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Short Communication

Solid-phase synthesis of combinatorial libraries based on enatiomerically pure (1*S*,2*S*,4*R*,5*S*)-4,5-dihydroxycyclohexan-1,2-dicarboxylic acid scaffolds

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Abstract

The conditions for solid-phase functionalization of the new enantio-pure scaffold **1** to give libraries of general formula **4** have been derived.

Keywords: Cyclohexanediols; Enantiopure compounds; Polyfunctional scaffolds; Solid-phase synthesis

The synthesis of large libraries of novel compounds is often based on the combinatorial functionalization (decoration) of template scaffolds anchored to insoluble supports [1]. Many heterocyclic and carbocyclic scaffolds have been used to this end, and the introduction of new molecular scaffolds with a high potential of molecular diversity is of great interest for the production of new collections of compounds.

We have recently reported the facile synthesis of the three polyfunctional enantio-pure cyclohexanes **1**–**3** (Fig. 1) [2]. These molecules have several properties that make them ideal for the use as scaffolds for the production of combinatorial libraries of highly diverse molecules with potential pharmaceutical activity. They have low molecular weight, which allows their decoration with many building blocks without violating Lipinski's rule [3], they contain four potential points of diversification (the two hydroxy and two carboxy groups) and they can be easily attached on solid-phase. Furthermore, the three diastereoisomeric scaffolds are conformationally defined molecules that populate a single chair conformation, and can fix the substituents in a predetermined disposition.

In this paper we report on the use of compound **1** for the solid-phase generation of libraries of type **4** (Scheme 1). In a first approach (Scheme 2), the equatorial function of **1** (R = Me) was protected as an allylether, the axial one as dimethyl-*t*-butylsilyl ether, and the carboxy groups were demasked to allow solid-phase anchoring.

The scaffold was attached to solid-phase using a commercially available PAL-PS resin [4], which gave better loading results than PS- or Tentagel based Rink amide resins (Scheme 2). As expected, a 1:1 regioisomeric mixture of **8** and **9** was obtained, as shown by nanoprobe NMR analysis of the resin and MS/HPLC analysis of the cleavage (20% TFA) mixture. This

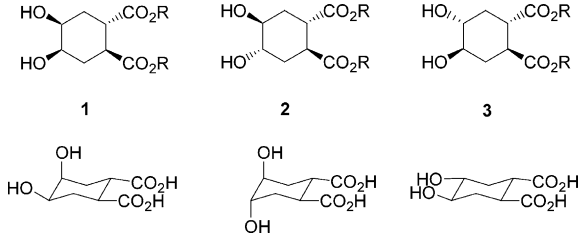

Fig. 1. The polyfunctional scaffolds **1**–**3**.

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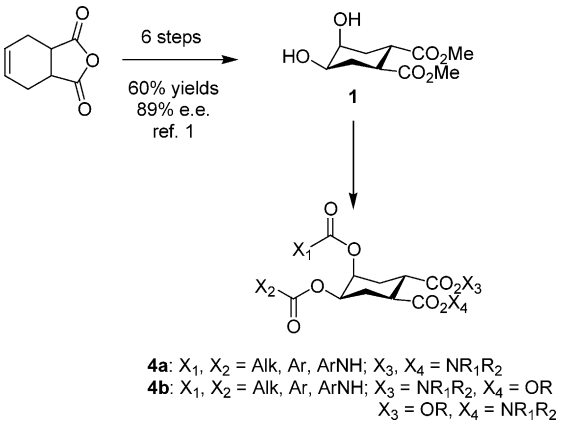
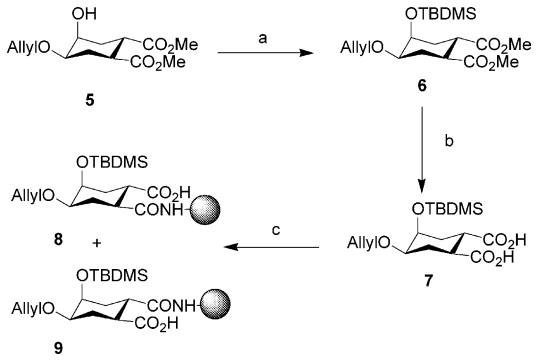


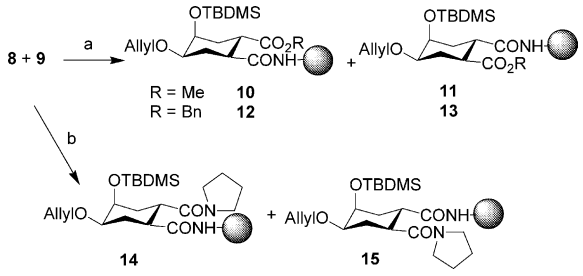
Scheme 1. General scheme of the library generation.



Scheme 2. Solid-phase anchoring of the fully protected scaffold. (a) Compound **5** see ref. [2b], TBDMSCl, DMF, imidazole (96%); (b) LiOH, MeOH–H_2O 3:1; (c) PyBOP, DIPEA, DMF, PAL-PS resin.

problem can be circumvented by differentiating the carboxy group functionalities before loading onto the resin, using the diasteroselective hydrolysis of **1** that we have recently described [2b]. However, all the preliminary solid-phase chemistry and library rehearsals reported in this paper were carried out on regioisomeric mixtures of compounds.

The first reaction carried out on solid-phase was the functionalization of the free carboxy group, which was transformed into an ester **10**–**13**, or an amide **14**–**15**

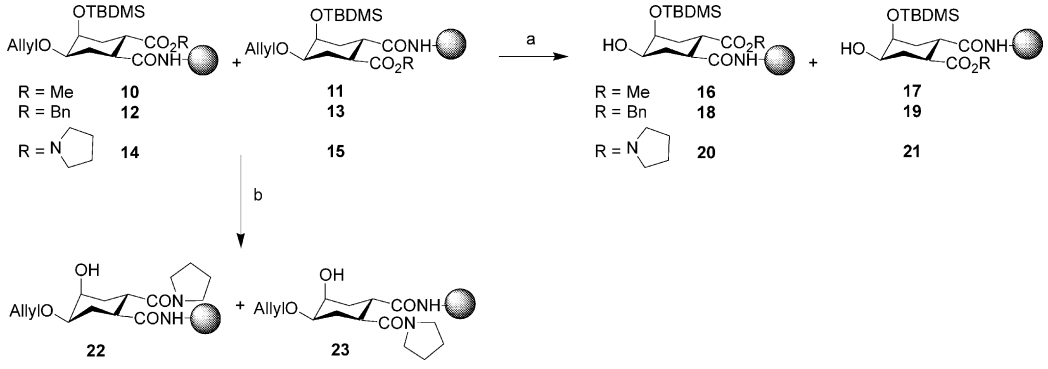


Scheme 3. Solid-phase functionalization of the free carboxy group. (a) DIC, DMAP, CH_2Cl_2–ROH 1:1; (b) PyBOP, DIPEA, DMF, pirrolidine.

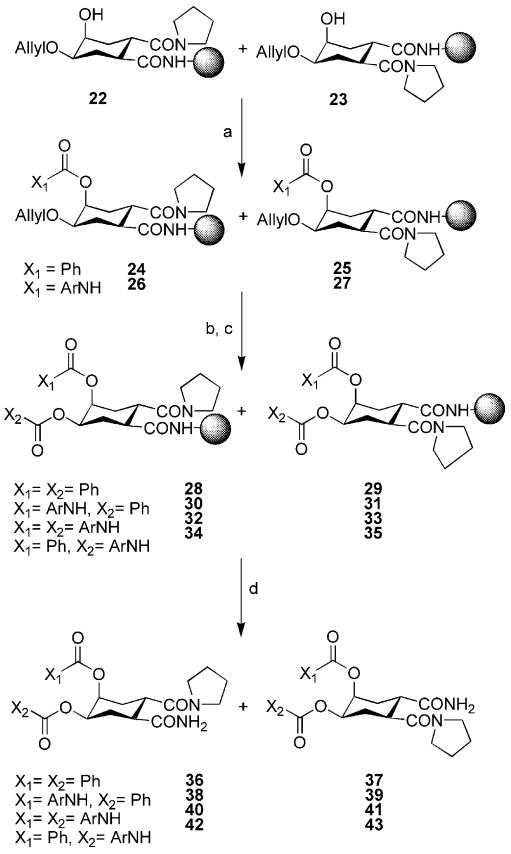
(Scheme 3). Selective deprotection of the hydroxy group functionalities was then studied (Scheme 4).

The deallylation of **10**–**15** to give **16**–**21** could be achieved in high yields and purity using $Pd(PPh_3)_4$ in CH_2Cl_2–AcOH–*N*-methylmorpholine [5]. The desilylation of the amides **14** and **15** also occurred uneventfully using 1 M TBAF in THF to give **22** and **23**. However, under these conditions the esters **10**–**13** were found to be unstable, and were extensively hydrolyzed before desilylation could take place. None of the experimental conditions attempted, using more diluted TBAF solution, shorter reaction times, or buffered F^- solutions (1:1 TBAF–AcOH or $Et_3N{\cdot}3HF$) could prevent the unwanted hydrolysis. Therefore this approach could only be used for the synthesis of the library **4a** (X_3, X_4 = NR_1R_2), and the reaction sequence of Scheme 5 had to be followed.

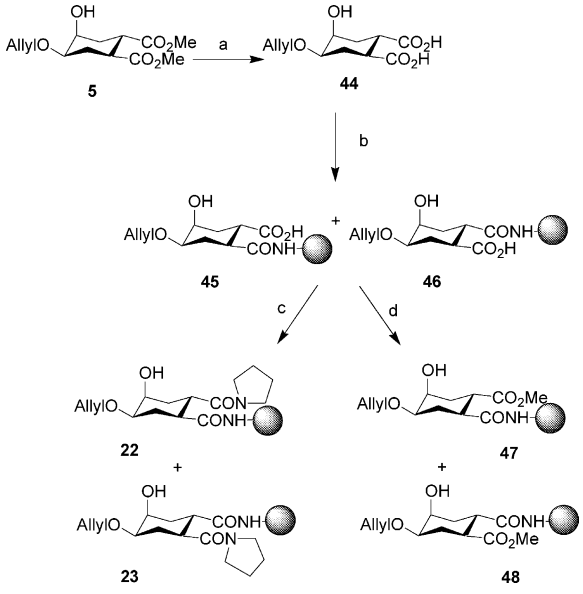
The free axial hydroxy group of **22** and **23** was transformed in the benzoate **24**, **25** (X_1 = Ph) or in carbamate **26**, **27** (X_1 = ArNH). This latter transformation was initially attempted using *p*-NO_2 phenylchloroformate followed by reaction with benzylamine. However, upon cleavage, the product was found to be contaminated by 15–20% of PNP-containing impurities, which could not be eliminated. Eventually the carbamates were synthesized in good yields and > 85% purity using ArNCO in the presence of stoichiometric amounts of DMAP [6]. Deallylation of **24**–**27** was performed under the conditions described for **10**–**15,** and the equatorial hydroxy group was in turn functionalized as



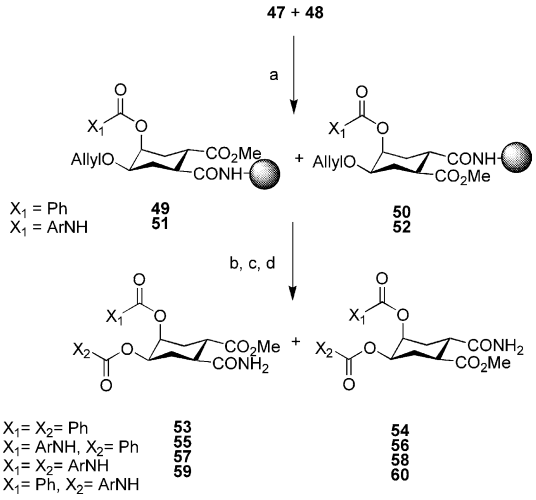
Scheme 4. Diol deprotection from **10** to **15**. (a) $(PPh_3)_4Pd$, NMM, AcOH, DCM; (b) 1 M TBAF in THF.



Scheme 5. Scheme for the synthesis of the library of amides **4a**. (a) $X_1 = Ph$: $PhCO_2H$, DIC, DMAP, DCM; $X_1 = NHAr$: ArNCO, DMAP, DCM; (b) $(PPh_3)_4Pd$, NMM, AcOH, DCM; (c) $X_2 = Ph$: $PhCO_2H$, DIC, DMAP, DCM; $X_2 = NHAr$: ArNCO, DMAP, DCM; (d) 20% TFA in DCM, 2% Me_2S scavanger.



Scheme 6. Solid-phase anchoring of the partially protected scaffold. (a) LiOH, MeOH–H_2O 3:1; (b) PyBOP, DIPEA, DMF, PAL-PS resin; (c) PyBOP, DIPEA, pirrolidine, DMF; (d) $TMSCHN_2$, MeOH–THF 1:1.



Scheme 7. Scheme for the synthesis of the library of ester **4b**. (a) $X_1 = Ph$: $PhCO_2H$, DIC, DMAP, DCM; $X_1 = NHAr$: ArNCO, DMAP, DCM; (b) $(PPh_3)_4Pd$, NMM, AcOH, DCM; (c) $X_2 = Ph$: $PhCO_2H$, DIC, DMAP, DCM; $X_2 = NHAr$: ArNCO, DMAP, DCM; (d) 20% TFA in DCM, 2% Me_2S scavenger.

a benzoate **28**–**31** ($X_2 = Ph$) or a carbamate **32**–**35** ($X_2 = PhNH$) following the procedure described above. TFA cleavage from the PAL resin (20% TFA, 2% Me_2S) yielded compounds **36**–**43** in >80% purity by MS/HPLC.

In order to synthesize the library of esters **4b**, loading of the unprotected diacid **44** onto the PAL resin was attempted (Scheme 6). Under the usual reaction conditions (2 equiv. of diacid, PyBOP, DIPEA, 18 h) a 1:1 mixture of **45** and **46** was cleanly obtained.

The two acids could be activated with PyBOP and treated with pirrolidine to give the corresponding amides **22** and **23**. However attempts to synthesize the ester **47** and **48** via carboxy group activation with DIC, followed by reaction with MeOH and DMAP led to the formation of byproducts possibly due to the internal competition of the free hydroxy group in **46**. The transformation was cleanly accomplished using TMS–diazometane [7] in 1:1 THF–MeOH (Scheme 6).

Further manipulation of these substrates using the same protocols discussed for **22** and **23** led to the desired ester **53**–**60**, in a >80% purity by MS/HPLC (Scheme 7).

In conclusion, conditions have been defined by which largely diverse libraries of type **4** can be built starting from the polyfunctional scaffold **1**. Several hundred compounds are being prepared using this strategy and will be tested for biological activity.

1. Definitions and abbreviations

DCM	dichloromethane
DIC	diisopropylcarbodiimide

DIPEA	*N*,*N*-diisopropylethylamine
DMAP	4-(dimethylamino)pyridine
DMF	*N*,*N*-dimethylformamide
NMM	4-methylmorpholine
PAL-PS	5-(4-(9-fluorenylmethyloxycarbonil)aminomethyl-3,5-dimetoxyphenoxy)-valeric acid-polystirenic resin
PyBOP	(benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate
TBAF	tetrabutylammonium fluoride
TBDMSCl	*tert*-butyldimethylsilyl chloride
TFA	trifluoroacetic acid
THF	Tetrahydrofuran
$TMSCHN_2$	(trimethylsilyl)diazomethane

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