A Pentaerythritol-Based Molecular Scaffold for Solid-Phase Combinatorial Chemistry

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A convergent synthesis has been developed for the preparation of solid-phase bound construct 1, consisting of an orthogonally protected trifunctional core structure that is attached to TentaGel via a photocleavable linker.

The development of multifunctional template structures, commonly known as multipodal scaffolds, for the construction of chemical libraries via combinatorial techniques is a timely challenge in organic synthesis.¹ In general, polyfunctional scaffolds have been developed in the context of binding studies whereby a receptor-like derivative consists of a rigid template structure² possessing two or more functionalities for the attachment of strands that will create an appropriate environment for binding of the ligand. When the generation of a large receptor-like library is considered using a combinatorial approach such as the mix-split procedure, a supplementary functional group for attachment of the scaffold to the solid phase must be incorporated. There are examples of constructs in which these functional features are present

and that allow at the same time the independent generation of strands via orthogonal protection, but they all involve a rigid template structure.³ Herein we wish to describe the convergent synthesis of the flexible and orthogonally protected solid-phase bound trifunctional construct **1**, in racemic form, in which a photocleavable linker is incorporated.⁴

Central in the scaffold are the pseudo- C_3 -symmetrical core structures **2** and **3** (Scheme 1). These are characterized by

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^{*a*} Reaction conditions: (a) TBDPSCl, Hlm, DMF, 85%; (b) **5**, NaH, THF, 48%; (c) TBAF, THF, 84%; (d) **6**, NaH, THF, 37%; (e) **7**, NaH, THF, 32%; (f) succinic anhydride, DMAP, CH₂Cl₂, 90%.

the presence of a stereogenic quaternary center, to which are connected three *para*-substituted benzylic chains, each one of them terminated by a differently protected primary alcohol. The choice of the protective groups, i.e., tetrahydropyranyl (THP), 3,4-dimethoxyphenylmethyl (DMPM), and *tert*-butyldiphenylsilyl (TBDPS) ethers, allows for a separate deprotection so that each hydroxyl group in turn can be used for the introduction of molecular diversity.

Starting from pentaerythritol, the first benzylic chain was introduced via a three-step sequence involving prior temporary protection of one of the hydroxymethyl groups as *tert*-butyldiphenylsilyl ether.⁵ Subsequently a classical Williamson ether synthesis, followed by silyl ether deprotection, led to triol **4**. The two other benzylic chains were introduced afterward in a consecutive way by similar ether formation. The required benzylic bromides **5**, **6**, and **7** were readily prepared from the commercially available 4-(bromomethyl)-phenylacetic acid via reduction of the carboxylic acid function with borane–methyl sulfide complex⁶ and introduction of the three different protective groups according to the usual procedures.

By treatment of alcohol 2 with succinic anhydride, the required carboxylic acid function (3) for eventual attachment to the solid phase was introduced. It was also expected that the simultaneous incorporation of a spacer would facilitate the connection to the solid phase.

An important feature of **1** is the presence of a photocleavable linker.⁷ The well-documented α -methyl-o-nitroveratryl structural moiety⁸ was introduced on TentaGel-S-NH₂ via condensation with acid **8** (Scheme 2).^{8a} After Fmoc deprotection, the resulting amine was reacted with acid scaffold **3** (EDC, DMAP). The coupling and deprotection steps were monitored in a qualitative way using the colorimetric TNBS⁹ and NF31¹⁰ tests. In our hands, the NF31 test appeared to



 a Reaction conditions: (a) DIC, HOBt, DMF; (b) 20% piperidine, DMF; (c) **3**, EDC, DMAP, CH₂Cl₂; (d) AcOH/CH₂Cl₂/H₂O 80:15:5, 16 h, 60 °C; (e) DDQ, 1 h, 0 °C; (f) TBAF, AcOH, molecular sieves (4 Å), THF.

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be more sensitive to control the completeness of the reaction step involving the coupling of acid 3 with the sterically hindered amine obtained after Fmoc deprotection.



At this point the photolytic release of the scaffold was investigated. Exposure of resin **1** (50 mg) in 1,4-dioxane (1.5 mL) containing 1% DMSO to UV light (365 nm) for 20 h gave primary amide **9** (86% yield). In this known procedure, the presence of DMSO was shown to have a beneficial influence on the rate of the cleavage.^{8d}

The development of appropriate reaction conditions for the selective deprotection of the three protective groups required extensive optimization. In a first stage, the efficiency of each deprotection step was assessed in a qualitative way by ¹³C gel-phase NMR (see Supporting Information).¹¹ **THP deprotection:** The use of *p*-toluenesulfonic acid^{12a} led to deprotection of both THP and DMPM ethers, whereas pyridinium *p*-toluenesulfonic acid was not strong enough to effect complete deprotection.^{12b} Treatment of the resin with a solution of AcOH/CH₂Cl₂/H₂O in a ratio of 80:15:5 at 60 °C led on the other hand to complete and selective deprotection of the THP ether.^{12c} **DMPM deprotection:** Complete and selective deprotection was achieved using dichlorodicyanoquinone (DDQ) at 0 °C for 1 h.¹³ Longer reaction times or higher temperatures led to cleavage of the benzyl ethers present in the scaffold **3**. The DMPM group proved to be superior over an earlier investigated 4-methoxyphenylmethyl benzyl ether protective group as a result of its known higher sensitivity toward oxidative conditions. **TB-DPS deprotection:** The procedure for deprotection of silyl ethers using tetrabutylammonium fluoride (TBAF) led to hydrolysis of the ester function present in **3**. However, the addition of 1 equiv of acetic acid led to a successful selective deprotection.¹⁴

Although the on-resin deprotection of the protective groups could be followed by ¹³C gel-phase NMR,¹¹ we wished to control the efficiency and the reproducibility of the above procedures in a quantitative way. Therefore, in each case after deprotection the free hydroxyl function was capped as the acetate, and the resulting intermediate was subjected to photocleavage. After chromatographic purification, the released acetates **10**, **11**, and **12** were obtained in 55%, 62%, and 56% overall yield, respectively. These isolated yields involving a six-step sequence were calculated taking into account the original loading of the commercial resin. The latter was determined by Fmoc UV—vis spectroscopy¹⁵ and by the picric acid test.¹⁶

In summary, a new flexible scaffold 3 containing four functionalities was developed. The carboxylic acid function is used for the coupling on the solid support TentaGel via a photocleavable linker 8, and the three protected hydroxyl functions can be deprotected in an orthogonal way, allowing for the introduction of molecular diversity. The use of this tripodal scaffold in the development of chemical libraries is currently under investigation.

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Supporting Information Available: Experimental procedures and characterization data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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