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Biology-Oriented Synthesis of Stereochemically Diverse Natural-Product-Derived Compound Collections by Iterative Allylations on a Solid Support

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Abstract: A strategy aiming at the introduction of stereocenters into polymer-bound natural-product-derived and -inspired compound collections is presented. Treatment of immobilized aldehydes with Brown's pinene-derived allylboranes results in the stereoselective formation of homoallylic alcohols with up to 89% *ee* (*ee* = enantiomeric excess). Subsequent iterative ozonolysis–allylation sequences with up to three allylations on a solid support give access to 1,3-polyols with different relative configurations. Esterification with acryloyl chloride and final ring-closing metathesis yields α,β-unsaturated δ-lactones with multiply oxygenated side chains, a substructure found in a group of natural products with a broad range of biological activity. The flexibility of the approach is exemplified by the parallel synthesis of all eight diastereomers of cryptocarya diacetate on a solid support. The individual isomers are obtained in overall yields of 40–60% over 10 steps and with 63–85% diastereoselectivity for the major isomer.

Keywords: 1,3-polyols · asymmetric synthesis · natural products · solid-phase synthesis

Introduction

The use of small molecules for the study of biological phenomena lies at the heart of medicinal chemistry and chemical biology research.[1] To investigate the response of biological systems to variations of the chemical structure of a probe, synthesis strategies for rapid and efficient variation and diversification of the target compound are in high demand. Combinatorial chemistry may give access to compound collections with a high degree of substituent variation on a given scaffold. More recently, this concept was extended leading to molecule architectures with high skeletal diversity[2] for diversity-oriented synthesis (DOS)[3] and biology-oriented synthesis (BIOS),[4] and of natural-product-derived and -inspired compound collections.[2,4] BIOS refers to natural products as evolutionary selected starting points for compound-collection synthesis. Due to their biosynthetic origin and their manifold interactions with sterically defined protein structures, natural products exhibit a broad stereochemical complexity. Particularly, multiple stereocenters are present in many target molecules, which require steroselective methods for their synthesis. The fact that altering the stereochemistry of a given molecule can drastically change its overall shape, and consequently its biological profile, can be taken as an incentive for diversification. Beyond substituent and skeleton variation, we hypothesized that a systematic reconfiguration of individual stereocenters of a given molecule might be of additional benefit. We felt that the synthesis and biological evaluation of all diastereomeric isomers, that is, a stereocomplementary synthesis, might further enlighten the potency of a molecule in biological assays.

However, only in relatively few cases have compound collections been synthesized in which a set of stereochemical descriptors of a given scaffold was systematically varied to explore the full stereochemical "descriptor space" of a molecule. In such synthetic endeavors, powerful enantiocomple-

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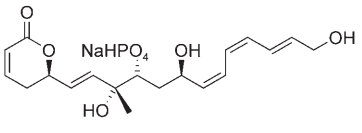
mentary transformations are indispensable which give access to stereoisomer libraries (for example, all diastereomers) of a given (natural) product and analogues thereof. Notably, Tietze et al. introduced stereoselective combinatorial synthesis employing enantiocomplementary chiral catalysts for the solution-phase synthesis of twelve stereoisomers of emetine[5] and Curran and co-workers prepared a sixteen-membered stereoisomer library of the pinesaw fly sex pheromone[6] as well as an eight-membered collection of Passifloricin in solution employing fluorous tagging en route as key technology.[7] Schreiber and co-workers synthesized a 4320-membered library of dihydropyrancarboxamides in both enantiomeric forms.[8]

For the synthesis of natural-product-inspired and -derived compound collections[4] solid-phase organic synthesis is a viable technology. Immobilization of the substrate on a polymeric carrier enables efficient and straightforward removal of all surplus reagents required in the multistep sequences typical for the synthesis of such compound collections and thereby facilitates purification of the desired compounds.

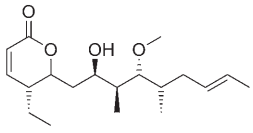
Thus, we[4,9] and others[10] have used this approach for the synthesis of different natural-product-derived and -inspired compound collections in >10 steps on the polymeric carrier. However, in general, to date only very few enantioselective synthetic methods have been developed for solid-phase synthesis in general.[11]

For instance, the generation of polyketide-type linear, functionalized carbon chains on a solid support was accomplished by Paterson et al.[12] and our group[13] by using an aldol-based strategy and by Panek et al. with chiral allylsilanes,[14] but applications of these transformations to the stereocomplementary synthesis of compound collections are still unknown.

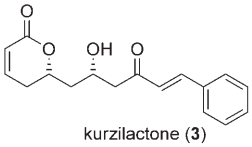
In the context of employing natural-product-inspired compound collections in chemical biology, we became interested in the synthesis and biological evaluation of natural-product-derived molecules which contain an α,β-unsaturated δ-lactone moiety. Such molecules can, for instance, act as Michael acceptors for nucleophilic protein side chains and display a broad range of biological properties. Fostriecin **1** is a



fostriecin (**1**)



pironetin (**2**)



kurzilactone (**3**)

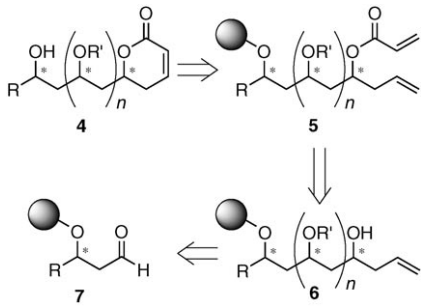
potent inhibitor of protein phosphatase 2 A,[15] pironetin **2** is an inhibitor of tubulin assembly.[16] Apart from these rather complex structures, structurally simpler natural products exist which also have biological activity, such as kurzilactone (**3**), which is cytotoxic to KB cells.[17] Many of these small molecules feature a carbon chain functionalized with at least one 1,3-diol unit.

In a preliminary communication,[18] we reported our work on stereocomplementary enantioselective reagent-controlled carbonyl allylation on the solid phase[19] employing chiral allylboranes[20] and applications to the synthesis of the natural product cryptocarya diacetate and all its stereoisomers.

Herein, we give a full record on the synthesis of stereochemically diverse 1,3-polyol collections on the solid phase and their use in the synthesis of different natural products and analogues thereof. The development of the allylation method as such on solid support is described in full in an accompanying article.[21]

Retrosynthetic Analysis

We planned to synthesize the target structures, such as **4**, by means of a ring-closing metathesis (RCM) reaction of the open acrylate **5** (Scheme 1). This approach is known from



Scheme 1. Retrosynthetic analysis of the target dehydrolactones.

different solution-phase approaches towards this class of molecules.[22] Iterative cycles of allylation, protection, and ozonolysis should deliver the molecular skeleton, such as **6**, with the correct and predictable stereochemical pattern. The appropriate starting point of such a sequence would be an immobilized aldehyde **7**. Along with the availability of the D- and L-enantiomers of Ipc_2BAll, the stereochemical space around the *syn*/*anti*-1,3-polyol-based α-pyrone natural products can be explored rapidly once the sequence is established on solid support.

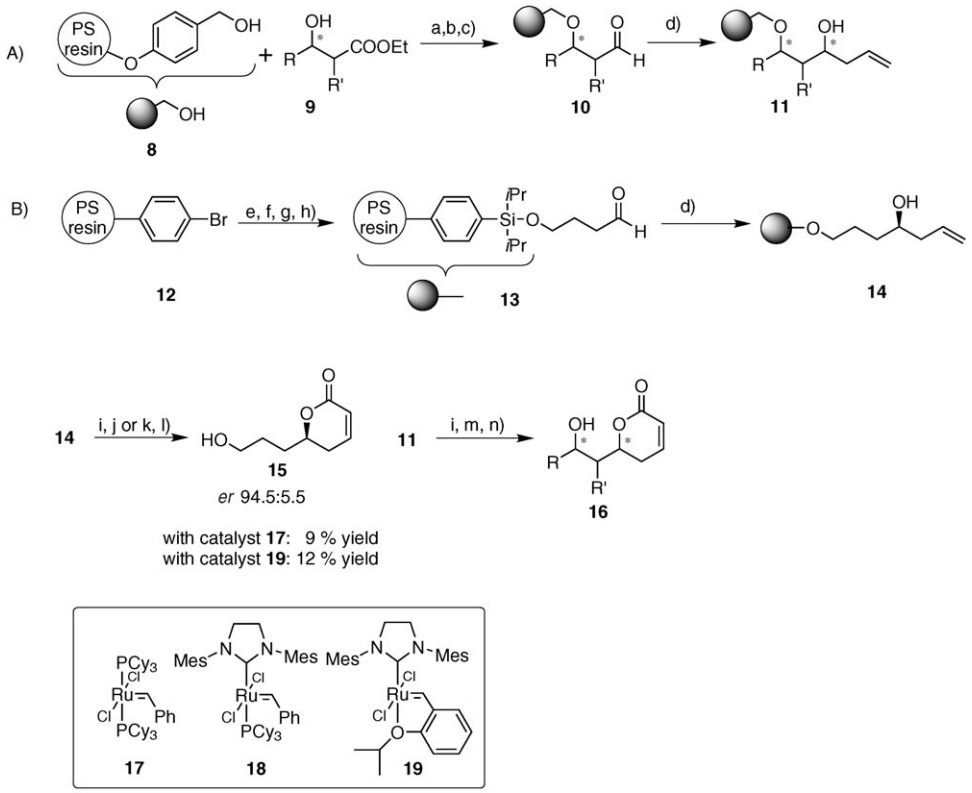
Two different linker concepts were considered for application in this approach. The acid- and oxidant-labile Wang linker should be orthogonal to the silyl protecting groups on the hydroxyl groups of the growing carbon chain. Compounds can be released from the resin and further modified before final deprotection. Alternatively, attachment to the resin by means of a silicon-based linker would allow global deprotection and concomitant release of the final target compounds from the resin in a single step, delivering the desired molecules after only one purification step.

Establishment of the RCM sequence on the solid support: In a recent report, we have shown that the asymmetric allylation can be successfully applied to immobilized aldehydes, giving rise to homoallylic alcohols that can be converted into compound collections.[21] This methodology turned out to be applicable also to an iterative approach, resulting in the synthesis of 1,3-*syn* diols and polyols on substrates that were linked to the polymeric carrier via an ester bond. This allowed quick release of the substrates and straightforward analysis of the resulting methyl esters; however, the sensitivity of the α,β-unsaturated δ-lactone moiety towards nucleophiles demanded different modes of substrate immobilization (Scheme 2). We chose the well-established Wang-linker **8** as an acid-labile and oxidatively cleavable attachment system. Commercial, enantiomerically pure β-hydroxyesters **9** were attached by activation of the linker as a trichloroaetimidate (Scheme 2A) and subsequent nucleophilic substitution by the respective alcohol **9**.[23] The immobilized esters were converted to aldehydes **10**[9f] by means of a reduction–oxidation sequence with loadings of 0.7 mmol g^{-1} in the case of primary alcohols and 0.4 to 0.5 mmol g^{-1} in the case of secondary alcohols.[24]

Alternatively, we made use of a phenyldialkylsilyl system.[25] Commercial bromopolystyrene resin **12** was lithiated, quenched with diisopropyldichlorosilane and coupled to the alcohol (Scheme 2B). Ozonolysis of the terminal double bond led to the desired aldehyde **13** with a loading of 0.5 mmol g^{-1}.[24]

The immobilized aldehydes were treated with the established allylation conditions (3 equiv of the chiral allyl boron reagent, −78 °C to room temperature, 16 h) and were converted to the corresponding homoallylic alcohols **11** or **14**, as indicated by the disappearance of the carbonyl band at ≈1732 cm^{-1} in the FTIR spectrum. Thereby, the stage was set for further steps towards the desired α,β-unsaturated δ-lactones. Esterification of the homoallylic alcohols was achieved with acryloyl chloride in the presence of an amine base and DMAP (DMAP = 4-dimetylaminopyridine) in dichloromethane and could be monitored by the appearance of a carbonyl band at 1732 cm^{-1} in the FTIR spectrum.

Although ring-closing metathesis on these kind of substrates was reported with the use of Grubbs first-generation catalyst in solution,[22a,b,d] in some cases Ti(O*i*Pr)$_4$ is used as an additive[22c] or the more reactive Grubbs second-generation or Hoveyda–Grubbs catalysts are employed.[7] In the case of our immobilized substrates, the use of the Grubbs first-generation catalyst **17** alone was not sufficient to achieve full conversion of the substrate. Addition of one equivalent of Ti(O*i*Pr)$_4$ led to the desired lactone **15** (Scheme 2) in 9% yield (based on the aldehyde loading of the resin). However, the reaction could be carried out without additive when catalysts **18** or **19** were used. As a standard protocol, the catalyst was added in two portions of 20 mol% each over a period of 24 h in refluxing dichloromethane. Release of the compounds was achieved by subjecting the resins to pyridine-buffered HF (**15**) or DDQ (DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone) (**16**).[13b] In the case of lactone **15**, an enantiomeric ratio of 94.5:5.5 (89% *ee*) could be determined by GC analysis on a chiral Lipodex E column.



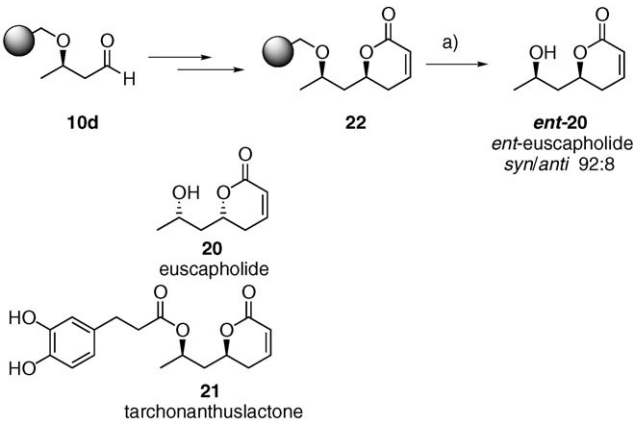
Scheme 2. Establishment of the allylation/RCM sequence on a solid support. A) synthesis on Wang resin. B) synthesis on a diisopropylsilyl resin. a) Resin **8** (1.2 mmol g^{-1}), trichloroacetonitrile, DBU, CH_2Cl_2, then **9**, $BF_3{\cdot}OEt_2$, cyclohexane/CH_2Cl_2; b) DIBAL-H, THF, −78 °C to RT, 16 h, c) IBX, DMSO/THF, RT, 16 h; d) i) D-Ipc_2BAll (3 equiv), THF, −78 °C; ii) pH 7 buffer, H_2O_2 30%, DMF/MeOH 1:1, 0 °C, 2 h; e) *n*BuLi (6 equiv), toluene, 60 °C, 15 h; f) iPr_2SiCl_2 (2 equiv), THF, 0 °C to RT, 2 h; g) DMAP (0.5 equiv), 2,6-lutidine (5 equiv), 4-pentene-1-ol (3 equiv), CH_2Cl_2, RT, 15 h; h) O_3, CH_2Cl_2, −78 °C then PPh_3 (5 equiv), −78 °C to RT, 12 h; i) acryloyl chloride (5 equiv), NEt_3 (5 equiv), cat. DMAP, CH_2Cl_2, 0 °C to RT, 16 h; j) **17** (2×20 mol%), Ti(O*i*Pr)$_4$ (1 equiv), CH_2Cl_2, reflux, 24 h; k) **19** (2×20 mol%), CH_2Cl_2, reflux, 24 h; l) HF/pyridine, pyridine, THF, RT, 8 h; m) **18** (2×20 mol%), CH_2Cl_2, reflux, 24 h; n) DDQ (10 equiv), CH_2Cl_2, pH 7 buffer, 0 °C to RT, 16 h. DIBAL-H = diisobutylaluminium hydride; IBX = *o*-iodoxybenzoic acid.

Having found conditions for the RCM, we were able to generate a first set of small molecules bearing the α,β-unsaturated δ-lactone moiety

(Table 1). Interestingly, for aldehydes bearing an α-stereocenter, the *anti*-directed allylation gave rise to higher selectivity than the *syn*-directed transformation (entry 2 versus 3). As expected, the sequence worked equally well for crotylated compounds (entry 6 and 7).

After the RCM reaction, the resin usually had turned brown to black because of the adsorption of ruthenium particles. After cleavage, the ruthenium content of the product was still high (indicated by the brown color of the crude product), but careful flash chromatography or preparative HPLC served to remove the ruthenium.

Synthesis of euscapholide and all stereoisomers of cryptocarya diacetate: With these results in hand, we approached the synthesis of natural products and their stereoisomers. Euscapholide (**20**) (Scheme 3) is a small pyrone natural product which was isolated from the leaves of *Euscaphis japonica*.[26] Compound **20** is the enantiomer of the lactone substructure of tarchonathuslactone **21**.[27] The synthesis of *ent*-**20** followed the route described above and delivered the desired product in 44% overall yield from **10d** and with a *syn*/*anti* ratio of 92:8 (determined by integration of the methyl group signals in the ^{1}H NMR spectrum).



Scheme 3. Synthesis of *ent*-euscaphlide on a solid support. a) DDQ (10 equiv), CH_2Cl_2, pH 7 buffer, 0 °C to RT, 16 h.

The absolute configuration of *ent*-**20** was deduced from the comparison of the specific rotation $[\alpha]_D^{20} = -100$ ($c = 1.37$ in MeOH) measured for synthetic *ent*-**20** with the reported value for the isolated natural product euscapholide (**20**) ($[\alpha]_D^{30} = +115.5$ ($c = 1.52$ in MeOH).[26]

Table 1. Asymmetric allylation and crotylation of immobilized aldehydes according to Scheme 2.

Entry	Aldehyde	Reagent	Alcohol	Lactone	Yield [%][a]	dr[b]
1	10a	D-Ipc$_2$BAll	11a	16a	30	–
2	10b	D-Ipc$_2$BAll	11b	16b	28	90:10
3	10c	L-Ipc$_2$BAll	11c	16c	18	80:20
4	10d	L-Ipc$_2$BAll	11d	16d	34	90:10
5	11a	L-Ipc$_2$BAll	11e	16e	37	80:20
6	10b	L-Ipc$_2$B(*E*-)Crot	11f	16f	38	95:5
7	10d	L-Ipc$_2$B(*E*-)Crot	11g	16g	48	95:5

[a] Isolated yield. [b] Determined by integration of the signals recorded for the methyl groups in the ^{1}H NMR spectrum.

This synthesis describes also the assembly of the stereochemically demanding alcohol of tarchonanthuslactone **21**[27] and further confirms that the allylation on solid support proceeds with the same sense of induction as in solution-phase synthesis.

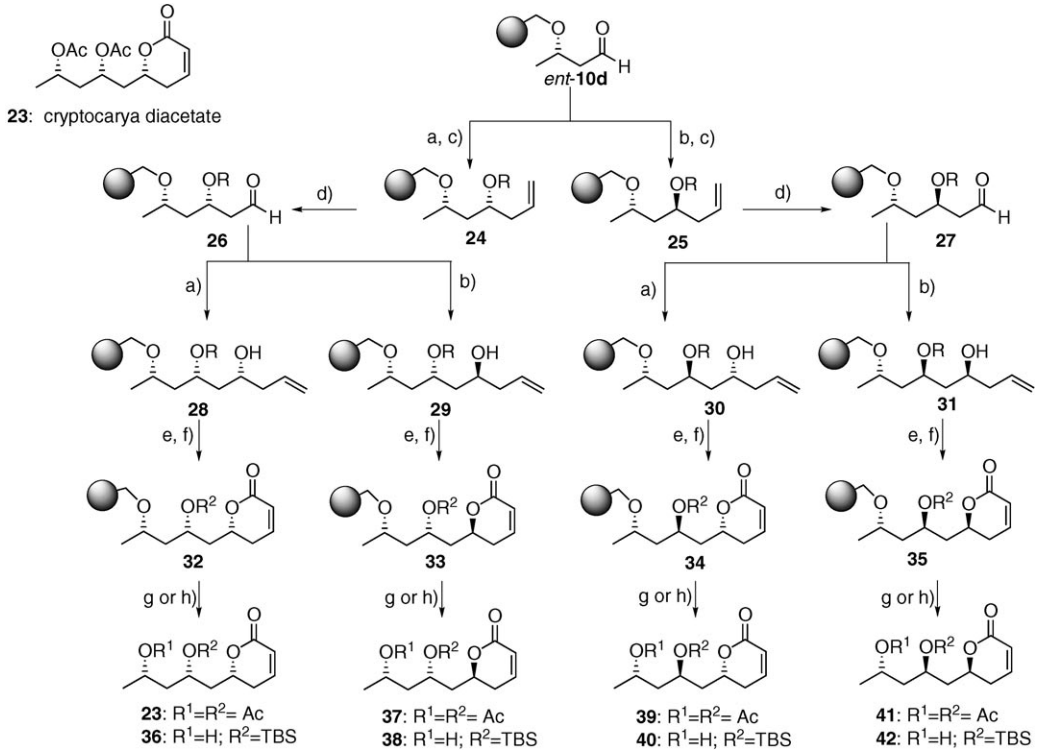
The successful synthesis of *ent*-**20** on solid support demonstrated the applicability of the allylation and RCM sequence to the synthesis of natural products and prompted us to carry out the iterative allylation and ozonolysis sequence for the generation of a natural-product-derived compound collection. Cryptocarya diacetate **23**[28] (Scheme 4), a natural product isolated from the African tree *Cryptocarya latifolia*, was chosen as the target. It embodies an α,β-unsaturated δ-lactone moiety and two additional acetoxy groups, all in relative *syn* configuration. Moreover, we strived to synthesize all stereoisomers of the polyol framework present in the natural product by using the appropriate combinations of the chiral allyl boranes.

Towards this end, aldehyde *ent*-**10d** (Scheme 4), obtained by the same sequence as delineated above, underwent allylation with L- and D-Ipc_2BAll and afforded diols **24** (*syn*/*anti* ratio of 90:10, determined by ^1H NMR spectroscopic analysis after release from the polymeric carrier) and **25** (*syn*/*anti* ratio of 20:80). The immobilized homoallylic alcohols were protected as TBS ethers and subsequently transformed to aldehydes **26** and **27** by careful ozonolysis for six minutes. A second allylation was performed with both of the enantiomers of Ipc_2BAll and yielded triols **28**, **29**, **30**, and **31**, which were acylated with acryloyl chloride and then treated to the RCM protocol by using catalyst **18**. The immobilized lactones **32**–**35** were released from the solid support in two different ways.

Acidic conditions (TFA/dichloromethane 1:2, 20 min) did not only lead to release from the solid support, but also to partial deprotection. When immobilized compound **32** was treated in this way, the resulting diol could be isolated by filtration through a short silica column. It was acetylated to give a diastereomeric mixture of products, from which the major all-*syn* isomer **23** was isolated by careful flash chromatography in 11% overall yield after a total of 11 steps. Comparison of the specific rotation of **23** ($[\alpha]_D^{20}=47.2$ ($c=0.5$ in $CHCl_3$)) with literature data for the synthetic material ($[\alpha]_D^{29}=45.4$ ($c=0.33$ in $CHCl_3$),[28b] $[\alpha]_D^{20}=47.5$ ($c=0.6$ in $CHCl_3$)[28c] and the isolated natural product $[\alpha]_D^{25}=55.8$ ($c=1.06$ in $CHCl_3$)[28a] confirmed the absolute configuration.

Accordingly, the three non-natural stereoisomers of cryptocarya diacetate **37**, **39**, and **41** were obtained following identical cleavage and acetylating conditions.

In a different approach, the compounds could be released by oxidative treatment of the resin with DDQ. In these cases, the TBS (TBS = *tert*-butyldimethylsilyl) protecting groups were not affected by the cleavage procedure, and monoprotected compounds **36**, **38**, **40**, and **42** could be isolated in high overall yields (40–60% after a total of 10 steps).



Scheme 4. Stereocomplementary synthesis of all (4′*S*)-isomers of cryptocarya diacetate. a) i) L-Ipc_2BAll (3 equiv), THF, −78°C; ii) pH 7 buffer, H_2O_2 30%, DMF/MeOH 1:1, 0°C, 2 h; b) i) D-Ipc_2BAll (3 equiv), THF, −78°C; ii) pH 7 buffer, H_2O_2 30%, DMF/MeOH 1:1, 0°C, 2 h; c) TBSCl, imidazole, cat. DMAP, CH_2Cl_2, RT, 16 h; d) O_3, CH_2Cl_2, −78°C, then PPh_3, −78°C to RT; e) acryloyl chloride, DIPEA, cat. DMAP, CH_2Cl_2, 0°C to RT, 16 h; f) Grubbs second-generation catalyst (2×20 mol%) (**18**), CH_2Cl_2, reflux, 24 h; g) i) trifluoroacetic acid/CH_2Cl_2 1:2, 20 min, RT; (ii Ac_2O, NEt_3, cat. DMAP, CH_2Cl_2, 0°C to RT, 3 h; h) DDQ (10 equiv), CH_2Cl_2, pH 7 buffer, 0°C to RT, 16 h; DIPEA = diisopropyl ethyl amine.

In all cases, flash chromatography provided the major isomer of the acylated compounds in pure form with yields ranging from 10 to 20%, and with generally more than 90% purity in the case of the TBS-protected compounds.

Starting from aldehyde **10d**, the enantiomeric series of compounds was synthesized in an analogous way to that described above. Following this route, we could enlarge our compound collection with four diastereomers of **23** and TBS-protected analogues (Figure 1).[29] Further, the released

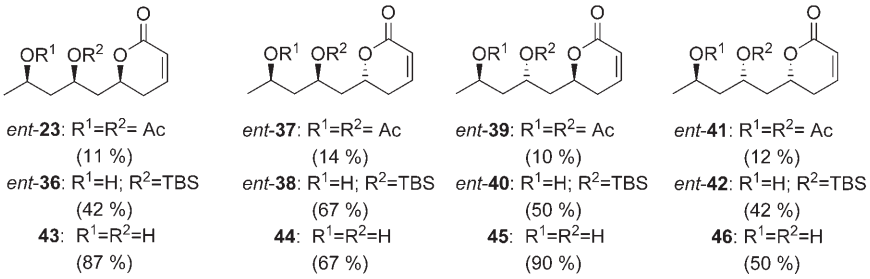


Figure 1. (4′*R*)-isomers of cryptocarya diacetate (see Table 2 for yields and diastereomeric ratios).

TBS-protected analogues could be transformed in solution-phase synthesis to their corresponding diol lactones **50**, **51**, **52**, and **53** by treating them with PPTS (PPTS = pyridinium *p*-toluene sulfonic acid) in refluxing aqueous MeOH in 50 to 90% yield.

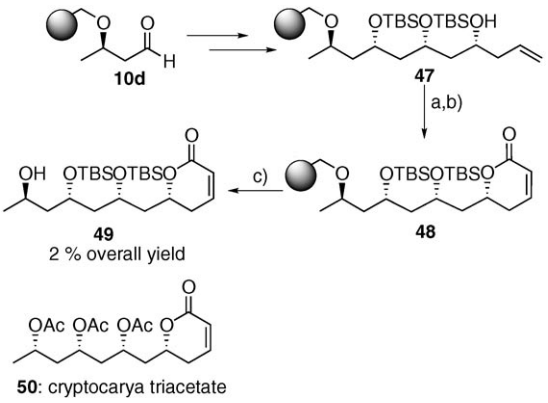
^{1}H NMR spectroscopic analysis of the crude monoprotected products allowed the determination of the diastereomer ratio. The isomer distributions of all reaction products are summarized in Table 2. The first allylation of **10d** with D-Ipc$_2$BAll gave a 90:10 ratio of *syn*/*anti* selectivity, whereas the allylation of **10d** with L-Ipc$_2$BAll gave an 80:20 ratio of *anti*/*syn* isomers. Thus, the 1,3-*syn* stereochemical pattern is the matched case and the 1,3-*anti* isomer is the mismatched case. A similar trend was also observed for the second allylation and was evident from the product distribution in the final products. As a result, all-*syn*-hydroxyl-derived compounds **36** and *ent*-**36** showed good diastereomeric purity whereas the other isomers showed lower stereoisomer ratios.

Table 2. Results of the synthesis of stereoisomers.

Entry	Compound (config.)	Yield [%][a]	Ratio *syn*/*syn*-**36**:*syn*/*anti*-**38**:*anti*/*syn*-**40**:*anti*/*anti*-**42**[b]
1	**36** (4′*S*,2′*S*,6*R*)	40	≥80:≤5:13:2
2	**38** (4′*S*,2′*S*,6*S*)	50	18:67:1:14
3	**40** (4′*S*,2′*R*,6*R*)	57	13:2:77:8
4	**42** (4′*S*,2′*R*,6*S*)	60	2:13:5:80
5	*ent*-**36** (4′*R*,2′*R*,6*S*)	42	≥85:≤=5:7:3
6	*ent*-**38** (4′*R*,2′*R*,6*R*)	67	27:63:6:9
7	*ent*-**40** (4′*R*,2′*S*,6*S*)	50	13:2:63:22
8	*ent*-**42** (4′*R*,2′*S*,6*R*)	42	2:13:10:75

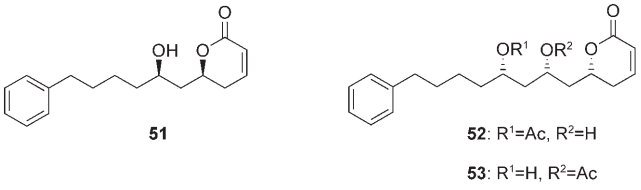
[a] Isolated overall yield based on the loading of aldehyde **16**. [b] Determined by integration of the signals of the protons at C-6, C-4′, and C-2′ in the 500 MHz ^{1}H NMR spectrum.

Finally, this route could be further extended to obtain compound **49** (Scheme 5) which represents a selectively protected version of a stereoisomeric analogue of the natural product cryptocarya triacetate **50**.[28a,b,30] The synthesis of compound **49** required a total of 14 consecutive steps on the polymeric carrier including three stereoselective carbonyl allylation reactions. It was obtained in stereoisomerically pure form in an overall yield of 1.6 mg (2%) after chromatographic purification. The decrease in yield might be attributed to partial release of the substrate during the repeated ozonolysis reactions.



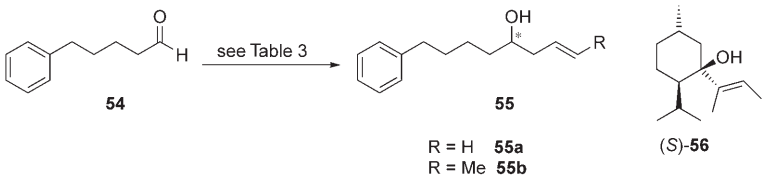
Scheme 5. Synthesis of a diastereomeric analogue of cyrptocarya triacetate on a solid support. a) acryloyl chloride, NEt_3, cat. DMAP, CH_2Cl_2, 0°C to RT, 16 h; b) **19** (2×20 mol%), CH_2Cl_2, reflux, 24 h; c) DDQ (10 equiv), CH_2Cl_2, pH 7 buffer, 0°C to RT, 16 h.

Synthesis of natural products isolated from *Ravensara anisata* and their stereoisomers: The potential of this method can be further demonstrated by the rapid synthesis of several natural products and their steroisomers from a single immobilized precursor. (6*S*)-5,6-Dihydro-6-[(2*R*)-2-hydroxy-6-phenylhexyl]-2*H*-pyran-2-one **51** was isolated by Hostettmann and co-workers from the tree *Ravensara crassifolia*.[31]



It exhibits antifungal activity against the phytopathogenic fungus *Cladosporium cucumarinum* in a bioautographic TLC assay. The closely related natural products **52** and **53** were isolated from leaves and bark extract from *Ravensara anisata*.[32]

The synthesis of these natural products and their analogues was conducted on both Wang and silyl linker. It started with the solution-phase synthesis of the homoallylic alcohols (*R*)- and (*S*)-**55** (Scheme 6), which were synthesized in solution by applying L-Ipc$_2$BAll, a Keck allylation,[33] or the Nokami crotyl-transfer method[34] (Table 3). In our hands, the use of a Ti-BINOL (BINOL = 1,1′-bi-2-naphthol) catalyst furnished variable results with respect to yield and selectivity, but after some experimentation, reaction conditions recently reported by Kurosu et al.[33b] turned out to be suitable (entry 2). However, application of the Nokami crotyl transfer agent (*S*)-**56** delivered the desired product in a straightforward way in high selectivity (entry 3).



Scheme 6. Asymmetric allylation of aldehyde **61**.

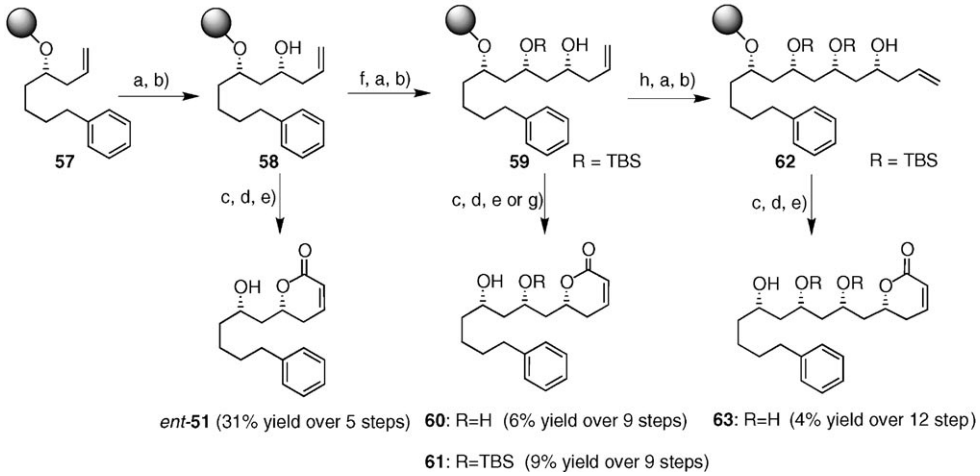
Synthesis on Wang resin: The allylic alcohol (*S*)-**55** (obtained by allylation with L-Ipc$_2$BAll, Table 3, entry 1) was immobilized on Wang imidate to afford resin **57** (Scheme 7). The resin-bound allylic alcohol **57** was converted to the corresponding aldehyde by ozonolysis, leading to an aldehyde loading of 0.5 mmol g^{-1}.[23] Subsequent allylation resulted in the homoallylic alcohol **58**, which was acylated with acryloyl chloride and underwent RCM by using catalyst **18** to yield the resin-bound lactone. Subsequent release of the substrate by using TFA (TFA = trifluoroacetic acid) afforded unsaturated δ-lactone *ent*-**51** in 31% overall yield with high diastereoselectivity (*syn*/*anti* ratio 91:9). The absolute configuration of synthetic *ent*-**51** was determined by comparison of the specific rotation measured for *ent*-**51** ($[\alpha]_D^{20} = +66$ ($c = 1.0$ in $CHCl_3$)) with literature data for synthetic **51** ($[\alpha]_D = -66$ ($c = 2$ in $CHCl_3$)).[31a]

Table 3. Asymmetric allylation of aldehyde **61**.

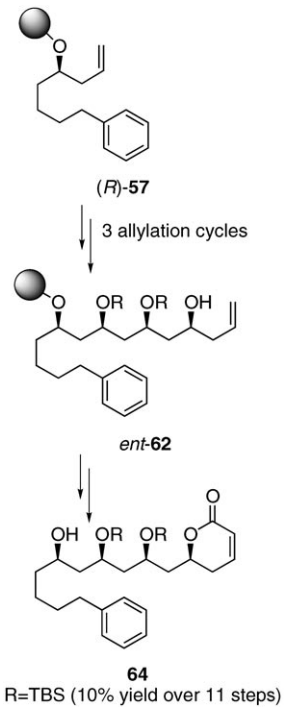
Entry	Reagent	Product	Conditions	Yield [%][a]	er (*R*/*S*)[b]
1	L-IpcBAll	**55a**	−100 °C, 6 h	73	3:97
2	Bu_3Sn(allyl), 5 mol% Ti(O*i*Pr)$_4$, 10 mol%, (*S*)-BINOL, toluene, MS 4 Å	**55a**	−15 °C, 38 h	67	98:2
3	(*S*)-**56**	**55b**	RT, 18 h	70	< 1:99[c]

[a] Isolated yield. [b] Determined by HPLC on a Daicel Chirapak AD column, flow 0.5 mL min^{-1}, hexane/isopropanol 97:3. [c] Determined by HPLC as above, hexane/isopropanol 98:2.

Furthermore, the resin-bound allylic alcohol **58** was protected as a TBS ether after the first allylation. Another ozonolysis/allylation cycle with L-Ipc$_2$BAll delivered alcohol **59**, which was further transformed and finally released with TFA or DDQ to yield unsaturated δ-lactones **60** and **61**, respectively. The diol lactone



Scheme 7. Iterative allylations in the synthesis of natural-product-derived compounds on a solid support. a) O_3, CH_2Cl_2, −78 °C, then PPh_3, −78 °C to RT; b) i) L-Ipc$_2$BAll (3 equiv), THF, −78 °C; ii) pH 7 buffer, H_2O_2 30%, DMF/MeOH 1:1, 0 °C, 2 h; c) acryloyl chloride, DIPEA, cat. DMAP, CH_2Cl_2, 0 °C to RT, 16 h; d) **25** (2 × 20 mol%), CH_2Cl_2, reflux, 24 h; e) TFA/CH_2Cl_2, RT, 15 min; f) TBSCl, imidazole, cat. DMAP, CH_2Cl_2, RT, 16 h; g) DDQ, CH_2Cl_2, pH 7 buffer, 0 °C to RT, 16 h; h) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C to RT, 10 h.



Scheme 8. Extension of the methodology to three *syn*-selective allylations on solid support.

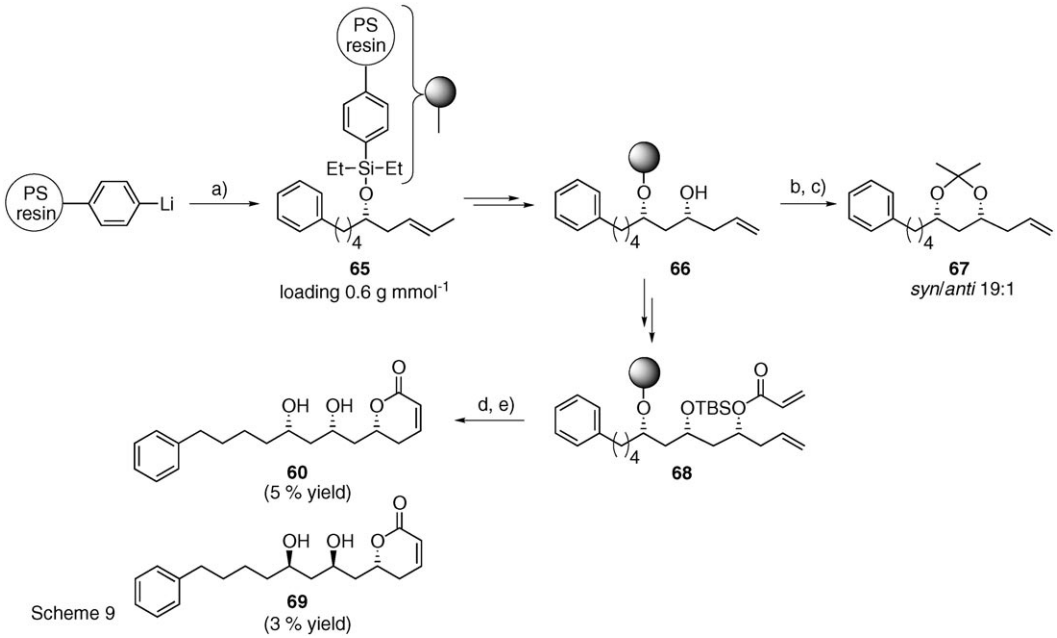
61 was obtained in 6% overall yield. It is the deacetylated analogue[32c] of the natural products **52** and **53**.

Finally, a third ozonolysis and allylation on the immobilized material furnished triol **62**, which could be converted into the corresponding lactone **63** as a single product after chromatographic purification on silica with an overall yield of 4% after 11 linear steps on the solid support.

Similarly, starting from (*R*)-**57** and applying the iterative allylation sequence with D-Ipc_2BAll (Scheme 8), the TBS-protected derivative **64** was obtained as a single diastereomer (as judged by ^{1}H NMR spectroscopy) in 10% overall yield.

Synthesis on a silyl linker: As shown above, attachment of the substrates via the Wang linker is a successful strategy. However, while cleavage with DDQ gave rise to the desired products in a protected form, release of the substrates with TFA led only to partial deprotection. In order to have substrate release and removal of all protecting groups in one step, we developed this synthesis also on a silyl linker.

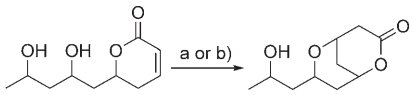
Lithiated PS resin[23] was quenched with dichlorodiethylsilane (Scheme 9) and subsequently loaded with (5*S*,2*E*)-5-hydroxy-9-phenyl-non-2-ene (**55b**) to give rise to resin **65** (loading ≈ 0.6 mmol g^{-1}, determined by HPLC analysis after release of a sample). Application of the allylation sequence gave rise to immobilized diol **66**, which could be released in 63% overall yield. GCMS analysis of the corresponding acetonide **67** indicated a *syn/anti* ratio of 19:1. Further allylation and acylation afforded the immobilized acrylate **68**, and application of catalyst **19** resulted in the immobilized lactone, which could be released and simultaneously deprotected with pyridine-buffered hydrogen fluoride (40 °C, 18 h). After flash chromatography, the final compound **60** was obtained in 5% overall yield, based on the original loading of **65**. Separation of the diastereomers by analytical HPLC analysis (Nucleodur C18 ISIS column) resulted in a distribution of 85:9:3:2.



Scheme 9. Synthesis of natural-product-derived compounds on a diethylsilylpolystyrene resin. a) i) Et_2SiCl_2 (6 equiv), THF, 0 °C to RT, 2 h; ii) (5*S*,2*E*)-5-hydroxy-9-phenyl-non-2-ene (3 equiv), 2,6-lutidine (3 equiv), DMAP (0.5 equiv), CH_2Cl_2, RT, 16 h; b) HF/pyridine, pyridine, THF, RT, 8 h; c) 2,2-dimethoxypropane, cat. (+)-CSA; d) **19** (2×20 mol%), CH_2Cl_2, reflux, 24 h; e) HF/pyridine, pyridine, THF, 40 °C, 16 h. CSA = camphorsulfonic acid.

Accordingly, the diastereomeric compound **69** could be obtained in 3% yield by analogy. The different structures of the compounds could best be detected by means of ^{13}C NMR spectroscopy, in which the carbon-bearing hydroxyl groups of the *syn*, *anti*-isomer **69** displayed a shift of $\delta =$ 74.7, 73.0, and 68.1 ppm, while the corresponding carbon atoms in the all-*syn*-compound **60** appeared at $\delta = 76.3$, 72.9, and 69.7 ppm.

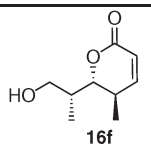
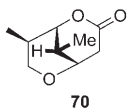
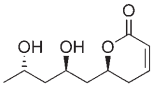
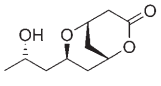
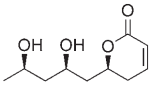
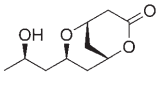
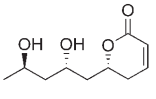
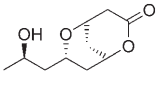
Structurally diverse lactones: As the developed synthetic strategy provides α,β-unsaturated δ-lactones with high diastereoselectivity, it was appealing to exploit their stereochemical integrity for further diversification. Intramolecular acid-catalyzed ring closure[30] should yield functionalized bicyclic compounds (Scheme 10). Such bicyclic compounds can be found as substructures of natural products like cryptocaryolone.[28a]



Scheme 10. Synthesis of bicyclic derivatives. a) TsOH (0.12 equiv); benzene, RT, 16 h; b) DBU, CH_2Cl_2, RT, 6 h.

Thus, exposure of unsaturated lactone **16f** to PTSA (PTSA = *para*-toluenesulfonic acid) resulted in formation of the saturated bicyclic lactone **70** in 66% yield (Table 4, entry 1). Similarly, the exposure of unsaturated lactone *ent*-**46** (obtained from resin **35**) to PTSA led to the formation of (1*R*,5*S*,7*R*)-3-oxo-7-[(*R*)-2-hydroxypropyl]-2,6-dioxabicyclo-[3.3.1]nonane (**71**) (entry 2). In this case, the conversion of the substrate *ent*-**46** was not complete, and the resulting yield was only moderate (38%). Gratifyingly, we found a more efficient procedure. Exposure of compounds **43** and **46** to DBU (DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene) in dichloromethane at room temperature delivered smoothly the desired bicyclic compounds **72** and *ent*-**71** in high yields (entries 3 and 4).

Table 4. Cyclization of α,β-unsaturated δ-lactones according to Scheme 10.

Entry	Reactant	Method	Product	Yield [%]
1	 **16f**	a	 **70**	66
2	 *ent*-**46**	a	 **71**	38
3	 **43**	b	 **72**	80
4	 **46**	b	 *ent*-**71**	75

Conclusion

We have shown that enantioselective allylation of polymer-bound aldehydes is an efficient solid-phase synthesis method for the stereocomplementary synthesis of collections of multiply functionalized carbon chains. This methodology should enable the synthesis of various natural productlike structures, as we have demonstrated for selected examples of the family of α,β-unsaturated δ-lactones. The synthesis of all of the diastereomers of cryptocarya diacetate demonstrates the complementarity and selectivity of the single reaction steps, whereas the synthesis of the *ravensara* lactones further exemplifies the flexibility of this route.

We believe that such stereocomplementary syntheses beneficially extend the more established solid-phase methodologies of introducing diversity into compound collections. Notably, we expect this concept to add favorably to our current efforts in biology-oriented synthesis (BIOS), in which biologically prevalidated and often stereochemically demanding natural products are taken as starting points for the synthesis of compound collections. In such endeavors, control over the stereochemical course of a reaction is an indispensable tool in order to specifically investigate the biological potency of each single stereoisomer.

Experimental Section

General: Unless otherwise noted, chemicals were obtained from Aldrich, Acros, or Fluka and were used without further purification. Regular hydroxymethylpolystyrene (0.98 mmol g^{-1}, 1% DVB, 100–200 mesh) and Wang resin (1.10 mmol g^{-1}, 1% DVB, 100–200 mesh) were purchased from Novabiochem, Bromopolystyrene resin (2.68 mmol g^{-1}, 100–200 mesh) was purchased from Rapp Polymers. All solvents were distilled by standard procedures. All reactions were performed under argon with freshly distilled and dried solvents. Analytical chromatography was performed by using Merck silica gel 60 F_{254} aluminum sheets. Flash chromatography was performed by using Acros silica gel(0.035–0.07 mm). ^1H and ^{13}C NMR spectrascopic data were recorded on a Bruker DRX 500 or Varian Mercury VX 400 spectrometer at RT. NMR spectra were calibrated to the solvent signals of $CDCl_3$ ($\delta = 7.26$ and 77.00 ppm) and the next abbreviations are used to indicate signal multiplicities: s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), sext (sextet), sept (septet), br (broad), ap (apparent). GCMS (EI) analysis was performed on a Hewlett–Packard 6890 series gas chromatograph connected to a Hewlett–Packard 5973 series mass spectrometer; column: H&W 19091σ-102 HP-5MS, capillary: 25.0×201μ×0.33μmm nominal. Chiral GC analysis was performed on an Agilent Technologies 6890N; column Lipodex-E (25 m, 0.025 mm). LCMS was performed on a Hewlett–Packard 1100 series connected to a Finnigan LCQ ESI-spectrometer. Preparative HPLC was performed on a Hewlett–Packard Agilent Series 1100 System equipped with a Nucleodur C18 gravity 5 μm column of Macherey&Nagel. High resolu-

tion mass spectra (HRMS) were measured on a Jeol SX 102 A spectrometer. IR spectra were measured on a Bruker Vector 22 spectrometer with an A527 diffuse reflectance head from Spectra Tech. UV spectra were measured on a Varian Cary 100 Bio spectrometer. The optical rotation was determined with a Schmidt+Haensch Polartronic HH8 polarimeter.

Representative experimental procedures for the attachment of substrate to the polymeric support, ozonolysis, allylation, crotylation, TBDMS protection, acylation with acryloyl chloride and ring-closing metathesis (RCM), and different substrate release procedures from the solid support are given below.

General procedure for the loading on bromopolystyrene resin: Bromopolystyrene resin (2.68 mmol g^{-1}) was dried by azeotropic distillation with toluene prior to use. It was swollen in toluene (5 mL g^{-1} resin) and *n*BuLi (3 equiv, 2.5 M in hexane) was added. After gentle stirring at 60 °C for 3 h, additional *n*BuLi (3 equiv) was added, and the mixture was stirred at 60 °C for 15 h. The resulting black resin was filtered and washed with toluene and THF. THF was added (1.5 mL g^{-1} resin) and the mixture was cooled to 0 °C. The appropriate dichlorosilane (4 equiv) was slowly added, and the mixture was stirred for 2 h and subsequently filtered and washed with THF and CH_2Cl_2. The resulting immobilized silylchloride was swollen in CH_2Cl_2 and DMAP (0.5 equiv), 2,6-lutidine (2 equiv), and alcohol (2 equiv) were added. The mixture was shaken for 16 h. The resin was filtered and washed with CH_2Cl_2, dimethylformamide, CH_2Cl_2, and MeOH and was then dried in vacuo.

General procedure for the ozonolysis on solid support: The resin was swollen for 15 min in CH_2Cl_2 and cooled to −78 °C. Ozone was bubbled through until the color turned deep green or blue and for an additional 8–10 min. When the polymeric support was the Wang resin, ozone was bubbled through for only 2–3 min after observation of the blue color (ca. 6 min in total). Argon was then bubbled through the mixture to remove excess ozone, PPh_3 (5 equiv) was added and the mixture was shaken from −78 °C to RT overnight. The resin was then filtered and washed with CH_2Cl_2 and MeOH and dried in vacuo.

General procedure for the asymmetric allylation on solid support: The supported aldehydes were dried by azeotropic distillation with toluene (2–3 times) and high vacuum for at least 3 h. The resin was suspended in THF (10–15 mL g^{-1} resin) and the allylborane (1 M in Et_2O solution, 4 equiv) was added at −78 °C. The resulting mixture was shaken overnight allowing the temperature to warm up slowly to 0 °C. After quenching the reaction with MeOH (4 mL g^{-1} resin), the resin was filtered and washed consecutively with pH 7 buffer, H_2O, THF, Et_2O, CH_2Cl_2, and MeOH. The resin was suspended in a mixture of DMF/MeOH 1:1 (12 mL g^{-1} resin each) and at 0 °C H_2O_2 (30 %, 2.5 mL g^{-1} resin) and pH 7 buffer (2.5 mL g^{-1} resin) were added. The resulting mixture was shaken for 2 h at RT (when the resin was hydroxymethylpolystyrene) or at 0 °C (when the Wang resin was used). The resin was filtered and washed with H_2O, THF, CH_2Cl_2, and MeOH and was then dried in vacuo.

Asymmetric crotylation on solid support: *trans*-Butene (excess, 0.5 mL) was added to a solution of *t*BuOK (1 M in THF, 5 equiv, 1.5 mmol) at −78 °C. A solution of *n*BuLi (2.5 M in hexane, 6 equiv, 1.8 mmol) was added dropwise and the mixture was stirred at −78 °C for 5 min then at −45 °C for 40 min. The resulting solution was cooled to −78 °C, a solution of (−)-MeOBIpc$_2$ (7 equiv, 2.1 mmol, 665 mg) in Et_2O (1.5 mL) was added dropwise over 15 min and the stirring was maintained for 45 min. $BF_3{\cdot}Et_2O$ (7.5 equiv, 2.25 mmol, 284 μL) was added dropwise and after 5 min to the aldehyde resin (≈400 mg, 0.3 mmol), which had beforehand been swollen in THF (10 mL) and cooled at −78 °C. The mixture was stirred overnight with the temperature rising slowly to 0 °C. After quenching by the addition of MeOH (0.5 mL), the resin was washed consecutively with pH 7 buffer, H_2O, THF, Et_2O, dichloromethane, and MeOH. DMF (3 mL), MeOH (3 mL), pH 7 buffer (1 mL), and H_2O_2 (30 %, 1 mL) were added to the resin at 0 °C. The mixture was then shaken at 0 °C for 2 h and filtered. The resin was washed with H_2O, THF, Et_2O, CH_2Cl_2, and MeOH and was then dried overnight in vacuo.

General procedure for the protection of secondary alcohols with a *tert*-butyldimethylsilyl group on solid support: The resin-bound secondary alcohol (1 g) was swollen in a mixture of CH_2Cl_2 (10 mL) and DMF (10 mL) at RT. After addition of TBSCl (1.13 g, 7.5 mmol), DMAP (5 mg, 0.075 mmol), and imidazole (0.51 g, 7.5 mmol), the resin was shaken for 24 h. The resin was filtered and washed with DMF, THF/H_2O, THF, and CH_2Cl_2 and was then dried in vacuo for 5 h (until the disappearance of the bands at 3504 and 3062 cm^{-1} was detected by FTIR spectroscopy).

General procedure for the introduction of the acrylate on solid support: The resin-bound secondary alcohol (0.5 g) was swollen in CH_2Cl_2 (5 mL) and the mixture was cooled to 0 °C. Diisopropylethyl amine (0.75 mL, 4.3 mmol), DMAP (10 mg, 0.08 mmol), and acryloyl chloride (0.36 mL, 4 mmol) were added to the cold mixture and it was shaken for 24 h at RT. The resin was filtered and washed successively with THF, THF/H_2O, THF, and CH_2Cl_2 and was then dried in vacuo for 5 h (The reaction was monitored by FTIR spectroscopy which showed the disappearance of bands at approximately 3500 cm^{-1} and the appearance of a broad peak at 1725 to 1730 cm^{-1}).

General procedure for RCM on the solid support: The resin-bound acrylic acid ester (0.25 g, ≈0.5 mmol g^{-1} loading) was suspended in CH_2Cl_2 (10 mL) and the mixture was degassed with argon. To the degassed mixture, the RCM catalyst (0.02 mmol) was added, the mixture was warmed to 40 °C and stirred for 12 h. A second portion of catalyst was added (0.02 mmol) and the mixture was stirred at reflux for another 12 h. The mixture was allowed to reach RT, and was then filtered. The filtrate was washed successively with CH_2Cl_2, THF, and CH_2Cl_2 and was then dried in vacuo.

General procedure for release from the solid support by using TFA: The resin (430 mg, loading 0.4 mmol g^{-1}) was swollen in CH_2Cl_2 and was subsequently treated with TFA/CH_2Cl_2 1:2 (20 mL g^{-1} resin, 8.6 mL) solution for 5 min at RT. The resin was filtered and washed with CH_2Cl_2. The filtrate was co-evaporated with toluene and the brown residue was purified by silica-gel column chromatography to yield the product.

General procedure for release from the solid support by using DDQ: The resin (250 mg, loading 0.4 mmol g^{-1}) was swollen in a mixture of CH_2Cl_2 (10 mL) and pH 7 phosphate buffer (0.5 mL) and recrystallized DDQ (180 mg, 0.8 mmol) was added at 0 °C. The mixture was shaken for 10 h while allowing the temperature to rise to RT. The resin was then filtered off and washed with CH_2Cl_2. The filtrate was washed with a saturated solution of $NaHCO_3$ (3×15 mL) and brine and was then dried over Na_2SO_4. After removal of solvent under reduced pressure, the required lactone was obtained in 80–90 % purity. The lactones were further purified by silica-gel column chromatography.

General procedure for the release from the dialkylsilylpolystyrene resins: The resin was swollen in THF (5 mL g^{-1} resin) in a 15 mL Falcon tube equipped with a magnetic stirring bar and a septum. Pyridine (75 μL g^{-1} resin) and HF/pyridine (100 μL g^{-1} resin) were added, and the suspension was stirred for 16 h at 40 °C. Excess reagent was quenched with trimethylsilylmethanol (2 mL g^{-1} resin). Filtration through a pad of silica afforded the crude product, which was further purified by flash chromatography or preparative HPLC.

(*R*)-6-(3-Hydroxypropyl)-5,6-dihydro-2*H*-pyran-2-one (15): After release from the resin, the compound was purified by preparative HPLC (lin. gradient 10 to 95 % acetonitrile + 0.1 % TFA in H_2O + 0.1 % TFA). Yield: 11.7 mg (from 589 mg diisopropylsilylpolystyrene resin), 12 %; R_f = 0.18 (silica gel, CH_2Cl_2/MeOH 95:5); $[\alpha]_D^{20} = -102$ (c = 0.2 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.91–6.86 (m, 1H), 6.03 (ddd, ^3J = 9.7, ^4J = 2.1, 1.5 Hz, 1H), 4.51–4.44 (m, 1H), 3.72–3.69 (m, 2H), 2.38–2.34 (m, 2H), 1.91–1.66 ppm (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.4 (CO), 145.0 (CH), 121.4 (CH), 77.8 (CH), 62.8 (CH_2), 31.2 (CH_2), 29.5 (CH_2), 28.0 ppm (CH_2); MS (FAB): m/z: 157.1 $[M+H]^+$; HRMS (FAB): m/z: calcd for $C_8H_{13}O_3$: 157.0865 $[M+H]^+$; found: 157.0880.

(*S*)-6-(2-Hydroxyethyl)-5,6-dihydro-2*H*-pyran-2-one (16a): Yield: 4 mg (from 120 mg resin), 30 %; R_f = 0.4 (silica gel, ethyl acetate/petroleum ether 1:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.90 (td, J = 9.7, 3.9 Hz, 1H), 6.06 (td, J = 9.7, 1.9 Hz, 1H), 4.62–4.55 (m, 3H), 2.42–2.39 (m, 2H), 2.25–2.12 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.39 (CO), 144.51 (CH), 121.57 (CH), 73.86 (CH), 63.60 (CH_2), 33.51 (CH_2), 29.37 ppm (CH_2); LCMS: m/z: 124 $[M-H_2O]^+$.

(*S*)-6-[(*R*)-1-Hydroxypropan-2-yl]-5,6-dihydro-2*H*-pyran-2-one (16b): Yield: 10 mg (from 300 mg resin), 28%; R_f=0.2 (silica gel, ethyl acetate/petroleum ether 1:1); $[\alpha]_D^{25}=-120.6$ (c=0.95 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ=6.92–6.90 (m, 1H), 6.01 (d, J=9.4 Hz, 1H), 4.45–4.43 (m, 1H), 3.74–3.70 (m, 2H), 2.40–2.39 (m, 2H), 2.06–2.03 (m, 1H), 1.00 ppm (d, J=6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=164.30 (C), 145.43 (CH), 121.19 (CH), 79.87 (CH), 64.23 (CH_2), 39.54 (CH), 26.87 (CH_2), 12.68 ppm (CH_3); LCMS: m/z: 157 $[M+H]^+$.

(*R*)-6-[(*R*)-1-Hydroxypropan-2-yl]-5,6-dihydro-2*H*-pyran-2-one (16c): Yield: 4 mg (from 200 mg resin), 18%; R_f=0.2 (silica gel, ethyl acetate/petroleum ether 1:1); ^{1}H NMR (500 MHz, $CDCl_3$): δ=6.94 (ddd, J=9.5, 6.4, 2.1 Hz, 1H), 6.06 (ddd, J=9.5, 2.9, 0.9 Hz, 1H), 4.53 (td, J=12.6, 3.72 Hz, 1H), 4.45 (dd, J=10.9, 7.4 Hz, 1H), 4.39 (dd, J=10.9, 5.8 Hz, 1H), 2.56–2.47 (m, 1H), 2.36–2.30 (m, 2H), 1.13 ppm (d, J=7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=163.77 (C), 144.95 (CH), 121.48 (CH), 77.00 (CH), 68.43 (CH_2), 36.20 (CH), 26.66 (CH_2), 11.01 ppm (CH_3); LCMS: m/z: 157 $[M+H]^+$.

(*R*)-6-[(*S*)-1-Hydroxypropan-2-yl]-5,6-dihydro-2*H*-pyran-2-one (16d): Yield: 10 mg (from 300 mg resin), 34%; R_f=0.2 (silica gel, ethyl acetate/petroleum ether 1:1); $[\alpha]_D^{25}=+60.3$ (c=0.9 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ=6.93–6.89 (m, 1H), 6.02 (td, J=9.9, 1.7 Hz, 1H), 4.47–4.41 (m, 1H), 3.76 (dd, J=10.9, 4.6 Hz, 1H), 3.71 (dd, J=10.9, 5.6 Hz, 1H), 2.39 (t, J=6.4 Hz, 2H), 2.10–2.03 (m, 1H), 1.00 ppm (d, J=6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=164.34 (C), 145.46 (CH), 121.18 (CH), 79.89 (CH), 64.25 (CH_2), 39.54 (CH), 26.88 (CH_2), 12.69 ppm (CH_3); LCMS: m/z: 157 $[M+H]^+$; HRMS (FAB): m/z: calcd for $C_8H_{13}O_3$: 157.0865 $[M+H]^+$; found: 157.0847.

(*R*)-6-[(*R*)-2-Hydroxypropyl]-5,6-dihydro-2*H*-pyran-2-one (16e): Yield: 6 mg (from 225 mg resin), 37%; R_f=0.2 (silica gel, ethyl acetate/petroleum ether 1:1); $[\alpha]_D^{25}=+59.6$ (c=0.6 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ=6.93–6.86 (m, 1H), 6.03 (d, J=9.9 Hz, 1H), 4.74–4.67 (m, 1H), 4.20–4.12 (m, 1H), 2.39–2.36 (m, 2H), 2.20 (brs, 1H), 1.90 (dd appears as t, J=9.8 Hz, 1H), 1.68 (dd appears as t, J=9.8 Hz, 1H), 1.25 ppm (d, J=6.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=164.39 (C), 145.30 (CH), 121.33 (CH), 75.05 (CH), 63.57 (CH), 43.79 (CH_2), 29.85 (CH_2), 24.15 ppm (CH_3); LRMS: m/z: 157.1 $[M+H]^+$.

(5*R*,6*R*)-6-[(*R*)-1-Hydroxypropan-2-yl]-5-methyl-5,6-dihydro-2*H*-pyran-2-one (16f): Yield: 8 mg (from 200 mg resin), 38%; R_f=0.2 (silica gel, ethyl acetate/petroleum ether 1:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ=6.68 (dd, J=9.6, 1.7 Hz, 1H), 5.95 (dd, J=9.6, 2.5 Hz, 1H), 4.35 (d, J=10.9 Hz, 1H), 3.80–3.67 (m, 1H), 3.66–3.63 (m, 1H), 2.70–2.65 (m, 1H), 2.04–2.01 (m, 1H), 1.17 (d, J=7.2 Hz, 3H), 1.02 ppm (d, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=164.70 (C), 152.67 (CH), 119.95 (CH), 82.96 (CH), 64.24 (CH_2), 36.13 (CH), 30.54 (CH), 15.68 (CH_3), 9.67 ppm (CH_3); LCMS m/z: 171 $[M+H]^+$.

(5*R*,6*S*)-6-[(*R*)-2-Hydroxypropyl]-5-methyl-5,6-dihydro-2*H*-pyran-2-one (16g): Yield: 6 mg (from 225 mg resin), 48%; R_f=0.2 (silica gel, ethyl acetate/petroleum ether 4:1); $[\alpha]_D^{25}=-52.6$ (c=0.53 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ=6.67 (dd, J=9.7, 2.5 Hz, 1H), 5.96 (dd, J=9.7, 2.3 Hz, 1H), 4.37 (dd appears as a t, J=8.4 Hz, 1H), 4.23 (brs, 1H), 2.49–2.44 (m, 1H), 1.82–1.70 (m, 2H), 1.24 (d, J=6.2 Hz, 3H), 1.14 ppm (d, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=164.19 (CO), 151.80 (CH), 119.99 (CH), 80.52 (CH), 63.40 (CH), 41.91 (CH_2), 33.61 (CH), 24.03 (CH_3), 16.36 ppm (CH_3); LCMS: m/z: 171 $[M+H]^+$; HRMS (FAB): calcd for $C_9H_{15}O_3$: 171.1021 $[M+H]^+$; found: 171.0996.

***ent*-Euscapholide (*ent*-20)**: Yield: 14.2 mg (from 450 mg resin), 44%; R_f=0.2 (silica gel, ethyl acetate/petroleum ether 1:1); $[\alpha]_D^{25}=-100.5$ (c=1.37 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ=6.91–6.86 (m, 1H), 6.01 (td, J=12.5, 1.6 Hz, 1H), 4.67–4.60 (m, 1H), 4.12–4.04 (m, 1H), 2.42–2.38 (m, 2H), 2.01 (td, J=14.4, 8.0 Hz, 1H), 1.75 (ddd, J=14.4, 5.2, 4.1 Hz, 1H), 1.25 ppm (d, J=6.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=163.99 (C), 145.21 (CH), 121.21 (CH), 76.80 (CH), 65.21 (CH), 43.54 (CH_2), 29.46 (CH_2), 23.71 ppm (CH_3); HRMS (FAB): m/z: calcd for $C_8H_{13}O_3$: 157.0865 $[M+H]^+$; found 157.0888.

General procedure for the synthesis of cryptocarya diacetate stereoisomers: Resin **32** (430 mg, 0.13 mmol) was swollen in TFA/CH_2Cl_2 1:2 (20 mL g^{-1} resin, 8.6 mL) for 20 min at RT. The resin was filtered and washed with CH_2Cl_2. The filtrate was co-evaporated with toluene. The residue was filtered through silica gel (CH_2Cl_2/MeOH 9:1) to yield a mixture of the free diol and the monoprotected compound as a byproduct. The diol was acetylated with Ac_2O (0.05 mL), Et_3N (0.07 mL), and a catalytic amount of DMAP in CH_2Cl_2 (1 mL). The mixture was stirred for 3 h from 0°C to RT, after which time 1 mL of a saturated solution of $NaHCO_3$ was added. The aqueous layer was extracted with CH_2Cl_2 (3× 10 mL). The combined organic extracts were dried over Na_2SO_4. The solvent was removed under reduced pressure and the crude product was purified by silica-gel chromatography (CH_2Cl_2 to CH_2Cl_2/EtOAc 2:1) to yield cryptocarya diacetate **30** with other minor isomers. After a second chromatography (petroleum ether/ethyl acetate 1:1) 4 mg (11%) of pure cryptocarya diacetate **30** were obtained.

The other diastereomers of cryptocarya diacetate were obtained following the same protocol.

General procedure for the synthesis of TBS-protected cryptocarya analogues: Release from the resin was achieved with DDQ as described above. The lactones were further purified by silica-gel column chromatography (ethyl acetate/petroleum ether 2:3) to yield the major diastereoisomer as an enriched diastereomer (>90% purity).

General procedure for the removal of a TBS group in solution to yield diol lactone analogues of cryptocarya diacetate: A catalytic amount of PPTS (3 mg, 0.01 mmol) was added to a stirred solution of the TBS-protected lactone (0.17 mmol) in MeOH (3 mL) and water (20μL). The reaction mixture was stirred at reflux for 16 h. The mixture was cooled and neutralized with saturated $NaHCO_3$ solution. The solution was evaporated and the residue underwent column chromatography on silica gel (ethyl acetate) to furnish the diol lactone in high yield (80–90%). Following this protocol, the four diastereomeric diol analogues **43**, **44**, **45**, and **46** of cryptocarya were obtained.

Cryptocarya diacetate 23: Yield: 10 mg (from 430 mg resin), 27%; $[\alpha]_D^{20}=+47.2$ (c=0.5 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ=6.86 (ddd, J=9.8, 5.9, 2.5 Hz, 1H), 6.02 (ddd, J=9.8, 2.7, 1.0 Hz, 1H), 5.10 (dddd, J=8.4, 7.0, 6.0, 3.7 Hz, 1H), 4.98 (ap sext, J=6.0 Hz, 1H), 4.49 (ddt, J=10.4, 6.6, 3.9 Hz, 1H), 2.45 (dddd, J=18.2, 5.9, 3.9, 1.0 Hz, 1H), 2.31 (ddt, J=18.4, 11.5, 2.6 Hz, 1H), 2.16 (ddd, J=14.8, 8.6, 6.6 Hz, 1H), 2.07 (s, 3H), 2.04 (s, 3H), 2.01 (ddd, J=14.4, 7.4, 7.4 Hz, 1H), 1.94 (ddd, J=14.7, 6.5, 3.7 Hz, 1H), 1.79 (dt, J=14.3, 5.8 Hz, 1H), 1.26 ppm (d, J=6.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=170.6 (CO), 170.5 (CO), 163.8 (CO), 144.7, 121.4, 74.9, 67.8, 67.7, 66.6, 40.5 (CH_2), 39.2 (CH_2), 29.2 (CH_2), 21.1, 20.1 ppm; IR (KBr): $\tilde{\nu}$=2925, 2857, 1731 (CO), 1373, 1241, 1038, 956, 815 cm^{-1}; MS (ESI): m/z: 302 $[M+NH_4]^+$; HRMS (FAB, m-NBA=m-nitrobenzoic acid): calcd for $C_{14}H_{21}O_6$: 285.1338 $[M+H]^+$; found: 285.1367.

(2*R*,4*R*)-1-[(*S*)-6-Oxo-3,6-dihydro-2*H*-pyran-2-yl]pentane-2,4-diyl diacetate (*ent*-23): Yield: 3.7 mg (from 250 mg resin), 11%; $[\alpha]_D^{20}=-44$ (c=0.46 in $CHCl_3$); HRMS (FAB): m/z: calcd for $C_{14}H_{21}O_6$: 285.1338 $[M+H]^+$; found: 285.1315.

(*S*)-6-[(2*R*,4R)-2-(*tert*-Butyldimethylsilyloxy)-4-hydroxypentyl]-5,6-dihydro-2*H*-pyran-2-one (*ent*-36): Yield: 11.4 mg (from 250 mg resin), 42%; R_f=0.25 (silica gel, ethyl acetate/petroleum ether 2:3); $[\alpha]_D^{20}=-33.6$ (c=1.14 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ=6.88 (ddd, J=9.7, 5.2, 3.1 Hz, 1H), 6.03 (td, J=9.7, 1.4 Hz, 1H), 4.54 (m, 1H), 4.22 (sep, J=3.5 Hz, 1H), 3.99–3.94 (m, 1H), 2.37–2.32 (m, 2H), 2.08 (ddd, J=14.0, 8.9, 4.2 Hz, 1H), 1.74 (1/2ABq, J=2.6, 1H), 1.70 (1/2ABq, J=2.6, 1H), 1.58 (td, J=14.0, 8.8 Hz, 1H), 1.18 (d, J=6.2 Hz, 3H), 0.89 (s, 9H), 0.13 (s, 3H), 0.11 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=164.06 (C), 144.88 (CH), 121.44 (CH), 74.81 (CH), 68.81 (CH), 66.53 (CH), 44.31 (CH_2), 42.99 (CH_2), 30.05 (CH_2), 25.74 (CH_3), 23.81 (CH_3), 17.80 (C), −4.2 (CH_3), −4.7 ppm (CH_3); LCMS: m/z: 315 $[M+H]^+$; HRMS (FAB): m/z: calcd for $C_{16}H_{31}O_4Si$: 315.1992 $[M+H]^+$; found: 315.1970.

(*R*)-6-[(2*S*,4*S*)-2-(*tert*-Butyldimethylsilyloxy)-4-hydroxypentyl]-5,6-dihydro-2*H*-pyran-2-one (36): Yield: 15 mg (from 420 mg resin), 38%; $[\alpha]_D^{20}=+29.65$ (c=1.4 in $CHCl_3$); IR (KBr): $\tilde{\nu}$=3355 (br, OH), 2925, 2880, 1720 (CO), 1459, 1260, 1070, 809 cm^{-1}; MS (ESI): m/z: 315 $[M+H]^+$, 332 $[M+NH_4]^+$; HRMS (FAB): m/z: calcd for $C_{16}H_{31}O_4Si$: 315.1992 $[M+H]^+$; found: 315.2016.

(2*S*,4*S*)-1-[(*S*)-6-Oxo-3,6-dihydro-2*H*-pyran-2-yl]pentane-2,4-diyl diacetate (37): Characterized from the isomer mixture. Yield: 31 mg (from 2.0 g resin), 18%; dr: 88:12; $[\alpha]_D^{20}=-20.5$ ($c=0.75$ in $CHCl_3$) (lit.[28c] $[\alpha]_D^{20}=-35.6$ ($c=0.75$ in $CHCl_3$)); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=6.85$ (m, 1H), 6.01 (dd, $J=10.0$, 2.0 Hz, 1H), 5.17 (m, 1H), 4.96 (ap sext, $J=$ 6.1 Hz, 1H), 4.48 (ddd, $J=9.0$, 6.2, 3.3 Hz, 1H), 2.34 (m, 2H), 2.10–1.99 (m, 2H), 2.05 (s, 3H), 2.04 (s, 3H), 1.88 (m, 1H), 1.77 (m, 1H), 1.26 ppm (d, $J=6.2$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=170.5$ (CO), 170.3 (CO), 163.6 (CO), 144.4, 121.5, 74.5, 67.9, 67.6, 40.4 (CH_2), 39.6 (CH_2), 29.6 (CH_2), 21.3, 21.1, 20.1 ppm; IR (KBr): $\tilde{\nu}=2924$, 2853, 1736 (CO), 1374, 1243, 1022, 816 cm^{-1}; MS (ESI): *m*/*z*: 302 $[M+NH_4]^+$; HRMS (FAB): *m*/*z*: calcd for $C_{14}H_{21}O_6$: 285.1338 $[M+H]^+$; found: 285.1327.

(2*R*,4*R*)-1-[(*R*)-6-Oxo-3,6-dihydro-2*H*-pyran-2-yl]pentane-2,4-diyl diacetate (*ent*-37): Yield: 4.8 mg (from 250 mg resin), 14%; $[\alpha]_D^{20}=+25.6$ ($c=$ 0.6 in $CHCl_3$); HRMS (FAB): *m*/*z*: calcd for $C_{14}H_{21}O_6$: 285.1338 $[M+H]^+$; found: 285.1322.

(*R*)-6-[(2*R*,4*R*)-2-(*tert*-Butyldimethylsilyloxy)-4-hydroxypentyl]-5,6-dihydro-2*H*-pyran-2-one (*ent*-38): Yield: 18 mg (from 250 mg resin), 67%; $R_f=0.26$ (silica gel, ethyl acetate/petroleum ether 2:3); $[\alpha]_D^{20}=+3.8$ ($c=$ 1.79 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=6.88$–6.86 (m, 1H), 6.03 (td, $J=9.9$, 1.9 Hz, 1H), 4.6–4.5 (m, 1H), 4.23–4.16 (m, 1H), 3.98–3.91 (m, 1H), 2.33–2.30 (m, 2H), 1.99 (ddd, $J=14.2$, 9.3, 3.3 Hz, 1H), 1.73 (ddd, $J=14.2$, 8.8, 2.9 Hz, 1H), 1.66–1.59 (series of d, 2H), 1.18 (d, $J=$ 6.2 Hz, 3H), 0.86 (s, 9H), 0.09 (s, 3H), 0.07 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=164.13$ (C), 145.19 (CH), 121.37 (CH), 74.57 (CH), 66.60 (CH), 65.15 (CH), 46.74 (CH_2), 42.85 (CH_2), 30.02 (CH_2), 25.79 (CH_3), 24.28 (CH_3), 17.89 (C), −4.40 (CH_3), −4.60 ppm (CH_3); LCMS: *m*/*z*: 315 $[M+H]^+$; HRMS (FAB): *m*/*z*: calcd for $C_{16}H_{31}O_4Si$: 315.1992 $[M+H]^+$; found: 315.1973.

(*S*)-6-[(2*S*,4*S*)-2-(*tert*-Butyldimethylsilyloxy)-4-hydroxypentyl]-5,6-dihydro-2*H*-pyran-2-one (38): Yield: 15 mg (from 420 mg resin), 38%; $[\alpha]_D^{20}=$ +4.3 ($c=0.84$ in $CHCl_3$); IR (KBr): $\tilde{\nu}=3468$ (br, OH), 2929, 2857, 1717 (CO), 1462, 1385, 1252, 1058, 825 cm^{-1}; MS (ESI): *m*/*z* (%): 315 $[M+1]^+$ (100), 332 $[M+NH_4]^+$; HRMS (FAB): *m*/*z*: calcd for $C_{16}H_{31}O_4Si$: 315.1992 $[M+H]^+$; found: 315.1974.

(2*R*,4*S*)-1-[(*R*)-6-Oxo-3,6-dihydro-2*H*-pyran-2-yl]pentane-2,4-diyl diacetate (39): Yield: 7 mg (from 350 mg resin), 23%; $[\alpha]_D^{20}=+43.5$ ($c=0.80$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=6.85$ (ddd, $J=9.6$, 5.1, 3.2 Hz, 1H), 6.02 (ddd, $J=9.8$, 2.3, 1.4 Hz, 1H), 5.17 (ddd, $J=13.5$, 8.0, 4.1 Hz, 1H), 4.94 (ap sept, $J=3.5$ Hz, 1H), 4.48 (m, 1H), 2.34 (m, 2H), 2.08–1.99 (m, 2H), 2.03 (s, 3H), 2.02 (s, 3H), 1.90 (m, 1H), 1.78 (ddd, $J=14.4$, 6.6, 3.5 Hz, 1H), 1.24 ppm (d, $J=6.2$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=170.7$ (C), 170.4 (C), 163.7 (C), 144.5, 121.6, 74.7, 67.3, 66.7, 40.9 (CH_2), 40.2 (CH_2), 29.7 (CH_2), 21.2, 21.0, 20.4 ppm; IR (KBr): $\tilde{\nu}=2935$, 2853, 1736 (CO), 1375, 1246, 1023, 822 cm^{-1}; MS (ESI): *m*/*z*: 302 $[M+NH_4]^+$; HRMS (FAB): *m*/*z*: calcd for $C_{14}H_{20}O_6$: 284.1260 $[M+H]^+$; found: 285.1350.

(2*S*,4*R*)-1-[(*S*)-6-Oxo-3,6-dihydro-2*H*-pyran-2-yl]pentane-2,4-diyl diacetate (*ent*-39): Yield: 3 mg (from 250 mg resin), 10%; $[\alpha]_D^{20}=-32$ ($c=0.17$ in $CHCl_3$); HRMS (FAB): *m*/*z*: calcd for $C_{14}H_{21}O_6$: 285.1338 $[M+H]^+$; found: 285.1316.

(*S*)-6-[(2*S*,4*R*)-2-(*tert*-Butyldimethylsilyloxy)-4-hydroxypentyl]-5,6-dihydro-2*H*-pyran-2-one (*ent*-40): Yield: 13.5 mg (from 250 mg resin), 50%; $R_f=0.26$ (silica gel, ethyl acetate/petroleum ether 4:6); $[\alpha]_D^{20}=-2.3$ ($c=$ 1.2 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=6.91$–6.85 (m, 1H), 6.01 (td, $J=9.7$, 1.9 Hz, 1H), 4.54 (dd, $J=8.2$, 4.8 Hz, 1H), 4.33 (m, 1H), 4.12 (m, 1H), 2.35–2.32 (m, 2H), 1.91 (ddd, $J=7.4$, 3.8, 1.7 Hz, 1H), 1.74 (ddd, $J=14.6$, 10.1, 4.4 Hz, 1H), 1.55 (1/2ABq, $J=2.7$, 1H), 1.52 (1/2ABq, $J=2.7$, 1H), 1.16 (d, $J=6.1$ Hz, 3H), 0.87 (s, 9H), 0.14 (s, 3H), 0.08 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=163.94$ (C), 145.17 (CH), 121.39 (CH), 74.27 (CH), 66.32 (CH), 64.66 (CH), 44.40 (CH_2), 41.49 (CH_2), 29.70 (CH_2), 25.79 (CH_3), 23.93 (CH_3), 17.82 (C), −4.47 (CH_3), −4.96 ppm (CH_3); LCMS: *m*/*z*: 315 $[M+H]^+$; HRMS (FAB): *m*/*z*: calcd for $C_{16}H_{31}O_4Si$: 315.1992 $[M+H]^+$; found: 315.1985.

(*R*)-6-[(2*R*,4*S*)-2-(*tert*-Butyldimethylsilyloxy)-4-hydroxypentyl]-5,6-dihydro-2*H*-pyran-2-one (40): Yield: 20 mg (from 362 mg resin), 57%; $[\alpha]_D^{20}=$ +6.84 ($c=1.17$ in $CHCl_3$); IR (KBr): $\tilde{\nu}=3450$ (br, OH), 2959, 1720 (CO), 1471, 1382, 1253, 1059, 836 cm^{-1}; MS (ESI): *m*/*z* (%): 315 $[M+H]^+$ (100), 332 $[M+NH_4]^+$; HRMS (FAB): *m*/*z*: calcd for $C_{16}H_{31}O_4Si$: 315.1992 $[M+H]^+$; found: 315.2022.

(2*R*,4*S*)-1-[(*S*)-6-Oxo-3,6-dihydro-2*H*-pyran-2-yl]pentane-2,4-diyl diacetate (41): Yield: 8 mg (from 300 mg resin), 20%; $[\alpha]_D^{20}=-41.5$ ($c=1.02$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=6.86$ (ddd, $J=9.6$, 6.0, 2.5 Hz, 1H), 6.01 (ddd, $J=9.8$, 2.8, 1.0 Hz, 1H), 5.15 (ap sept, $J=4.2$ Hz, 1H), 4.99–4.87 (m, 1H), 4.47 (ddd, $J=18.2$, 6.4, 3.9 Hz, 1H), 2.50 (dddd, $J=$ 19.2, 6.1, 3.9, 1.0 Hz, 1H), 2.31 (ddt, $J=18.4$, 11.7, 2.5 Hz, 1H), 2.15 (ddd, $J=14.6$, 8.4, 6.2 Hz, 1H), 2.05 (s, 3H), 2.03 (m, 1H), 2.02 (s, 3H), 1.93–1.83 (m, 2H), 1.23 ppm (d, $J=6.2$ Hz, 3H); ^{13}C NMR/APT (100 MHz, $CDCl_3$): $\delta=170.8$ (CO), 170.6 (CO), 163.8 (CO), 144.7, 121.4, 74.9, 66.7, 66.6, 40.8 (CH_2), 39.9 (CH_2), 29.2 (CH_2), 21.2, 21.0, 20.4 ppm; IR (KBr): $\tilde{\nu}=2927$, 2860, 1732 (CO), 1429, 1374, 1245, 1024, 956, 814 cm^{-1}; MS (ESI): *m*/*z*: 302 $[M+NH_4]^+$; HRMS (FAB, *m*-NBA): *m*/*z*: calcd for $C_{14}H_{21}O_6$: 285.1338 $[M+H]^+$; found: 285.1355.

(2*S*,4*R*)-1-[(*R*)-6-Oxo-3,6-dihydro-2*H*-pyran-2-yl]pentane-2,4-diyl diacetate (*ent*-41): Yield: 5 mg (from 300 mg resin), 12%; $[\alpha]_D^{20}=+30$ ($c=0.62$ in $CHCl_3$); HRMS (FAB): *m*/*z*: calcd for $C_{14}H_{21}O_6$: 285.1338 $[M+H]^+$; found: 285.1329.

(*R*)-6-[(2*S*,4*R*)-2-(*tert*-Butyldimethylsilyloxy)-4-hydroxypentyl]-5,6-dihydro-2*H*-pyran-2-one (*ent*-42): Yield: 11.5 mg (from 250 mg resin), 42%; $R_f=0.25$ (silica gel, ethyl acetate/petroleum ether 40:60); $[\alpha]_D^{20}=+45$ ($c=$ 1.15 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=6.89$–6.84 (m, 1H), 6.01 (td, $J=9.9$, 1.7 Hz, 1H), 4.51–5.45 (m, 1H), 4.33 (m, 1H), 4.08–4.00 (m, 1H), 2.37–2.34 (m, 2H), 2.08 (ddd, $J=11.5$, 7.5, 3.5 Hz, 1H), 1.91 (ddd, $J=12.0$, 7.0, 3.6 Hz, 1H), 1.67 (d, $J=3.6$ Hz, 1H), 1.52 (d, $J=2.5$ Hz, 1H), 1.17 (d, $J=6.2$ Hz, 3H), 0.88 (s, 9H), 0.11 (s, 3H), 0.08 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=163.99$ (C), 144.82 (CH), 121.44 (CH), 74.93 (CH), 67.40 (CH), 64.35 (CH), 42.95 (CH_2), 41.33 (CH_2), 29.96 (CH_2), 25.73 (CH_3), 24.02 (CH_3), 17.82 (C), −4.68 (CH_3), −4.83 ppm (CH_3); LCMS: *m*/*z*: 315 $[M+H]^+$; HRMS (FAB): *m*/*z*: calcd for $C_{16}H_{31}O_4Si$: 315.1992 $[M+H]^+$; found: 315.2027.

(*S*)-6-[(2*R*,4*S*)-2-(*tert*-Butyldimethylsilyloxy)-4-hydroxypentyl]-5,6-dihydro-2*H*-pyran-2-one (42): Yield: 19 mg (from 318 mg resin), 60%; $[\alpha]_D^{20}=$ −37.98 ($c=1.04$ in $CHCl_3$); IR (KBr): $\tilde{\nu}$3441 (br, OH), 2956, 2840, 1722 (CO), 1462, 1379, 1254, 1063, 836 cm^{-1}; MS (ESI): *m*/*z* (%): 315 $[M+H]^+$ (100), 332 $[M+NH_4]^+$; HRMS (FAB): *m*/*z*: calcd for $C_{16}H_{31}O_4Si$: 315.1992 $[M+H]^+$; found: 315.1963.

(*S*)-6-[(2*R*,4*R*)-2,4-Dihydroxypentyl]-5,6-dihydro-2*H*-pyran-2-one (43): Yield: 30 mg (from 54 mg of *ent*-**36**), 87%; $R_f=0.2$ (silica gel, ethyl acetate); $[\alpha]_D^{25}=-88.1$ ($c=1.13$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=$ 6.90–6.86 (m, 1H), 5.98 (d, $J=9.9$ Hz, 1H), 4.68–4.60 (m, 1H), 4.13–4.02 (m, 2H), 2.43–2.36 (m, 2H), 2.01 (td, $J=14.4$, 7.4 Hz, 1H), 1.78–1.72 (m, 1H), 1.58–1.55 (m, 2H), 1.19 ppm (d, $J=6.2$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=164.27$ (C), 145.47 (CH), 121.05 (CH), 76.17 (CH), 69.37 (CH), 68.79 (CH), 44.46 (CH_2), 42.31 (CH_2), 29.32 (CH_2), 24.18 ppm (CH_3); LCMS: *m*/*z*: 200.9 $(M)^+$; HRMS (FAB): *m*/*z*: calcd for $C_{10}H_{17}O_4$: 201.1127 $[M+H]^+$; found: 201.1106.

(*R*)-6-[(2*R*,4*R*)-2,4-Dihydroxypentyl]-5,6-dihydro-2*H*-pyran-2-one (44): Yield: 20 mg (from 47 mg of *ent*-**38**), 67%; $R_f=0.2$ (silica gel, ethyl acetate); $[\alpha]_D^{25}=+41$ ($c=0.98$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=$ 6.88 (ddd, $J=9.7$, 5.6, 2.9 Hz, 1H), 6.01–5.97 (m, 1H), 4.76–4.69 (m, 1H), 4.24–4.18 (m, 1H), 4.10–4.03 (m, 1H), 2.37–2.32 (m, 2H), 1.85 (ddd, $J=$ 14.4, 9.6, 2.8 Hz, 1H), 1.68 (ddd, $J=14.4$, 9.9, 2.8 Hz, 1H), 1.58–1.52 (m, 2H), 1.19 ppm (d, $J=6.2$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=$ 164.59 (C), 145.54 (CH), 121.19 (CH), 76.69 (CH), 68.83 (CH), 67.78 (CH), 44.97 (CH_2), 43.02 (CH_2), 29.87 (CH_2), 24.30 ppm (CH_3); LCMS: *m*/*z*: 200.9 $[M]^+$; HRMS (FAB): *m*/*z*: calcd for $C_{10}H_{17}O_4$: 201.1127 $[M+H]^+$; found: 201.1147.

(*S*)-6-[(2*S*,4*R*)-2,4-Dihydroxypentyl]-5,6-dihydro-2*H*-pyran-2-one (45): Yield: 15.5 mg (from 27 mg of *ent*-**40**), 90%; $R_f=0.2$ (silica gel, ethyl acetate); $[\alpha]_D^{25}=-68.8$ ($c=1.0$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=$ 6.92–6.87 (m, 1H), 6.02–5.98 (m, 1H), 4.79–4.72 (m, 1H), 4.34–4.28 (m, 1H), 4.17–4.10 (m, 1H), 2.40–2.36 (m, 2H), 1.85 (ddd, $J=14.4$, 9.3, 2.7 Hz, 1H), 1.75 (ddd, $J=14.4$, 9.9, 2.9 Hz, 1H), 1.62–1.57 (m, 2H), 1.23 ppm (d, $J=6.4$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=164.73$ (C), 145.66 (CH), 121.20 (CH), 75.08 (CH), 65.29 (CH), 64.32 (CH), 44.74 (CH_2), 42.34 (CH_2), 29.90 (CH_2), 23.55 ppm (CH_3); LCMS: *m*/*z*:

200.9 $[M]^+$; HRMS (FAB): m/z: calcd for $C_{10}H_{17}O_4$: 201.1127 $[M+H]^+$; found: 201.1088.

(*R*)-6-[(2*S*,4*R*)-2,4-Dihydroxypentyl]-5,6-dihydro-2*H*-pyran-2-one (46): Yield: 15 mg of **46** (from 50 mg of *ent*-**42**), 50% (8 mg, 25% of **73** was also obtained as a minor product); $R_f=0.2$ (silica gel, ethyl acetate); $[\alpha]_D^{25}=+73.6$ ($c=1.2$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=6.92$–6.87 (m, 1H), 6.02–5.99 (m, 1H), 4.71–4.64 (m, 1H), 4.22–4.13 (m, 2H), 2.44–2.40 (m, 2H), 2.08 (ddd, $J=16.2$, 8.8, 7.4 Hz, 1H), 1.77 (ddd, $J=16.2$, 5.6, 3.7 Hz, 1H), 1.66–1.57 (m, 2H), 1.23 ppm (d, $J=6.2$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=164.25$ (C), 145.47 (CH), 121.11 (CH), 76.68 (CH), 66.20 (CH), 65.11 (CH), 44.30 (CH_2), 41.84 (CH_2), 29.36 (CH_2), 23.51 ppm (CH_3); LCMS: m/z: 200.9 $[M]^+$; HRMS (FAB): m/z: calcd for $C_{10}H_{17}O_4$: 201.1127 $[M+H]^+$; found: 201.1103.

(*R*)-6-[(2*R*,4*S*,6*R*)-2,4-Bis(*tert*-butyldimethylsilyloxy)-6-hydroxyheptyl]-5,6-dihydro-2*H*-pyran-2-one (49): Yield: 1.6 mg (from 450 mg resin), 2%; $R_f=0.08$ (petroleum ether/ethyl acetate 4:1+0.1% MeOH); $[\alpha]_D^{20}=+10.5$ ($c=0.19$ in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=6.87$ (ddd, $^3J=9.5$, 4.9, 3.6 Hz, 1H), 6.02 (ddd, $^3J=9.9$, $^4J=1.9$, 1.9 Hz, 1H) 4.64–4.55 (m, 1H), 4.17–4.07 (m, 2H), 4.01–3.93 (m, 1H), 2.37–2.32 (m, 2H), 2.06 (ddd, $^2J=14.4$, $^3J=8.3$, 4.2 Hz, 1H), 1.90 (ddd, $^2J=13.6$, $^3J=7.0$, 5.3 Hz, 1H), 1.81–1.57 (m, 4H), 1.18 (d, $^3J=6.1$ Hz, 3H), 0.90 (s, 9H), 0.88 (s, 9H), 0.12 (s, 3H), 0.09 (s, 3H), 0.07 (s, 3H), 0.65 ppm (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=144.4$ (CO), 121.2 (CH), 74.4 (CH), 68.8 (CH), 66.0 (CH), 64.5 (CH), 42.9 (CH_2), 42.8 (CH_2), 42.1 (CH_2), 30.1 (CH_2), 25.9 (CH_3), 24.1 (C), −4.4 ppm (C); LCMS: m/z: 473.1 $[M+H]^+$; MS (FAB): m/z: 473.5 $[M+H]^+$; HRMS (FAB): m/z: calcd for $C_{24}H_{49}O_5Si_2$: 473.3119 $[M+H]^+$; found: 473.3141.

(*S*,*E*)-9-Phenylnon-2-en-5-ol ((*S*)-55b): Compound (*S*)-**56**[34] (2.76 g, 13.11 mmol) and PPTS (217 mg, 1.14 mmol) were added to a stirred solution of 5-phenylpentanal (1.85 g, 11.42 mmol) in CH_2Cl_2 (11 mL, 0°C). After stirring at RT for 20 h, solid $NaHCO_3$ (450 mg, 5.36 mmol) was added and the turbid mixture was stirred for an additional 2 h. Filtration from the precipitate and flash chromatography of the concentrated filtrate (petroleum ether/ethyl acetate 95:5+0.1% MeOH) afforded 1.75 g (8.01 mmol, 70%) of a colorless oil. $R_f=0.19$ (petroleum ether/ethyl acetate 9:1+0.1% MeOH); $[\alpha]_D^{20}=-1.0$ ($c=1.02$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.30$–7.25 (m, 2H), 7.19–7.38 (m, 3H), 5.56 (dtq, $^2J=15.2$, $^3J=6.3$, $^4J=1.2$ Hz, 1H), 5.43 (dddq, $^2J=15.2$, $^3J=7.8$, 6.3, $^4J=1.4$ Hz, 1H), 3.61–3.55 (m, 1H,), 2.62 (t, $^3J=7.7$ Hz, 2H), 2.22 (dddt, $^2J=13.9$, $^3J=6.3$, 4.0, $^4J=1.3$ Hz, 1H), 2.05 (dddt, $^2J=14.0$, $^3J=7.8$, 7.8, $^4J=0.9$ Hz, 1H), 1.70 (brd, $^3J=6.4$ Hz, 1H), 1.68–1.35 ppm (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=142.62$ (C), 129.01 (CH), 128.4 (CH), 128.2 (d, CH), 127.1 (d, CH), 125.6 (d, CH), 70.8 (d, CH), 40.7 (CH_2), 36.6 (CH_2), 35.9 (CH_2), 31.5 (CH_2), 25.4 (CH_2), 18.1 ppm (CH_3); HRMS (FAB): m/z: calcd for $C_{15}H_{23}O$: 219.1749 $[M+H]^+$; found: 219.1739.

Determination of the loading of 55b on diethylsilylpolystyrene resin: A sample of the resin was treated with HF/pyridine as described and the resulting solution in THF was compared to a calibration curve taken from different concentrations of **55b** in THF on a Daicel Chirapak AD column, eluent: *n*-hexane/isopropanol 98:2, flow 0.5 mL min^{-1}.

(*R*)-6-[(*S*)-2-Hydroxy-6-phenylhexyl]-5,6-dihydro-2*H*-pyran-2-one (*ent*-51): Yield: 11 mg (from 300 mg resin), 31%; $R_f=0.2$ (silica gel, ethyl acetate/petroleum ether 1:1); $[\alpha]_D^{25}=+66$ ($c=1.0$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.29$–7.25 (m, 2H), 7.19–7.15 (m, 3H), 6.90–6.86 (m, 1H), 6.02 (brd, $J=9.9$ Hz, 1H), 4.65–4.62 (m, 1H), 3.91–3.80 (m, 1H), 2.62 (t, $J=7.6$ Hz, 2H), 2.40–2.38 (m, 2H), 1.98–1.93 (m, 2H), 1.79–1.75 (m, 1H), 1.67–1.62 (m, 2H), 1.50–1.47 (m, 3H), 1.40–1.36 ppm (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=163.92$ (C), 145.12 (CH), 142.39 (C), 128.35 (CH), 128.26 (CH), 125.67 (CH), 121.26 (CH), 76.90 (CH), 69.02 (CH), 41.91 (CH_2), 37.47 (CH_2), 35.82 (CH_2), 31.31 (CH_2), 29.46 (CH_2), 25.01 ppm (CH_2); LCMS: m/z: 275 $[M+H]^+$.

(*R*)-6-[(2*S*,4*S*)-2,4-Dihydroxy-8-phenyloctyl]-5,6-dihydro-2*H*-pyran-2-one (60): Yield: 2.2 mg (from 270 mg Wang resin), 6.3%; 8.9 mg (from 900 mg diethylsilylpolystyrene resin, loading 0.6 mmol g^{-1}), 5%; $R_f=0.2$ (silica gel, ethyl acetate); $[\alpha]_D^{20}=+55.6$ ($c=0.27$ in $CHCl_3$) (lit.[32b,c] $[\alpha]_D^{25}=+62.1$ ($c=1.0$ in $CHCl_3$)); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=7.29$–7.26 (m, 2H), 7.18–7.16 (m, 3H), 6.89 (ddd, $^3J=9.4$, 4.7, 3.9 Hz, 1H), 6.02 (ddd, $^3J=9.6$, $^4J=1.6$, 1.6 Hz, 1H) 4.70–4.64 (m, 1H), 4.15–4.10 (m, 1H), 3.90–3.85 (m, 1H), 2.62 (t, $^3J=7.6$ Hz, 2H), 2.43–2.41 (m, 2H), 2.02 (ddd, $^2J=15.0$, $^3J=7.5$, 7.5 Hz, 1H), 1.77 (ddd, $^2J=14.4$, $^3J=5.4$, 3.9 Hz, 1H), 1.67–1.31 ppm (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=164.1$ (C), 145.3 (CH), 142.4 (CH), 128.4 (CH), 128.3 (CH), 125.7 (CH), 121.2 (CH), 76.3 (CH), 72.9 (CH), 69.8 (CH), 42.8 (CH_2), 42.3 (CH_2), 38.1 (CH_2), 35.8 (CH_2), 31.3 (CH_2), 29.4 (CH_2), 24.9 ppm (CH_2); LCMS: m/z: 319.1 $[M+H]^+$; HRMS (FAB): m/z: calcd for $C_{19}H_{27}O_4$: 319.1909 $[M+H]^+$; found: 319.1935.

(*R*)-6-[(2*S*,4*S*)-2-(*tert*-Butyldimethylsilyloxy)-4-hydroxy-8-phenyloctyl]-5,6-dihydro-2*H*-pyran-2-one (61): Yield: 10 mg (from 720 mg resin), 9.3%; $R_f=0.2$ (silica gel, ethyl acetate/petroleum ether 1:1); $[\alpha]_D^{20}=+23.2$ ($c=0.96$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.28$–7.25 (m, 2H), 7.18–7.16 (m, 3H), 6.87 (ddd, $J=9.6$, 5.2, 3.6 Hz, 1H), 6.03 (ddd, $J=9.6$, 2.4, 1.2 Hz, 1H), 4.58–4.51 (m, 1H), 4.26–4.20 (m, 1H), 3.80–3.74 (m, 1H), 2.62 (t, $J=7.6$ Hz, 2H), 2.37–2.30 (m, 2H), 2.07 (ddd, $J=8.8$, 8.8, 4.4 Hz, 1H), 1.82–1.45 (m, 9H), 0.89 (s, 9H), 0.13 (s, 3H), 0.11 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=164.06$ (C), 144.85 (CH), 142.63 (C), 128.40 (CH), 128.38 (CH), 128.23 (CH), 128.21 (CH), 125.60 (CH), 121.47 (CH), 74.84 (CH), 70.27 (CH), 68.87 (CH), 42.98 (CH_2), 42.65 (CH_2), 37.77 (CH_2), 35.88 (CH_2), 31.51 (CH_2), 30.04 (CH_2), 25.77 ($CH_3\times3$), 25.07 (CH_2), 17.81 (C), −4.23 (CH_3), −4.63 ppm (CH_3); LCMS: m/z: 432 $[M]^+$; HRMS (FAB): m/z: calcd for $C_{25}H_{41}O_4Si$: 433.2774 $[M+H]^+$; found: 433.2769.

(*R*)-6-[(2*S*,4*S*,6*S*)-2,4,6-Trihydroxy-10-phenyldecyl]-5,6-dihydro-2*H*-pyran-2-one (63): Yield: 4.5 mg (from 700 mg resin), 4.3%; $R_f=0.2$ (silica gel, ethyl acetate + 2% MeOH); $[\alpha]_D^{20}=+25.6$ ($c=0.44$ in $CHCl_3$); ^{1}H NMR (400 MHz, CD_3COCD_3): $\delta=7.25$–7.21 (m, 2H), 7.18–7.12 (m, 3H), 7.01–6.97 (m, 1H), 5.89 (dd, $J=9.9$, 2.3 Hz, 1H), 4.65–4.60 (m, 1H), 4.14–4.07 (m, 2H), 3.86–3.81 (m, 1H), 2.59 (t, $J=7.6$ Hz, 2H), 2.55–2.49 (m, 1H), 2.39–2.30 (m, 1H), 2.06–2.04 (m, 2H), 1.90–1.78 (m, 2H), 1.70–1.45 ppm (m, 8H); ^{13}C NMR (100 MHz, CD_3COCD_3): $\delta=164.32$ (C), 146.71 (CH), 143.54 (C), 129.17 (CH), 129.16 (CH), 129.03 (CH), 126.38 (CH), 121.51 (CH), 76.28 (CH), 72.11 (CH), 68.43 (CH), 44.56 (CH_2), 43.34 (CH_2), 38.80 (CH_2), 36.50 (CH_2), 31.75 (CH_2), 25.10 ppm (CH_2); LCMS: m/z: 363 $[M+H]^+$; HRMS (FAB): m/z: calcd for $C_{21}H_{31}O_5$: 363.2171 $[M+H]^+$; found: 363.2166.

(*S*)-6-[(2*S*,4*R*,6*R*)-2,4-Bis(*tert*-butyldimethylsilyloxy)-6-hydroxy-10-phenyldecyl]-5,6-dihydro-2*H*-pyran-2-one (64): Yield: 12.2 mg (from 700 mg resin), 10.5%; $R_f=0.2$ (silica gel, ethyl acetate/petroleum ether 1:4); $[\alpha]_D^{20}=-34.4$ ($c=1.22$ in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=7.28$–7.18 (m, 2H), 7.18–7.16 (m, 3H), 6.91–6.88 (m, 1H), 6.01 (dd, $J=9.7$, 1.7 Hz, 1H), 4.72–4.69 (m, 1H), 4.10–4.07 (m, 2H), 3.68–3.66 (m, 1H), 2.61 (t, $J=7.7$ Hz, 2H), 2.40–2.37 (m, 1H), 2.28 (t 1/2ABq, $J=18.7$, 4.5 Hz, 1H), 2.11 (ddd, $J=14.7$, 8.7, 3.0 Hz, 1H), 1.91–1.85 (m, 1H), 1.71–1.56 (m, 6H), 1.52–1.46 (m, 2H), 1.42–1.38 (m, 2H), 0.89 (s, 9H), 0.88 (s, 9H), 0.11 (s, 3H), 0.09 (s, 3H), 0.05 ppm (brs, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=164.67$ (C), 145.36 (CH), 142.88 (C), 128.38 (CH), 128.18 (CH), 125.50 (CH), 121.20 (CH), 74.16 (CH), 69.03 (CH), 68.93 (CH), 66.45 (CH), 45.01 (CH_2), 43.92 (CH_2), 41.10 (CH_2), 38.16 (CH_2), 36.00 (CH_2), 31.62 (CH_2), 30.26 (CH_2), 25.82 ($CH_3\times6$), 25.47 (CH_2), 17.98 (C), 17.88 (C), −4.05 (CH_3), −4.27 (CH_3), −4.53 (CH_3), −4.54 ppm (CH_3); LCMS: m/z: 590 $[M]^+$; HRMS (FAB): m/z: calcd for $C_{33}H_{59}O_5Si_2$: 591.3901 $[M+H]^+$; found: 591.3944.

(4*R*,6*S*)-4-Allyl-2,2-dimethyl-6-(4-phenylbutyl)-1,3-dioxane (67): Resin **66** (270 mg, 0.16 mmol) was treated with HF/pyridine and subsequent column chromatography yielded 24.2 mg (0.10 mmol, 63%) of the free diol as a colorless oil. This diol (22.8 mg, 0.09 mmol) was dissolved in 2,2-dimethoxypropane (2 mL). (+)-Camphorsulfonic acid was added (1.8 mg, 0.007 mmol) and the mixture was stirred for 3.5 h at RT. The reaction mixture was diluted with ethyl acetate (5 mL) and washed with a saturated aqueous $NaHCO_3$ solution and brine. The organic phase was dried over magnesium sulfate, concentrated, and then underwent column chromatography (silica gel, petroleum ether/ethyl acetate 99:1) to yield 12.0 mg (0.04 mmol, 46%) of a colorless oil. $R_f=0.27$ (petroleum ether/ethyl acetate 95:5); $[\alpha]_D^{20}=+4.3$ ($c=1.40$ in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=7.29$–7.26 (m, 2H), 7.19–7.17 (m, 3H), 5.85–5.77 (m, 1H), 5.11–5.04 (m, 2H), 3.89–3.83 (m, 1H), 3.81–3.76 (m, 1H), 2.61 (t, $^3J=7.6$ Hz, 2H), 2.31 (ddd, $^2J=13.9$, $^3J=6.3$, 6.3 Hz, 1H), 2.15 (ddd, $^2J=13.8$,

$^3J=7.0$, 6.9 Hz, 1H), 1.65–1.52 (m, 4H), 1.49 (ddd, $^2J=12.8$, $^3J=2.4$, 2.4 Hz, 1H), 1.43 (s, 3H), 1.41–1.34 (m, 2H), 1.40 (s, 3H), 1.12 ppm (ddd, $^2J=12.2$, $^3J=12.0$, 12.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=142.7$ (C), 134.3 (CH), 128.4 (CH), 128.2 (CH), 125.6 (CH), 117.0 (CH_2), 98.4 (C), 68.9 (CH), 68.7 (CH), 40.9 (CH_2), 36.5 (CH_2), 36.3 (CH_2), 35.9 (CH_2), 31.5 (CH_2), 30.3 (CH_3), 24.7 (CH_2), 19.8 ppm (CH_3); MS (FAB): m/z: 289.3 $[M+H]^+$; HRMS (FAB): m/z: calcd for $C_{19}H_{29}O_2$: 289.2168 $[M+H]^+$; found: 289.2139.

(*R*)-6-[(2*R*,4*R*)-2,4-Dihydroxy-8-phenyloctyl]-5,6-dihydro-2*H*-pyran-2-one (69): Yield: 5.3 mg (from 875 mg of diethylsilylpolystyrene resin), 3%; $R_f=0.25$ (silica gel, ethyl acetate + 0.1% MeOH); $[\alpha]_D^{20}=+33.9$ ($c=0.59$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.29$–7.25 (m, 2H), 7.20–7.16 (m, 3H), 6.89 (ddd, $^3J=9.7$, 5.4, 3.1 Hz, 1H), 6.02 (ddd, $^3J=9.8$, $^4J=2.3$, 1.2 Hz, 1H) 4.78–4.71 (m, 1H), 4.26–4.20 (m, 1H), 3.92–3.87 (m, 1H), 2.62 (t, $^3J=7.7$ Hz, 2H), 2.38–2.33 (m, 2H), 1.86 (ddd, $^2J=14.4$, $^3J=9.6$, 2.5 Hz, 1H), 1.71 (ddd, $^2J=14.4$, $^3J=10.1$, 3.0 Hz, 1H), 1.69–1.33 ppm (m, 8H); ^{13}C NMR (100.71 MHz, $CDCl_3$): $\delta=164.4$ (CO), 145.3 (CH), 142.4 (C), 128.4, 128.3, 125.7 (3×CH), 121.3 (CH), 74.7 (CH), 73.0 (CH), 68.1 (CH), 43.2 (CH_2), 43.0 (CH_2), 38.2 (CH_2), 35.8 (CH_2), 31.3 (CH_2), 29.9 (CH_2), 24.9 ppm (CH_2); LCMS: m/z: 319.1 $[M+H]^+$; MS (FAB): m/z: 319.3 $[M+H]^+$; HRMS (FAB): m/z: calcd for $C_{19}H_{27}O_4$: 319.1909 $[M+H]^+$; found: 319.1898.

(1*S*,5*S*,8*R*,9*R*)-8,9-Dimethyl-2,6-dioxabicyclo[3.3.1]nonan-3-one (70): The alcohol **23f** (6 mg, 0.03 mmol) was dissolved in anhydrous benzene (1.5 mL) and treated with *p*TsOH (2 mg). The mixture was stirred overnight at RT and was worked up with solid $NaHCO_3$. Filtration, washing with EtOAc, and removal of the solvent in vacuo afforded a crude product which was purified by silica-gel chromatography (ethyl acetate/petroleum ether 1:10) to yield **70** (4 mg, 66%). $R_f=0.5$ (silica gel, ethyl acetate/petroleum ether 1:4); $[\alpha]_D^{20}=-2.3$ ($c=0.42$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=4.32$ (brs, 1H), 4.03 (brs, 1H), 3.85 (d 1/2ABq, $J=13.1$, 3.5 Hz, 1H), 3.50 (1/2ABq, $J=13.1$ Hz, 1H), 2.80 (d 1/2ABq, $J=19.5$, 4.8 Hz, 1H), 2.04–2.01 (brd, $J=19.5$ Hz, 1H), 2.36–2.29 (m, 1H), 2.15–2.08 (m, 1H), 1.17 (d, $J=7.2$ Hz, 3H), 1.03 ppm (d, $J=7.2$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=169.49$ (C), 82.26 (CH), 70.59 (CH), 60.82 (CH_2), 34.19 (CH), 32.15 (CH_2), 27.72 (CH), 15.52 (CH_3), 14.09 ppm (CH_3); HRMS (FAB): m/z: calcd for $C_9H_{15}O_3$: 171.1021 $[M+H]^+$; found: 171.0999.

(1*R*,5*S*,7*S*)-7-[(*R*)-2-Hydroxypropyl]-2,6-dioxabicyclo[3.3.1]nonan-3-one (*ent*-71): DBU (2–5 μL) was added to a stirred solution of diol lactone **46** (8 mg, 0.04 mmol) in CH_2Cl_2 (3 mL) and the reaction mixture was stirred at RT for 6 h. The solvent was evaporated and the residue underwent column chromatography on silica gel (ethyl acetate) to furnish bicyclic lactone *ent*-**71** (6 mg, 75%). $R_f=0.25$ (silica gel, ethyl acetate); $[\alpha]_D^{25}=-35.8$ ($c=0.77$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=4.91$–4.88 (m, 1H), 4.38–4.36 (m, 1H), 4.13–4.08 (m, 1H), 4.07–4.01 (m, 1H), 2.89 (brd, $J=19.1$ Hz, 1H), 2.77 (dd, $J=19.1$, 5.2 Hz, 1H), 2.04–1.90 (m, 3H), 1.72–1.61 (m, 3H), 1.20 ppm (d, $J=6.2$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=169.50$ (C), 72.90 (CH), 65.94 (CH), 64.42 (CH), 63.54 (CH), 43.52 (CH_2), 36.65 (CH_2), 36.29 (CH_2), 29.67 (CH_2), 23.60 ppm (CH_3); LCMS: m/z: 200.9 $[M]^+$; HRMS (FAB): calcd for $C_{10}H_{17}O_4$: 201.1127 $[M+H]^+$; found: 201.1103.

(1*S*,5*R*,7*R*)-7-[(*S*)-2-Hydroxypropyl]-2,6-dioxabicyclo[3.3.1]nonan-3-one (71): A mixture of resin **35** (319 mg, 0.10 mmol) in TFA/CH_2Cl_2 1:2 (20 mL g^{-1} resin, 6.4 mL) was shaken for 15 min at RT. The resin was filtered off and washed with CH_2Cl_2. The filtrate was co-evaporated with toluene. The residue was filtrated through silica gel (CH_2Cl_2/MeOH 9:1) to obtain the diol *ent*-**46**, which was dissolved in anhydrous benzene (1.5 mL) and treated with *p*TsOH (0.12 equiv, 0.012 mmol, 2 mg). The mixture was stirred overnight at RT and was then worked up by addition of solid $NaHCO_3$. Filtration, washing with ethyl acetate, and removal of the solvent in vacuo afforded a crude product which was purified by silica-gel chromatography (CH_2Cl_2/MeOH 0–5%) to yield **71** (7.5 mg, 38%). $[\alpha]_D^{20}=+26.35$ ($c=0.63$ in $CHCl_3$); IR (KBr): $\tilde{\nu}=3437$, 2926, 2860, 1731 (CO), 1353, 1070, 986 cm^{-1}; MS (EI): m/z: 141 $[M-C_3H_7O]^+$, 156 $[M-C_2H_5O]^+$, 167 $[M-CH_4O]^+$; HRMS (FAB): m/z: calcd for $C_{10}H_{17}O_4$: 201.1049 $[M+H]^+$; found: 201.1114.

(1*S*,5*R*,7*R*)-7-[(*R*)-2-Hydroxypropyl]-2,6-dioxabicyclo[3.3.1]nonan-3-one (72): DBU (2–5 μL) was added to a stirred solution of diol lactone **43** (5 mg, 0.025 mmol) in CH_2Cl_2 (3 mL) and the reaction mixture was stirred at RT for 6 h. The solvent was evaporated and the residue underwent column chromatography on silica gel (ethyl acetate) to furnish bicyclic lactone **72** (4 mg, 80%). $R_f=0.25$ (silica gel, ethyl acetate); $[\alpha]_D^{25}=+7.8$ ($c=0.25$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=4.89$–4.87 (m, 1H), 4.42–4.40 (m, 1H), 4.06–3.96 (m, 2H), 2.90 (brd, $J=19.1$ Hz, 1H), 2.80 (dd, $J=19.1$, 5.2 Hz, 1H), 2.07–2.00 (m, 2H), 1.97–1.92 (m, 1H), 1.71–1.65 (series of d, 1H), 1.63 (dd appears as a t, $J=2.2$ Hz, 1H), 1.60 (dd, appears as a t, $J=2.9$ Hz, 1H), 1.17 ppm (d, $J=6.2$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=169.25$ (C), 72.56 (CH), 67.66 (CH), 67.06 (CH), 65.96 (CH), 44.13 (CH_2), 37.32 (CH_2), 36.45 (CH_2), 29.53 (CH_2), 23.36 ppm (CH_3); LCMS: m/z: 200.9 $[M]^+$; HRMS (FAB): m/z: calcd for $C_{10}H_{17}O_4$: 201.1127 $[M+H]^+$; found: 201.1091.

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