Stereocomplementary synthesis of a natural product-derived compound collection on a solid phase†

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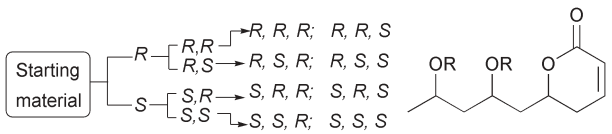
Enantiocomplementary allylation of solid phase-bound aldehydes gives rise to a natural product-derived compound collection, including all stereoisomers of cryptocarya diacetate.

The development of synthetic methodologies giving access to complex molecule architectures of high skeletal diversity[1] for diversity-oriented synthesis (DOS)[2] and biology-oriented synthesis (BIOS)[3] is of major importance to chemical biology and medicinal chemistry research. For such synthetic endeavours, which give access to stereoisomer libraries (*i.e.* all diastereomers, see Scheme 1), *e.g.*, of a given natural product and analogues thereof, powerful enantiocomplementary transformations are indispensable. However, solutions to this demanding problem have so far only been scarcely provided.[4–6]

For the synthesis of natural product-inspired and -derived compound collections, solid phase organic synthesis is a viable technology, enabling the efficient removal of all surplus reagents required in multi-step sequences.[1,2,3,7] However, to date, very few enantioselective synthetic methods have been developed for solid phase synthesis in general,[8] and their application to the stereocomplementary synthesis of compound libraries has remained virtually unexplored.[9]

Here we disclose the development of stereocomplementary, enantioselective, reagent-controlled carbonyl allylation[10] on a solid phase employing chiral allylboranes,[11] and its application to the synthesis of a natural product-derived compound collection, including the combinatorial synthesis of all eight isomers of the natural product cryptocarya diacetate.



Scheme 1 Synthetic pathway to stereoisomer libraries.

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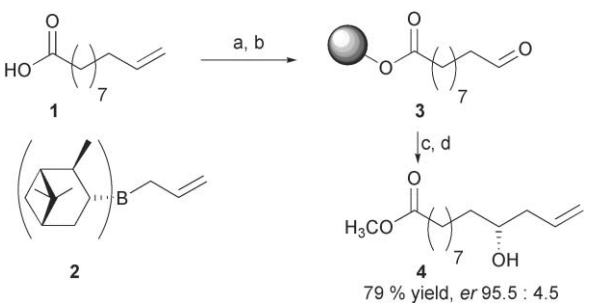
In order to identify the reaction conditions that would give rise to allylation products with high enantioselectivity and in high yield, immobilized aldehyde **3** was synthesized as a model compound on a polystyrene resin and subjected to allylation with *B*-allyl(diisopinocampheyl)borane (Ipc_2BAll, **2**)[12] (Scheme 2) under different conditions. After oxidative work-up, homoallyl alcohol **4** was released from the resin by treatment with sodium methoxide and isolated by simple filtration of the crude reaction mixture through a plug of silica gel. For results of the enantioselective allylation reactions, see ESI Table 1.†

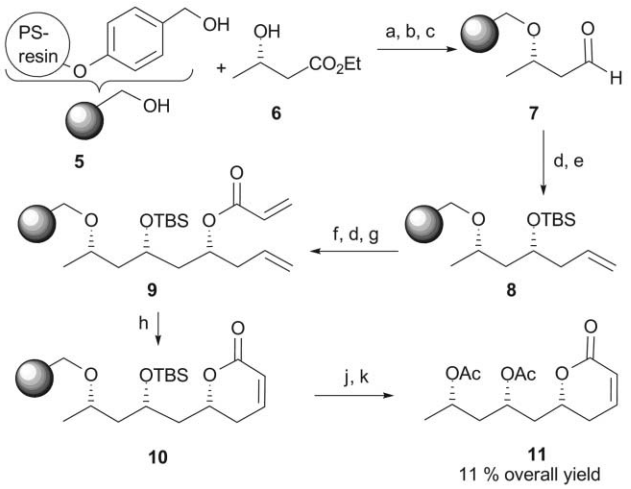
If four equivalents of **2** are employed at −78 °C in THF/ether 8 : 1.5 (v/v), the homoallylic alcohol **4** is obtained in 79% yield, in >95% purity and with an enantiomer ratio of 95.5 : 4.5.[13]

Encouraged by this finding, we sought to synthesize a natural product and a collection of stereoisomers derived from it by means of multiple stereocomplementary allylation reactions on the polymeric carrier. The target cryptocarya diacetate (**11**)[14] (Scheme 3) was chosen as it is an α,β-unsaturated lactone isolated from *Cryptocarya latifolia* that is representative of a large group of biologically-active secondary metabolites.[15]

For the synthesis of cryptocarya diacetate, (*S*)-3-hydroxybutyric acid ester (**6**) was immobilized on Wang resin **5**, activated as the trichloroacetimidate and converted into polymer-bound aldehyde **7** in two steps (loading 0.5 mmol g^{-1}, determined with 4-(9-fluorenylmethoxycarbonyl)-phenylhydrazine[16]). Allylation with *l*-Ipc_2BAll, as described above, and protection of the secondary alcohol as a silyl ether yielded resin **8**, which was formed in a *syn* : *anti* ratio of 85 : 15 (determined after release from the resin by



Scheme 2 Development of the enantioselective allylation on a solid support employing Ipc_2BAll (**2**) as a chiral allylation reagent. (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},[7a] 60% yield (two steps); (c) (i) 4 equiv. **2**, THF, −78 °C, (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.



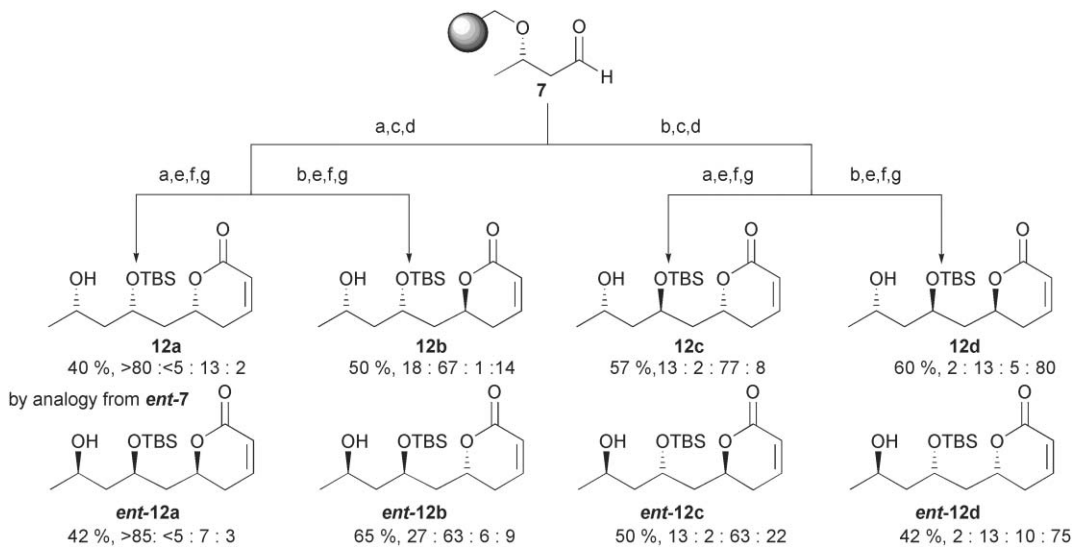
Scheme 3 Enantioselective synthesis of cryptocarya diacetate (**11**) on a solid support. (a) **5** (1.2 mmol g^{-1}), trichloroacetonitrile, DBU, CH_2Cl_2, then **6**, $BF_3{\cdot}OEt_2$, cyclohexane/CH_2Cl_2; (b) DIBAL–H, THF, −78 °C to rt, 16 h, (c) IBX, DMSO/THF, rt, 16 h; (d) (i) 3 equiv. **2**, THF, −78 °C, (ii) pH 7 buffer, H_2O_2 30%, DMF/MeOH 1 : 1, 0 °C, 2 h; (e) TBS–Cl, imidazole, cat. DMAP, CH_2Cl_2, rt, 16 h; (f) O_3, CH_2Cl_2, −78 °C, then PPh_3, −78 °C to rt; (g) acryloyl chloride, NEt_3, cat. DMAP, CH_2Cl_2, 0 °C to rt, 16 h; (h) 2 × 20 mol% Grubbs II catalyst, CH_2Cl_2, reflux, 24 h; (j) trifluoroacetic acid/CH_2Cl_2 1 : 2, 20 min, rt; (k) Ac_2O, NEt_3, cat. DMAP, CH_2Cl_2, 0 °C to rt, 3 h. DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene, DIBAL–H: di-*iso*-butylaluminiumhydride, IBX: *ortho*-iodoxybenzoic acid, TBS: *tert*-butyldimethylsilyl, DDQ: 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.

means of integration of the methyl signal intensities in the 500 MHz ^{1}H NMR spectrum). After careful ozonolysis of the double bond for 6 min, the resulting aldehyde was subjected to a second allylation with *l*-Ipc_2BAll and the formed secondary alcohol was converted to acrylic ester **9**. Ring closing metathesis employing the Grubbs II catalyst induced formation of the α,β-unsaturated lactone **10**.[17] Release from the solid support, with consecutive cleavage of the silyl group by treatment with trifluoroacetic acid and subsequent acetylation, yielded a mixture of four stereoisomers, from which the all-*syn* isomer of cryptocarya diacetate was isolated in 11% overall yield after 11 steps by means of simple flash chromatography. Formation of the *syn*-isomer was ascertained by formation of the acetonide, obtained after the second allylation.[18] The absolute configuration of **11** was determined by comparison of the specific rotation measured for synthetic **11** ($[\alpha]_D^{20}$ = 47.2 (*c* 0.5, $CHCl_3$)) with literature data ($[\alpha]_D^{29}$ = 45.4 (*c* 0.33, $CHCl_3$),[14b] $[\alpha]_D^{20}$ = 47.5 (*c* 0.6, $CHCl_3$),[14c] and $[\alpha]_D^{25}$ = 55.8 (*c* 1.06, $CHCl_3$)[14a]).

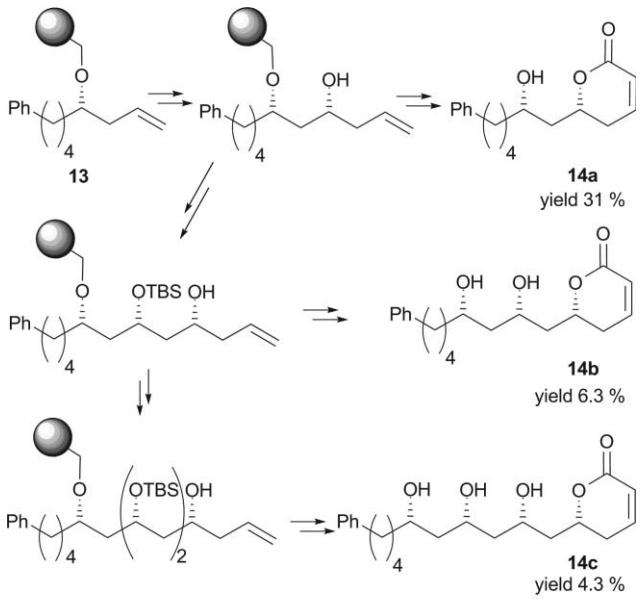
Based on this reaction sequence, all eight stereoisomeric configurations possible for the scaffold of the natural product were generated in a reaction sequence by employing the allylation reactions in a stereocomplementary fashion (Scheme 4). To this end, aldehyde **7** was synthesized, as described above, and subjected to allylation with *d*- or *l*-Ipc_2BAll. After silylation of the secondary alcohols and ozonolysis, the resulting aldehydes were subjected to a second allylation with either enantiomer of the allylborane. Formation of the acrylic acid ester, ring closing metathesis, as described above, and final release from the polymeric carrier with DDQ (CH_2Cl_2, pH 7 buffer, 0 °C to rt, 16 h) yielded TBS-protected stereoisomers **12a–d**. The yields and stereoisomeric ratios are given in Scheme 4. By analogy, isomers *ent*-**12a–d** were obtained from aldehyde *ent*-**7**. All isomers were obtained in fairly high overall yields for a 7-step sequence, as shown in Scheme 4.

In order to explore whether the synthesis sequence delineated above can be extended even further and used for the synthesis of whole families of natural product-derived and -inspired compound collections, we synthesized lactones **14a–c** (Scheme 5), embodying up to four stereocenters.

Employment of phenylbutyl-substituted immobilized alcohol **13**[19] in the multiple allylation sequence delineated above allows us to demonstrate that from one reaction sequence, several different



Scheme 4 Enantiocomplementary solid phase synthesis of eight stereoisomers based on the structure of cryptocarya diacetate. (a) (i) 3 equiv. *ent*-**2**, THF, −78 °C; (ii) pH 7 buffer, H_2O_2 30%, DMF/MeOH 1 : 1, 0 °C, 2 h; (b) (i) 3 equiv. **2**, THF, −78 °C; (ii) pH 7 buffer, H_2O_2 30%, DMF/MeOH 1 : 1, 0 °C, 2 h; (c) TBS–Cl, 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, NEt_3, cat. DMAP, CH_2Cl_2, 0 °C to rt, 16 h; (f) 2 × 20 mol% Grubbs II catalyst, CH_2Cl_2, reflux, 24 h; (g) 10 equiv. DDQ, CH_2Cl_2, pH 7 buffer, 0 °C to rt, 16 h.



Scheme 5 Enantioselective solid phase synthesis of natural product-derived lactones **14a–c**.

natural products (and consequently also their stereoisomers, if the sequence is carried out in a stereocomplimentary fashion) can be obtained (Scheme 5). Thus, after the first allylation, ring closing metathesis and release from the polymeric carrier by treatment with DDQ, as described above, gave compound **14a** in 31% overall yield, which is the enantiomer of a natural product isolated from *Ravensara anisata*.[20] After a second allylation, compound **14b**, which represents the deacetylated version of a natural product isolated from the same plant,[21] was obtained in 6.3% overall yield. After a third allylation, lactone **14c** was obtained in an overall yield of 4.3%. The synthesis of compound **14c** required a total of 12 consecutive steps on the polymeric carrier, including three stereoselective carbonyl allylation reactions.

These results convincingly demonstrate the applicability of the allylation reaction on solid supports to the stereocomplementary synthesis of natural product-derived and -inspired compound collections.

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