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Polymer-Supported (2,6-Dichloro-4-alkoxyphenyl)(2,4-dichlorophenyl)methanol: A New Linker for Solid-Phase Organic Synthesis

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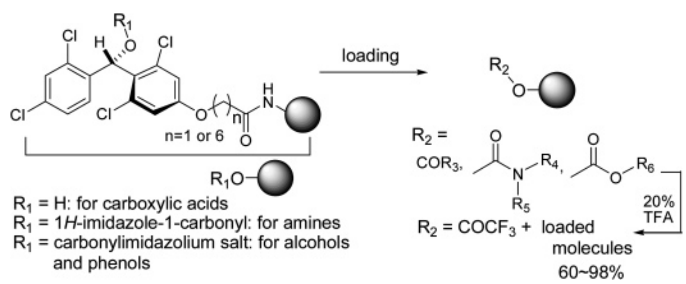
ABSTRACT



An acid and base stable hydroxytetrachlorodiphenylmethyl (HTPM) linker is developed for polymer-supported organic synthesis. The linkers reported here are utilized for loading carboxylic acids, amines, alcohols, and phenols, and are stable to Brønsted and Lewis acids, Brønsted bases, and a wide variety of nucleophiles. However, the HTPM linkers can conveniently be cleaved by the solvolytic displacement reactions with 20% TFA.

Since introduction of the concept of solid-phase synthesis in the late 1950s,[1] a variety of linkers for immobilizing organic molecules (the first building blocks or natural product derivatives) and organic reactions amenable to polymer-supported chemistries have been developed, greatly advancing research in biochemistry, molecular biology, pharmacology, and drug discovery.[2] Although recent advances in analysis and purification methods dramatically enhanced the usefulness of solid-phase synthesis,[3] development of a new linker that allows delivering target molecules in high yield and purity is still required. The linkers should be stable against a planned set of reaction conditions, but be cleaved under mild conditions that do not degrade the products. To date, many useful linkers for solid-phase synthesis have been developed.[4] However, the choice of spacer and linker requires careful consideration when applying diverse organic reactions on the solid phase.[4f]

In connection with the ongoing studies on the development of novel MraY inhibitors,[5] we have delivered a set of small optimized libraries based on uridine-β-hydroxyamino acid

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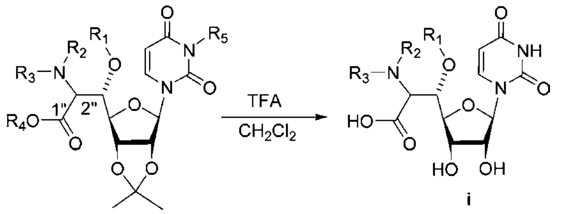
Scheme 1. General Structures of MraY Inhibitors **i**



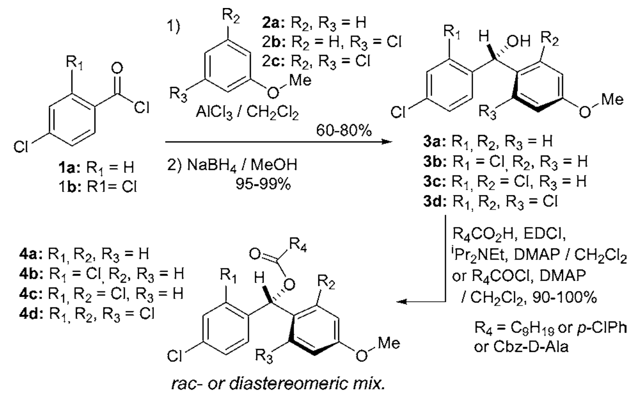
R_1, R_2, R_3 = building blocks
R_4 = acid-cleavable protecting group
R_5 = BOM or H

(Scheme 1).[6] To efficiently generate such libraries in solution or on polymer-support, we sought a protecting group or a linker for the carboxylic acid that can be cleaved simultaneously with the acetonide by a volatile and mild acid such as TFA. In addition, a protecting group (or a linker) for the carboxylic acid should have susceptibility to relatively strong Brønsted and Lewis acids, and a wide variety of nucleophiles. Although a large number of acid cleavable protecting groups (i.e., trityl, TBDPS, methoxymethyl, tetrahydropyranyl, 2-(trimethylsilyl)ethyl, *tert*-butyl, *p*-methoxybenzyl, ortho esters, and their related protecting groups) for carboxylic acids have been utilized in organic syntheses, these protecting groups did not meet our needs: trityl, silyl, and MPM protecting groups are too labile to acids being utilized in the library production and MOM, SEM, *tert*-butyl, and ortho esters require harsh acidic conditions for the regeneration of the carboxylic acids.[7] Because of the reasons mentioned above we have developed a new protecting group for carboxylic acid functional groups that can be selectively cleaved by TFA but is stable to a variety of acids.

Diphenylmethyl ester is an acid-labile functional group and has been utilized as a temporary protecting group for carboxylic acids. In our experiments diphenylmethanol exhibited similar nucleophilicity to allylic alcohol and is not esterified efficiently with carboxylic acids via conventional carboxylic acid activation methods (i.e., DCC, BOPCl, and mixed anhydride). To stabilize diphenylmethyl esters by tuning electronic properties of dibenzene moieties, several chloro-substituted diphenylmethyl esters were synthesized and tested for stability against representative acids such as $TsOH{\cdot}H_2O$ (20% in CH_2Cl_2−THF), HF (10% in CH_3CN), $BF_3{\cdot}OEt_2$ (10% in CH_2Cl_2), and $La(OTf)_3$ (10% in aq THF). Interestingly, as summarized in Scheme 2 all (4-methoxyphenyl)(chlorophenyl)methanols **4a**−**d**, conveniently synthesized by Friedel−Crafts reactions followed by $NaBH_4$ reductions, could be efficiently esterified by using EDCI, DCC, or acid chloride methods. The esters **4a**−**c** regenerated the corresponding acids by treatment with 20% TsOH within 1 h and were also not stable under 10% HF, 15% TFA, 10% $BF_3{\cdot}OEt_2$, and 10% $La(OTf)_3$.

However, the tetrachloro-substituted 4-methoxydiphenylmethyl esters **4d** showed an unusual acid stability: no

Scheme 2. Syntheses of Chlorosubstituted Diphenylmethyl Esters and Their Stability against the Representative Acids



entry	TsOH[a]	HF[b]	TFA[c]	$BF_3{\cdot}OEt_2$[d]	$La(OTf)_3$[d]
4a	H	H	H	H	H
4b	H	H	H	H	H
4c	H	H	H	H	H
4d	L	L	L	M[e]	L

[a] 20% in CH_2Cl_2−THF (1/1). [b] 10% in CH_3CN. [c] 15% in CH_2Cl_2. [d] 10% in aq THF. H indicates the protecting group is readily cleaved. M indicates that the protecting group is cleaved very slowly. L indicates that the protecting group is stable. [e] ∼5% of regeneration of the carboxylic acids was observed after 1 h.

regeneration of the acids from the esters **4d** was observed under 20% TsOH for over 20 h. The esters **4d** also exhibited excellent stablility to 15% TFA, 10% HF, and a variety of Lewis acids such as $AlCl_3$, $B(C_6F_5)_3$, BCl_3, TMSOTf, and $La(OTf)_3$. Moreover, the esters **4d** (1) were photolytically stable (no change by the irradiation at 200−350 nm in DMF for 72 h), (2) showed stability under basic conditions (no saponifications were observed under 40% NH_4OH in aq THF, 10% LiOH in aq THF−MeOH, 10% KOH in MeOH−THF, and 10% DBU in aq THF at rt for over 12 h), and (3) showed excellent stability to nucleophiles (the esters **4d** were not susceptible to the nucleophilic attacks of *primary* and *secondary* amines (in aq THF at 80 °C), NH_2NH_2 (in aq THF at rt), alkylthiols (in THF at 80 °C), and NaN_3 (90 °C in DMF) for over 12 h).[8] However, the esters **4d** slowly reacted with 10% $BF_3{\cdot}OEt_2$ to furnish the carboxylic acids (∼5% after 1 h) and 1,3-dichloro-2-((2,4-dichlorophenyl)-fluoromethyl)-5-methoxybenzene. The esters **4d** could conveniently be cleaved by using 20% TFA in CH_2Cl_2 to afford the corresponding acids and the trifluoroacetate (R_1, R_2, and R_3 = Cl, R_4 = CF_3 in **4d**).[9] Thus, we succeeded in stabilizing diphenylmethyl ester, enabling a wide range of organic reactions for the generation of small optimized libraries of MraY inhibitors in solution (Scheme 1). Taking advantage of excellent chemical stability of esters of (2,6-dicholoro-

(6) Kurosu, M.; Narayanasamy, P.; Crick, D. C. *Heterocycles* **2007**, *72*, in press.

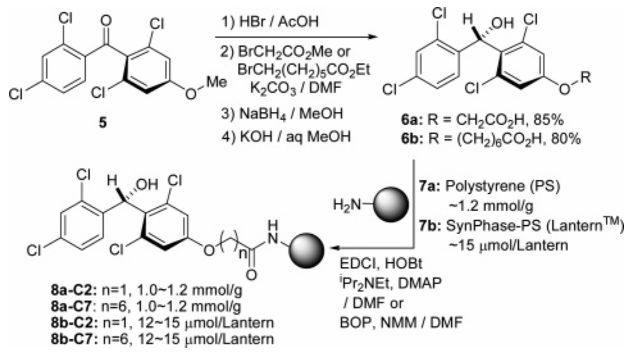
(7) (a) Pearson, A. J.; Roush, W. R., Eds. *Handbook of Reagents for Organic Synthesis*: *Activating and Agents and Protecting Groups*; Wiley: New York, 1999.

(8) The MM2 calculation of **4d** (R_4 = Me) indicated that the dihedral angle formed by two planar chloro-substituted benzenes is 76.4°. The −CO−O− linkage and the ether methine proton would preferentially be in a common plane. Thus, the chloro atoms at ortho positions of two benzenes hinder the nucleophilc attack on the carbonyl group of the esters.

(9) For solvolytic displacement reactions with TFA, see: (a) Milne, J. B. *J. Chem. Non-Aqueous Solvents* **1978**, *5B*, 1. (b) Nordlander, J. E.; Gruetzmacher, R. R.; Miller, F. *Tetrahedron Lett.* **1973**, *12*, 927.

4-methoxyphenyl)(2,4-dichlorophenyl)methanol, we have developed a new linker to immobilize carboxylic acids, amines, and alcohols which can, however, be cleaved by 20% TFA.

Scheme 3. Synthesis of the Hydroxytetrachlorodiphenylmethyl (HTPM) Linkers

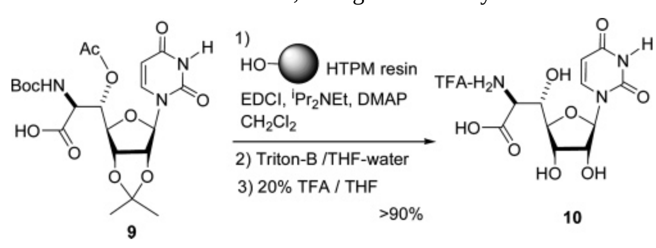


As illustrated in Scheme 3 the 3,5-dichloro-4-((2,4-dichlorophenyl)(hydroxy)methyl)phenol group could be efficiently linked with (aminomethyl)polystyrene **7a** and aminomethyl-Lantern **7b**[10] through C2 and C7 spacers without using sophisticated procedures. Available alcohol-linkers on the polymer surface after derivatization of the polymers **7a** (~1.2 mmol/g) and **7b** (~15 μmol/Lantern) were determined to be 1.0−1.2 mmol/g for **8a-C2** and **8a-C7**, and 12−15 μmol/Lantern for **8b-C2** and **8b-C7** by coupling of the linkers with Fmoc-β-Ala-OH and subsequent release of Fmoc chromophore and elemental analyses of the Cl atoms for **8a** and **8b**.

We first investigated the reactivity of the hydroxytetrachlorodiphenylmethyl (HTPM) linkers **8a** and **8b** to carboxylic acids. We have not observed noticeable differences in the rates of esterification with *N*-blocked amino acids between **8a-C2** and **8a-C7** or between **8b-C2** and **8b-C7**; a variety of Cbz or Boc-protected amino acids could be loaded onto **8a-C2**, **8a-C7**, **8b-C2**, and **8b-C7** within 6 h in >95% yields via a 4−5-fold excess of *N*-protected amino acids and EDCI or DICI.[11] It is worthwhile mentioning that Cbz-D-alanyl esters of **8a-C2** and **8b-C2** showed excellent stability to $BF_3 \cdot OEt_2$; on the other hand, ~10% of the same esters of **8a-C7** and **8b-C7** were cleaved after 2 h. Thus, we utilized **8a-C2** and **8b-C2** for further studies. Robustness of the linkers **8a-C2** and **8b-C2** to an acid (20% TsOH) was demonstrated by synthesizing the pentapeptide moiety of Park's nucleotide (UDP-*N*-acetylmuramyl-L-alanyl-D-isoglutamyl-L-lysinyl-D-alanyl-D-alanine),[12] using the Boc-strategy. One gram of the Boc-D-Ala-HTPM resin (~1.0 mmol/g) was used for the following sequential ligation reactions with Boc-D-Ala-OH, Boc-L-Lys($COCF_3$)-OH, Boc-γ-D-Glu(OMe)-OH, and Cbz-L-Ala-OH. The generated pentapeptide on the HTPM resin was cleaved with 20% TFA in CH_2Cl_2 for 1 h followed by methylation with CH_2N_2 to afford Cbz-L-Ala-γ-D-Glu(OMe)-L-Lys($COCF_3$)-D-Ala-D-Ala-OMe in over 90% overall yield after SiO_2-plug filtration ($CHCl_3$:MeOH 3:1).[13] As observed in the esters **4d**, **8a-C2** could be regenerated by ammonolysis of the recovered resins and the regenerated HTPM linker was reused two times for the synthesis of Cbz-L-Ala-γ-D-Glu(OMe)-L-Lys($COCF_3$)-D-Ala-D-Ala-OMe; the overall yields with the regenerated resins were 90% (first reuse) and 89% (second reuse), respectively.[14]

Solid-phase peptide synthesis has proven to be a practical method of producing synthetic oligo to longer peptides and the Boc-strategy is a popular method currently used for oligo peptide synthesis.[15] However, the Boc-solid-phase peptide synthesis suffers from low overall yield and low purity due to (1) partial cleavage of the anchor peptides in the cycle of the deprotection of Boc groups and (2) inefficient cleavage of the products when applied to photolabile linkers.[4g] We could demonstrate the synthesis of the oligopeptide using the HTPM linker **8a-C2** with excellent yield and purity. In addition, the appropriately protected uridine-β-hydroxyamino acid **9** could also be loaded completely via 1.3 equiv of the HTMP resin **8a-C2**. The ester linker was stable to the basic conditions such as Triton B or NH_4OH in aq THF−MeOH. The acetonide deprotection and concomitant cleavage of the linker under 20% TFA provided the fully deprotected uridine-β-hydroxyamino acid **10** in over 90% yield (Scheme 4).

Scheme 4.[a] A Demonstration of Loading onto and Cleavage from the HTPM-Resin, Using the Carboxylic Acid **9**



[a] 1.3 equiv of the HTPM resin against **9** was used.

The HTPM linker **8a-C2** could be converted to the carbonylimidazole linker **8a-C2-CI** by the reaction with CDI, which could further be converted to the carbonylimidazolium salts **8a-C2-CI-Me** by the treatment with MeI in CH_3CN or MeOTf in CH_2Cl_2. The resin **8a-C2-CI**[16] exhibited excellent reactivity against *primary* and *secondary* amines but much less reactivity toward alcohol nucleophiles; the primary

(10) Lantern (trademark of Mimotopes Pty, Ltd) is cylindrical in appearance and polystyrene grafted surface.

(11) The yield was determined by ^{1}H NMR analysis, using an internal standard (1-bromo-4-methoxybenzene).

(12) (a) Kurosu, M.; Mahapatra, S.; Narayanasamy, P.; Crick, D. C. *Tetrahedron Lett*. **2007**, *48*, 799. (b) Kurosu, M.; Crick, D. C. *Tetrahedron Lett*. **2006**, *47*, 5325 and references therein.

(13) In our hands, the synthesis of the same pentapetide with the HMBA linker employing the Fmoc-strategy afforded the desired product in ~15%.

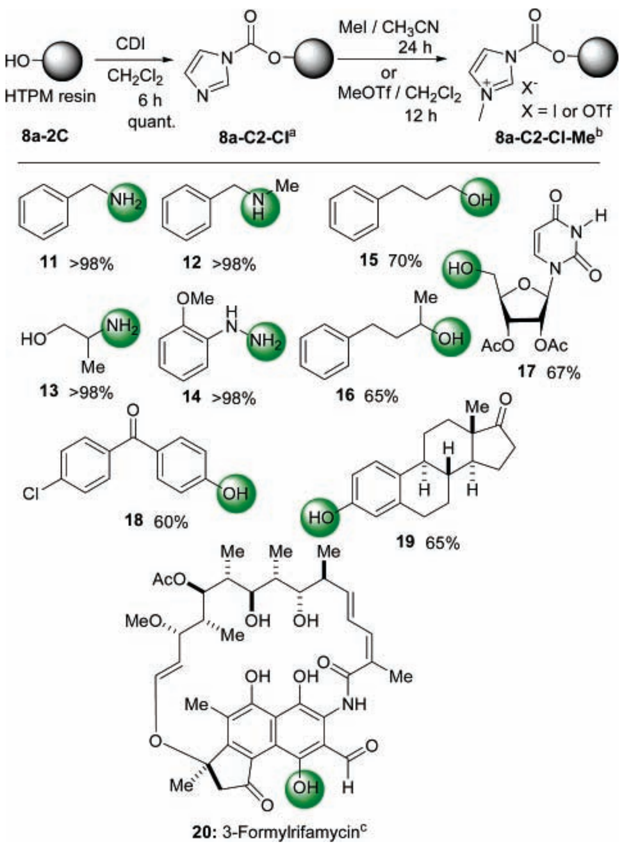
(14) The same experiments were performed using **8b-C2** and we obtained compatible results that were observed with **8a-C2**.

(15) Shin, D.-S.; Kim, D.-H.; Chung, W.-J.; Lee, Y.-S. *J. Bio. Mol. Biol*. **2005**, *38*, 517.

(16) The resin **8a-Cl** could be stored for over 20 days without decrease of the loading efficiency.

alcohols did not react with the carbonylimidazole resin even in the presence of *tertiary* amines at elevated temperatures. Thus, the resin **8a-C2-CI** can be utilized in loading amino groups selectively in the presence of alcohol groups in the same molecule. On the other hand, the corresponding carbonylimidazolium salts **8a-C2-CI-Me** could be utilized in the immobilization of alcohols and phenols in the presence of DMAP in CH_2Cl_2 at rt; we did not observe a difference in the loading efficiency of **8a-C2-CI-Me** due to the difference of the counterion (I vs OTf). As summarized in Scheme 5 benzylamine (**11**), *N*-methylbenzylamine (**12**), 2-aminopropan-1-ol (**13**), and (2-methoxyphenyl)hydrazine (**14**) were successfully loaded onto and cleaved from the **8a-C2-CI** linker; overall yields for two steps were over 98%.[11]

Scheme 5. The Linkers **8a-C2-Cl** and **8a-C2-Cl-Me** for the Immobilizations of Amines, Alcohols, and Phenols



[a] 5 equiv of the amine was used in CH_2Cl_2. [b]5 equiv of the alcohol and DMAP were used in CH_2Cl_2. [c]2 equiv of the resin was used.

3-Phenylpropan-1-ol (**15**), 4-phenylbutan-2-ol (**16**), the partially protected uridine **17**, (4-chlorophenyl)(4-hydroxyphenyl)methanone (**18**), and estrone (**19**) were also loaded onto and cleaved from **8a-C2-CI-Me** in 60−70% yield. Interestingly, 3-formylrifamycin (**20**) could be completely loaded by using an excess of **8a-C2-CI-Me**.[17] The yields for loading the alcohols and phenols were lower than those achieved for amines with the **8a-C2-CI** linker. It may be explained by the following reasons: (1) the imidazolium salt formation may be incomplete due to the lower swelling nature of **8a-C2-CI-Me**, which would significantly slow down the imidazolium salt formation on the polymer surface in the course of the reaction, and (2) adventitious water in the reaction is also activated by DMAP to hydrolyze the carbonylimidazolium salts. Nonetheless, we could achieve a useful level of loading of alcohols and phenols onto the **8a-C2-CI-Me**. As expected, the carbamate and the carbonate linkers exhibited excellent stability to acids, bases, and a variety of nucleophiles as demonstrated for the esters **4d**.

In conclusion, we have developed acid and base stable hydroxytetrachlorodiphenylmethyl (HTPM) linkers, which have significant advantages over currently utilized linkers for loading carboxylic acids in that (1) the ester linker is stable to a wide variety of nucleophiles, (2) the loaded molecules can be cleaved by solvolytic cleavage with 20% TFA within 1 h, and (3) the linker can be regenerated by treatment with aq NH_3 in THF. The utility of the HTPM linker was also demonstrated for loading amines, alcohols, and phenols, using a carbonylating reagent. These new linkers should be a valuable asset for polymer-supported organic synthesis. Applicability of these linkers to the generation of diverse structures of libraries defining the scope and limitations of the linkers will be reported elsewhere.

Acknowledgment. This paper is dedicated to Professor Yoshito Kishi (Harvard University) on the occasion of his 70th birthday. We thank the National Institutes of Health (NIAID grants AI049151, AI018357, and AI06357) and Colorado State University for generous financial support. We also thank Dr. Narayanasamy (Colorado State University) for providing the intermediates for the synthesis of MraY inhibitors.

Supporting Information Available: Experimental procedures and copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) Phenolic alcohols reacted with **8a-C2-Cl-Me** much faster than alkanols; greater than 90% selectivity was observed in the competition experiments with **15** and **19**.