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Combinatorial Chemistry and Natural Products. Teicoplanin Aglycone as a Molecular Scaffold for Solid Phase Synthesis of Combinatorial Libraries.

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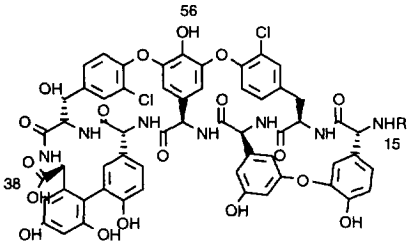
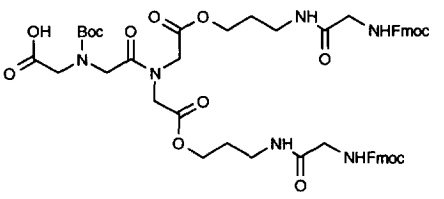
Abstract: Teicoplanin aglycone **1** has been linked to a solid support via two different double cleavable linkers. The attachment was realized selectively on the ^{38}COOH function of **1**. Two molecules of **1** were attached on each linker moiety and could be separately released with different mechanisms. The release properties of the resin bound entities were determined by means of analytical and biological characterization.

Combinatorial chemistry was exploited in the recent past as a powerful tool to produce a large number of diversified molecules in a short time. This was done either randomly (generic libraries screened in many biological assays) or non-randomly (biased libraries inspired by a certain structure and tested on a specific biological assay)[3].

Much less exploited is the use of a natural product as scaffold for the generation of combinatorial libraries. An example where a steroidal scaffold was used is reported[4]. We selected teicoplanin aglycone (TD[5] Fig. 1, **1**), an inhibitor of bacterial cell wall biosynthesis[6], as representative of complex scaffolds from natural sources.



1 R=H Teicoplanin aglycone
2 R=Boc

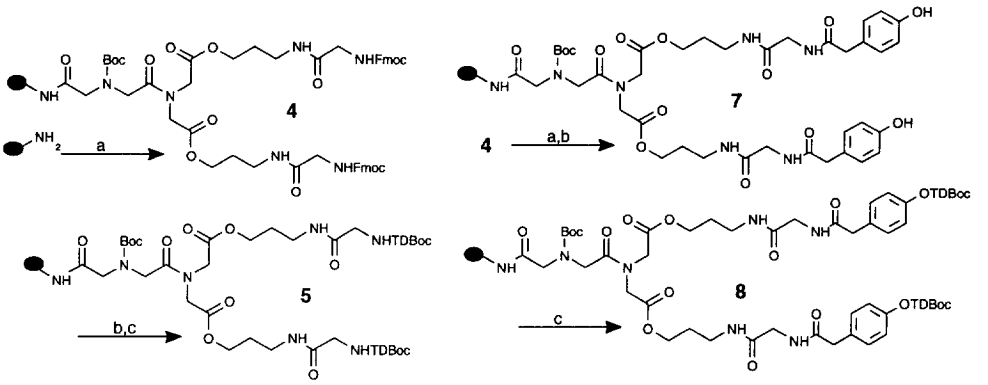


3 IDA-DC (Iminodiacetic acid based double cleavable linker)

Figure 1

Here we report two methods for the attachment of teicoplanin aglycone **1** to resin beads via double cleavable linkers. We utilized ^{15}N-Boc teicoplanin aglycone (TDBoc[5] Fig.1, **2**) to be coupled via IDA-DC linker[8] (Fig.1, **3**) to the solid phase support. The synthetic strategies leading to resin bound **5** and **8** are reported in Scheme 1.

Scheme 1



a) **3**, DIC/HOBt/DMF, 16h, RT; b) Piperidine/DMF 1/1, 20', RT; c) **2**, BOP/HOBt/DIEA/DMF, 4h, RT.

a) Piperidine/DMF 1/1, 20', RT; b) pOHPheAcOH (**6**), DIC/HOBt/DMF, 6h, RT; c) **2**, DIC/HOBt/DMF, 16h, RT.

These solid phase-bound scaffolds will be used to synthesize chemical libraries through selective randomizations on the $^{15}NH_2$ or the ^{56}OH groups via acylation or reductive amination of the amino group, acylation or alkylation of the phenol[7]. The linker stability of resin bound **5** when the reactions are carried out in anhydrous conditions is complete; the two aromatic ester bonds contained in structure **8** will require a careful adjustment of the experimental conditions for some of the above mentioned reactions.

The double cleavage of **5** is shown in Scheme 2, left. HPLC and MS spectra of the releasates (data not shown) confirmed the presence of the hydroxypropylamide **9** as major compound in both releasates.

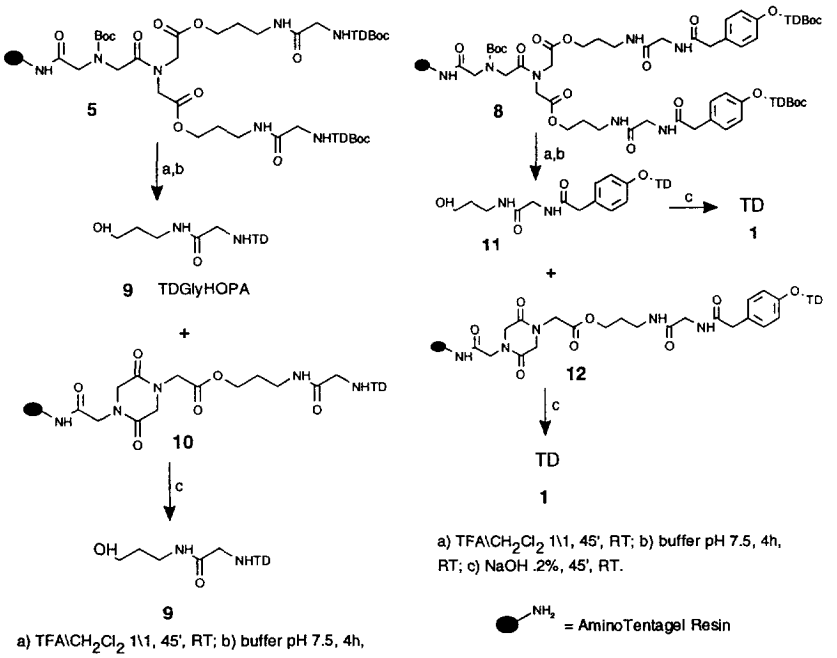
Structure **8** allowed direct access to aglycone **1** (Scheme 2, right).

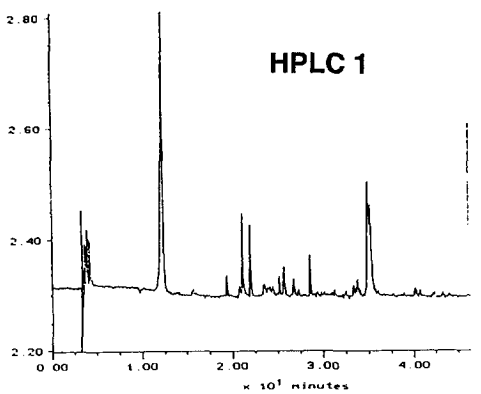
The HPLC traces corresponding to the releasates from compound **8** are reported in Fig.2.

First release at pH 7.5 produced the poorly water soluble phenol ester **11** that was not extracted from the beads by the aqueous buffer (no peaks in HPLC). The cleaved **11** was removed from the beads by DMSO washing, then the DMSO solution was freeze-dried and treated with base to give aglycone **1** (HPLC 1, Fig.2). Second release at pH 13 (NaOH) cleaved the aglycone **1** as its sodium salt that was solubilized by the aqueous solution (HPLC 2, Fig.2). The lower quantity of **1** and the presence of various impurities in HPLC 1 were attributed respectively to incomplete solubilization of **11** by the DMSO washing and to solubilization of water insoluble impurities, produced by the release conditions or by the resin itself, by DMSO.

The biological activity of the modified derivatives either resin bound or in solution was investigated and is reported elsewhere[9].

Scheme 2





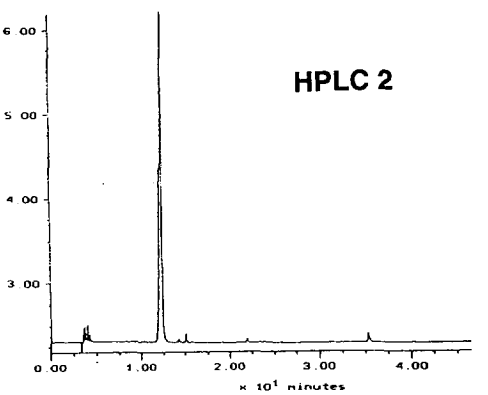


Figure 2

In conclusion, we have shown that **1**, representing an example of a complex natural product, can be bound to resin beads via double cleavable linkers through selective attachment of the ^{38}COOH functional group. The release of the molecule can produce either the hydroxypropylamide of **1** (from compound **5**) or compound **1** itself (from compound **8**). The issue of poor solubilization of **1** at neutral pH has been resolved by DMSO washing. We feel that this could be an important finding for any library where the cleaved materials are sufficiently lipophilic and/or hydrophobic to stick to the resin rather than dissolving in aqueous cleavage solutions.

Utilization of these resin bound TD derivatives as natural product based molecular scaffolds for library generation through randomizations on other functional groups ($^{15}NH_2$, ^{56}OH, etc.) and application of this strategy to other natural products are undergoing.

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