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Tetrahydropyran synthesis by palladium(II)-catalysed hydroxycarbonylation of hexenols: synthesis of (±)-diospongin A and (+)-civet cat compound

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ABSTRACT

A diastereoselective synthesis of 2,6-*cis*-tetrahydropyranyl acetic acids has been developed based on the palladium(II)-catalysed intramolecular hydroxycarbonylation of hexenols. This domino Pd-cyclisation/carbonylation/hydroxylation of (2*S*)-hept-6-en-2-ol **15** and *O*-TBDPS protected 1-phenylhex-5-en-1,3-diol **12**, respectively, was used as a key step in the total syntheses of two natural products, civet cat (+)-2-[(2*S*,6*S*)-(6-methyltetrahydro-2*H*-pyran-2-yl)] acetic acid **1** and diospongin A **2**. Moreover, an efficient synthesis of **2** using a multi Pd-cyclisation/carbonylation/cross-coupling transformation has been achieved.

1. Introduction

The synthesis and medicinal chemistry of substituted tetrahydropyrans have attracted considerable attention due to the prevalence of the THP-ring backbone in natural products and biologically active compounds.[1] The *cis*-2,6-substituted tetrahydropyran ring features in a large variety of biologically interesting natural products, such as (+)-2-[(2*S*,6*S*)-(6-methyltetrahydro-2*H*-pyran-2-yl)] acetic acid **1** and diospongin A **2** (Fig 1). The acetic acid derivative **1** was isolated by Maurer and co-workers from perianal glandular pheromone secretion of the African civet cat (*Vivierra civetta*).[2] Together with ambergris, castoreum and musk, it is one of the few very expensive animal perfume materials.[3] Diospongin A **2**, along with its 2-epimer diospongin B, have been found in rhizomes of *Dioscorea spongiosa*.[4] Both diastereomers have been showed to exhibit an inhibitory activity against the bone resorption induced by parathyroid hormone in a bone organ culture. Several synthetic-strategies have already been employed for construction of 2,6-*cis*-disubstituted THP-rings of diospongin A[5] and the civet compound,[6] including an intramolecular oxa-Michael addition,[5c] Prins reaction,[5d,e,6j] tandem cross-metathesis/termal S_N2'reaction,[5h] palladium-catalysed cyclisation of hept-2-ene-1,5,7-triols,[5f] and Pd(II)-catalysed methoxycarbonylation.[6a]

Recently we described the Pd(II)-catalysed oxycarbonylative lactonisation of unsaturated polyols with an α-allylic hydroxyl group[7] and its application in natural product synthesis.[8] In the course of our long term program directed towards the exploitation of Pd-catalysed oxidative carbonylation in domino reactions, we have been interested in the transformation of homoallylic alcohols. In this paper we report on the new intramolecular hydroxycarbonylation of hex-5-enols and its application in the synthesis of civet compound **1** and diospongin A **2**.

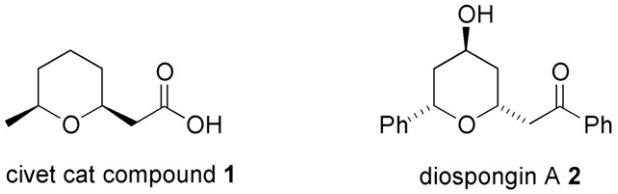

Fig. 1. Structures of diospongin A and civet cat compound.

2. Results and discussion

The intramolecular Pd(II)-catalysed oxidative carbonylation is of interest due to the facility of its incorporation into the multi-transformation processes. Early examples of such domino reactions include: Pd(II)-promoted cyclisation–methoxycarbonylation[6a,9] and/or intramolecular alkoxylation–lactonisation[10] as described for alkenols and 5-aminoalkenes providing heterocycles or fused

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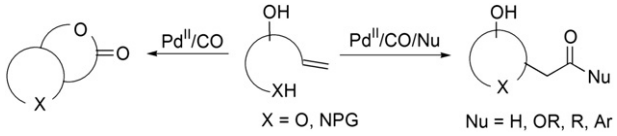
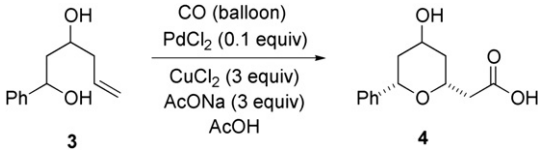
bicyclic lactones. Intermediate acylpalladium complexes are trapped by a second nucleophile, usually the solvent or react intramolecularly to give the product. Recently, oxidative formylation and ketonylation of alkenyl amines and alkenyl alcohols were found,[11] in which intermediate Pd-acyl species were transmetallated by a suitable organometallic reagent affording aldehydes or ketones (Scheme 1).



Scheme 1. Pd(II)-catalysed oxycarbonylations of unsaturated polyols.

As a part of our recent project dealing with the synthesis of tetrahydropyran derivatives, we discovered the reaction of 1-phenylhex-5-en-1,3-diol **3** with palladium(II) chloride (catalyst, 0.1 equiv), copper(II) chloride (oxidant, 3 equiv) and sodium acetate (buffer, 3 equiv) in acetic acid under carbon monoxide at normal pressure and rt. This system, used in various Pd(II)-catalysed reactions earlier,[7,8,10] had been shown to be advantageous for carbonylative bicyclisation. Surprisingly, we obtained diastereomeric 2-tetrahydropyranyl acetic acids **4**, products of hydroxycarbonylation (Scheme 2).



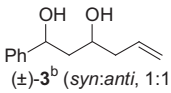
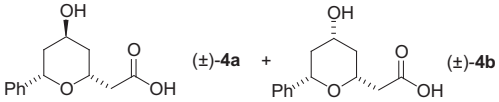
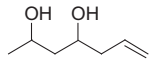
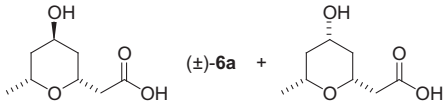
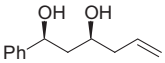
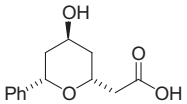
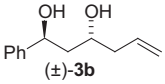
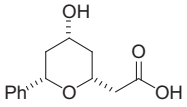
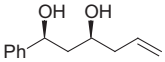
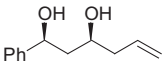
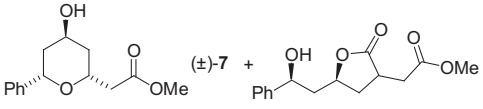
Scheme 2. Pd(II)-catalysed hydroxycarbonylation of 1-phenylhex-5-en-1,3-diol.

With this unexpected initial result, we decided to perform screening of the substrate scope of the reaction and composition of the catalytic mixture. Thus, we scrutinised the influence of the nature of the *O*-protecting group, catalyst/re-oxidant and solvent on the yield of **4** as well as the diastereoselectivity of hydroxycarbonylation. The results are summarised in Table 1.

In all successful cases (entries 1–4, 10), the predominant formation of 2,6-*cis*-THP-rings with high diastereoselectivity was observed.[12] All diastereomers of the unprotected 1-phenyl and 1-methyl diols **3**, **5** were found to participate efficiently in this process providing THP-ring containing acetic acids **4**, **6** in good yields (entries 1–4). The catalytic system based on $PdCl_2$–$CuCl_2$ in AcOH worked well (entries 1–4, 10), while employment of $Pd(OAc)_2$-BQ in THF totally failed (entry 5). Interestingly, a solvent change from AcOH to MeOH had an expressive effect on the course of the reaction. The diols **3a** and **9** were transformed to the lactones **8** and **10**, respectively, instead to the expected sole tetrahydropyranyl methyl acetate[6a,9] **7** (entries 6–8). Moreover, using acetic acid as a solvent after preliminary migration of the benzyl group, the 3-*O*-benzyl protected diol **9** provided only the biscarbonylation product **11** (entry 9). Likewise, the hexe-5-en-1,3-diols proved viable substrates for carbonylation, leading to lactones with incorporation of 2 equiv of carbon monoxide. This constitutes a new mode of the carbonylation path of α,γ-diols that has only been observed in the reaction of α,β-diols.[7b] The benzyl protecting group having failed, *O*-silyl protection was tested. However, although the *tert*-butyldiphenylsilyl moiety was more stable for deprotection, the yield of **13** dropped (entry 10).

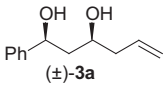
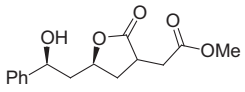
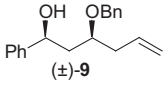
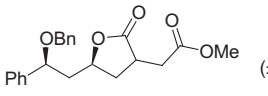
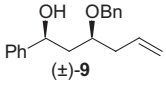
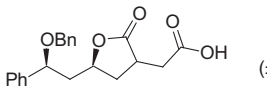
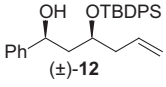
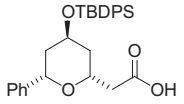
As a demonstration of the utility of the intramolecular hydroxycarbonylation reaction for one-pot synthesis, we applied the transformation to the synthesis of the civet cat compound **1**. The synthesis commenced with a regioselective ring-opening of the

Table 1
Pd(II)-catalysed oxycarbonylation of hex-5-enols

Entry	Substrate	Conditions	Product(s)	Yield %	dr[a]
1	 (±)-**3**[b] (*syn*:*anti*, 1:1)	$PdCl_2$ (0.1 equiv), $CuCl_2$ (3 equiv), AcONa (3 equiv), AcOH, CO (balloon), rt, 22 h	 (±)-**4a** + (±)-**4b**	63	>20:1
2	 (±)-**5**[b] (*syn*:*anti*, 1:1)	$PdCl_2$ (0.1 equiv), $CuCl_2$ (3 equiv), AcONa (3 equiv), AcOH, CO (balloon), rt, 20 h	 (±)-**6a** + (±)-**6b**	53	>20:1
3	 (±)-**3a**	$PdCl_2$ (0.1 equiv), $CuCl_2$ (3 equiv), AcONa (3 equiv), AcOH, CO (balloon), rt, 12 h	 (±)-**4a**	88	>20:1
4	 (±)-**3b**	$PdCl_2$ (0.1 equiv), $CuCl_2$ (3 equiv), AcONa (3 equiv), AcOH, CO (balloon), rt, 12 h	 (±)-**4b**	65	>20:1
5	 (±)-**3a**	$Pd(OAc)_2$ (0.1 equiv), benzoquinone (2.5 equiv), THF, CO (balloon), rt to rfx, 7 days	decomposition	—	—
6	 (±)-**3a**	$PdCl_2$ (0.1 equiv), $CuCl_2$ (3 equiv), AcONa (3 equiv), MeOH, CO (balloon), rt, 72 h	 (±)-**7** + (±)-**8**	26 32	>20:1 2:1

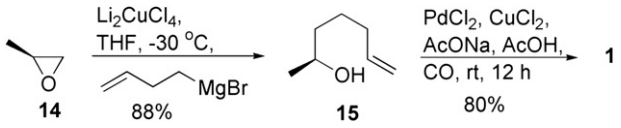
(*continued on next page*)

Table 1 (*continued*)

Entry	Substrate	Conditions	Product(s)	Yield %	dr[a]
7	 (±)-**3a**	$PdCl_2$ (0.1 equiv), $CuCl_2$ (3 equiv), AcONa (3 equiv), MeOH, CO (balloon), 40 °C, 10 h	 (±)-**8**	62	2:1
8	 (±)-**9**	$PdCl_2$ (0.1 equiv), $CuCl_2$ (3 equiv), AcONa (3 equiv), MeOH, CO (balloon), rt, 3 days	 (±)-**10**	59	2:1
9	 (±)-**9**	$PdCl_2$ (0.1 equiv), $CuCl_2$ (3 equiv), AcONa (3 equiv), AcOH, CO (balloon), rt, 3 days	 (±)-**11**	73	>20:1
10	 (±)-**12**	$PdCl_2$ (0.1 equiv), $CuCl_2$ (3 equiv), AcONa (3 equiv), AcOH, CO (balloon), rt, 12 h	 (±)-**13**	40	>20:1

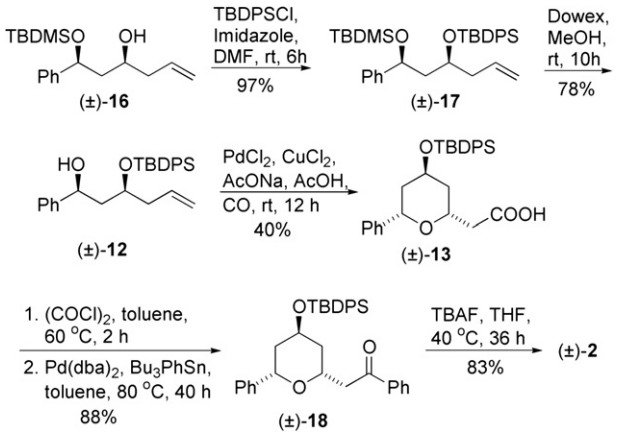
[a] Dr of 2,6-*cis* to 2,6-*trans*-derivatives determined by ^{1}H NMR analysis on crude reaction mixtures.
[b] Commercially available.

commercially available epoxide **14** to give (2*S*)-hept-6-en-2-ol **15**,[6g] followed by Pd(II)-catalysed hydroxycarbonylation to produce target compound **1** in 70% overall yield (Scheme 3). Synthetic **1**, $[\alpha]_D^{25}$ +21.9 (*c* 1.108, $CHCl_3$), lit.,[6g] $[\alpha]_D^{31}$ +20 (*c* 1.23, $CHCl_3$), lit.,[6h] $[\alpha]_D^{25}$ +26 (*c* 0.18, $CHCl_3$), lit.,[6k] $[\alpha]_D^{25}$ +21 (*c* 0.3, $CHCl_3$), showed physical and spectroscopic data corresponding to the reported values.[2,6]



Scheme 3. Synthesis of the civet cat compound **1**.

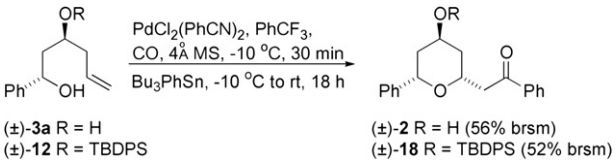
This new domino transformation was also applied to the synthesis of dispongin A (Scheme 4). The key *syn*-diol **12** was obtained from the known homoallylic alcohol **16**[5c] by a series of simple protection and deprotection steps with high yields. The allylic alcohol function was first protected as a TBDPS ether followed by selective cleavage of the TBDMS-protecting group with strong acidic Dowex in methanol to afford **12** (76% over two steps). Hydroxycarbonylation of partially protected diol **12** with carbon monoxide in acetic acid using $PdCl_2$ gave exclusively 2,6-*cis*-diastereomer **13** in moderate yield (entry 10, Table 1,). Next, the carboxylic acid **13** was subjected to a two-step sequence in one-pot to convert the carboxylic function to the ketone. Chlorination of **13**



Scheme 4. Synthesis of dispongin A **2**.

with oxalyl chloride in toluene, followed by the Stille[13] coupling with Bu_3PhSn in the presence of $Pd(dba)_2$ (0.2 equiv) afforded **18** in 88% yield over two steps. Finally, deprotection of **18** using TBAF in THF gave the target molecule **2** (83%).

In order to improve the efficiency of the diospongin synthesis, we decided to explore the utility of the ketonylation methodology[11] for obtaining required tetrahydropyranylmethyl phenyl ketone. Both partially protected and unprotected *syn*-diols **3a** and **12**, respectively, were exposed to $PdCl_2(PhCN)_2$ (1.05 equiv) and Bu_3PhSn in α,α,α-trifluorotoluene under carbon monoxide at −10 °C for 18 h (Scheme 5). The domino reaction of **3a** and **12** under Lambert's reaction conditions proceeded smoothly to provide the corresponding 2,6-*cis*-THP ketones **2** and **18** with excellent diastereoselectivity (dr>20:1). In fact, utilisation of this process as a key step of the synthesis rapidly enhanced the access to target molecule.



Scheme 5. Pd(II)-catalysed ketonylation of 1-phenylhex-5-en-1,3-diol.

3. Conclusions

In summary, we have explored the palladium(II)-catalysed intramolecular hydroxycarbonylation of hexenols. The domino Pd-cyclisation/carbonylation/hydroxylation reaction provides a new synthetic tool for the stereoselective synthesis of 2,6-*cis*-tetrahydropyranyl acetic acids. The capability of such a domino process has been demonstrated in the short and efficient syntheses of two natural products, civet compound (+)-2-[(2*S*,6*S*)-(6-methyltetrahydro-2*H*-pyran-2-yl)] acetic acid **1** (two steps, 70% yield) and diospongin A **2** (five steps, 22% from **16**).

Next, Pd(II)-catalysed carbonylative ketonylation[11] of hex-5-en-1,3-diols has been explored and applied to a markedly shortened and improved synthesis of diospongin A (56% br sm from **3a**).

The method presents a practical entry to diverse THP-based natural compounds and analogues. A special feature of these methods is that no protection/deprotection of the hydroxyl groups is necessary.

4. Experimental section

4.1. General methods

Commercial reagents were used without further purification. All solvents were distilled before use. Hexanes refer to the fraction boiling at 60–65 °C. Dowex 50 ionic resin was used in acidic H^+ form. Flash column liquid chromatography (FLC) was performed on silica gel Kieselgel 60 (40–63 μm, 230–400 mesh) using Buchi Sepacore® preparative MPLC system and analytical thin-layer chromatography (TLC) was performed on aluminium plates precoated with either 0.2 mm (DC-Alufolien, Merck) or 0.25 mm silica gel 60 F_{254} (ALUGRAM® SIL G/UV_{254}, Macherey–Nagel). The compounds were visualised by UV fluorescence and by dipping the plates in an aqueous H_2SO_4 solution of cerium sulfate/ammonium molybdate followed by charring with a heat-gun. Optical rotations were measured with a JASCO P-2000 polarimeter and are given in units of 10^{-1} deg cm^2 g^{-1}. High resolution mass spectra (HRMS) were recorded on a Q-Tof PremierTM mass spectrometer with nanoACQUITY UPLCTM (Waters), and are accurate to ±3 ppm. Elemental analyses were run on FISONS EA1108 instrument. FTIR spectra were obtained on a Nicolet 5700 spectrometer (Thermo Electron) equipped with a Smart Orbit (diamond crystal ATR) accessory, using the reflectance technique (4000–400 cm^{-1}). ^1H and ^{13}C NMR spectra were recorded on either 300 (75) MHz MercuryPlus or 600 (150) MHz Unity Inova spectrometers from Varian. Chemical shifts (δ) are quoted in parts per million and are referenced to the tetramethylsilane (TMS) as internal standard.

4.2. (±)-(1*S*,3*S*)-1-Phenylhex-5-en-1,3-diol[(±)-3a]

Dowex 50 (2 g) was added to a solution of TBDMS ether (±)-**16**[5c] (457 mg, 1.575 mmol) in ethanol (10 mL). The mixture was stirred vigorously overnight; Dowex was then filtered off, washed with EtOH and the washings concentrated. The crude product was purified by flash chromatography (50% AcOEt/hexanes) affording unprotected diol (±)-**3a** as an off-white solid (280 mg, 93%); R_f 0.5 (50% AcOEt/hexanes); ν_{max} (ATR) 3252, 2891, 1640, 1065, 1032, 1002, 916, 757, 702, 648, 588 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.66–1.82 (m, 2H, H-2), 2.13–2.19 (m, 2H, H-4), 3.84–3.94 (m, 1H, H-3), 4.82 (dd, 1H, $J_{1,2A}$ 4.5, $J_{1,2B}$ 8.5 Hz, H-1), 4.99–5.03 (m, 1H, H-6A), 5.05 (m, 1H, H-6B), 5.64–5.79 (m, 1H, H-5), 7.15–7.30 (m, 5H, Ph); δ_C (75 MHz, $CDCl_3$) 42.4, 44.7 (all t, C-2, C-4), 71.5, 75.1 (all d, C-1, C-3), 118.3 (t, C-6), 125.6, 127.5, 128.4, (all d, Ph), 134.1 (d, C-5), 144.3 (s, *i*-Ph). HRMS (ESI^+) *m*/*z* found 215.1088 ($[M+Na]^+$, $C_{12}H_{16}NaO_2^+$ requires 215.1048).

4.3. Synthesis of (±)-(1*S*,3*R*)-1-phenylhex-5-en-1,3-diol [(±)-3b]

The title compound was obtained from **16**[5c] using Shi's[14] protocol for inversion of secondary alcohol in two steps.

*4.3.1. Mesylation of (±)-**16**.* To the solution of **16** (200 mg, 0.652 mmol) and pyridine (192 μL, 2.39 mmol) in CH_2Cl_2 (6 mL) methanesulfonyl chloride (53 μL, 0.685 mmol) was added dropwise at 0 °C. Reaction mixture was allowed to warm to rt and then heated up to 40 °C for 24 h. Mixture was concentrated, redissolved in CH_2Cl_2 washed with water and with brine, dried over $MgSO_4$ and concentrated. After flash chromatography (5% EtOAc in hexanes) the corresponding mesylate was obtained (217 mg, 86%) as a slightly yellow oil; R_f 0.5 (10% AcOEt/hexanes); ν_{max} (ATR) 2954, 2928, 2856, 1643, 1357, 1335, 1333, 1172, 1085, 902, 835, 776, 701, 526 cm^{-1}; δ_H (300 MHz, $CDCl_3$) −0.19, 0.04 (2× s, 6H, $Si(CH_3)_2$), 0.88 (s, 9H, $C(CH_3)_3$), 2.01 (ddd, 1H, $J_{2A,3}$=$J_{1,2A}$ 6.2, $J_{2A,2B}$ 13.8 Hz, H-2A), 2.23 (ddd, 1H, $J_{2B,3}$=$J_{1,2B}$ 6.4 $J_{2A,2B}$ 13.8 Hz, H-2B), 2.44 (ddd, 1H, $J_{3,4A}$=$J_{4A,5}$ 7.1, $J_{4A,4B}$ 14.6 Hz, H-4A), 2.60 (m, 1H, H-4B), 2.89 (s, 3H, SO_2CH_3), 4.74–4.84 (m, 2H, H-3, H-1), 5.11–5.20 (m, 2H, H-6), 5.70–5.87 (m, 1H, H-5), 7.20–7.38 (m, 5H, Ph); δ_C (75 MHz, $CDCl_3$) −5.1, −4.6 (all q, $Si(CH_3)_2$), 18.1 (s, $C(CH_3)_3$), 25.8 (q, $C(CH_3)_3$), 38.6 (q, SO_2CH_3), 38.9, 44.9 (all t, C-2, C-4), 71.6, 79.6 (all d, C-1, C-3), 119.1 (t, C-6), 126.1, 127.5, 128.3, 132.3 (all d, Ph, C-5), 143.8 (s, *i*-Ph). HRMS (ESI^+) *m*/*z* found 402.2128 ($[M+NH_4]^+$, $C_{19}H_{36}NO_4SSi^+$ requires 402.2134).

4.3.2. Nucleophilic displacement of the mesyl group. A mixture of Et_3N (0.234 μL, 1.69 mmol) and benzoic acid (414 mg, 3.39 mmol) were stirred in toluene (1 mL) at rt. After 30 min mesylate (217 mg, 0.564 mmol) was added and mixture was stirred at 80 °C for 5 days. After being cooled down to rt, the reaction mixture was diluted with toluene (5 mL) and washed successively with aqueous HCl solution (2 M, 2 mL), aqueous K_2CO_3 solution (10%, 3 mL) and brine (10 mL). After the organic solution was dried over anhydrous $MgSO_4$, the solvent was removed by distillation in vacuo to give the crude product, which was purified by flash chromatography to afford corresponding benzoate (126 mg, 64%) as a colourless oil; R_f 0.9 (10% AcOEt/hexanes); ν_{max} (ATR) 2953, 2928, 2856, 1716, 1693, 1643, 1451, 1269, 1096, 1068, 1026, 835, 776, 709, 700, 686 cm^{-1}; δ_H (300 MHz, $CDCl_3$) −0.32, −0.08 (2× s, 6H, $Si(CH_3)_2$), 0.85 (s, 9H, $C(CH_3)_3$), 1.97–2.03 (m, 2H, H-2), 2.45–2.53 (m, 2H, H-4), 4.77 (m, 1H, H-1), 5.02–5.10 (m, 2H, H-6), 5.31–5.41 (m, 1H, H-3), 5.73–5.89 (m, 1H, H-5), 7.17–7.33 (m, 5H, Ph), 7.40–7.48 (m, 2H, Ph), 7.51–7.59 (m, 1H, Ph), 8.02–8.07 (m, 2H, Ph); δ_C (75 MHz, $CDCl_3$) −5.3, −4.6 (all q, $Si(CH_3)_2$), 18.0 (s, $C(CH_3)_3$), 25.8 (q, $C(CH_3)_3$), 39.1, 45.2 (all t, C-2, C-4), 71.5, 71.8 (all d, C-1, C-3), 118.0 (t, C-6), 125.8, 127.2, 128.2, 128.3, 129.4, 130.1, 132.7, 133.3 (all d, Ph, C-5), 130.8, 145.4 (all s, *i*-Ph), 166.0 (s, CO). HRMS (ESI^+) *m*/*z* found 411.2387 ($[M+H]^+$, $C_{25}H_{35}O_3Si^+$ requires 411.2355).

*4.3.3. (±)-(1S,3R)-1-Phenylhex-5-en-1,3-diol[(±)-**3b**].* To the solution of benzoate (60 mg, 0.146 mmol) in MeOH (5 mL) sodium methoxide (24 mg, 0.44 mmol) was added. Mixture was stirred at rt for 24 h, then 5 days at 40 °C. After reaction was completed Dowex 50 (2 g) was added and mixture was stirred until complete conversion (TLC control). When finished, reaction mixture was filtered off, concentrated and the crude product purified by flash chromatography to yield unprotected *anti*-diol **3b** (19 mg, 68%) as a gel oil; R_f 0.3 (40% AcOEt/hexanes); ν_{max} (ATR) 3253, 3063, 2950, 2924, 1639, 1494, 1454, 1065, 1002, 909, 757, 702, 667, 605, 558 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.85–1.93 (m, 2H, H-2), 2.23–2.31 (m, 2H, H-4), 3.87–3.97 (m, 1H, H-3), 5.05 (dd, 1H, $J_{1,2A}$ 3.7, $J_{1,2B}$ 7.7 Hz, H-1), 5.08–5.16 (m, 2H, H-6), 5.70–5.85 (m, 1H, H-5), 7.22–7.38 (m, 5H, Ph); δ_C (75 MHz, $CDCl_3$) 41.9, 44.0 (all t, C-2, C-4), 68.0, 71.6 (all d, C-1, C-3), 118.4 (t, C-6), 125.5, 125.7, 127.3, 128.4 (all d, Ph), 134.3 (d, C-5), 144.4 (s, *i*-Ph). HRMS (ESI^+) *m*/*z* found 215.1094 ($[M+Na]^+$, $C_{12}H_{16}O_2Na^+$ requires 215.1048).

4.4. Synthesis of (±)-(1*S*,3*S*)-3-Benzyloxy-1-phenylhex-5-en-1-ol [(±)-9]

The title compound was obtained in two steps, benzylation of (±)-**16** followed by removal of TBDMS-protecting group.

*4.4.1. Benzylation of (±)-**16**.* A suspension of hexanes washed NaH (60% in paraffin, 157 mg, 3.92 mmol, 1.2 equiv) in dry DMF (5 mL) was cooled to −30 °C and the solution of (±)-**16**[5c] (1 g, 3.26 mmol) in DMF (5 mL) was added dropwise over 10 min. The resulting mixture was stirred for 15 min and benzyl bromide (470 μL, 3.92 mmol, 1.2 equiv) was added at once via syringe. The reaction was left to stir at rt for 5 h, quenched with water (20 mL) and extracted with ether (4×10 mL). Combined organic layers were washed with water (2×10 mL) to remove DMF, dried over

anhydrous $MgSO_4$ and concentrated. The remainder was purified by flash chromatography (silica gel, hexanes). Yield of benzyl-protected diol was 1.2 g (93%), colourless oil; R_f 0.8, (10% EtOAc/hexanes); ν_{max} (ATR) 2936, 2860, 1639, 1453, 1087, 1061, 1020, 760, 699 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.01, 0.03 (2× s, 6H, $Si(CH_3)_2$), 0.87 (s, 9H, $C(CH_3)_3$), 1.79 (ddd, 1H, $J_{3,A}$ 5.4, $J_{4,5}$ 6.7, $J_{A,4}$ 14.0 Hz, H-2A or H-4A), 2.05 (ddd, 1H, $J_{3,B}$ 5.5, $J_{B,5}$ 8.2, $J_{A,B}$ 13.8 Hz, Hz, H-2B or H-4B), 2.08–2.18 (m, 1H, H-2A or H-4A) 2.22–2.34 (m, 1H, H-2B or H-4B), 3.82 (qd, 1H, $J_{2B,3}$=$J_{3,4A}$=$J_{3,4B}$=5.6, $J_{2A,3}$ 11.2 Hz, H-3), 4.21 (d, 1H, J 11.9 Hz, CH_2Ph), 4.42 (d, 1H, J 11.7 Hz, CH_2Ph), 4.44 (dd, 1H, $J_{1,2A}$ 2.8, $J_{1,2B}$ 5.4 Hz, H-1), 4.93–5.04 (m, 2H, H-6), 5.71–5.87 (m, 1H, H-5) 7.22–7.40 (m, 10H, 2× Ph); δ_C (75 MHz, $CDCl_3$) −4.5, −4.2 (all q, $Si(CH_3)_2$), 18.1 (s, $C(CH_3)_3$), 25.0 (q, $C(CH_3)_3$), 41.4, 45.4 (all t, C-2, C-4), 70.1 (t, CH_2Ph), 69.0, 78.1 (all d, C-1, C-3), 116.8 (t, C-6), 126.9, 127.4, 127.6, 127.8, 128.3, 128.5 (all d, Ph), 135.2 (d, C-5), 138.5, 142.3 (all s, *i*-Ph). HRMS (ESI^+) *m*/*z* found 397.2590 ($[M+H]^+$, $C_{25}H_{37}O_2Si^+$ requires 397.2563).

*4.4.2. (±)-(1S,3S)-3-Benzyloxy-1-phenylhex-5-en-1-ol [(±)-**9**].* For removal of the TBDMS-group the benzylated diol (1.2 g, 3.03 mmol) was dissolved in MeOH (20 mL), then Dowex 50 (4.5 g) was added and the mixture was stirred vigorously at rt. After 12 h Dowex was filtered off, washed with methanol and resulting solution was concentrated. The crude product was purified by flash chromatography (10% AcOEt/hexanes) to give (±)-**9** as a colourless oil (854 mg, 88%); R_f 0.3 (10% AcOEt/hexanes); ν_{max} (ATR) 3445, 3063, 3029, 2912, 2865, 1640, 1494, 1454, 1086, 1063, 1025, 996, 759, 699, 627, 568 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.77 (ddd, 1H, $J_{2A,3}$ 2.0, $J_{1,2A}$ 3.8, $J_{2A,2B}$ 14.6 Hz, H-2A), 1.97 (td, 1H, $J_{2B,3}$=$J_{1,2B}$ 9. 8, $J_{2A,2B}$ 14.6 Hz, H-2B), 2.10–2.31 (m, 2H, H-4), 3.73 (s, 1H, OH), 3.87 (m, 1H, H-3), 4.25 (d, 1H, J 11.5 Hz, CH_2Ph), 4.45 (d, 1H, J 11.5 Hz, CH_2Ph), 4.60 (dd, 1H, $J_{1,2A}$ 3.8, $J_{1,2B}$ 9.9 Hz, H-1), 5.01–5.10 (m, 2H, H-6), 5.72–5.88 (m, 1H, H-5) 7.23–7.43 (m, 10H, 2× Ph); δ_C (75 MHz, $CDCl_3$) 41.9, 44.5 (all t, C-2, C-4), 70.5 (t, CH_2Ph), 70.8, 82.1 (all d, C-1, C-3), 117.4 (t, C-6), 126.6, 127.8, 127.9, 128.0, 128.5, 128.6 (all d, Ph), 134.7 (d, C-5), 137.6, 141.4 (all s, *i*-Ph). HRMS (ESI^+) *m*/*z* found 305.1508 ($[M+Na]^+$, $C_{19}H_{22}NaO_2^+$ requires 305.1517).

4.5. (±)-(1S,3S)-1-(*tert*-Butydimethylsilyloxy)-3-(*tert*-butydiphenylsilyloxy)-1-phenylhex-5-ene [(±)-17]

TBDPSCl (425 μL, 1.63 mmol, 1 equiv) was added dropwise to the solution of (±)-**16** (500 mg, 1.63 mmol) and imidazole (297 mg, 4.36 mmol, 2.7 equiv) in dry DMF (5 mL). The resulting mixture was stirred for 6 h then water (10 mL) was added and the mixture extracted with ether (4×10 mL). Combined organic layers were washed with water (3×10 mL) to remove DMF, dried over anhydrous $MgSO_4$ and concentrated. The product was purified by flash chromatography (1% AcOEt/hexanes) and isolated as colourless oil (862 mg, 97%); R_f 0.9 (10% AcOEt/hexanes); ν_{max} (ATR) 2928, 2856, 1639, 1427, 1104, 1089, 1061, 835, 775, 699, 505 cm^{-1}; δ_H (300 MHz, $CDCl_3$) −0.3, −0.1 (2× s, 6H, $Si(CH_3)_2$), 0.77, 1.07 (2× s, 18H, 2× $C(CH_3)_3$), 1.78 (ddd, 1H, $J_{1,2A}$ 5.0, $J_{2A,3}$ 7.8, $J_{2A,2B}$ 13.8 Hz, H-2A), 1.97 (ddd, 1H, $J_{2B,3}$ 5.0, $J_{1,2B}$ 8.5, $J_{2A,2B}$ 13.7 Hz, H-2B), 2.19 (ddd, 1H, $J_{3,4A}$ 4.6, $J_{4A,5}$ 7.7, $J_{4A,4B}$ 14.0 Hz, H-4A), 2.34 (td, 1H, $J_{3,4B}$=$J_{4B,5}$ 6.0, $J_{4A,4B}$ 14.1 Hz, H-4B), 3.95 (qd, 1H, $J_{2B,3}$=$J_{3,4A}$=$J_{3,4B}$ 5.1, $J_{2A,3}$ 7.9 Hz, H-3), 4.68 (dd, 1H, $J_{1,2A}$ 4.9, $J_{1,2B}$ 8.5 Hz, H-1), 4.97 (br d, 1H, $J_{5,6A}$ 17.0 Hz, H-6A), 5.00 (br d, 1H, $J_{5,6B}$ 10.0 Hz, H-6B), 5.79 (dddd, 1H, $J_{4B,5}$ 6.5, $J_{4A,5}$ 7.7, $J_{5,6B}$ 10.3, $J_{5,6A}$ 16.8 Hz, H-5), 7.07–7.12 (m, 2H, Ph), 7.17–7.27 (m, 3H, Ph), 7.32–7.45 (m, 6H, Ph), 7.65–7.71 (m, 4H, Ph); δ_C (75 MHz, $CDCl_3$) −5.0, −4.5 (all q, $Si(CH_3)_2$), 18.0, 19.4 (all s, 2× $C(CH_3)_3$), 25.8, 27.1 (all q, 2× $C(CH_3)_3$), 40.5, 46.9 (all t, C-2, C-4), 70.0, 72.4 (all d, C-1, C-3), 117.0 (t, C-6), 126.0, 126.9, 127.4, 127.5, 127.9, 129.4 (all d, Ph, C-5), 134.4, 134.5 (all s, *i*-Ph), 134.7, 135.9 (all d, Ph, C-5), 145.3 (s, *i*-Ph). HRMS (ESI^+) *m*/*z* found 545.3322 ($[M+H]^+$, $C_{34}H_{49}O_2Si_2^+$ requires 545.3271).

4.6. (±)-(1S,3S)-3-(*tert*-Butydiphenylsilyloxy)-1-phenylhex-5-en-1-ol [(±)-12]

Dowex 50 (2 g) was added to a solution of silylated diol (±)-**17** (824 mg, 1.512 mmol) in methanol (10 mL). After 10 h vigorous stirring at rt the ionex was filtered off, washed with MeOH and solution was concentrated. The crude product was purified by flash chromatography (10% AcOEt/hexanes). The yield of (±)-**17** as a colourless oil: 510 mg (78%); R_f 0.5 (10% AcOEt/hexanes); ν_{max} (ATR) 3419, 2929, 2856, 1639, 1427, 1105, 1062, 1028, 998, 822, 738, 700, 611, 506 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.09 (s, 9H, $C(CH_3)_3$), 1.85–1.93 (m, 2H, H-2), 2.08–2.22 (m, 2H, H-4), 4.00–4.11 (m, 1H, H-3), 4.72–4.94 (m, 3H, H-1, H-6), 5.47–5.64 (m, 1H, H-5) 7.22–7.35 (m, 5H, Ph), 7.35–7.50 (m, 6H, Ph), 7.70–7.80 (m, 4H, Ph); δ_C (75 MHz, $CDCl_3$) 19.3 (s, $C(CH_3)_3$), 27.0 (q, $C(CH_3)_3$), 41.8, 45.1 (all t, C-2, C-4), 72.9, 73.1 (all d, C-1, C-3), 117.6 (t, C-6), 125.7, 127.3, 127.6, 127.7, 128.3, 129.7, 129.9, 133.9, 134.0, 135.9 (all d, Ph, C-5), 133.4, 134.8, 144.5 (all s, *i*-Ph). HRMS (ESI^+) *m*/*z* found 453.2271 ($[M+Na]^+$, $C_{28}H_{34}NaO_2Si^+$ requires 453.2226).

4.7. (*S*)-Hept-6-ene-2-ol (15)

Following the procedure given by Ley and co-workers,[6g] a solution of (*S*)-propylene oxide (269 mg, 4.63 mmol) in dry THF (8 mL) was cooled to −30 °C and the catalytic amount of freshly prepared Li_2CuCl_4 (0.463 mmol) in THF (5 mL) was added followed by dropwise addition of the freshly prepared butenylmagnesium bromide (6.945 mmol) in dry THF (15 mL). After 40 min the reaction was quenched at −30 °C by the addition of aqueous solution of NH_4Cl (6 mL). After warming up to rt the mixture was extracted with Et_2O (3×10 mL), combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated. The crude product was purified by distillation on Kugelrohr (20 mbar, 100 °C). Product was isolated as a colourless liquid in 88% yield (465 mg); $[\alpha]_D^{25}$ 11.5 (*c* 1.43, $CHCl_3$), lit.,[6g] $[\alpha]_D^{31}$ +6.5 (*c* 1.60, $CHCl_3$). Spectral data were in accordance with those previously reported.[6g]

4.8. General procedure for Pd(II)-catalysed hydroxycarbonylation of hexenols

A 25 mL flask equipped with side inlet with stopcock was charged with AcONa (anhydrous, 3 equiv), $CuCl_2$ (anhydrous, 3 equiv), and $PdCl_2$ (0.1 equiv). The flask was evacuated; filled with CO via balloon and solution of substrate (1.0 equiv) in glacial AcOH (10–15 mL) was added. The mixture was vigorously stirred at rt under CO atmosphere (balloon) until the colour of the mixture changed from green to pale brown. The reaction mixture was diluted with EtOAc, filtered through a bed of Celite and concentrated. Crude product was extracted between 1% water solution of NH_3 and EtOAc. Water layer was then acidified with aqueous HCl (5%) and released free acid was extracted with EtOAc (3×). Purification by flash column chromatography on silica afforded the appropriate compound.

*4.8.1. (±)-(2′R,4′S,6′S)-(4′-Hydroxy-6′-phenyltetrahydropyran-2′-yl)-acetic acid [(±)-**4a**].* Following the general procedure the mixture of AcONa (384 mg, 4.68 mmol), $CuCl_2$ (630 mg, 4.68 mmol), $PdCl_2$ (30 mg, 0.156 mmol) and *syn*-diol (±)-**3a** (300 mg, 1.56 mmol) in AcOH (15 mL) was stirred at rt for 12 h under CO atmosphere. Workup in the described manner gave residue that was purified by flash column chromatography (66% AcOEt/hexanes) to yield title compound (±)-**4a** (320 mg, 88%) as a viscous oil; R_f 0.3 (50% AcOEt/hexanes); ν_{max} (ATR) 3392, 3060, 3031, 2918, 1706, 1378, 1213, 1190, 1166, 1082, 1054, 979, 753, 697, 531 cm^{-1}; δ_H (600 MHz, acetone-d_6) 1.58 (dt, 1H, $J_{3A',4'}$ 5.0, $J_{3A',3B'}$=$J_{2',3A'}$ 13.5 Hz, H-3A′), 1.65 (ddd, 1H, $J_{4'5A'}$ 5.0, $J_{5'A,6'}$ 11, $J_{5A',5B'}$ 13.5 Hz, H-5A′), 1.84 (br dd, 1H, $J_{3B',4'}$ 2.0, $J_{3A',3B'}$ 13.5 Hz, H-3B′), 1.92 (br dd, 1H, $J_{4'5B'}$ 1.9,

$J_{5A',5B'}$ 13.3 Hz, H-5B′), 2.47 (dd, 1H, $J_{2A,2'}$ 5.0, $J_{2A,2B}$ 15.3 Hz, H-2A), 2.54 (dd, 1H, $J_{2B,2'}$ 8.0, $J_{2A,2B}$ 15.3 Hz, H-2B), 4.28 (m, 1H, H-4′), 4.47 (m, 1H, H-2′), 4.91 (br d, 1H, $J_{5A',6'}$ 11 Hz, H-6′), 7.21 (t, 1H, *J* 7.3 Hz, Ph), 7.29 (t, 2H, *J* 7.5 Hz, Ph), 7.34 (d, 2H, *J* 7.4 Hz, Ph); δ_C (150 MHz, acetone-d_6) 39.4 (t, C-3′), 42.2 (t, C-5′), 42.7 (t, C-2), 65.3 (d, C-2′), 70.9 (d, C-4′), 75.3 (d, C-6′), 127.5, 128.6, 129.8 (all d, Ph), 144.3 (s, *i*-Ph), 173.8 (s, C-1). HRMS *m*/*z* calcd for $C_{13}H_{17}O_4^+$: 237.1127, found 237.1169 $[M+H]^+$.

*4.8.2. (±)-(2′R,4′R,6′S)-(4′-Hydroxy-6′-phenyltetrahydropyran-2′-yl)-acetic acid [(±)-**4b**].* According to general procedure: mixture of *anti*-diol (±)-**3b** (100 mg, 0.52 mmol), AcONa (128 mg, 1.56 mmol), $CuCl_2$ (210 mg, 1.56 mmol), and $PdCl_2$ (10 mg, 0.052 mmol) in AcOH (5 mL); reaction at rt for 12 h; after flash column chromatography (10% MeOH/CH_2Cl_2) a viscous oil was obtained. The yield of (±)-**4b** (80 mg, 65%); R_f 0.7 (10% MeOH/CH_2Cl_2); ν_{max} (ATR) 3350, 2921, 1709, 1372, 1240, 1184, 1151, 1043, 989, 756, 698, 605 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.33 (t, 1H, $J_{3A',3B'}$=$J_{2',3A'}$ 11.4 Hz, H-3A′), 1.48 (t, 1H, $J_{5A',5B'}$=$J_{5A',6'}$ 11.5 Hz, H-5A′), 2.05–2.23 (m, 2H, H-3B, H-5B), 2.55 (dd, 1H, $J_{2A,2'}$ 5.7, $J_{2A,2B}$ 15.7 H-2A), 2.73 (dd, 1H, $J_{2B,2'}$ 7.2, $J_{2A,2B}$ 15.8 Hz, H-2B), 3.88–4.03 (m, 2H, H-2′, H-4′), 4.39 (dd, 1H, $J_{5B',6'}$, 1.9, $J_{5A',6'}$ 11.5 Hz, H-6′), 7.24–7.35 (m, 5H, Ph); δ_C (75 MHz, $CDCl_3$) 40.1 (t, C-3′), 40.7 (t, C-5′), 42.2 (t, C-2), 67.9, 72.1 (all d, C-2′, C-4′), 77.6 (d, C-6′), 125.8, 127.7, 128.4 (all d, Ph), 141.3 (s, *i*-Ph), 175.5 (C-1). HRMS *m*/*z* calcd for $C_{13}H_{20}NO_4^+$: 254.1392, found 254.1422 $[M+NH_4]^+$.

*4.8.3. (±)-(2′R,4′S,6′S)-(4′-Hydroxy-6′-methyl-tetrahydropyran-2′-yl)-acetic acid [(±)-**6a**] and (±)-(2′R,4′R,6′S)-(4′-hydroxy-6′-methyl-tetrahydropyran-2′-yl)-acetic acid [(±)-**6b**].* Following the general procedure; the mixture of diasteromers (*syn*/*anti* 1:1) (±)-**5** (200 mg, 1.536 mmol), $PdCl_2$ (27 mg, 0.154 mmol), $CuCl_2$ (619 mg, 4.609 mmol), AcONa (378 mg, 4.609 mmol) in AcOH (8 mL); reaction at rt for 20 h; after flash chromatography (silica gel, elution with 50% AcOEt/hexanes); fraction **2** (R_f 0.1) gave analytically pure **6** (140 mg, 53%, colourless oil). The product consisted of a 2:1 mixture of **6a**/**6b** as determined by ^{1}H NMR; [Found: C, 55.24; H, 8.08. $C_8H_{14}O_4$ requires C, 55.16; H, 8.0]; ν_{max} (ATR) 3402, 3090, 2972, 2936, 2642, 1717, 1419, 1381, 1242, 1201, 1174, 1109, 1078, 1059, 1006, 989 cm^{-1}; δ_H (600 MHz, $CDCl_3$) for **6a** (major isomer): 1.19 (d, 3H, $J_{6',Me}$ 6.2 Hz, Me), 1.47 (ddd, 1H, $J_{3A',4'}$ 2.9, $J_{2',3A'}$ 11.5, $J_{3A',3B'}$ 14.2 Hz, H-3A′), 1.52 (ddd, 1H, $J_{4',5A'}$ 2.9, $J_{5A',6'}$ 11.5, $J_{5A',5B'}$ 14.2 Hz, H-5A′), 1.70 (dddd, 1H, $J_{2',3B'}$=$J_{3B',5B'}$ 2.1, $J_{3B',4'}$ 3.1, $J_{3A',3B'}$ 14.1 Hz, H-3B′), 1.75 (dddd, 1H, $J_{4',5B'}$=$J_{5B',6'}$ 2.1, $J_{4',5B'}$ 3.1, $J_{5A',5B'}$ 14.1 Hz, H-5B′), 2.47 (dd, 1H, $J_{2A,2'}$ 5.4, $J_{2A,2B}$ 15.7 Hz, H-2A), 2.58 (dd, 1H, $J_{2B,2'}$ 7.6, $J_{2A,2B}$ 15.7 Hz, H-2B), 4.01 (ddq, 1H, $J_{5B',6'}$ 2.0, $J_{Me,6'}$ 6.2, $J_{5A',6'}$ 11.6 Hz H-6′), 4.25 (dddd, 1H, $J_{2',3B}$ 2.0, $J_{2A,2'}$ 5.4, $J_{2B,2'}$ 7.6, $J_{2',3A'}$ 11.8 Hz, H-2′), 4.27 (m, 1H, H-4′); δ_H for **6b** (minor isomer): 1.23 (d, 3H, $J_{6',Me}$ 6.2 Hz, Me), 1.14–1.44 (m, 2H, H-3A′, H-5A′), 1.96 (dddd, 1H, $J_{2',3B'}$=$J_{3B',5B'}$ 2.0, $J_{3B',4'}$ 4.7, $J_{3A',3B'}$ 12.5 Hz, H-3B′), 2.03 (dddd, 1H, $J_{3B',5B'}$=$J_{5B',6'}$ 2.0, $J_{4',5B'}$ 4.7, $J_{5A',5B'}$ 12.5 Hz, H-5B′), 2.31 (dd, 1H, $J_{2A,2'}$ 5.4, $J_{2A,2B}$ 15.7 Hz, H-2A), 2.65 (dd, 1H, $J_{2B,2'}$ 7.6, $J_{2A,2B}$ 15.7 Hz, H-2B), 3.53 (ddq, 1H, $J_{5B',6'}$ 2.0, $J_{Me,6'}$ 6.2, $J_{5A',6'}$ 11.0 Hz H-6′), 3.78 (dddd, 1H, $J_{2',3B'}$ 2.0, $J_{2A,2'}$ 5.4, $J_{2B,2'}$ 7.6, $J_{2',3A'}$ 11.4 Hz, H-2′), 3.85 (dddd, 1H, $J_{3B',4'}$=$J_{4',5B'}$4.7, $J_{3A',4'}$=$J_{4',5A'}$ 11.0 Hz, H-4′); δ_C (150 MHz, $CDCl_3$, mixture of **6a**/**6b**) 21.6, 21.7 (all q, Me), 37.7, 39.6, 40.4, 40.7, 40.8, 42.3 (all t, C-3′, C-5′, C-2), 64.3, 67.6, 68.2, 68.4, 71.7, 72.1 (all d, C-2′, C-4′, C-6′), 174.7, 174.9 (all s, C-1).

*4.8.4. [5′-(2″-Benzyloxy-2″-phenylethyl)-2′-oxo-tetrahydrofuran-3′-yl]-acetic acid [(±)-**11**].* The general procedure was followed: benzylated diol (±)-**9** (147 mg, 0.52 mmol), AcONa (128 mg, 1.56 mmol), $CuCl_2$ (210 mg, 1.56 mmol), $PdCl_2$ (10 mg, 0.052 mmol) in AcOH (5 mL); reaction at rt for 3 days; after purification by flash chromatography (30% AcOEt/hexanes) a single diastereomer (±)-**11** was obtained (131 mg, 72%) as a viscous oil; R_f 0.2 (50% AcOEt/hexanes); ν_{max} (ATR) 3271, 2918, 2850, 1776, 1738, 1713, 1454, 1088, 1065, 1026, 1012, 699, 541 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.81 (ddd, 1H, $J_{1A'',5'}$ 5.7, $J_{1A'',2''}$ 7.5, $J_{1A'',1B''}$ 13.6 Hz, H-1A″), 1.91 (ddd, 1H, $J_{5',4A'}$ 4.4, $J_{4A',3'}$ 9.1, $J_{4A',4B'}$ 13.1 Hz, H-4A′), 2.10 (ddd, 1H, $J_{5'4B'}$ 3.4, $J_{4B',3'}$ 9.6, $J_{4A',4B'}$ 12.9 Hz, H-4B′), 2.28 (ddd, 1H, $J_{1B'',2''}$ 6.8, $J_{1B'',5'}$ 8.2, $J_{1A'',1B''}$ 14.2 Hz, H-1B″), 2.48 (dd, 1H, Hz, $J_{2A,3'}$ 8.5, $J_{2A,2B}$ 17.4 Hz, H-2A), 2.75 (dd, 1H, $J_{2B,3'}$ 4.2, $J_{2A,2B}$ 17.4 Hz, H-2B), 2.92 (dddd, 1H, $J_{2B,3'}$ 4.2, $J_{2A,3'}$=$J_{4A',3'}$=$J_{4B',3'}$ 9.3 Hz, H-3′), 4.13 (d, 1H, *J* 12.9 Hz, CH_2Ph), 4.28–4.38 (m, 2H, H-5′, CH_2Ph), 4.42 (t, 1H, $J_{1A'',2''}$=$J_{1B'',2''}$=7.1 Hz, H-2″) 7.10–7.55 (m, 10H, Ph); δ_C (75 MHz, $CDCl_3$) 32.6 (t, C-4′), 34.5 (t, C-2), 35.1 (d, C-3′), 43.3 (t, C-1″), 70.4 (t, CH_2Ph), 75.7 (d, C-5′), 77.8 (d, C-2″), 127.0, 127.7, 127.8, 128.2, 128.4, 128.7 (all d, Ph), 137.9, 140.5 (all s, *i*-Ph), 176.2, 177.8 (all s, 2× CO). HRMS *m*/*z* calcd for $C_{21}H_{26}NO_5^+$: 372.1811, found 372.1842 $[M+NH_4]^+$.

*4.8.5. (±)-(2′R,4′S,6′S)-(4′-tert-Butyldiphenylsilyloxy-6′-phenyl-tetrahydropyran-2′-yl)-acetic acid [(±)-**13**].* According to general procedure: mixture of diol (±)-**12** (223 mg, 0.52 mmol), AcONa (128 mg, 1.56 mmol), $CuCl_2$ (210 mg, 1.56 mmol) and $PdCl_2$ (10 mg, 0.052 mmol) in AcOH (5 mL); reaction at rt for 12 h; after flash column chromatography (10% AcOEt/hexanes) a viscous oil was obtained. Yield of (±)-**13** (101 mg, 40%); R_f 0.2 (10% AcOEt/hexanes); ν_{max} (ATR) 3068, 2928, 2855, 1684, 1597, 1427, 1104, 1058, 1026, 998, 741, 698, 505 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.13 (s, 9H, $C(CH_3)_3$), 1.44 (t, 1H, $J_{2'3A'}$=$J_{3A',3B'}$ 12.5 Hz, H-3A′), 1.56 (dd, 1H, $J_{5'A,6'}$ 10.7, $J_{5A',5B'}$ 13.5 Hz, H-5A′), 1.74 (br d, 1H, $J_{3A',3B'}$ 13.2 Hz, H-3B′), 1.84 (br d, 1H, $J_{5A',5B'}$ 13.5 Hz, H-5B′), 2.52 (dd, 1H, $J_{2A,2'}$ 5.4, $J_{2A,2B}$ 15.7 Hz, H-2A), 2.68 (dd, 1H, $J_{2B,2'}$ 7.5, $J_{2A,2B}$ 15.7 Hz, H-2B), 4.29 (br s, 1H, H-4′), 4.62 (m, 1H, H-2′), 5.1 (br d, 1H, $J_{5A',6'}$ 10.7 Hz, H-6′), 7.20–7.72 (m, 15H, 3× Ph); δ_C (75 MHz, $CDCl_3$) 19.3 (s, $C(CH_3)_3$), 27.0 (q, $C(CH_3)_3$), 38.0 (t, C-3′), 40.5 (t, C-5′), 41.0 (t, C-2), 65.8 (d, C-4′), 69.0 (d, C-2′), 74.2 (d, C-6′), 125.7, 127.3, 127.7, 128.3, 129.8, 135.7 (all d, Ph), 133.7, 133.8, 142.3 (all s, *i*-Ph), 175.9 (s, C-1). HRMS *m*/*z* calcd for $C_{29}H_{35}O_4Si^+$: 475.2305, found 475.2344 $[M+H]^+$.

*4.8.6. (+)-2-[(2S,6S)-(6-Methyltetrahydro-2H-pyran-2-yl)] acetic acid (civet cat compound) (**1**).* Following general procedure the mixture of AcONa (321 mg, 3.91 mmol), $CuCl_2$ (526 mg, 3.91 mmol), $PdCl_2$ (23 mg, 0.13 mmol) and alcohol **15** (149 mg, 1.3 mmol) in AcOH (10 mL) was stirred at rt for 12 h under CO atmosphere. Workup in the usual manner gave residue that was purified by flash column chromatography (50% AcOEt/hexanes) to yield title compound **1** (164 mg, 80%) as a yellow viscous oil; $[\alpha]_D^{25}$ +21.9 (*c* 1.108, $CHCl_3$), lit.,[6g] $[\alpha]_D^{31}$ +20 (*c* 1.23, $CHCl_3$), lit.,[6h] $[\alpha]_D^{25}$ +26 (*c* 0.18, $CHCl_3$), lit.,[6k] $[\alpha]_D^{25}$ +21 (*c* 0.3, $CHCl_3$); δ_H (300 MHz, $CDCl_3$) 1.19 (d, 3H, *J* 6.2 Hz, CH_3), 1.22–1.35 (m, 2H), 1.46–1.70 (m, 3H), 1.79–1.89 (m, 1H), 2.49 (ddd, 1H, *J* 1.0, *J* 5.1, *J* 15.7 Hz, H-2A), 2.58 (dd, 1H, *J* 7.6, *J* 15.7 Hz, H-2B), 3.51–3.58 (m, 1H), 3.73–3.83 (m, 1H). Physical and spectroscopic data were corresponding to the reported values.[2,6]

4.9. General procedure for Pd(II)-catalysed methoxycarbonylation of hexenols

Using the Semmelhack protocol[6a] for methoxycarbonylation a 25 mL flask with stopcock equipped side inlet was charged with $PdCl_2$ (10 mg, 0.052 mmol, 0.1 equiv), $CuCl_2$ (210 mg, 1.56 mmol, 3 equiv) and AcONa (128 mg, 1.56 mmol, 3 equiv). Diol (±)-**3a** (100 mg, 0.52 mmol) in MeOH (5 mL) was added and the flask was purged with CO from a balloon. The mixture was vigorously stirred under CO atmosphere overnight. Reaction mixture was diluted with EtOAc, filtered through a bed of Celite and concentrated. The residue was purified by chromatography (10% AcOEt/hexanes). Fraction 1, THP-derivative (±)-**7** (33 mg, 26%, a viscous oil); R_f 0.6 (10% AcOEt/hexanes). Fraction 2, a diastereomeric mixture of lactones (±)-**8** in the ratio 2:1 (46 mg, 32%) as a colourless oil; R_f 0.1 (10% AcOEt/hexanes).

*4.9.1. (±)-(2′R,4′S,6′S)-Methyl (4′-hydroxy-6′-phenyltetrahydropyran-2′-yl)-acetate [(±)-**7**].* Data of (±)-**7**; ν_{max} (ATR) 3435, 3030, 2949, 2918, 1732, 1437, 1192, 1055, 754, 699, 532 cm^{-1}; δ_H (600 MHz, $CDCl_3$) 1.65 (dt, 1H, $J_{3A',4'}$ 2.5, $J_{2',3A'}$=$J_{3A',3B'}$ 12.8 Hz, H-3A′), 1.65 (ddd, 1H, $J_{4',5A'}$ 2.5, $J_{5'A,6'}$ 11.7, $J_{5A',5B'}$ 14.0 Hz, H-5A′), 1.83 (br dd, 1H, $J_{2',3B'}$ 2.0, $J_{3A',3B'}$ 13.8 Hz, H-3B′), 1.93 (br dd, 1H, $J_{5B',6'}$ 2.0, $J_{5A',5B'}$ 14.0 Hz, H-5B′), 2.48 (dd, 1H, $J_{2A,2'}$ 6.1, $J_{2A,2B}$ 15.8 Hz, H-2A), 2.67 (dd, 1H, $J_{2B,2'}$ 7.1, $J_{2A,2B}$ 15.2 Hz, H-2B), 3.68 (s, 3H, Me), 4.36 (br s, 1H, H-4′), 4.45 (m, 1H, H-2′), 4.91 (dd, 1H, $J_{5B',6'}$ 1.5, $J_{5A'6'}$ 11.7 Hz, H-6′), 7.23–7.40 (m, 5H, Ph); δ_C (150 MHz, $CDCl_3$) 37.9 (t, C-3′), 40.0 (t, C-5′), 41.1 (t, C-2), 51.7 (q, Me), 64.6 (d, C-4′), 68.8 (d, C-2′), 73.5 (d, C-6′), 125.8, 127.3, 128.3 (all d, Ph), 142.6 (s, *i*-Ph), 171.6 (s, C-1). HRMS *m*/*z* calcd for $C_{14}H_{19}O_4^+$: 251.1283, found 251.1307 $[M+H]^+$.

*4.9.2. Methyl [5′-(2″-hydroxy-2″-phenylethyl)-2′-oxo-tetrahydrofuran-3′-yl]-acetate [(±)-**8**].* Data of (±)-**8**; ν_{max} (ATR) 3435, 3030, 2952, 1763,1732, 1437, 1372, 1266, 1196, 1169, 1026, 993, 761, 702, 560 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.87–2.32 (m, 4H), 2.45–2.60 (m, 1H), 2.62 (br s, 1H, OH), 2.73 (dd, 1H, *J* 4.2, *J* 17.0 Hz), 2.82–2.90 (m, 1H, minor) 2.97 (ddd, 1H, *J* 4.2, 9.2, 18.2 Hz, major), 3.61 (s, 3H, Me), 4.28 (ddd, 1H, *J* 5.2, 8.2, 10.4 Hz, H-5′ minor), 4.36–4.46 (m, 1H, H-5′ major), 4.75–4.86 (m, 1H, H-2″), 7.16–7.36 (m, 5H, Ph); δ_C (150 MHz, $CDCl_3$) 32.9 (major), 34.0 (minor), 34.5 (major), 35.0 (all t, C-2, C-4′ minor), 35.2 (major), 37.1 (all d, C-3′ minor), 44.2 (t, C-1″), 51.9 (minor), 52.0 (all q, Me major), 71.4, 76.3 (major), 76.7 (all d, C-2″, C-5′ minor), 125.9 (minor), 126.0 (major), 127.9, 128.6 (all d, Ph), 143.2 (major), 143.3 (all s, *i*-Ph minor), 171.5 (major), 171.6 (minor), 177.3 (minor), 177.8 (all s, 2× CO, major). HRMS *m*/*z* calcd for $C_{15}H_{22}NO_5^+$: 296.1498, found 296.1517 $[M+NH_4]^+$.

*4.9.3. Methyl [5′-(2″-benzyloxy-2″-phenylethyl)-2′-oxo-tetrahydrofuran-3′-yl]-acetate [(±)-**10**].* According to general procedure: mixture of diol (±)-**9** (147 mg, 0.52 mmol), AcONa (128 mg, 1.56 mmol), $CuCl_2$ (210 mg, 1.56 mmol) and $PdCl_2$ (10 mg, 0.052 mmol) in MeOH (5 mL); reaction at rt for 3 days; after flash column chromatography (10% AcOEt/hexanes) a viscous oil was obtained. Yield of (±)-**10** (112 mg, 59%); R_f 0.1 (10% AcOEt/hexanes); ν_{max} (ATR) 3030, 2951, 2866, 1768, 1735, 1454, 1436, 1257, 1198, 1168, 1090, 1067, 1012, 762, 738, 701 cm^{-1}; δ_H (300 MHz, $CDCl_3$, mixture of diasteromers in ratio 2:1) 1.83–2.06 (m, 2H), 2.19 (ddd, 1H, *J* 3.5, 9.5, 13.1 Hz) 2.30–2.58 (m, 2H), 2.80 (dd, 1H, *J* 4.2, 17.2 Hz), 2.85–3.07 (m, 1H), 3.67 (s, 3H, Me), 4.18–4.26 (m, 2H, CH_2Ph, H-3 minor), 4.36–4.46 (m, 2H, CH_2Ph, H-3 major) 4.48–4.58 (m, 1H, H-2″), 7.22–7.44 (m, 10H, Ph); δ_C (150 MHz, $CDCl_3$) 32.6 (major), 34.0 (minor), 34.5 (major), 34.8 (all t, C-2, C-4′, minor), 35.2 (major), 37.3 (all d, C-3′, minor), 43.2 (minor), 43.3 (all t, C-1″, major), 51.8 (minor), 51.9 (q, Me major), 70.3 (t, CH_2Ph), 75.4 (major), 75.9 (minor), 77.7 (minor), 77.8 (all d, C-5′, C-2″ major), 126.8 (minor), 126.9 (major), 127.6, 127.7, 128.0, 128.3, 128.6 (all d, Ph), 137.9, 140.5 (major), 140.6 (all s, *i*-Ph minor), 171.3 (major), 171.4 (minor), 177.2 (minor), 177.7 (all s, 2× CO major). HRMS *m*/*z* calcd for $C_{22}H_{25}O_5^+$: 369.1702, found 369.1699 $[M+H]^+$.

4.10. Ketone [(±)-18] from acid (±)-13

To the solution of (±)-**13** (100 mg, 0.211 mmol) in toluene (5 mL) oxalyl chloride (362 μL, 4.22 mmol) was added dropwise and reaction mixture was heated up and stirred at 80 °C for 2 h. Mixture was concentrated and crude chloride was dissolved in toluene (5 mL) then $Pd(dba)_2$ (24 mg, 0.042 mmol) and $PhSnBu_3$ (87 μL, 0.254 mmol) were added and mixture was heated at 80 °C overnight. After removal of solvent a colourless oil of (±)-**18** (100 mg, 88%) was obtained and without further purification used in the next step.

4.11. Diospongin A [(±)-2]

TBAF×$3H_2O$ (65 mg, 0.206 mmol) was added to the solution of (±)-**18** (55 mg, 0.103 mmol) in THF (2 mL). The mixture was stirred at 40 °C for 5 days, then concentrated and after chromatography diospongin (±)-**2** was isolated (25 mg, 83%); δ_H (300 MHz, $CDCl_3$) 1.56–1.75 (m, 2H), 1.89 (br d, 2H, *J* 13.7 Hz), 3.00 (dd, 1H, $J_{2A,2'}$ 6.9, $J_{2A,2B}$ 16.0 Hz, H-2A), 3.35 (dd, 1H, $J_{2B,2'}$ 5.8, $J_{2A,2B}$ 16.0 Hz, H-2B), 4.28–4.33 (m, 1H), 4.52–4.63 (m, 1H), 4.86 (dd, 1H, *J* 1.9, 11.7 Hz), 7.12–7.96 (m, 10H, Ph). The ^{13}C NMR and IR spectral data were in good agreement with those reported.[4,5]

4.12. General procedure for Pd(II)-catalysed ketonylation of hexenols

Following the procedure given by Lambert and co-workers,[11] a round-bottom flask with a magnetic stir bar was charged with $PdCl_2(PhCN)_2$ (1.05 equiv) and flame-dried, ground 4 Å MS (238 mg). The flask was evacuated and backfilled with CO via balloon (3×) and $PhCF_3$ (4 mL) was added. The mixture was cooled to −10 °C in a salt–ice bath and stirred in the CO atmosphere (balloon) for 30 min. A solution of a hexenol (1.0 equiv) in $PhCF_3$ (2 mL) was added. The mixture was stirred for 30 min tributylphenylstanane was then added at −10 °C and the mixture was stirred at this temperature overnight, then filtered through a plug of Celite and concentrated in vacuo. The product was purified by flash chromatography (AcOEt/hexanes).

*4.12.1. Compound [(±)-**18**].* Compound (±)-**18** (74 mg, 39%, 52% br sm) was obtained from (±)-**12** (200 mg, 0.464 mmol) as a colourless oil; R_f 0.7 (10% AcOEt/hexanes); ν_{max} (ATR) 3062, 2918, 1720, 1688, 1595, 1449, 1283, 1197, 1058, 1000, 978, 749, 700, 689, 530 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.9–1.9 (m, 13H, $C(CH_3)_3$, H-3′, H-5′), 3.00 (dd, 1H, $J_{2A,2'}$ 6.6, $J_{2A,2B}$ 15.4 Hz, H-2A), 3.39 (dd, 1H, $J_{2B,2'}$ 6.2, $J_{2A,2B}$ 15.4 Hz, H-2B), 4.29 (br s, 1H, H-4′), 4.82 (dddd, 1H, $J_{2',3B'}$ 1.1, $J_{2A,2'}$=$J_{2B,2'}$ 6.4, $J_{2',3A'}$, 11.2 Hz, H-2′), 5.08 (br d, 1H, $J_{5A',6'}$ 11.1 Hz, H-6′), 7.25–7.60 (m, 14H, Ph) 7.65–7.74 (m, 4H, Ph), 7.97–8.02 (m, 2H, Ph); δ_C (75 MHz, $CDCl_3$) 19.3 (s, $C(CH_3)_3$), 27.0 (q, $C(CH_3)_3$), 38.5, 40.7, 45.3 (all t, C-3′, C-5′, C-2), 66.1, 69.6, 73.9 (all d, C-4′, C-2′, C-6′), 125.7, 127.1, 127.6, 128.2, 128.4, 128.5, 129.7, 132.9, 135.7, 135.8 (all d, Ph), 133.9, 134.1, 137.4, 142.9 (s, *i*-Ph), 198.3 (s, C-1). HRMS *m*/*z* calcd for $C_{35}H_{39}O_3Si^+$: 535.2668, found 535.2677 $[M+H]^+$.

*4.12.2. Diospongin A [(±)-**2**].* Diospongin A (±)-**2** was prepared from (±)-**3a** (100 mg, 0.52 mmol) using $PdCl_2(PhCN)_2$ (200 mg, 0.52 mmol), tributylphenylstannane (187 μL, 0.572), 4 Å MS (250 mg) in $PhCF_3$ (5 mL). Purification by flash chromatography (10% AcOEt/hexanes) gave the product (±)-**2** (50 mg, 40%, 56% br sm) as a colourless oil; R_f 0.1 (20% AcOEt/hexanes); δ_H (300 MHz, $CDCl_3$) 1.62–1.81 (m, 2H), 1.92 (br dd, 2H, *J* 1.8, 14.0 Hz), 3.09 (dd, 1H, $J_{2A,2'}$ 6.9, $J_{2A,2B}$ 16.1 Hz, H-2A), 3.43 (dd, 1H, $J_{2B,2'}$ 5.8, $J_{2A,2B}$ 16.1 Hz, H-2B), 4.35–4.40 (m, 1H), 4.62–4.72 (m, 1H), 4.95 (dd, 1H, *J* 1.8, 11.8 Hz), 7.20–8.03 (m, 10H, Ph). HRMS *m*/*z* calcd for $C_{19}H_{21}O_3^+$: 297.1491, found 297.1503 $[M+H]^+$. The ^{13}C NMR and IR spectral data were in good agreement with those reported.[4,5]

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