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Enantioselective Catalysis on the Solid Phase: Synthesis of Natural Product-Derived Tetrahydropyrans Employing the Enantioselective Oxa-Diels–Alder Reaction

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Abstract: Aliphatic aldehydes were synthesized on a solid support and subjected to an enantioselectively catalyzed oxa-Diels–Alder reaction with Danishefsky's diene. Employing 5 mol% of a Cr(III)-salen catalyst enantiomeric ratios up to >99% and yields up to 40% over five steps were achieved. Further elaboration of the polymer-bound dihydropyrones was performed by subsequent conjugate cuprate addition, reduction of the ketone and transformation of the resulting alcohol to a carbamate yielding 2,4,6-trisubstituted tetrahydropyrans after cleavage from the solid support.

Keywords: combinatorial chemistry; enantioselectivity; oxa-Diels–Alder reaction; solid phase synthesis; tetrahydropyrans

Significance in nature and biological prevalidation are the dominant criteria to be met by the underlying chemical structures of compound libraries for chemical biology and medicinal chemistry research and provide guidance for biology-oriented synthesis (BIOS).[1]

These preconditions are fulfilled by classes of natural products enriched in biological activity. Such natural products can be regarded as ligands selected by evolution for structurally conserved yet genetically mobile protein domains or their ligand sensing cores.[1,2] For these reasons natural product-guided compound library development should provide promising starting points for chemical biology and medicinal chemistry research.

Cheminformatics analysis of natural product structures[3] reveals that the tetrahydropyran motif belongs to the most frequently occurring scaffolds in nature. For instance, it occurs as a characteristic underlying structural element in antibiotics, marine toxins and pheromones.[4] In particular, tetrahydropyrans that belong to the cyclic diarylheptanoids[5] like the blepharocalyxins (see Figure 1) have recently attracted considerable attention. They display multiple biological activities, e.g., inhibition of NO production, antiproliferative activity against human and murine colon carcinoma cells and human fibrosarcoma cells and inhibition of platelet aggregation.

Due to the widespread occurrence of the underlying tetrahydropyran motif in nature and the 2,4,6-trisubstitution pattern found in the cyclic diarylheptanoids, we embarked on the development of an asymmetric synthesis method that would give access to related compound collections in a format amenable to combinatorial synthesis.

In planning the synthesis, we envisioned that a reaction sequence carried out on a solid support beginning with an enantioselective oxa-Diels–Alder reaction between a polymer-bound aldehyde and Danishefsky's diene would give a rapid and flexible access to the core structure of the target compounds. This cycloaddition would be followed by a subsequent diastereoselective conjugate addition of an aryl cuprate to the formed pyrone and concluded by stereoselective reduction of the remaining ketone (Scheme 1).[6] Oxa-Diels–Alder reactions have previously been employed in solid phase chemistry.[7,8] However, enantioselective versions of this cycloaddition employing a polymer-bound aldehyde have not yet been reported.[8] The use of organocuprates in solid-phase synthesis has been reported only in a few cases.[9]

In order to establish a reaction sequence following the outline delineated above and giving rise to the diarylheptanoid tetrahydropyran system, polystyrene beads **1** functionalized with the Wang linker (loading 1.23 mmol g^{-1}; obtained from Novabiochem) were

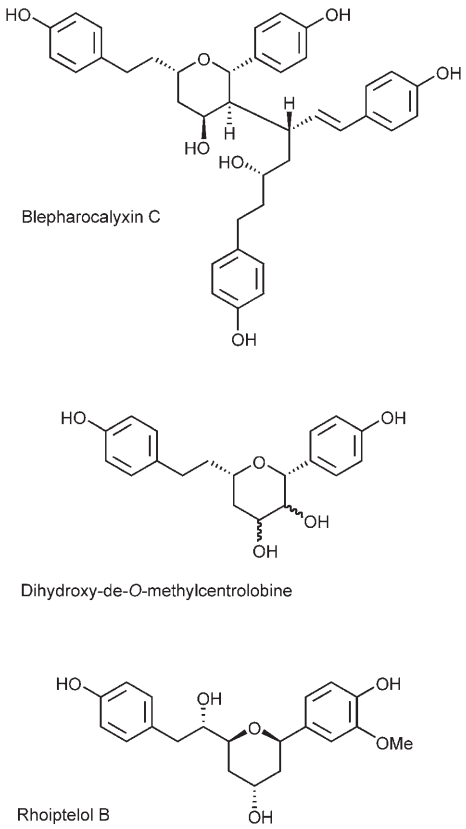
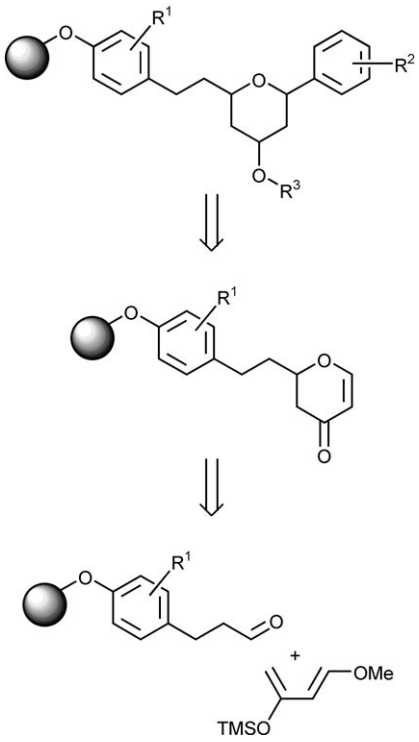


Figure 1. Natural cyclic diarylheptanoids embodying a tetrahydropyran core.

coupled with phenolic esters **2** by means of the Mitsunobu protocol (Scheme 2; loading *ca.* 1 mmol g^{-1}, determined by means of the Fmoc method to quantify the amount of remaining alcohol on the resin). Subsequent reduction of the esters **3** with lithium borohydride and oxidation of the formed alcohols with *o*-iodosobenzoic acid (IBX) yielded aldehyde resins **4**.

For the execution of the crucial enantioselective hetero-Diels–Alder reaction on the solid support chromium catalysts **7** and **8** developed by Katsuki et al.[10] and Jacobsen et al.,[11] respectively, were investigated. While in general both compounds catalyzed the cycloaddition, in the presence of **8** conversion of the aldehydes remained incomplete. The best results were obtained when 5 mol% of catalyst **7** and 3 equivalents of Danishefsky's diene were used at room temperature. After release from the solid support by treatment with acid, the desired dihydropyrones **6** were obtained in 10–40% overall yield over five steps and with enantiomeric ratios up to >99%. For four of the five compounds prepared the enantiomeric ratio was between 88% and >99% (Table 1). The direction of the stereoselection was identical with the stereochemical course of the corresponding reaction in solution.[12]

After the successful establishment of the highly enantioselective hetero-Diels–Alder reaction, the conjugate addition to polymer-bound pyrones was investigated. Initial experiments focussed on the use of higher-order cuprates since these reagents had proven before to be applicable in solid-phase synthesis.[9] However, after extensive variation of the reaction

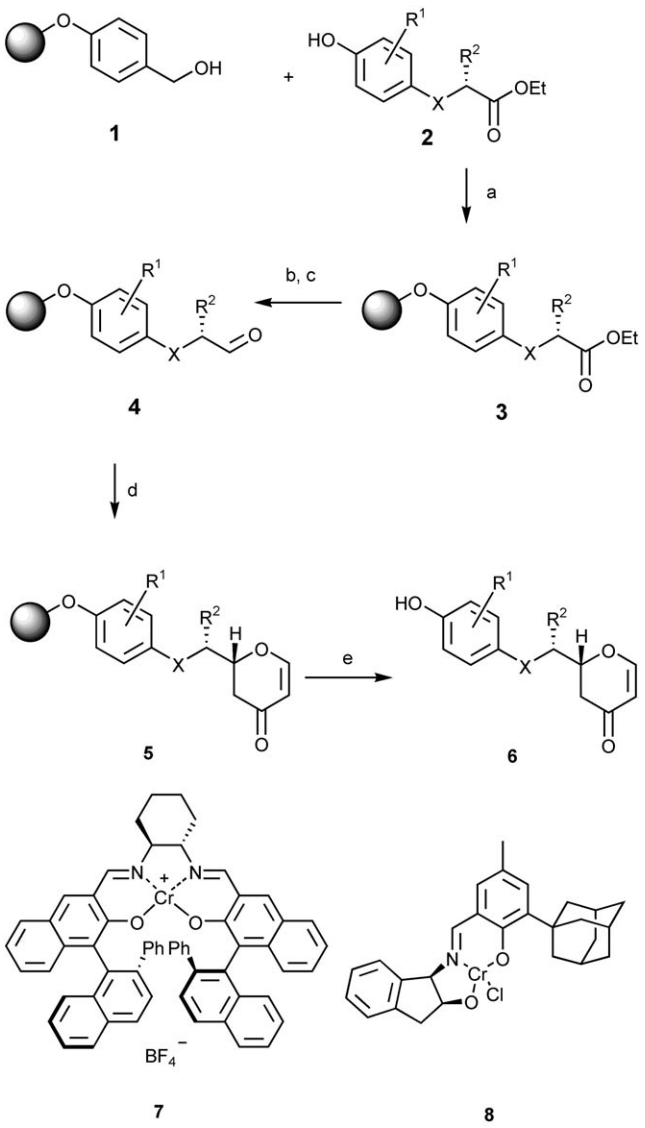


Scheme 1. Retrosynthetic analysis of diarylheptanoid tetrahydropyran target compounds.

Table 1. Dihydropyrones **6** synthesized on solid phase.

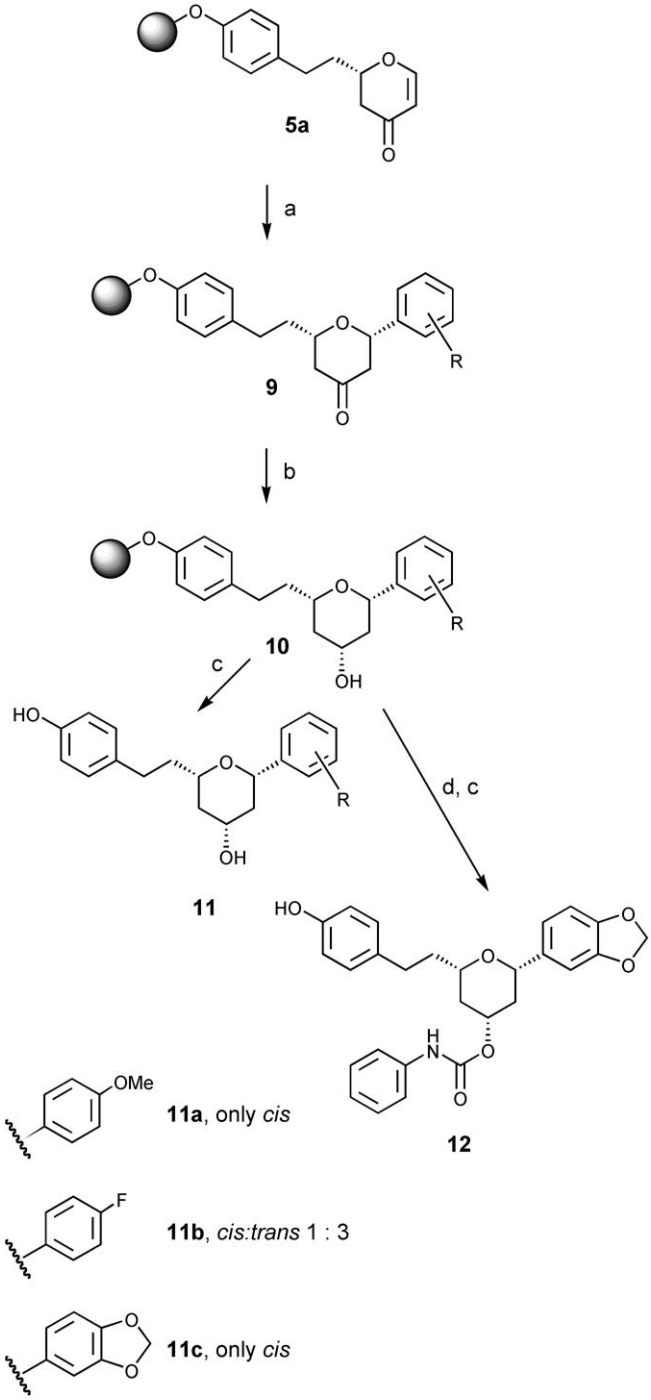
Compound	Substituents	Yield [%][a]	Enantiomeric ratio[b]	$[\alpha]_D^{20}$(*c*, MeOH)
6a	X = CH_2, R^1 = H, R^2 = H	14	94:6	−65.6 (0.50)
6b	X = CH_2, R^1 = 3-MeO R^2 = H	14	96:4	−99.2 (0.25)
6c	X = CH_2, R^1 = 3-Br, R^2 = H	40	75:25	−53.9 (0.56)
6d	X = CH_2, R^1 = 3,5-Br, R^2 = H	12	>99:1	−31.7 (1.18)
6e	X = O, R^1 = H, R^2 = CH_3	10	>99:1[c]	−50.7 (0.33)

[a] After HPLC purification and based on the initial loading of the resin.
[b] Determined by employing a chiral stationary phase HPLC.
[c] For **6e** the diastereoisomeric ratio was 88:12 (determined by ^{1}H NMR.)



Scheme 2. Enantioselective synthesis of dihydropyrones on the solid phase. *Reagents and conditions:* a) *i*-PrOC(O)N=NC(O)O-*i*-Pr (DIAD); PPh_3, CH_2Cl_2, room temperature, 24 h. b) $LiBH_4$, THF, room temperature, 48 h. c) IBX, THF/DMSO, room temperature, 24 h. d) Danishefsky's diene, MS 4 Å, Cr(III) catalyst (**7**) 5 mol%, CH_2Cl_2, room temperature, 96 h; ii) TFA, CH_2Cl_2, room temperature, 15 min. e) 10% TFA, CH_2Cl_2, room temperature, 3 h.

conditions we came to the conclusion that higher-order cuprates are not suitable for the conjugate addition to pyrones **5** on the solid phase. As an alternative, lower-order cuprates[13] were investigated, and, gratifyingly, conditions could be established for the successful execution of the conjugate addition. The conjugate addition proceeds well at −35 °C in THF. Of particular importance, however, is that the resin is very carefully dried, that the cuprate reagent is preformed at −78 °C in diethyl ether and that PBu_3 is employed as additive. The use of $BF_3{\cdot}Et_2O$ or TMSCl gave inferior results. The reaction was successfully carried out as shown in Scheme 3 and Table 2 for pyrone **5a** and three cuprate reagents. In two of the three cases the *syn*-diastereomer was formed exclusively. In order to increase the complexity of the molecules and to reduce their reactivity, ketones **9** were



Scheme 3. Conjugate additions to pyrone **5a** on the solid phase. a) Ar-Br, *t*-BuLi, CuI, PBu_3, 6 equivs. cuprate, THF, −35 °C, 16 h. b) L-Selectride, THF, −50 °C. c) 10% TFA, CH_2Cl_2, room temperature, 3 h. d) phenyl isocyanate, THF, room temperature, 24 h.

Table 2. Results of the syntheses of tetrahydropyrans **11** and **12**.

Compound	R	Yield [%][a]	Ratio *cis*:*trans*[b]	$[\alpha]_D^{20}$ (*c*, MeOH)
11a	4-methoxy	14	100:0	−37.0 (0.50)
11b	4-fluoro	14	25:75	n.d.
11c	3,4-methylene-dioxy	40	100:0	−23.0 (0.40)
12	3,4-methylene-dioxy	10	100:0	−3.5 (0.20)

[a] After HPLC purification and based on the initial loading of the resin.
[b] Determined by ^{1}H NMR.

reduced to the corresponding alcohols **10** before release from the solid support (Scheme 3).

To this end, the polymer-bound ketones **9** were treated with L-Selectride in THF, and after release from the solid support alcohols **11** were isolated as single diastereomers and in yields of 17–29% for the last three steps on the solid support.

Structure determination of **11c** by means of detection of NOE signal enhancements revealed that H-2, H-4 and H-6 are in *cis*-orientation (Figure 2). In addition, H-4 displays two large coupling constants in the NMR spectrum (triplet of 13.7 Hz). This result demonstrates that in the conjugate addition the cuprate approaches the double bond *cis* to the stereodirecting substituent. This finding is remarkable since in the corresponding reaction in solution we exclusively obtained the *trans* isomer. Thus, the solid phase in this case appears to have a major influence on the stereochemical course of the reaction.

Finally, in order to demonstrate that the tetrahydropyrans formed by the reaction sequence detailed above can be further functionalized on a solid support, intermediate **10c** was treated with phenyl isocyanate before release from the solid support to yield carbamate **12**.

In conclusion, we have developed a flexible method for the enantioselective synthesis of diarylheptanoids with a tetrahydropyran core on the solid support. The reaction sequence employs an enantioselective oxa-Diels–Alder reaction with resin-bound aldehydes as the key step. The target compounds resemble the core structure of a class of natural products enriched in biological activity. The production of a compound collection based on this transformation and its biological evaluation in a series of different biochemical and biological screens promise to yield highly relevant starting points for subsequent chemical biological investigations.

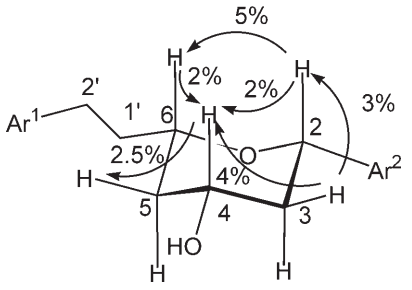


Figure 2. NOE signal enhancements observed for 4-tetrahydropyranol **11c**.

Experimental Section

Wang Resin-Bound 2,3-Dihydropyran-4-ones 5 *via* Enantioselective Oxa-Diels–Alder Reaction and Cleavage from Solid Support (6)

To a suspension of a resin-bound aldehyde **4** (4.0 g, approx. 4 mmol) and 4 Å molecular sieves (4.0 g) in dry CH_2Cl_2 (50 mL) was added the Cr(III) catalyst **7** (193 mg, 200 μmol) and the mixture was shaken for 5 min at room temperature whereupon Danishefsky's diene (2.07 g, 12.0 mmol) was added. After 48 h the same amount of diene was added and the reaction was shaken for further 48 h. TFA (50 μL) was added and the suspension was shaken for 15 min before the resin was filtered and washed with MeOH and CH_2Cl_2 several times. It was dried under vacuum overnight to give the polymer-bound 2,3-dihydropyran-4-ones **5** as brown resins. IR (SiC): $\nu = 1731–1727$, cm^{-1} (C=O).

The solid supported 2,3-dihydropyran-4-one **5** (0.40 g) was treated with a solution of 10% TFA in CH_2Cl_2 for 3 h at room temperature. The solution was filtered off, and the resin was washed twice with CH_2Cl_2. The combined organic phases were washed with saturated aqueous $NaHCO_3$ solution, dried over $MgSO_4$, the solvent was removed under reduced pressure and the residue was purified by reverse-phase HPLC.

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[12] For comparison compound **6a** was synthesized in solution employing chiral catalyst **7**. To this end, the corresponding TBDMS-protected phenol was subjected to the oxa-Diels–Alder reaction with Danishefsky's diene and subsequently the silyl protecting group was removed. The pyrone was obtained with an enantiomer ratio > 99:1 and displayed a specific rotation of −92° (*c* 0.5, CH_3OH), i. e., the sense of the specific rotation is the same as recorded for the product obtained from the solid-phase synthesis (see Table 1; **6a**). The absolute configuration was assigned based on the assumption that the stereodirecting influence of the chiral catalyst in these transformation is identical to its performance in closely related cases.[9].
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