_2$C=O, OCHC*H*$_2$CH$_2$, OCHCHC*H*$_2$, C*H*$_2$C=CH, C=CHC*H*$_2$), 2.02 (s, 3 H, CH_3C=O), 1.85 (t, J = 13.6 Hz, 1 H, OCHCHC*H*$_2$), 1.77 (s, 3 H, CCH_3), 1.76–1.79 (m, 1 H, C*H*$_2$C=CH), 1.66–1.73 (m, 1 H, CH_2C*H*$_2$CH$_2$CH$_2$), 1.51–1.62 (m, 3 H, CH_2C*H*$_2$CH$_2$CH$_2$, CH_2CH_2C*H*$_2$CH$_2$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 209.1 (C), 170.1 (C), 134.7 (C), 122.1 (CH), 81.3 (C), 79.1 (CH), 71.4 (CH), 42.8 (CH), 35.7 (CH_2), 33.5 (CH_2), 28.4 (CH_2), 25.3 (CH_2), 23.0 (CH_2), 22.9 (CH_3), 22.4 (CH_2), 22.2 (CH_3), 21.7 (CH_2).

HRMS (CI, CH_4): m/z [M^+] calcd for $C_{17}H_{24}O_4$: 292.1675; found: 292.1662.

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