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ScienceDirect
Tetrahedron 63 (2007) 5754–5767
Tetrahedron

# Stereoselective allylation of aldehydes on solid support and its application in biology-oriented synthesis (BIOS)

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Received 14 November 2006; revised 16 January 2007; accepted 22 January 2007
Available online 25 January 2007

**Abstract**—A systematic study on the asymmetric allylation of aldehydes on solid support is reported. Different kinds of chiral allylboron reagents with complementary direction of stereoinduction were applied successfully in this reagent-controlled transformation. The homoallylic alcohol products are generated with high levels of stereoselectivity and in high yields. The crotylation of aldehydes on solid support employing (*E*)- and (*Z*)-Ipc$_2$crotylborane also proceeds with very high levels of stereoinduction and in high yields. Applications of this methodology for the synthesis of compound collections by subsequent modifications of the allylic moiety are described. In particular, a collection of γ- and δ-lactones has been synthesized by means of a cyclo-release approach including a natural product. In addition, a procedure for the long-standing problem of the hydrogenation of double bonds on solid support is reported. We have also demonstrated the feasibility of applying the stereoselective allylation of aldehydes on solid support in an iterative fashion to generate polyol structures.


## 1. Introduction

The synthesis of compound collections has gained steadily increasing interest in both industry and academia.[1] As a result, new strategies for library design that focus for instance on natural product guided[2a–d] and biology-oriented[2e] or diversity-oriented[3] synthesis have emerged to gain access to more complex structures in library formats. In such endeavors, asymmetric synthesis, in particular employing enantioselective transformations, is needed as an integral part of the library development effort.

In addition, the synthesis of compound collections on solid support is a key enabling technique for medicinal chemistry and chemical biology research.[2a] The compounds employed in such programs very often are chiral. Therefore, the availability of efficient reaction sequences proceeding with a degree of efficiency and stereoselectivity comparable to established solution-phase methods is of major interest. The application of asymmetric transformations to immobilized substrates is challenged by the fact that minor products cannot be separated in the course of the synthesis. Therefore, asymmetric transformations that provide high levels of stereoinduction for solid-phase organic synthesis need to be developed. However, asymmetric syntheses on solid support have been scarcely investigated.[4]

The allylation of carbonyl compounds is one of the most useful carbon–carbon bond-forming asymmetric transformations in organic synthesis, which is receiving intense attention. This is due to the fact that the resulting homoallylic alcohols have proven to be valuable reagents and intermediates for synthesis.[5] For instance, they have found numerous applications in natural product total synthesis. In particular, asymmetric allylboration of aldehydes employing tartrate- and pinane-derived reagents has been widely exploited.[6] More recently, allylboron reagents have been applied to the allylation of imines[7] and to the catalytic enantioselective allylation of both aldehydes and ketones.[8] New chiral boron reagents embodying a bicyclic structure (9-borabicyclo[3.3.2]decanes) have also been successfully applied.[9]

Whereas the allylation reaction is well documented and widely used in solution phase, very few reports on allylations on the solid support are known. For instance, some examples employing the Nozaki–Hiyama–Kishi protocol,[10] allylstannanes[11] or allylboronic acid pinacolate[11] have been reported.

*Keywords*: Asymmetric solid-phase synthesis; Allylation; Boranes; Lactones; Hydrogenation on solid support.
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0040–4020/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2007.01.041

However, the asymmetric variant of the allylation of carbonyl compounds on the solid support remains almost elusive.[12] In particular, Panek et al. described the asymmetric crotyl transfer reaction to aldehydes on solid support using a chiral (*E*)-crotylsilane reagent in the presence of TMSOMe via reaction with in situ generated oxocarbenium ions.[12a,13] While our work on the stereoselective allylation on solid support[4b] was in progress, Tan et al.[12b] reported the asymmetric allylation of an aliphatic polymer-supported aldehyde using a strained allylsilacycle developed by Leighton.[14]

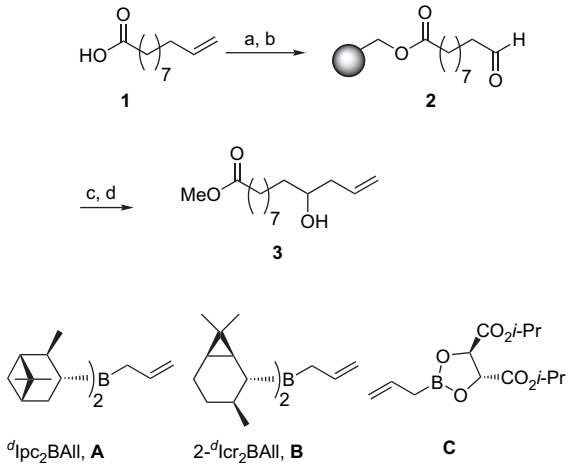
The lack of reports on the enantioselective allylboration of aldehydes on solid support together with our interest in the development of new asymmetric transformations on solid phase[4b–j] prompted us to undertake a systematic study of these transformations and develop applications in the generation of compound collections on solid support.

Herein we describe in full experimental detail the results of our investigations on the stereoselective allylboration of aldehydes on solid support.[4b]

## 2. Results and discussion

### 2.1. Allylboration of aldehydes on solid support

In order to identify reaction conditions that would give rise to the allylation products with high enantioselectivity and in high yield, immobilized aldehyde **2** was synthesized as model compound (Scheme 1). To this end, regular hydroxymethyl polystyrene resin (PS-OH, loading 0.98 mmol $g^{-1}$) was subjected to esterification with undec-10-enoic acid **1** followed by ozonolysis of the double bond (loading of the aldehyde resin 0.6 mmol $g^{-1}$;[15] 60% yield for the two-step sequence). Polymer-bound aldehyde **2** was then subjected to allylation with three representative chiral allylboron reagents: $^{D}$*B*-allyldiisopinocampheylborane **A** ($^{D}$Ipc$_2$BAll), $^{D}$*B*-allylbis(2-isocaranyl)borane **B** (2-$^{D}$Icr$_2$BAll)[16] and




**Scheme 1**. Synthesis and enantioselective allylation of polymer-bound aldehyde **2**. Reagents and conditions: (a) hydroxypolystyrene resin (loading 0.98 mmol $g^{-1}$), DCC, cat. DMAP, $CH_2Cl_2$, rt, 16 h; (b) $O_3$, $CH_2Cl_2$, −78 °C, then $PPh_3$, −78 °C to rt; loading of the aldehyde resin 0.6 mmol $g^{-1}$, 60% yield (two steps); (c) (i) allylborane **A**, **B** or **C** (*n* equiv), THF, *T* (°C) and time (see Table 1), (ii) pH 7 buffer, $H_2O_2$ 30%, DMF/MeOH 1:1, rt, 2 h; (d) MeONa (2 equiv), THF/MeOH 2:1, rt, 12 h. DCC: dicyclohexylcarbodiimide.

(−)-*B*-allyl(diisopropyltartrate)boronate **C** (Scheme 1).[17] After some experimentation we found that an oxidative workup in a buffered medium followed by release from the resin by treatment with sodium methoxide and isolation by simple filtration of the crude reaction mixture through a plug of silica gel gave rise to the desired homoallylic alcohol **3**.

The results of the enantioselective allylation reactions are shown in Table 1. When 4 equiv of $^{D}$Ipc$_2$BAll **A** was employed at −78 °C in THF/ether 5:1 (v/v), the homoallylic alcohol **3** was obtained in high yield, high purity, and with very high enantioselectivity (Table 1, entry 1). Raising the temperature from −78 to −40 °C or −20 °C or allowing the reaction to warm up to 0 °C overnight led to a slight decrease in stereoselectivity (Table 1, entries 2–4). The analogous reaction in solution employing the methyl ester corresponding to **2** as starting material at −78 °C and 1 equiv of the allylation reagent **A** yielded the homoallyl alcohol **3** in 83% yield and with an enantiomer ratio of 92.5:7.5. In all cases, the (*R*)-enantiomer was formed predominantly.[18] Thus, both in solution and on the solid phase the reaction does follow the same stereochemical course to give the product with very comparable stereoselection levels. When the less reactive allylborane **B** (2-$^{D}$Icr$_2$BAll) was employed, (*S*)-**3** was obtained as expected with an enantiomer ratio of 90.5:9.5 and the allyl boronate **C** also gave the expected (*R*)-enantiomer with lower stereoselectivity than **A** (Table 1, entries 5 and 6).

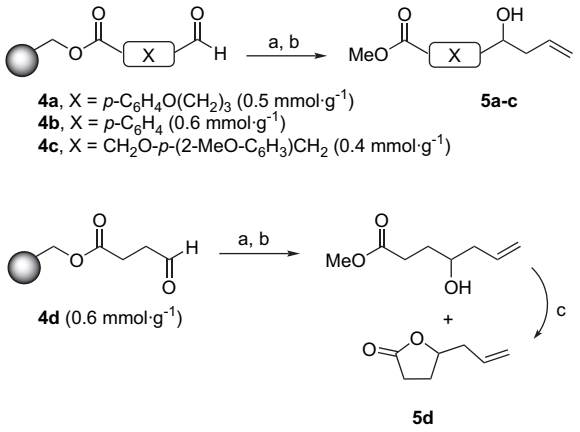
Once favorable experimental conditions were established and the stereochemical outcome on solid support was identified, we decided to study the generality of this enantioselective transformation and the influence of the temperature on the enantioselectivity. Thus, immobilized aldehydes **4a–d** (Scheme 2) were synthesized by analogy to the synthesis of **2** except for **4b**. In this case, the aromatic aldehyde was introduced directly without the need for an ozonolysis step. The four resulting resins were then subjected to enantioselective allylation reactions with reagents **A**, **B**, and **C**. The results for the allylation products **5a–c**[18] and **5d** obtained after oxidative workup and release from the solid support as described above are summarized in Table 2. In all cases, the expected reaction products were isolated in high yield with high purity and very appreciable enantiomer ratios. Interestingly, the allylation of aldehyde **4d** and subsequent release from the polymeric carrier led to the formation of the corresponding homoallyl alcohol along with the lactone **5d**. The open-chain compound cyclized completely to **5d** upon standing in chloroform

**Table 1**. Variation of the reaction conditions for the enantioselective allylation of **2**

| Entry | Allylborane (equiv) | *T* [°C], time | Purity[a] [%] | Yield[b] [%] | er[c] [%] (*R*:*S*) |
|---|---|---|---|---|---|
| 1 | **A** (4) | −78, 5 h | >95 | 79 | 95.5:4.5 |
| 2 | **A** (4) | −78, 3 h then to −40 for 2 h | >95 | 83 | 94:6 |
| 3 | **A** (4) | −78, 3 h then to −20 for 2 h | >95 | 66 | 93:7 |
| 4 | **A** (3) | −78 to 0, 12 h | >95 | 71 | 94.5:5.5 |
| 5 | **B** (4) | −78 to −50, 6 h | >95 | 95 | 9.5:90.5 |
| 6[d] | **C** (5) | −78 to 0, 12 h | >95 | 95 | 88.5:11.5 |

[a] Based on GC–MS analysis.
[b] Isolated yield after allylation and cleavage from the resin.
[c] Enantiomer ratio (er) determined by $^1$H NMR analysis of the Mosher esters.
[d] Toluene was used as solvent.

solution (ca. 2 days) and silica gel. Several trends are apparent from the data. In general, the allylborane **A** is more reactive in reactions on the solid phase (as it is in solution-phase reactions). In contrast to the observation for aldehyde **2**, for aldehydes **4a–c**, reagent **B** gives higher enantioselectivity. This is in accordance with findings for solution-phase reactions employing these reagents.[19] In all cases, Brown's allylborane reagents **A** and **B** give higher enantiomer ratios than the Roush reagent **C**. We can also conclude that the enantioselectivity of the process is hardly affected by a slow increase of reaction temperature (even from −78 to 0 °C overnight) provided the addition of the allyl borane is done at −78 °C and the mixture is kept at this temperature for ca. 2 h. However, the enantioselectivity is highly dependent on the quality of the chiral borane reagent. The best results were obtained when the reagent was freshly prepared from solid $Ipc_2BAll$.




**Scheme 2**. Development of the enantioselective allylation on solid support employing allylboranes. Reagents and conditions: (a) (i) allylborane **A**, **B** or **C** (4 equiv), THF, *T* (°C) and time (see Table 2), (ii) pH 7 buffer, $H_2O_2$ 30%, DMF/MeOH 1:1, rt, 2 h; (b) MeONa (2 equiv), THF/MeOH 2:1, rt, 12 h; (c) $CHCl_3$ solution or $SiO_2$ chromatography.

## 2.2. Asymmetric crotylboration of aldehydes on solid support

In order to further explore the generality of the method for asymmetric synthesis of homoallylic alcohols on the solid support, the enantio- and diastereoselective crotylation of polymer bound aldehydes **2** and **4b** with (*E*)- and (*Z*)-*B*-crotyldiisopinocampheylborane[20] was investigated (Table 3).

The reactions were carried out under the conditions described above for the allylation with the analogous crotylboron reagents.[21] For entries 1–4, (*E*)- and (*Z*)-crotylborane were used yielding the diastereomeric homoallyl alcohols **6–9** in high yields and with high diastereomer ratios. The major diastereomers were formed with high enantiomer ratios.[22] The direction of the diastereoselection parallels the observations made for analogous crotylation reactions in solution.[20]

## 2.3. Allylboration in the generation of compound collections

After having achieved satisfactory enantioselective allyl and crotylboration of aldehydes on solid support, we demonstrated the potential and attractiveness of these asymmetric transformations on resin for the synthesis of compound collections through subsequent modifications of the homoallylic alcohol products. We envisioned that the supported homoallylic alcohols having an appropriate linker between the resin and the hydroxyl group could give access to lactones by a cyclo-release approach. A collection of γ- and δ-lactones could be obtained by introducing modifications into the skeleton (size, stereochemistry, and substitution pattern) as well as in the allyl side chain (strategy I, Scheme 3). In addition, this methodology could be extended to the synthesis of polypropionate-like units found in numerous bioactive natural products through an iterative asymmetric allylation- or crotylation–ozonolysis sequence (strategy II, Scheme 3). Thereby, natural product-derived compound libraries could be obtained.[4b,23]

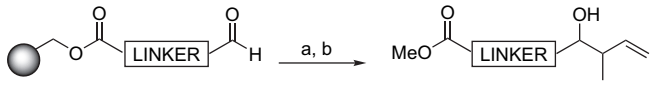
**2.3.1. Synthesis of a collection of γ- and δ-lactones and hydrogenation on solid support.** The general strategy to synthesize the saturated lactones included the preparation of aldehydes embodying a four or five carbon skeleton attached to the polymeric support through an ester linkage. Subsequently, the stereoselective allylation of the aldehydes, modifications of the double bond and finally the release from the resin with in situ cyclization should give the

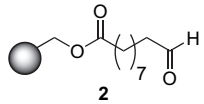
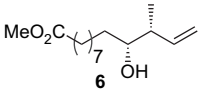
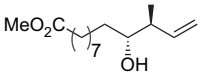
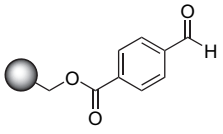
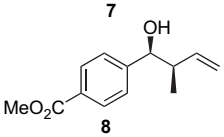
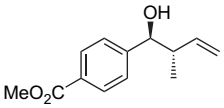
**Table 2**. Scope of the enantioselective allylation reaction with chiral allylation reagents **A**, **B**, and **C**

| Aldehyde | Allylborane (equiv) | *T* [°C], time | Product | Yield[a] [%] | Purity[b] [%] | er[c] [%] (*R*:*S*) |
|---|---|---|---|---|---|---|
| **4a** | **A** (4) | −78, 6 h | **5a** | 73 | >95 | 89:11 |
| | **B** (4) | −78 to −50, 6 h | | 54 | >95 | 6:94 |
| | **C** (5)[d] | −78 to 0, 12 h | | 85 | >95 | 85:15 |
| **4b** | **A** (4) | −78, 6 h | **5b** | 94 | 94 | 10:90 |
| | **B** (4) | −78 to −20, 12 h | | 95 | >95 | 94:6 |
| | **C** (5)[d] | −78, 6 h | | 66 | >95 | 16:84 |
| **4c** | **A** (4) | −78 to 0, 12 h | **5c** | 64 | 94 | 12:88 |
| | **B** (4) | −78 to −20, 12 h | | 56 | >95 | 97:3 |
| | **C** (5)[e] | −78 to 0, 12 h | | — | Mixture | — |
| **4d** | **A** (4) | −78, 6 h | **5d** | 71 | 87 | 82:18[e] |
| | **B** (4) | −78 to 0, 12 h | | 70 | >95 | 19:81[e] |
| | **C** (5)[e] | −78 to 0, 12 h | | 60 | >95 | 75:25[e] |

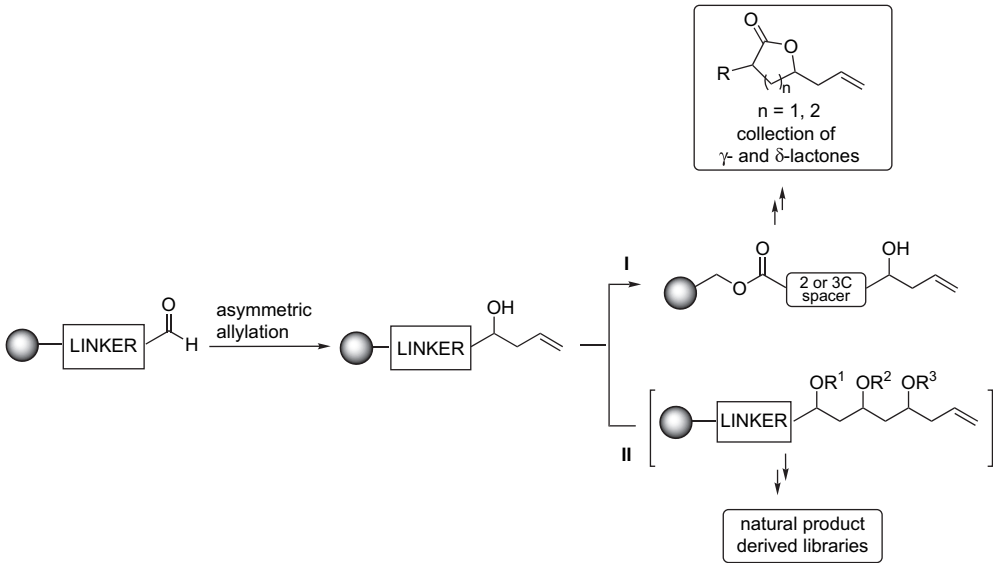
[a] Isolated yield after allylation and cleavage from the resin.
[b] Based on GC–MS analysis.
[c] Determined by $^1H$ NMR analysis of the Mosher esters if not otherwise noted.
[d] Toluene was used as solvent.
[e] Determined by NMR shift experiments employing 0.8 equiv of the chiral shift reagent $Eu(tfc)_3$ and with chiral GC.

**Table 3**. Results of the asymmetric crotylation reactions on solid support




| Entry | Aldehyde | Crotylborane | Yield[a] (%) | Product | dr[b] (er) |
|---|---|---|---|---|---|
| 1 |  **2** | $^{D}Ipc_2B$-(*Z*)-crotyl | 78 |  **6** | 96 (95:5):4 |
| 2 | | $^{D}Ipc_2B$-(*E*)-crotyl | 95 |  **7** | 93 (88:12):7 |
| 3 |  **4b** | $^{D}Ipc_2B$-(*Z*)-crotyl | 94 |  **8** | 96 (94:6):4 |
| 4 | | $^{D}Ipc_2B$-(*E*)-crotyl | 91 |  **9** | 96 (83:17):4 |

(a) (i) crotylborane (5 equiv), THF, −78 °C to 0 °C; (ii) pH 7 buffer, $H_2O_2$ 30%, DMF/MeOH 1:1, rt, 2 h; (b) MeONa (2 equiv), THF/MeOH 2:1, rt, 12 h.
[a] Yields of pure isolated compounds.
[b] Diastereomer ratios were determined by $^1H$ NMR analysis and enantiomer ratios of the main diastereomers in compounds **6–9** by Mosher ester derivatisation.



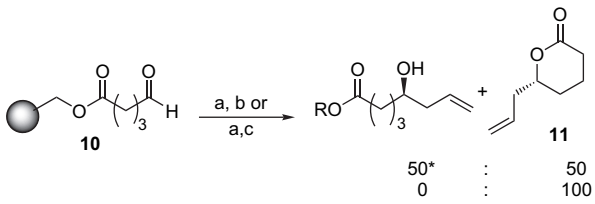

**Scheme 3**. Strategies for the generation of compound collections on solid support employing the asymmetric allylation as a key step.

corresponding γ-lactones (4C aldehydes) or δ-lactones (5C aldehydes). Introduction of diversity into the ring could be achieved by means of α-substituents. Therefore, α-substituted 4-pentenoic or 5-hexenoic acids were chosen as building blocks. These enantiopure building blocks can be synthesized using Evans' alkylation methodology. The double bond serves as precursor for the aldehyde group and the carboxylic acid enables the attachment to the resin as ester.

The viability of the approach was investigated for the synthesis of six-membered-ring lactones starting from the supported aldehyde **10**, which was derived from the commercially available 5-hexenoic acid. Release from the resin with NaOMe after allylation (which occurred with an enantiomeric ratio of 80:20) gave rise to a mixture of the expected lactone and the open-chain compound paralleling the behavior of the aldehyde **4d** (see Scheme 2). Instead, cleavage under acidic conditions yielded the lactone **11** exclusively (Scheme 4).

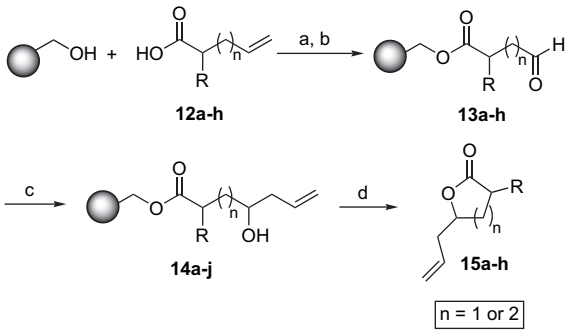
Thus, the carboxylic acids **12a–h** with an alkyl group in α-position were synthesized following the Evans protocol[24,25] and employing (4*R*,5*S*)-4-methyl-5-phenyl-2-oxazolidinone as chiral auxiliary[26] (see Supplementary data).

They were anchored to the polymeric support by activation with carbodiimides. Subsequent ozonolysis of the double bond afforded the supported aldehydes **13a–h**, which were




**Scheme 4**. Release-cyclization approach. Reagents and conditions: (a) (i) $^{D}Ipc_2BAll$ (4 equiv), THF, (ii) pH 7 buffer, $H_2O_2$ 30%, DMF/MeOH 1:1, rt, 2 h; (b) MeONa (2 equiv), THF/MeOH 2:1, rt, 12 h; (c) TFA/$CH_2Cl_2$ 4:1, 2 h. *The open-chain compound was slowly converted into the lactone upon standing in chloroform solution or by treatment with silica gel.

subjected to allylation with both enantiomers of $Ipc_2BAll$ to yield the corresponding supported homoallylic alcohols **14a–j**. Release from the resin with TFA yielded the five- and six-membered-ring lactones with varied stereochemistry (Scheme 5). Table 4 summarizes the results for the synthesis of the lactone collection.[27] In general, all the lactones were obtained with high to very high overall yields.




**Scheme 5**. Solid-phase synthesis of five- and six-membered lactones **15**. Resin: hydroxymethyl polystyrene, loading=0.98 mmol $g^{-1}$. Reagents and conditions: (a) DCC or DIC, cat. DMAP, $CH_2Cl_2$, rt, 16 h; (b) $O_3$, $CH_2Cl_2$, −78 °C, then $PPh_3$, −78 °C to rt; (c) (i) 4 equiv L or D-$Ipc_2BAll$, THF, −78 °C to 0 °C overnight, (ii) pH 7 buffer, $H_2O_2$ 30%, DMF/MeOH 1:1, 0 °C to rt, 2 h; (d) TFA/$CH_2Cl_2$ 4:1 (v/v), rt, 2 h. DCC: dicyclohexylcarbodiimide, DIC: diisopropylcarbodiimide.

The allyl moiety in the supported intermediate can be further modified before cyclorelease. (*R*)-5-Heptyl-dihydrofuran-2-one **18**[30] (Scheme 6) is a natural product isolated from the red alga *Gracilaria corticata*. For the synthesis of this natural product on solid support, the homoallyl alcohol resin *ent*-**14b** was subjected to cross metathesis (CM) with hex-1-ene in the presence of 20% of the first generation Grubbs catalyst $Cl_2(Pcy_3)_2Ru{=}CHPh$ (cy=cyclohexyl). Initial attempts to reduce the double bond on the resin **16** failed. Therefore, to complete the synthesis, the lactone **17** was first released from the resin followed by hydrogenation of the double bond using 5% Pd/C without intermediary purification. The natural product **18** was obtained in 55% overall yield starting from resin **4d**.

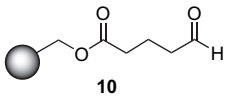
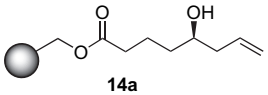
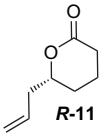
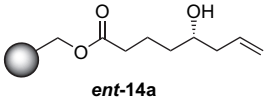
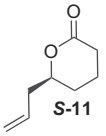
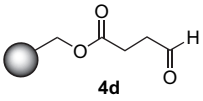
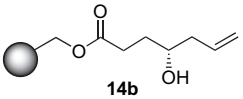
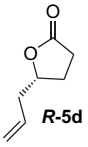
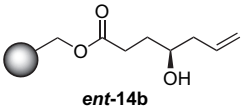
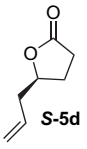
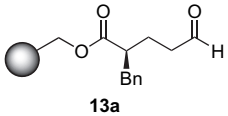
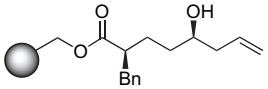
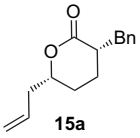
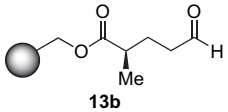
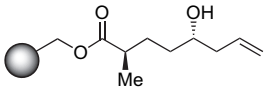
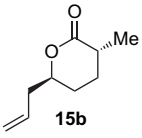
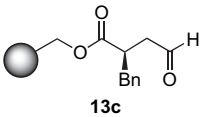
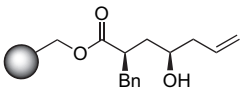
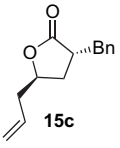
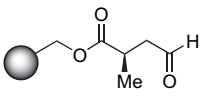
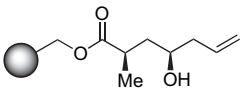
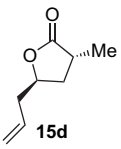
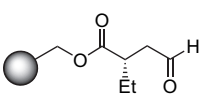
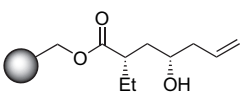
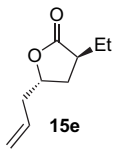
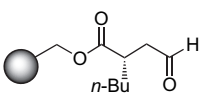
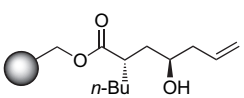
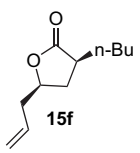
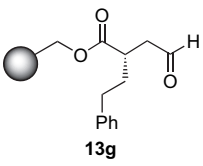
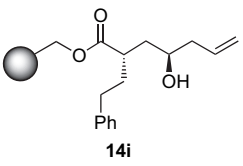
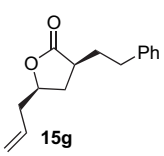
At this point we decided to investigate the long-standing problem of hydrogenation on solid support. Although the heterogeneous hydrogenation is routinely employed in solution-phase chemistry, reports on hydrogenation of alkenes on solid support with palladium catalysis are rare.[31] The hydrogenation of alkenes on solid phase is generally accomplished using soluble reagents, like diimide,[32a] or homogeneous catalysis.[32b–d] As envisaged, the supported homoallylic alcohol **19**[23] underwent smooth cross metathesis reaction with methyl acrylate to yield ca. 1:1 mixture of cis/trans esters **20** (Scheme 7, indicated by NMR of the released product). Diimide-based hydrogenation of unsaturated ester **20** employing sulfonyl hydrazide/DMF[32a] as reported led to only little conversion, and under drastic conditions (excess reagent and heating) very little product was recovered. The initial attempts to hydrogenate the olefin with in situ generated diimide from potassium azodicarboxylate (PAD) at room temperature were promising. However, the attempted hydrogenation of the olefin under various combinations in THF/MeOH as solvent and with varying amounts of PAD/AcOH (5–20 equiv) did not lead to complete conversion even after three reaction cycles. However, the use of pyridine as solvent finally resulted in 90–95% conversion in two cycles. The reaction could be monitored by IR (disappearance of the IR resonance at 1660 $cm^{-1}$ was indicative for completion of the reaction). The release of hydroxyester **21** from the resin under acidic conditions led to simultaneous formation of lactone **22** in 60% overall yield (Scheme 7).

## 2.4. Stereoselective synthesis of polyols

In order to additionally demonstrate the potential and attractiveness of the enantioselective allylation on solid support for the synthesis of natural product-derived compound libraries,[4,12] an iterative sequence of allylation and ozonolysis reactions was developed, which yielded polyols with high stereoselectivity. 1,3-Diol and polyol structures are found in numerous biologically active natural products. This iterative sequence opens up an opportunity for the synthesis of further natural product-derived compound collections.[4b,23]

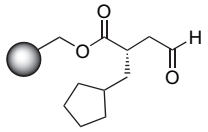
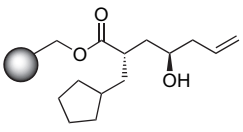
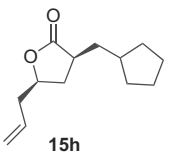
To this end, polymer-bound homoallyl alcohol **23** was synthesized as described above, and the secondary alcohol was protected as TBS ether[33,34] (Scheme 8). Ozonolysis of the double bond yielded a new aldehyde, which was subjected to further allylation reaction employing allyl borane **A**. The resulting monoprotected diol **25** was then desilylated and converted into acetonide **26**. On the one hand, the protected diol was released from the polymeric carrier to give masked compound **27** with an overall yield of 43% over seven steps and with a *syn*:*anti* ratio of 86:14 (determined by GC–MS and NMR). The *syn* and *anti* isomers were assigned using the [$^{13}$C]acetonide method.[35] Since the first allylation had proceeded with an enantiomer ratio of 90:10 (see above) the diastereomer ratio of 86:14 determined for **27** demonstrates that the second allylation proceeded with a diastereomer ratio of ca. 95:5. On the other hand, an additional cycle of ozonolysis, stereoselective allylation and release from the solid support yielded selectively protected triol **29** in 40% yield over nine steps as a mixture of four stereoisomers in a ratio of *syn*,*syn*/*syn*,*anti*/*anti*,*syn*/*anti*, *anti*=75:13:9:3 (determined by GC–MS). These values are in accordance with the assumption that the third allylation reaction proceeds with a degree of diastereoselectivity close to the result observed for the second allylation. In this case, an isomer ratio of 74:12:12:2 would be expected with the *syn*/*syn* isomer predominating and the *anti*/*anti* isomer formed as the minor diastereomer.

**Table 4**. Results for the synthesis of a collection of γ- and δ-lactones

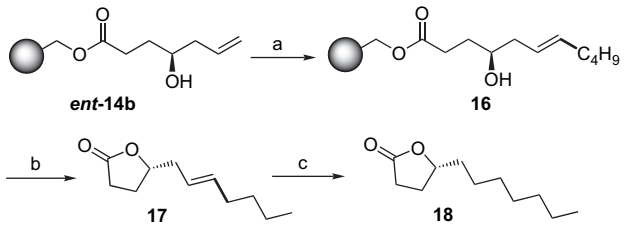
| Entry | Aldehyde | D- or L-$Ipc_2BAll$ | Homoallyl alcohol | Lactone | dr[a] (er) | Yield[b] (%) |
|---|---|---|---|---|---|---|
| 1 |  **10** | D |  **14a** |  ***R*-11** | (80:20) | 96 |
| 2 | | L |  ***ent*-14a** |  ***S*-11** | (92:8) | 85 |
| 3 |  **4d** | D |  **14b** |  ***R*-5d** | (82:18) | 64 |
| 4 | | L |  ***ent*-14b** |  ***S*-5d** | (95:5) | 65 |
| 5 |  **13a** | D |  **14c** |  **15a** | 86:14 (97:3) | 75 |
| 6 |  **13b** | L |  **14d** |  **15b** | 88:12 (98:2) | 85 |
| 7 |  **13c** | L |  **14e** |  **15c** | 87:13 (97:3) | 60 |
| 8 |  **13d** | L |  **14f** |  **15d** | 85:15 (98:2) | 87 |
| 9 |  **13e** | D |  **14g** |  **15e** | 87:13 (>99:1) | 37 |
| 10 |  **13f** | L |  **14h** |  **15f** | 91:9 (99:1) | 51 |
| 11 |  **13g** | L |  **14i** |  **15g** | 88:12 (99:1) | 66 |

(*continued*)

**Table 4**. (*continued*)

| Entry | Aldehyde | D- or L-$Ipc_2BAll$ | Homoallyl alcohol | Lactone | dr[a] (er) | Yield[b] (%) |
|---|---|---|---|---|---|---|
| 12 |  **13h** | L |  **14j** |  **15h** | 88:12 (99:1) | 86 |

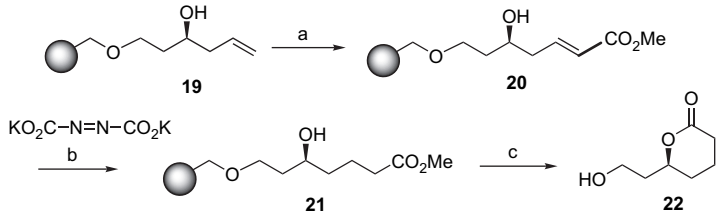
[a] The dr was determined by integration of signals in the $^1H$ NMR spectra recorded at 400 MHz. The er corresponds to the ratio found in the carboxylic acids **12a–h** (see Ref. 28).
[b] Overall yield of isolated compounds (mixture of diastereomers) from hydroxymethyl polystyrene (see Ref. 29).



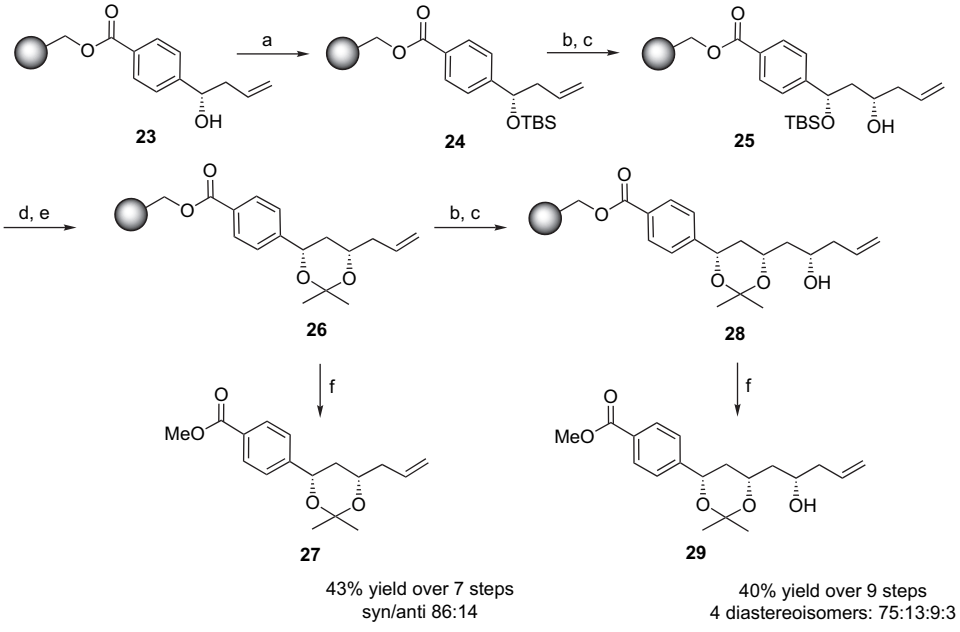

**Scheme 6**. Total synthesis of (*R*)-5-heptyl-dihydrofuran-2-one. Reagents and conditions: (a) $Cl_2(Pcy_3)_2Ru{=}CHPh$ (Grubbs I catalyst, 20 mol %), hex-1-ene (6 equiv), $CH_2Cl_2$, reflux, 20 h; (b) MeONa (2 equiv), THF/MeOH 2:1, rt, 12 h; (c) Pd/C (5 mol %), $H_2$ (1 bar), MeOH, rt, 20 h.

## 3. Conclusion

In conclusion, we have developed the asymmetric allylboration and crotylboration of aldehydes on the solid support. The transformations proceed with very high stereoselectivity, have a wide scope and yield homoallylic alcohols, which can be further modified to characteristic partial structures of natural products in multistep sequences. This reagent-controlled asymmetric methodology should open up numerous opportunities for the synthesis of natural product-derived and -inspired compound libraries for medicinal chemistry and chemical biology research.




**Scheme 7**. Hydrogenation on solid support. Reagents and conditions: (a) methyl acrylate (6 equiv), Grubbs II catalyst (12 mol %), $CH_2Cl_2$, reflux, 24 h; (b) PAD/AcOH 1:2 (10 equiv), pyridine, rt, 36 h (two cycles); (c) TFA/$CH_2Cl_2$ 1:2, rt, 10 min. Polymeric support: Wang resin, PAD: potassium azodicarboxylate.




**Scheme 8**. Iterative synthesis of polyols. Reagents and conditions: (a) TBSCl (10 equiv), DMAP (1 mol %), imidazole (10 equiv), $CH_2Cl_2$, rt, 20 h; (b) $O_3$, $CH_2Cl_2$, −78 °C then $PPh_3$ (5 equiv), −78 °C to rt, 12 h; (c) $^DIpc_2BAll$ (1 M in $Et_2O$, 3 equiv), THF, −78 to 0 °C, 12 h; (d) TBAF (1 M in THF, 3 equiv), THF, rt, 12 h; (e) 2,2-dimethoxypropane/$CH_2Cl_2$ 1:1, CSA (10 mol %), rt, 20 h; (f) MeONa (2 equiv), THF/MeOH 2:1, rt, 12 h. CSA: camphorsulfonic acid.

## 4. Experimental section

### 4.1. General

Unless otherwise noted, chemicals were obtained from Aldrich, Acros or Fluka and were used without further purification. Regular hydroxymethyl polystyrene (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. 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 Merck silica gel 60. $^{1}H$ and $^{13}C$ NMR data were recorded on a Bruker DRX 500 or Bruker DRX 400 spectrometer at room temperature. NMR spectra were calibrated to the solvent signals of $CDCl_3$ (7.26 and 77.00 ppm) and the following abbreviations are used to indicate signal multiplicities: s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), sext (sextet), sept (septet), br (broad), and ap (apparent). GC–MS (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: 25.0×201μm×0.33 μm nominal. Chiral GC analysis was performed on an Agilent Technologies 6890N; column Lipodex-E (25 m, 0.025 mm). LC-MS was performed on a Hewlett–Packard 1100 series connected to a Finnigan LCQ ESI-spectrometer. High-resolution mass spectra (HRMS) were measured on a Finnigan MAT 8200 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 but it was only measured for those compounds having an optical purity higher than 80%.

### 4.2. Synthesis of polymer-supported aldehydes 2, 4a–d, 10, 13a–h

**4.2.1. General procedure for esterification of the resin.** The hydroxypolystyrene resin (PSOH, 0.98 mmol $g^{-1}$, 4.9 mmol, 5 g) was swelled for 30 min in $CH_2Cl_2$. The carboxylic acid (2 equiv, 9.8 mmol) dissolved in $CH_2Cl_2$ or in a mixture $CH_2Cl_2$/DMF 1:1 (case of **4a**), DCC (1 M in $CH_2Cl_2$) or DIC (2 equiv, 9.8 mmol) and DMAP (10 mol %, 0.98 mmol) were successively added and the mixture was stirred overnight at room temperature. The resin was filtered off, washed successively with $CH_2Cl_2$, DMF, $CH_2Cl_2$, and MeOH and dried in vacuum for 12 h.

**4.2.2. General procedure for the ozonolysis on solid support.** The resin was swelled 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 then for additional 8–10 min. When Wang resin was used as the polymeric support, 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 to remove excess ozone, $PPh_3$ (5 equiv) was added and the mixture was shaken from −78 °C to room temperature overnight. The resin was filtered off, washed with $CH_2Cl_2$ and MeOH, and dried in vacuo.

**4.2.2.1. Determination of loading of the aldehydes on resins (DNPH method).**[4g] A standard solution of 2,4-dinitrophenylhydrazine (DNPH, 100 mg) in THF (100 mL) was prepared. The UV absorption $A_0$ of the 10-fold diluted solution was measured in a 1 mm quartz cuvette at 350 nm. Then a suspension of aldehyde resin (20 mg) in the DNPH standard solution (10 mL) was shaken overnight. The UV absorption $A_1$ of the 10-fold diluted supernatant solution was measured in a 1 mm quartz cuvette at 350 nm. The aldehyde loading was calculated by employing the following formula: $C=2.524(1-A_1/A_0)$ (mmol $g^{-1}$). See Ref. 4g.

All supported aldehydes were obtained following these procedures except for aldehyde **4b**, which was attached directly to the resin.

Aldehyde **2**—IR (SiC): $\nu_{max}$=3059 (CH alkene), 3024 (CH alkane), 2924 (CH alkane), 2715 (CH aldehyde), 1720 $cm^{-1}$ (C=O ester and aldehyde). Loading=0.9 mmol $g^{-1}$.

Aldehyde **4a**—IR (SiC): $\nu_{max}$=2722 (CH aldehyde), 1707 $cm^{-1}$ (C=O ester and aldehyde). Loading= 0.5 mmol $g^{-1}$.

Aldehyde **4b**—IR (SiC): $\nu_{max}$=2733 (CH aldehyde), 1706 $cm^{-1}$ (C=O ester and aldehyde). Loading= 0.6 mmol $g^{-1}$.

Aldehyde **4c**—IR (SiC): $\nu_{max}$=2720 (CH aldehyde), 1781 $cm^{-1}$ (C=O ester and aldehyde). Loading= 0.4 mmol $g^{-1}$.

Aldehyde **4d**—IR (SiC): $\nu_{max}$=2724 (CH aldehyde), 1711 $cm^{-1}$ (C=O ester and aldehyde). Loading= 0.6 mmol $g^{-1}$.

Aldehyde **10**—IR (SiC): $\nu_{max}$=2721 (CH aldehyde), 1747 $cm^{-1}$ (C=O ester and aldehyde). Loading= 0.8 mmol $g^{-1}$.

Aldehyde **13a**—IR (SiC): $\nu_{max}$=2721 (CH aldehyde), 1743 $cm^{-1}$ (C=O ester and aldehyde).

Aldehyde **13b**—IR (SiC): $\nu_{max}$=2721 (CH aldehyde), 1742 $cm^{-1}$ (C=O ester and aldehyde).

Aldehyde **13c**—IR (SiC): $\nu_{max}$=2725 (CH aldehyde), 1731 $cm^{-1}$ (C=O ester and aldehyde).

Aldehyde **13d**—IR (SiC): $\nu_{max}$=2723 (CH aldehyde), 1745 $cm^{-1}$ (C=O ester and aldehyde).

Aldehyde **13e**—IR (SiC): $\nu_{max}$=2724 (CH aldehyde), 1740 $cm^{-1}$ (C=O ester and aldehyde).

Aldehyde **13f**—IR (SiC): $\nu_{max}$=2723 (CH aldehyde), 1740 $cm^{-1}$ (C=O ester and aldehyde).

Aldehyde **13g**—IR (SiC): $\nu_{max}$=2724 (CH aldehyde), 1731 $cm^{-1}$ (C=O ester and aldehyde).

Aldehyde **13h**—IR (SiC): $\nu_{max}$=2722 (CH aldehyde), 1745 $cm^{-1}$ (C=O ester and aldehyde).

### 4.3. General procedure for the asymmetric allylation on solid support

The supported aldehydes were dried by azeotropic distillation with toluene (2–3 times) and application of high vacuum for at least 3 h. The resins were 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 suspension was shaken overnight allowing the reaction to warm up slowly to 0 °C. After quenching with MeOH (4 mL $g^{-1}$ resin), the resins were filtered and washed consecutively with pH 7 buffer, $H_2O$, THF, $Et_2O$, $CH_2Cl_2$, and MeOH. The resins were suspended in a mixture of DMF/MeOH 1:1 (12 mL $g^{-1}$ resin each) and at 0 °C were added $H_2O_2$ (30%, 2.5 mL $g^{-1}$ resin) and pH 7 buffer (2.5 mL $g^{-1}$ resin). The resulting mixture was shaken for 2 h at room temperature (when the resin was hydroxymethyl polystyrene) or at 0 °C (when the Wang resin was used). The resins were filtered, washed with $H_2O$, THF, $CH_2Cl_2$, and MeOH and dried in vacuo.

**4.3.1. Release from the resin.** Method A: The resin was suspended in THF (10 mL $g^{-1}$ resin). NaOMe (0.25 M in MeOH, 2 equiv) was added and the mixture was shaken overnight at room temperature. Water (1 mL $g^{-1}$ resin) was added, the mixture was filtered, and the product was extracted with $Et_2O$ or the solution was directly dried with $Na_2SO_4$. Method B: The resin was suspended in TFA/$CH_2Cl_2$ 4:1 (10 mL $g^{-1}$ resin) and the mixture was shaken for 2 h. The resin was filtrated off and washed with $CH_2Cl_2$. The filtrates were co-evaporated with toluene to yield the final products. Method C: When the polymeric support was the Wang resin, the cleavage was carried out with TFA/$CH_2Cl_2$ 1:2 (10 mL $g^{-1}$ resin) in two cycles of ca. 10 min following the same procedure as in method B. The final products were purified through a plug of silica gel.

### 4.4. Synthesis of homoallylic alcohols and lactones[36]

**4.4.1. Methyl (*R*)-10-hydroxytridec-12-enoate (*R*)-3[4b] (representative experimental procedure).** To the resin **2** (800 mg) in THF (8 mL) at −78 °C was added a 1 M solution of **A** in $Et_2O$ (1.5 mmol, 1.5 mL) and the mixture was shaken overnight while the temperature raised slowly to 0 °C. After quenching and oxidative workup as described in the general procedure, the homoallylic alcohol resin was obtained (monitored by IR). The cleavage was performed using method A [THF (8 mL), NaOMe (0.25 M, 4 mL, 1 mmol)]. After filtration through silica gel, product (*R*)-**3** was obtained as a colorless syrup (86 mg, 71%). $[\alpha]_D^{20}$ +4.3 (*c* 1, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$=1.29 (m, 1H), 1.42 (br s, 1H), 1.59 (m, 2H), 2.12 (m, 1H), 2.29 (m, 3H), 3.63 (m, 1H), 3.66 (s, 3H), 5.11 (ddd, *J*=4.5, 2.0, 1.0 Hz, 1H), 5.14 (ddd, *J*=7.3, 2.0, 1.0 Hz, 1H), 5.82 ppm (m, 1H); $^{13}$C NMR (100.6 MHz, $CDCl_3$): $\delta$=25.0, 25.7, 29.2, 29.3, 29.5, 29.6, 34.2, 36.9, 51.6, 70.7, 118.2, 135.0, 174.5 ppm (CO); MS (70 eV, EI) *m*/*z* (%): 201 (11) [$M^+-C_3H_5$], 169 (100), 81 (50), 67 (32), 55 (38); HRMS (FAB, *m*-NBA) *m*/*z* calcd for $C_{14}H_{26}O_3$: 242.1882, found 243.1946 [$M^+$+H].

**4.4.2. Methyl 4-(4-hydroxyhept-6-enyloxy)benzoate 5a.** From resin **4a** (500 mg, 0.25 mmol) and $^p$Ipc$_2$BAll (1 mmol) following the general procedure and the cleavage method A, **5a** (48 mg, 73%, er=89:11) was obtained as a colorless oil. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$=1.66 (m, 3H), 1.94 (m, 2H), 2.19 (m, 1H), 2.34 (m, 1H), 3.73 (sept, *J*=4.0 Hz, 1H), 3.88 (s, 3H), 4.05 (m, 2H), 5.14 (m, 1H), 5.18 (m, 1H), 5.84 (m, 1H), 6.90 (d, *J*=9.0 Hz, 2H), 7.98 ppm (d, *J*=9.0 Hz, 2H); $^{13}$C NMR (100.6 MHz, $CDCl_3$): $\delta$=25.5, 33.2, 42.1, 51.8, 68.0, 70.2, 114.0, 118.4, 122.5, 131.6, 134.5, 162.7, 166.9 ppm (CO); MS (70 eV, EI) *m*/*z* (%): 264 (4) [$M^+$], 223 (8) [$M^+-C_3H_5$], 191 (10), 152 (57), 121 (100), 95 (13), 71 (77); HRMS (FAB, *m*-NBA) *m*/*z* calcd for $C_{15}H_{20}O_4$: 264.1362, found 265.1469 [$M^+$+H].

**4.4.3. Methyl 4-(1-hydroxybutenyl)benzoate 5b.[18]** From resin **4b** (500 mg, 0.30 mmol) and $^p$Ipc$_2$BAll (1.2 mmol) following the general procedure and the cleavage method A, (*S*)-**5b** (50 mg, 81%, er=90:10) was obtained as a colorless syrup. $[\alpha]_D^{20}$ −27.6 (*c* 1.0, benzene), Ref. 18 for (*R*)-**5b**, $[\alpha]_D^{20}$ +28.1 (*c* 1.0, benzene); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$=2.04 (br s, 1H), 2.51 (m, 2H), 3.91 (s, 3H), 4.80 (dd, *J*=8, 4.7 Hz, 1H), 5.16 (m, 1H), 5.18 (m, 1H), 5.79 (m, 1H), 7.43 (d, *J*=8.5 Hz, 2H), 8.01 ppm (d, *J*=8.5 Hz, 2H); $^{13}$C NMR (100.6 MHz, $CDCl_3$): $\delta$=43.8, 52.1, 72.7, 119.0, 125.7, 129.7, 133.8, 144.9, 149.4, 185.4 ppm (CO); MS (70 eV, EI) *m*/*z* (%): 175 (8) [$M^+$−MeO], 165 (100) [$M^+-C_3H_5$], 105 (21), 91 (20), 77 (34), 59 (18).

**4.4.4. Methyl [4-(2-hydroxypent-4-enyl)-2-methoxyphenoxy]acetate 5c.** From resin **4c** (300 mg, 0.12 mmol) and $^p$Ipc$_2$BAll (0.48 mmol) following the general procedure and the cleavage method A, **5c** was obtained (28 mg, 83%, er=88:12) as a colorless oil. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$=1.75 (br s, 1H), 2.22 (dt, *J*=14.0, 7.7 Hz, 2H), 2.33 (m, 1H), 2.64 (dd, *J*=13.7, 8.2 Hz, 1H), 2.76 (dd, *J*=13.7, 4.7 Hz, 1H), 3.79 (s, 3H), 3.85 (m, 1H), 3.87 (s, 3H), 4.67 (s, 2H), 5.13 (d, *J*=1.2 Hz, 1H), 5.16 (d, *J*=6.5, 1.2 Hz, 1H), 5.86 (m, 1H), 6.71 (dd, *J*=8.2, 1.7 Hz, 1H), 6.77 ppm (m, 2H); $^{13}$C NMR (100.6 MHz, $CDCl_3$): $\delta$=41.2, 42.9, 52.1, 55.9, 66.6, 71.6, 113.3, 114.6, 118.1, 121.3, 132.8, 134.6, 147.0, 149.6, 171.0 ppm (CO); MS (70 eV, EI) *m*/*z* (%): 280 (20) [$M^+$], 209 (45), 137 (100); HRMS (FAB, *m*-NBA) *m*/*z* calcd for $C_{15}H_{19}O_5$: 279.1233, found 280.1293 [$M^+$+H].

**4.4.5. 5-Allyl-dihydrofuran-2-one 5d.[11]** From resin **4d** (280 mg, 0.17 mmol) and $^p$Ipc$_2$BAll (0.68 mmol) following the general procedure and the cleavage method A, the lactone **5d** was obtained (15 mg, 71%) after standing (ca. 2 days) in chloroform solution and purification through silica gel. The cleavage method B afforded directly the lactone (*R*)-**5d** (13.5 mg, 64%, er=82:18). From resin **4d** (200 mg, 0.12 mmol) and $^l$Ipc$_2$BAll (0.48 mmol) following the general procedure and the cleavage method B, the lactone (*S*)-**5d** was obtained (9.8 mg, 65%, er=95:5). (*S*)-**5d:** $[\alpha]_D^{20}$ +16.40 (*c* 1.50, $CHCl_3$), Ref. 11 for (*R*)-**5d**, $[\alpha]_D^{20}$ −17.22 (*c* 2.10, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$=1.91 (m, 1H), 2.29 (m, 1H), 2.39 (m, 1H), 2.45–2.54 (m, 2H), 4.54 (q, *J*=6.5 Hz, 1H), 5.14 (dd, *J*=10.2, 2.7 Hz, 1H), 5.15 (ddd, *J*=17.2, 3.0, 1.5 Hz, 1H), 5.77 ppm (ddt, *J*=17.2, 10.2, 7.0 Hz, 1H); $^{13}$C NMR (100.6 MHz, $CDCl_3$): $\delta$=27.0, 28.6, 39.4, 79.7, 118.8, 131.9, 177.0 ppm (CO); MS (70 eV, EI) *m*/*z* (%): 85 (100) [$M^+-C_3H_5$], 57 (10).

**4.4.6. 6-Allyl-tetrahydropyran-2-one 11.**[37] From resin **10** (240 mg, 0.19 mmol) and $^{D}Ipc_2BAll$ (0.80 mmol) following the general procedure and the cleavage method B, the lactone (*R*)-**11** was obtained (26 mg, 96%, er=80:20). From resin **10** (315 mg, 0.25 mmol) and $^{L}Ipc_2BAll$ (1 mmol) following the general procedure and the cleavage method B, the lactone (*S*)-**11** was obtained (30 mg, 85%, er=92:8) as a colorless oil. (*S*)-**11**: $[\alpha]_D^{20}$ +30.1 (*c* 1.50, $CHCl_3$), Ref. 37 for (*R*)-**11**, $[\alpha]_D^{20}$ −32.4 (*c* 1.73, $CHCl_3$); $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$=1.56 (m, 1H), 1.80 (m, 1H), 1.90 (m, 2H), 2.35–2.60 (m, 4H), 4.35 (ddd, *J*=17.0, 6.2, 2.7 Hz, 1H), 5.16 (m, 2H), 5.80 ppm (ddt, *J*=17.2, 10.4, 7.0 Hz, 1H); MS (70 eV, EI) *m/z* (%): 99 (100) [$M^+-C_3H_5$], 71 (70), 55 (30), 43 (32).

**4.4.7. (3*S*,6*R*)-6-Allyl-3-benzyl-tetrahydropyran-2-one 15a.** From resin **15a** and $^{D}Ipc_2BAll$ following the general procedure and the cleavage method B, the lactone **15a** (19 mg, 75%, dr=86:14, from 143 mg of **14c**) was obtained as a colorless oil. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$=1.46–1.67 (m, 2H), 1.79–1.92 (m, 2H), 2.25–2.37 (m, 1H), 2.38–2.48 (m, 1H), 2.62 (dd, *J*=13.7, 4.3 Hz, 1H), 2.68–2.75 (m, 1H), 3.31 (dd, *J*=13.7, 4.3 Hz, 1H), 4.30 (ddd, *J*=16.8, 6.2, 3.5 Hz, 1H), 5.07–5.13 (m, 2H), 5.72–5.83 (ddt, *J*=17.0, 9.2, 7.0 Hz, 1H), 7.16–7.30 ppm (m, 5H); $^{13}C$ NMR/DEPT (100 MHz, $CDCl_3$): $\delta$=22.5 ($CH_2$), 25.8 ($CH_2$), 36.8 ($CH_2$), 39.5 ($CH_2$), 40.1, 77.4, 126.4 ($CH_2$), 128.5 (2C), 129.1 (2C), 132.7, 139.0, 174.9 ppm; IR (KBr): $\nu_{max}$=2926, 1732 (C=O), 1644, 1538, 1454, 1383, 1184, 743 $cm^{-1}$; MS (70 eV, EI) *m/z* (%): 230 (21) [$M^+$], 189 (15) [$M^+$−allyl], 117 (60), 91 (100) [Bn]; MS (ESI) *m/z* (%): 230 (100) [$M^+$]; HRMS (FAB, *m*-NBA) calcd for $C_{15}H_{18}O_2$: 230.1307, found 231.1358 [$M^+$+H].

**4.4.8. (3*S*,6*R*)-6-Allyl-tetrahydro-3-methylpyran-2-one 15b.** From resin **15b** and $^{L}Ipc_2BAll$ following the general procedure and the cleavage method B, the lactone **15b** (42 mg, 85%, dr=87:13, from 377 mg of **14d**) was obtained as a colorless oil. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$=1.27 (d, *J*=6.8 Hz, 3H), 1.47–1.64 (m, 2H), 1.88–1.94 (m, 1H), 1.96–2.03 (m, 1H), 2.29–2.49 (m, 3H), 4.31 (ddd, *J*=17.2, 6.1, 3.3 Hz, 1H), 5.08–5.14 (m, 2H), 5.79 ppm (ddt, *J*=17.2, 10.4, 7.0 Hz, 1H); $^{13}C$ NMR/DEPT (100 MHz, $CDCl_3$): $\delta$=17.3, 28.3 ($CH_2$), 28.5 ($CH_2$), 36.1, 40.4 ($CH_2$), 80.9, 118.5 ($CH_2$), 132.6, 174.2 ppm (CO); IR (KBr): $\nu_{max}$=2924, 2854, 1732 (C=O), 1463, 1378, 1177, 917 $cm^{-1}$; MS (70 eV, EI) *m/z*: 113 (100) [$M^+$−allyl], 85 (65), 67 (54), 41 (61) [allyl]; HRMS (EI) *m/z* calcd for $C_9H_{14}O_2$: 154.0994, found 154.1004.

**4.4.9. (3*R*,5*R*)-5-Allyl-3-benzyl-dihydrofuran-2(*3H*)-one 15c.** From resin **15c** and $^{L}Ipc_2BAll$ following the general procedure and the cleavage method B, the lactone **15c** (50 mg, 60%, dr=88:12, from 477 mg of **14e**) was obtained as a colorless oil. $[\alpha]_D^{20}$ −19.67 (*c* 1.20, $CHCl_3$); $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$=1.95 (ddd, *J*=14.2, 9.2, 5.1 Hz, 1H), 2.05 (dt, *J*=15.4, 7.6 Hz, 1H), 2.24–2.32 (m, 1H), 2.36–2.43 (m, 1H), 2.76 (dd, *J*=13.8, 9.3 Hz, 1H), 2.92 (dtd, *J*=9.3, 7.4, 4.4 Hz, 1H), 3.16 (dd, *J*=13.8, 4.4 Hz, 1H), 4.36 (ap quint, *J*=6.2 Hz, 1H), 5.07–5.13 (m, 2H), 5.70 (ddt, *J*=13.9, 9.6, 6.8 Hz, 1H), 7.15 (m, 2H), 7.23 (m, 1H), 7.28 ppm (m, 2H); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$=31.6, 36.5, 39.4, 40.9, 77.4, 118.9, 126.8, 128.7 (2C), 128.9 (2C), 132.0, 138.2, 178.5 ppm; IR (KBr): $\nu_{max}$=3064, 3028, 2929, 1769 (C=O), 1496, 1355, 1160, 966, 921 $cm^{-1}$; MS (70 eV, EI) *m/z* (%): 216 (16) [$M^+$], 175 (44) [$M^+$−allyl], 157 (28), 148 (62), 129 (39), 91 (100) [Bn]; MS (ESI) *m/z* (%): 234 (100) [$M^+$+$NH_4$], 217 (20) [$M^+$+1]; HRMS (EI) calcd for $C_{14}H_{16}O_2$: 216.1150, found 216.1131.

**4.4.10. (3*R*,5*R*)-5-Allyldihydro-3-methylfuran-2(*3H*)-one 15d.** From resin **15d** and $^{L}Ipc_2BAll$ following the general procedure and the cleavage method B, the lactone **15d** (50 mg, 87%, dr=85:15, from 476 mg of **14f**) was obtained as a colorless oil. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$=1.25 (d, *J*=7.2 Hz, 3H), 1.96 (dt, *J*=12.9, 7.8 Hz, 1H), 2.16 (ddd, *J*=12.9, 9.2, 4.7 Hz, 1H), 2.30–2.39 (m, 1H), 2.40–2.50 (m, 1H), 2.67 (m, 1H), 4.55 (dtd, *J*=9.4, 6.2, 4.7 Hz, 1H), 5.11–5.17 (m, 2H), 5.75 ppm (m, 1H); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$=15.8, 33.9, 34.4 ($CH_2$), 39.3 ($CH_2$), 77.4, 119.0 ($CH_2$), 132.1, 180.1 ppm; IR (KBr): $\nu_{max}$=2936, 1770, 1455, 1353, 1174, 921 $cm^{-1}$; MS (70 eV, EI) *m/z* (%): 99 (100) [$M^+$−allyl], 71 (34), 43 (38); HRMS (FAB, *m*-NBA) *m/z* calcd for $C_8H_{12}O_2$: 140.0837, found 141.0926 [$M^+$+H].

**4.4.11. (3*S*,5*S*)-5-Allyl-3-ethyldihydrofuran-2(*3H*)-one 15e.** From resin **13e** and $^{D}Ipc_2BAll$ following the general procedure and the cleavage method B, the lactone **15e** (8 mg, 37%, dr=87:13, from 153 mg of **14g**) was obtained as a colorless oil. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$=0.98 (t, *J*=7.6 Hz, 3H), 1.45–1.57 (m, 1H), 1.78–1.88 (m, 1H), 1.97–2.14 (m, 2H), 2.30–2.39 (ap sext, *J*=6.8 Hz, 1H), 2.40–2.48 (ap sext, *J*=6.4 Hz, 1H), 2.49–2.57 (m, 1H), 4.53 (dddd, *J*=12.6, 6.4, 6.2, 2.4 Hz, 1H), 5.11–5.18 (m, 2H), 5.71–5.81 ppm (ddt, *J*=17.1, 7.0, 3.5 Hz, 1H); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$=11.6, 24.0, 32.1, 39.6, 40.1, 77.5, 118.9, 132.2, 179.1 ppm; IR (KBr): $\nu_{max}$=3079, 2965, 1769 (C=O), 1643, 1463, 1355, 1177, 923 $cm^{-1}$; MS (70 eV, EI) *m/z* (%): 113 (100) [$M^+$−allyl], 85 (25) [$M^+$−allyl−Et]; HRMS (EI) *m/z* $C_9H_{14}O_2$: 154.0994, found 154.0985.

**4.4.12. (3*S*,5*R*)-5-Allyl-3-butyldihydrofuran-2(*3H*)-one 15f.** From resin **13f** (839 mg) and $^{L}Ipc_2BAll$ (1.68 mmol) following the general procedure and the cleavage method B, the lactone **15f** (79 mg, 51%, dr=91:9) was obtained as a colorless oil. $[\alpha]_D^{20}$ +29.50 (*c* 2.0, $CHCl_3$); $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$=0.90 (t, *J*=7.2 Hz, 1H), 1.33 (m, 4H), 2.35–2.65 (m, 4H), 4.42 (ddd, *J*=11.9, 10.2, 6.2 Hz, 1H), 5.13–5.18 (m, 2H), 5.76 ppm (ddt, *J*=17.2, 10.2, 6.8 Hz, 1H); $^{13}C$ NMR/DEPT (100 MHz, $CDCl_3$): $\delta$=13.8, 22.4 ($CH_2$), 29.4 ($CH_2$), 29.9 ($CH_2$), 34.4 ($CH_2$), 39.4 ($CH_2$), 40.8, 77.6, 118.6 ($CH_2$), 132.1, 178.7 ppm (CO); IR (KBr): $\nu_{max}$=3080, 2932, 1770 (C=O), 1644, 1455, 1353, 1174, 920 $cm^{-1}$; MS (70 eV, EI) *m/z* (%): 141 (100) [$M^+$−allyl], 95 (20); HRMS (EI) *m/z* $C_{11}H_{18}O_2$: 182.1307; found 182.1315.

**4.4.13. (3*S*,5*R*)-5-Allyldihydro-3-phenylethylfuran-2(*3H*)-one 15g.** From resin **13g** (240 mg) and $^{L}Ipc_2BAll$ (0.5 mmol) following the general procedure and the cleavage method B, the lactone **15g** (35 mg, 66%, dr=82:18) was obtained as a colorless oil. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$=1.64 (dt, *J*=12.1, 10.6 Hz, 1H), 1.75–1.85 (dtd, *J*=19.6, 9.0, 5.8 Hz, 1H), 2.28–2.37 (m, 1H), 2.44–2.50

(m, 2H), 2.54–2.66 (m, 2H), 2.71–2.81 (m, 1H), 2.81–2.88 (m, 1H), 4.43 (ddd, $J$=11.9, 10.3, 6.0 Hz, 1H), 5.20–5.25 (m, 2H), 5.84 (dtd, $J$=17.2, 10.3, 7.0 Hz, 1H), 7.26 (m, 2H), 7.31–7.38 ppm (m, 3H); $^{13}$C NMR/DEPT (100 MHz, $CDCl_3$): $\delta$=31.9 ($CH_2$), 33.3 ($CH_2$), 34.6 ($CH_2$), 39.4 ($CH_2$), 40.0, 77.5, 118.8 ($CH_2$), 126.2, 128.4 (2C), 128.5 (2C), 132.1, 140.7, 178.5 ppm (CO); IR (KBr): $\nu_{max}$=3071, 2925, 2869, 1769 (C=O), 1454, 1353, 1175, 1011, 921 cm$^{-1}$; MS (70 eV, EI) $m/z$ (%): 230 (15) [M$^+$], 189 (100) [M$^+$−allyl], 108 (30), 91 (73); MS (ESI) $m/z$ (%): 248 (100) [M$^+$+NH$_4$]; HRMS (FAB, $m$-NBA) $m/z$ $C_{15}H_{18}O_2$: 230.1307, found 231.1394 [M$^+$+H].

**4.4.14. (3*S*,5*R*)-5-Allyl-3-(cyclopentylmethyl)dihydrofuran-2(*3H*)-one 15h.** From resin **13h** (946 mg) and $^{L}$Ipc$_2$BAll (1.9 mmol) following the general procedure and the cleavage method B, the lactone **15h** (139 mg, 86%, dr=88:12) was obtained as a colorless oil. After a second careful chromatography, the 'dr' was enriched to 92:8. $[\alpha]_D^{20}$ +37.95 ($c$ 2.10, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$=1.03–1.13 (m, 2H), 1.36–1.43 (m, 1H), 1.46–1.62 (m, 3H), 1.68–1.78 (m, 2H), 1.79–1.92 (m, 2H), 2.32–2.60 (m, 4H), 4.36 (ddd, $J$=18.0, 10.3, 5.7 Hz, 1H), 5.12 (m, 2H), 5.75 ppm (dtd, $J$=17.2, 10.2, 7.0 Hz, 1H); $^{13}$C NMR/DEPT (100 MHz, $CDCl_3$): $\delta$=24.8 ($CH_2$), 25.1 ($CH_2$), 31.8 ($CH_2$), 33.0 ($CH_2$), 35.5 ($CH_2$), 36.6 ($CH_2$), 38.2, 39.4 ($CH_2$), 40.3, 77.6, 118.6 ($CH_2$), 132.1, 179.0 ppm (CO); IR (KBr): $\nu_{max}$=2947, 2869, 1776 (C=O), 1452, 1372, 1170, 1015, 921 cm$^{-1}$; HRMS (FAB, $m$-NBA) $m/z$ $C_{13}H_{20}O_2$: 208.1463, found 209.1526 [M$^+$+H].

**4.4.15. Synthetic sequence to lactone 18.** Resin **14b** (700 mg) and the Grubbs catalyst (20 mol %, 0.084 mmol, 28 mg) were placed under argon in a flask equipped with a reflux condenser. A degassed solution (two freeze–thaw cycles) of hex-1-en (6 equiv, 2.52 mmol, 310 μL) in dichloromethane (7 mL) was then added and the mixture was heated to reflux for 20 h. After cooling to room temperature, the mixture was filtered, washed with $CH_2Cl_2$ and MeOH, and dried in vacuo overnight to give 720 mg of resin **16**. To resin **16** (470 mg) was added THF (5 mL) followed by a solution of NaOMe (0.56 mmol, 31 mg) in MeOH (2.5 mL) and the mixture was shaken overnight at room temperature. Water was added, the mixture was filtered, and the product was extracted with $Et_2O$. After concentration, the crude mixture containing **17** (45 mg) was dissolved in MeOH (10 mL) and Pd/C (5 mol %, 13.2 mg) was added. After degassing, the flask was filled with $H_2$ (1 bar) and the mixture was stirred for 20 h under $H_2$ atmosphere at room temperature. After filtration over Celite, the solvent was removed in vacuo and the residue was purified by flash chromatography (pentane/$Et_2O$ 9:1) to furnish the lactone **18** as a yellowish oil (25.5 mg, 55%). $[\alpha]_D^{20}$ −25.8 ($c$ 1, $CHCl_3$); $^1$H NMR (500 MHz, $CDCl_3$): $\delta$=0.87 (t, $J$=6.7 Hz, 3H), 1.20–1.40 (m, 9H), 1.45 (m, 1H), 1.59 (m, 1H), 1.72 (m, 1H), 1.84 (quint, $J$=8.2 Hz, 1H), 2.31 (sext, $J$=6.5 Hz, 1H), 2.52 (t, $J$=8 Hz, 2H), 4.48 (quint, $J$=6.8 Hz, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$=14.0, 22.6, 25.2, 28.0, 28.8, 29.1, 29.3, 31.7, 35.6, 81.0, 177.2. MS (70 eV, EI) $m/z$ (%): 128 (13) [M$^+$−$C_4H_8$], 85 (100), 55 (9).

**4.4.16. (*S*)-[Tetrahydro-6-(2-hydroxyethyl)]pyran-2-one 22.** The resin-bound homoallylic alcohol **19** (1.0 g, ~0.70 mmol) was swelled in $CH_2Cl_2$ (25 mL) and the suspension was degassed by bubbling argon through it. To the degassed suspension, methyl acrylate (0.4 mL, 4.20 mmol) and Grubbs second generation catalyst (45 mg, 0.05 mmol) were added and the mixture was refluxed under inert atmosphere for 12 h. Another portion of Grubbs catalyst (20 mg, 0.02 mmol) and methyl acrylate (0.2 mL, 2.1 mmol) was added and the suspension was further stirred under reflux for 12 h. The resulting resin **20** was then filtered, washed successively with THF (25 mL×2) and $CH_2Cl_2$ (60 mL), and dried in vacuo for 5 h. The resin **20** (0.75 g, ~0.50 mmol) was suspended in dry pyridine (15 mL) and potassium azodicarboxylate (1.20 g, 6.2 mmol) was added. The suspension was shaken, cooled to 0 °C, and acetic acid (0.6 mL, 10 mmol) was added dropwise over a period of 2 h. The mixture was then shaken at room temperature for 24 h. The resin was filtered, washed with a cold solution of THF/$H_2O$ (2:1), DMF (25 mL), THF (25 mL×2), and $CH_2Cl_2$ (40 mL×2) and dried in vacuo. A portion of the dried resin **21** (0.12 g) was subjected to TFA/$CH_2Cl_2$ (2:1) release conditions (method C) to afford saturated lactone **22** (7 mg, 60% yield. $[\alpha]_D^{20}$ +18.8 ($c$ 0.33, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$=1.58–1.69 (m, 1H), 1.90–2.01 (m, 3H), 2.09 (ap q, $J$=6.6 Hz, 2H), 2.60–2.68 (m, 1H), 2.46–2.54 (m, 1H), 4.40–4.48 (m, 1H), 4.57 ppm (t, $J$=6.0 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$=18.5, 28.0, 29.3, 34.5, 76.3, 170.9 ppm; MS (ESI) $m/z$ (%): 127 [M$^+$−17] (100).

### 4.5. Asymmetric crotylation on solid support

**4.5.1. Methyl (10*R*,11*R*)-10-hydroxy-11-methyltridec-12-enoate 6 (representative procedure).** To a solution of KO-*t*-Bu (1 M in THF, 5 equiv, 1.5 mmol) at −78 °C was added *cis*-butene (excess, 0.5 mL). 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, the resin **2** (0.3 mmol pre-swelled in THF (10 mL)) was added and the mixture cooled to −78 °C. The mixture was stirred overnight while the temperature rose slowly to 0 °C. After quenching by adding MeOH (0.5 mL), the resin was washed consecutively with pH 7 buffer, $H_2O$, THF, $Et_2O$, DCM, and MeOH. To the resin at 0 °C were added DMF (3 mL), MeOH (3 mL), pH 7 buffer (1 mL), and $H_2O_2$ (30%, 1 mL). The mixture was shaken at room temperature for 2 h and filtered. The resin was washed with $H_2O$, THF, $Et_2O$, $CH_2Cl_2$, and MeOH and dried overnight in vacuo. For the cleavage, THF (5 mL) was added followed by a solution of NaOMe (0.6 mmol) in MeOH (2.5 mL) and the mixture was shaken overnight at room temperature. Water was added, the mixture was filtered, and the product was extracted with $Et_2O$. After filtration through silica gel, product **6** (60 mg, 78%, dr=95:5) was obtained as a colorless syrup. $[\alpha]_D^{20}$ +18.7 ($c$ 1, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$=1.00 (d, $J$=7.0 Hz, 3H), 1.25–1.35 (m, 10H), 1.46 (m, 2H), 1.59 (m, 2H), 2.22 (m, 1H), 2.25 (t, $J$=7.6 Hz, 2H), 3.44 (m, 1H), 3.64 (s, 3H), 5.01 (d, $J$=1.0 Hz, 1H), 5.05 (dt, $J$=5.3, 1.4 Hz, 1H), 5.75 ppm (m,

1H); $^{13}$C NMR (100.6 MHz, $CDCl_3$): $\delta$=14.0, 24.9, 26.0, 29.0, 29.05, 29.1, 29.3, 29.5, 34.0, 43.4, 51.4, 74.6, 115.1, 141.1, 174.3 ppm (CO); MS (70 eV, EI) *m/z* (%): 201 (14) [$M^+-C_4H_7$], 169 (100), 81 (21), 67(12), 55 (18); HRMS (FAB, *m*-NBA) *m/z* calcd for $C_{15}H_{28}O_3$: 256.2038, found 257.2148 [$M^+$+H].

**4.5.2. Methyl (10*R*,11*S*)-10-hydroxy-11-methyltridec-12-enoate 7.** From resin **2** (335 mg, 0.30 mmol) and $^{D}Ipc_2B$-(*E*)-crotyl generated following the representative procedure from *trans*-butene, homoallylic alcohol **7** (73 mg, 95%, dr=88:12) was obtained as a colorless syrup. $[\alpha]_D^{20}$ −54.8 (*c* 1, $CHCl_3$); $^1$H NMR (500 MHz, $CDCl_3$): $\delta$=1.00 (d, *J*=6.8 Hz, 3H), 1.20–1.40 (m, 10H), 1.46 (m, 2H), 1.59 (m, 2H), 2.18 (sext, *J*=7.0 Hz, 1H), 2.27 (t, *J*=7.2 Hz, 2H), 3.36 (m, 1H), 3.64 (s, 3H), 5.07 (d, *J*=9.0 Hz, 1H), 5.09 (s, 1H), 5.72 ppm (quint, *J*=8.8 Hz, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$=16.2, 24.9, 25.6, 29.0, 29.1, 29.3, 29.6, 34.0, 34.2, 44.0, 51.3, 76.6, 116.1, 140.3, 174.3 ppm (CO); MS (70 eV, EI) *m/z* (%): 201 (13) [$M^+-C_4H_7$], 169 (100), 81 (34), 67 (20), 55 (29); HRMS (FAB, *m*-NBA) *m/z* calcd for $C_{15}H_{28}O_3$: 256.2038, found 257.2116 [$M^+$+H].

**4.5.3. Methyl 4-[(1*S*,2*R*)-1-hydroxy-2-methylbut-3-enyl]-benzoate 8.** From resin **4b** (500 mg, 0.30 mmol) and $^{D}Ipc_2B$-(*Z*)-crotyl generated following the representative procedure from *cis*-butene, homoallylic alcohol **8** (62 mg, 94%, dr=94:6) was obtained as a colorless syrup. $[\alpha]_D^{20}$ −47.7 (*c* 2, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$=0.96 (d, *J*=7.0 Hz, 3H), 2.21 (br s, 1H), 2.54 (m, 1H), 3.89 (s, 3H), 4.66 (d, *J*=5.3 Hz, 1H), 4.99 (t, *J*=1.4 Hz, 1H), 5.03 (tt, *J*=5.3, 1.4 Hz, 1H), 5.72 (m, 1H), 7.35 (d, *J*=8.0 Hz, 2H), 7.97 ppm (d, *J*=8.0 Hz, 2H); $^{13}$C NMR (100.6 MHz, $CDCl_3$): $\delta$=13.6, 44.6, 52.0, 76.6, 115.9, 126.4, 129.3, 139.8, 147.8, 167.0 ppm (CO); MS (70 eV, EI) *m/z* (%): 189 (6) [$M^+$−MeO], 165 (100), 105 (10), 77 (12); HRMS (FAB, *m*-NBA) *m/z* calcd for $C_{13}H_{16}O_3$: 220.1099, found 221.1157 [$M^+$+H].

**4.5.4. Methyl 4-[(1*S*,2*S*)-1-hydroxy-2-methylbut-3-enyl]-benzoate 9.** From resin **4b** (500 mg, 0.30 mmol) and $^{D}Ipc_2B$-(*E*)-crotyl generated following the representative procedure from *trans*-butene, homoallylic alcohol **9** was obtained (60 mg, 91%, dr=83:17) as a colorless syrup. $[\alpha]_D^{20}$ +23.9 (*c* 1, $CHCl_3$); $^1$H NMR (500 MHz, $CDCl_3$): $\delta$=0.88 (d, *J*=6.8 Hz, 3H), 2.29 (br s, 1H), 2.46 (sext, *J*=7.0 Hz, 1H), 3.89 (s, 3H), 4.42 (d, *J*=7.2 Hz, 1H), 5.14 (d, *J*=6.0 Hz, 1H), 5.17 (s, 1H), 5.75 (quint, *J*=8.2 Hz, 1H), 7.38 (d, *J*=8 Hz, 2H), 7.98 ppm (d, *J*=8.0 Hz, 2H); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$=16.3, 46.1, 52.0, 77.3, 117.1, 126.7, 129.4, 139.8, 147.7, 167.0 ppm (CO); MS (70 eV, EI) *m/z* (%): 189 (9) [$M^+$−MeO], 165 (100), 105 (20), 91 (19), 77 (28), 59 (18); HRMS (FAB, *m*-NBA) *m/z* calcd for $C_{13}H_{16}O_3$: 220.1099, found 221.1157 [$M^+$+H].

### 4.6. Iterative sequence

**4.6.1. Resin 24 (protection as TBS ether).** The homoallylic alcohol resin **23** (derived from allylation of **4b** with $^{D}Ipc_2BAll$ following the general procedure, 1.5 g) was swelled in DMF (15 mL) for 15 min before the addition of imidazole (10 equiv, 9 mmol, 680 mg) and DMAP (10 mol %, 0.01 mmol, 12 mg). The mixture was cooled to 0 °C and TBSCl (10 equiv, 9 mmol, 1.5 g) was added. The temperature was raised to room temperature and the mixture was shaken overnight. The resin was filtered off, washed successively with DMF, $H_2O$, THF, $Et_2O$, $CH_2Cl_2$, and MeOH, and dried in vacuo for 12 h to yield the resin **24** (IR (SiC): $\nu_{max}$=1709 (C=O), 1641 $cm^{-1}$ (C=C)).

**4.6.2. Resin 25 (ozonolysis and allylation).** Resin **24** was ozonized using the general procedure (IR (SiC): $\nu_{max}$=1704 (C=O ester and aldehyde), 2722 $cm^{-1}$ (CH aldehyde)) and the resulting resin was submitted to allylation with $^{D}Ipc_2BAll$ following the general procedure (IR (SiC): $\nu_{max}$=3540 (OH), 1731 and 1710 (C=O), 1641 $cm^{-1}$ (C=C)).

**4.6.3. Resin 26 (TBS deprotection and acetonide formation).** Resin **25** (1.5 g) was swelled in THF (15 mL) for 15 min. A solution of TBAF (1 M in THF, 0.9 mL) was added and the mixture was shaken for 12 h. The resin was filtered off, washed with THF, $Et_2O$, $CH_2Cl_2$, and MeOH, and dried in vacuo for 12 h. The resulting resin (1.5 g) was suspended in $CH_2Cl_2$ (15 mL), 2,2-dimethoxypropane (15 mL) was added, and the mixture was shaken for 15 min. CSA (1.5 equiv, 1.4 mmol, 300 mg) was added and the shaking was maintained for 24 h. The resin was filtered off, washed with $CH_2Cl_2$ and MeOH, and dried in vacuo for 12 h (IR (SiC): $\nu_{max}$=1642 (C=C), 1709 $cm^{-1}$ (C=O)).

**4.6.4. Methyl 4-[(4*S*,6*S*)-6-allyl-2,2-dimethyl-1,3-dioxan-4-yl]benzoate 27.** To the resin **26** (500 mg) was added THF (5 mL) followed by a solution of NaOMe (0.6 mmol, 32.4 mg) in MeOH (2.5 mL) and the mixture was shaken overnight at room temperature. Water was added, the mixture was filtered, and the product was extracted with $Et_2O$. After filtration on silica gel, product **27** (*syn*/*anti* ratio=86:14) was obtained as a colorless syrup (37 mg, 43%). A pure sample of the major diastereoisomer *syn*-**27** could be obtained after a second careful chromatography. $[\alpha]_D^{20}$ −22.0 (*c* 1, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$=1.52 (s, 3H), 1.56 (s, 3H), 1.76 (dt, *J*=13.0, 2.5 Hz, 2H), 2.18 (m, 1H), 2.35 (m, 1H), 3.90 (s, 3H), 4.04 (m, 1H), 4.94 (dd, *J*=11.8, 2.5 Hz, 1H), 5.08 (m, 2H), 5.81 (m, 1H), 7.43 (d, *J*=8.3 Hz, 2H), 8.01 ppm (d, *J*=8.5 Hz, 2H); $^{13}$C NMR (100.6 MHz, $CDCl_3$): $\delta$=19.7, 30.1, 36.4, 38.6, 40.7, 52.0, 68.6, 71.0, 99.1, 117.4, 125.7, 129.7, 133.8, 147.5, 166.9 ppm; MS (70 eV, EI) *m/z* (%): 275 (67) [$M^+-CH_3$], 215 (93), 191 (81), 175 (69), 163 (100), 149 (40), 131 (57), 103 (24), 77 (25), 59 (46); HRMS (EI): *m/z* calcd for $C_{17}H_{22}O_4$: 290.1518, found 290.1581.

**4.6.5. Methyl 4-[(4*S*,6*S*)-6-((*S*)-2-hydroxypent-4-enyl)-2,2-dimethyl-1,3-dioxan-4-yl]benzoate 29.** The resin **26** (500 mg) was submitted to ozonolysis and allylation with $^{D}Ipc_2BAll$ following the general procedures to yield the resin **28**, which was released from the resin with NaOMe (method A). The product **29** (40 mg, 40%) was isolated as a mixture of diastereoisomers (75:13:9:3; determined by GC–MS). $^1$H NMR (500 MHz, $CDCl_3$): $\delta$=1.40–1.80 (m, 10H), 2.23 (m, 2H), 3.90 (s, 3H), 3.92 (m, 1H), 4.33 (m, 1H), 4.98 (d, *J*=11.5 Hz, 1H), 5.10 (m, 2H), 5.83 (m, 1H), 7.42 (d, *J*=8.0 Hz, 2H), 8.01 ppm (d, *J*=8.5 Hz, 2H); MS (70 eV, EI) *m/z* (%): 319 (55) [$M^+-CH_3$], 241 (38), 227 (68), 189 (95), 163 (100), 131 (66), 59 (56).

## Acknowledgements

This research was supported by the Deutsche Forschungsgemeinschaft, the Max Planck Gesellschaft, the Fonds der Chemischen Industrie, the European Union (Marie Curie Intra-European post-doctoral fellowship to A.B.G.) and the Alexander von Humboldt Stiftung (post-doctoral fellowship to J.D.U.).

## Supplementary data

Experimental procedures and data for new carboxylic acids are reported. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2007.01.041.

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21. In contrast to the allylation protocol with $Ipc_2BAll$, a pre-swelled and pre-cooled (−78 °C) resin in THF was added under argon to the solution of (*E*)- or (*Z*)-crotylborane at −78 °C to keep the temperature low and to avoid (*E*)–(*Z*) isomerization of the crotylborane. See: Kramer, G. W.; Brown, H. C. *J. Organomet. Chem.* **1977**, *132*, 9–27.
22. Diastereoisomer ratios were determined by $^1H$ NMR; *syn* and *anti* isomers were assigned according to the literature (see:

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25. The experimental procedure and data for new or partially characterized carboxylic acids **12** are collected in Supplementary data.
26. The ee was determined by $^1$H NMR analysis in the intermediates carrying the chiral auxiliary (see Supplementary data) and assuming that the dr observed there is the same as the ee after hydrolysis of the imide moiety. This assumption was checked by analysis in chiral GC of some of the carboxylic acids.
27. Entries 1–4 show that the L-enantiomer of the allylborane gave rise to higher enantioselectivity. This is mainly due to the quality of the reagent ($^L$Ipc$_2$BAll) in terms of enantiomeric purity. The starting material for its preparation, commercially available (+)-Ipc$_2$BOMe, is supplied as a solid while (−)-Ipc$_2$BOMe is a syrup more difficult to manipulate. This may have some influence in the enantiopurity of the resulting $^D$Ipc$_2$BAll and thereof in the selectivity of the allylation.
28. We assumed the same 'er' in the carboxylic acids **12a–h** as in the lactones **15a–h**. The assumption that no epimerization occurred either during the attachment to the resin or in the release with TFA was checked by comparison of the ee of the carboxylic acid **12e** (99%, determined by chiral GC analysis) and the ee after esterification to the polymeric support and release with TFA employing the same conditions as for the synthesis of lactones, which was also 99%.
29. The yields are calculated by comparison of the experimental loading of resins **14** (determined by cleavage) with the theoretical loading for those resins taking into account the increase of molecular weight between them and hydroxymethyl polystyrene following the next equation: $L_T = L_0/(1 + (\Delta MW/L_0 \times 1000))$, $L_T$=theoretical loading, $L_0$=initial loading; Chan, W. C.; White, P. D. *Fmoc Solid Phase Peptide Synthesis. A Practical Approach*; Hames, B. D., Ed.; Oxford University Press: New York, NY, 2000; Chapter 9, pp 61–63.
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