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Development of New Dihydropyran Linker for Solid-Phase Reaction

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The linker which plays a role in connecting a polymer with a scaffold has become an important part in solid-phase reaction. To develop a new linker for alcohols and carbohydrates, dihydropyran moiety was selected in this study.
New linker, 1-(4',5'-dihydro-5*H*-pyranyl)-7-hydroxyheptan-3-one (**5**) was synthesized *via* four steps from δ-valerolactone. This can be called as DDHP-linked Wang resin due to double dihy-dropyran rings. To the one pyran ring of new linker **5** was added Wang resin and other alcohols and carbohydrates as scaffolds were then added successfully to the another pyran ring. Carbohydrate and hydroxyl resins were connected *via* new linker in a 70% loading yield. The detachment of glucose moiety in the presence of PPTS (2 equiv.) in 1:1 *n*-butanol/1,2-dichloroethane at 60°C for 12 h was carried out quantitatively. When certain combinatorial chemical works are carried out using this dihydropyran linker, Wang resin itself can be recovered. Its fact is particularly very important in industry, because recovered resins can be recycled.

Key words: Dihydropyran linker, Carbohydrate library, Combinatorial chemistry, Solid-phase reaction, Wang resin, DDHP resin

INTRODUCTION

Drug discovery has involved the optimization of lead structures, usually derived from biological sources, through a painstaking process of serial synthesis followed by screening. This approach is sometimes not efficient and not economical, as each test compound will have been individually handled by a skilled synthetic chemist and biologist. The need to find more cost-effective methods of drug development, combined with recent advances in robotic screening which enable the testing of many kinds of compounds in short time, has led pharmaceutical companies to consider combinatorial synthetic strategies as a means of accelerating drug discovery programs and increasing the chemical diversity of their compound libraries.

Combinatorial chemistry should overcome several problems such as efficiency of solid-phase reaction for automation, development of applied polymer resin, linker or spacer, etc. (Dolle and Nelson Jr., 1999;Dewitt and Czarnik, 1996; Armstrong *et al.*, 1996; Ellman, 1996; Gordon *et al.*, 1996; Petsko, 1996; Thompson and Ellman, 1996; Balkenhohl, 1996; Kobayashi, 1996) A wide range of technologies have been employed of the generation of combinatorial libraries - new analytical methods, new computer modeling and database-related challenges, new synthetic approaches, new types of reagents, and new types of assays.

In several methods for combinatorial chemistry, the solid phase reaction is mostly used for rapid synthesis. Until the revolution in high-speed bioassays, the testing of new compounds was the rate-limiting step in the drug discovery process. While it might take a chemist one or two weeks to synthesize a single compound, it required a much longer time to carry out the biological assays. Now modern high-speed assays using robotic samplers can screen more than 10,000 compounds per week. The biological assay has evolved from the rate-limiting step to the driving force in the need for large numbers of compounds.

Until 1992, the combinatorial library field was exclusively the domain of peptide and oligonucleotide-based chemistry. The situation changed in 1992 with the report by Bunin and Ellman of the preparation of combinatorial libraries of organic molecules (Bunnin and Ellman, 1992; Bunnin *et al.*,1994).

The solid-phase technology used in combinatorial

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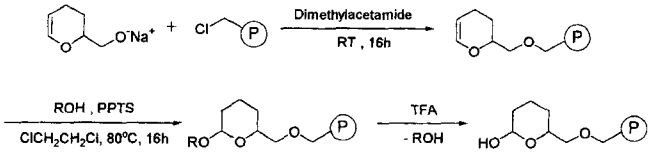
library can be broken down into three major components. First is the solid support that should be stable to a wide range of organic solvents and reagents. Second is the linker, which connects the support to the scaffold or target molecule. The linker should be cleavable under mild conditions but stable to proposed reaction conditions needed to build the desired product. The cleavage reaction should also be amenable to automation. Third is the scaffold or target molecule, which should be synthesized in high yield and purity.

In solid-phase synthesis, a linker is an important part which play a spacer to be reacted between scaffold with reagent and most of all, a linker connects resin with target molecules. There are a lot of linker types (halomethyl resin, hydroxy resin, amino resin, trityl resin, carboxy resin, arylsiloxy resin, pyran resin, etc). A great number of the commercially available linkers owe their existence to the field of solid-phase synthesis (Barany and Merrifield, 1980 ;Frechet, 1980).

Many of the methods used to cleave the bound component require the use of harsh acids such as trifluoroacetic acid. The total removal of trifluoroacetic acid, for example, typically requires incorporation in the cleavage protocol of a series of other precipitation steps. Such steps make automation of multiple simultaneous synthesis difficult. We have been interested in the development of linkers that not only can be cleaved selectively and under mild conditions but also chemistries that are easy to automate. We have been interested in creating a linker that cleaves product under more milder acidic condition and can let support to be recycled. One of the first to adapt these studies to a heterogeneous system for the purpose of cleaving product from a support was Wang (Wang, 1976).

To develop a new linker for alcohols and carbohydrates, dihydropyran moiety was selected in this study. Dihydropyran was one of the first generally useful protecting groups for alcohols to be adopted and they are still widely used today. The particular merits are its ease of introduction alcohol groups to dihydropyran moiety, its stability under a wide range of reaction conditions. An alcohol was attached to a 3,4-dihydro-5*H*-pyran (Miyashita *et al.*,1977). Ellman and co-workers were synthesized dihydropyran(DHP) Linker for coupling alcohols to solid supports (**Scheme 1**) (Thomson and Ellman, 1994). DHP-hydroxy-methyl (HM) resin consists of Ellman's 3,4-dihydro-2*H*-pyran-2-ylmethanol linker attached to 100-200 mesh chloromethyl polystyrene, and is a support for the reversible solid phase immobilization of primary and secondary alcohols (Wallace, 1997; Liu and Ellman, 1995), phenols (Pearson *et al.*, 1997) and purines (Nugiel *et al.*, 1997). A similar support has also been used to immobilize tetrazoles (Yoo *et al.*, 1997).



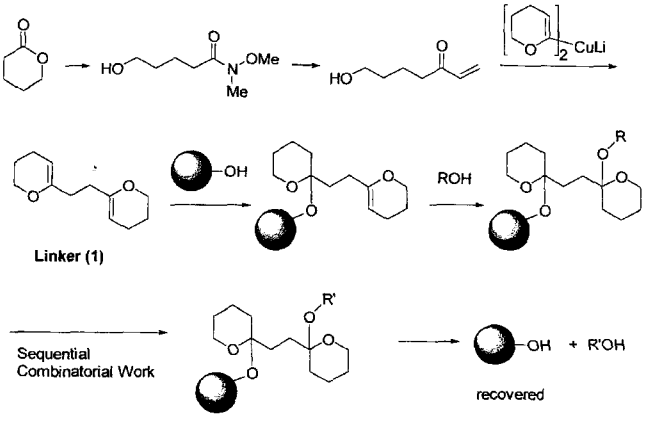
Scheme 1. DHP-HM Resin by Ellman

In contrast to trityl based supports, where the use of prolonged reactions times and elevated temperatures are often required to achieve satisfactory loadings, derivatization of DHP-HM resin is relatively straightforward, with even secondary alcohols being loaded without difficulty. Typically, this process involves treating the resin with an excess of alcohol or phenol in the presence of pyridinium *p*-toluenesulphonate (PPTS) in dichloroethane. The resin-bound THP ether is stable to basic and strongly nucleophilic reagents, but is easily cleaved by treating with 95%TFA/5%water (Wallace, 1997), TFA/dichloroethane/EtOH (Thompson and Ellman, 1994) or PPTS/ BuOH/ dichloroethane (Liu and Ellman, 1995). As shown in scheme 1, the starting resin was not recovered after the cleavage. On the point of Industrial case, the recovery of starting resin after reaction is very helpful economically and environmentally.

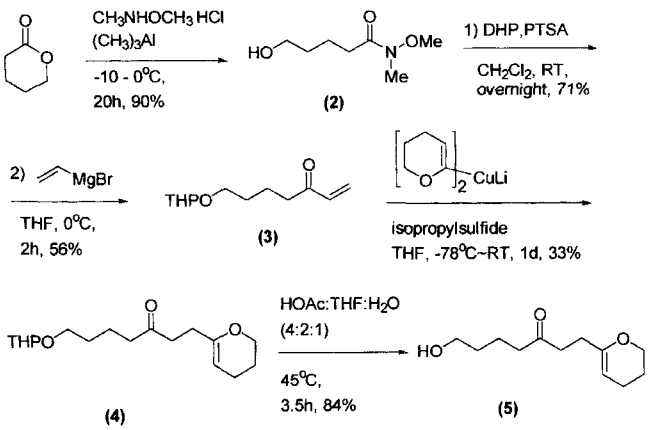
We design a new pyran-type linker (**1**) with hydroxyl type resins as shown in **Scheme 2**. Wang resin is common and fit in value to use. The hydroxyl moiety of carbohydrates as well as alcohols can be connected to new linker. New linker is expected to an important tool in carbohydrates combinatorial chemistry.

RESULTS AND DISCUSSION

To prepare new linker **1**, δ-valerolactone was used as a starting material (**Scheme 3**). The lactone ring was cleaved by *N,O*-dimethylhydroxylamine·HCl and trimethylaluminum with the Weinreb amide formation (Levin



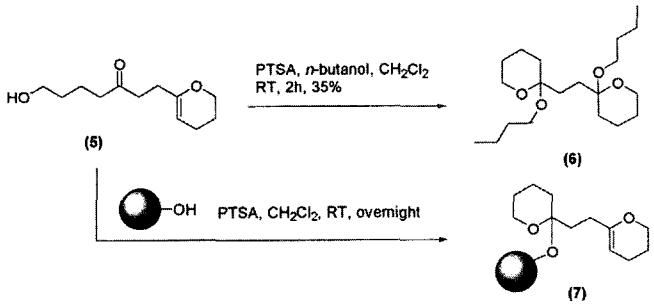
Scheme 2. Design of new dihydropyran linker **5** and its synthetic strategy



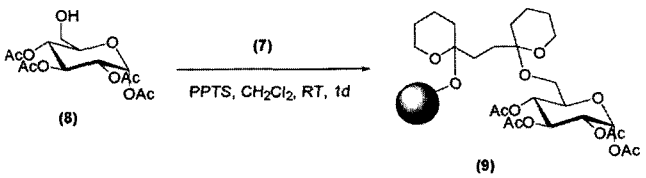
Scheme 3. Synthetic pathway to prepare a linker (**5**) which is equivalent to a designed linker (**1**)

et al., 1982; Basha *et al.*, 1977; Nahm and Weinreb, 1981) in chloroform as a solvent. This ring cleavage reaction generated 5-hydroxy-*N*-methoxy-*N*-methylpentamide (**2**) in a 90% yield. 3, 4-Dihydro-5*H*-pyran and a catalytic amount of *p*-toluenesulfonic acid was treated (Bernady *et al.*, 1979) to give 5-(2'-Tetrahydropyranoxy)-*N*-methoxy-*N*-methylpentanamide in a 71% yield and followed by an addition of vinyl magnesium bromide to give 7-(2'- tetrahydro pyranoxy)hepta-2-en-3-one (**3**) in a 56% yield.

The treatment of pyranylorganocuprate (Kociensky, 1983) produced 1,4-addition product,1-(4',5'-dihydro-5'*H*-pyranyl)-7-(2'-tetrahydropyranoxyl)heptan-3-one (**4**) (Corey and Enders, 1978) in a 33% yield. The tetrahydropyran protecting group was removed by treating with a mixture of acetic acid, THF, water (4:2:1) (Bernady *et al.*, 1979) to give 1-(4',5'-Dihydro-5*H*-pyranyl)-7-hydroxyheptan-3-one (**5**) in a 84% yield. The cyclization which form new linker **1** directly as well as the deprotection of tetra-hydropyran group was expected by treating with *p*-toluensulfonic acid (Corey *et al.*, 1978). However, it was not cyclized and just deprotected to offer compound **5** in a 34% yield. Even though we initially designed a



Scheme 4. Preparation of 1'-[1-(3'4'-dihydro-5'*H*-pyranyl)-2-(tetrahydro-5'*H*-pyranyl)ethanyl] Wang resin (7)



Scheme 5. Attachment of glucose moiety to new-linked Wang Resin 7

structure of 1,2-bis(3',4'-dihydro-5'*H*-pyranyl)ethane (**1**), compound **5** could be equivalent to compound **1**.

As a model study, *n*-butanol was added to compound **5** to offer bis-addition product **6** in a 35% yield as shown to **Scheme 4**. This yield was not optimized. Wang resin was selected, beacuse it is one of the most common resin of hydroxyl resin. We supposed that the Wang resin could be mono-adducted to compound **5**. Respectively, 1'-[1-(3'4'-Dihydro-5'*H*-pyranyl)-2-(tetrahydro-5'*H*-pyranyl) ethanyl] Wang resin (**7**) was formed. We hope to call this linker as DDHP linker (double DHP).

Secondly, glucose moiety was tried to be connected with the Wang resin using linker **5** (**Scheme 5**). The primary alcohol of D-(+)-glucose was protected selectively with TBDMS moiety by TBDMSCl and Imidazole in DMF (Kendall *et al.*,1979; Ronald *et al.*,1982). Other secondary alcohols were protected fully by acetic anhydride and pyridne at room temperature (Weber and khorana, 1972; Zhdanov and Zhenodarova, 1975). Deprotection of TBDMS group with tetrabutylammonium fluoride in THF (Corey and Benkateswarlu, 1972) gave 1,2,3,4-tetraacetyl-D-(+)-glucose (**8**). Compound **8** was treated with resin **7** in the presence of pyridinium *p*-toluenesulfonate to give compound **9**. It was identified by IR spectrum to speculate C=O peak due to acetyl group of compound **9**.

Eventually, carbohydrate and hydroxyl resins were connected *via* new linker in a 70% loading yield. The detachment of glucose moiety in the presence of PPTS (2 equiv.) in 1:1 *n*-butanol/1,2-dichloroethane at 60°C for 12 h was carried out quantitatively (Thompson and Ellman, 1994). The cyclization with diacetone alcohol (*tert*-alcohol) was not successful. In the case of Ellaman's DHP-HM resin, tertiary alcohol was not successful as well.

Other primary and secondary alcohols or carbohydrates were applied to give similar results. This report will be done soon or later. Particularly, we will examine that carbohydrate library works can be done by using DDHP linked Wang resin. After the cleavage of new linker DDHP, the Wang resin was recovered in contrast to the other pyran linker. When certain combinatorial chemical works are carried out using this DDHP linker, Wang resin itself can be recovered. Its fact is particularly very important in industry, because recovered resins can be recycled.

MATERIALS AND METHODS

Materials

Reactions were generally carried out under a positive pressure of dried nitrogen gas; for moisture sensitive reactions the glassware was flame-dried under a stream of dried nitrogen gas. Dried nitrogen gas was supplied by Shin Yang Co., dried through Silica gel, blue (Shinyo Pure Chemicals Co. LTD., practical grade)and inlet to the reaction vessel by the silicon tubing connected a stainless steel needle. Air and moisture sensitive liquid reagents were transferred by disposable sylinge. and were introduced into reaction vessels through Suba Seal white-rubber septa (William Freeman LTD.) Solid reagents were added either in a nitrogen-filled glove bags or under a stream of dried nitrogen gas. All reactions were stirred with a Teflon covered magnetic stirring bar. The resin for solid-phase synthesis was Wang resin (Novabiochem, 100-200 mesh). Anhydrous solvents were distilled before use. They were typically purchased from Oriental Chemical Ind. (extra pure grade). Dichloromethane and dichloroethane (Yakuri chemical) were distilled from calcium hydride (Sigma) powder under a stream of dried argon gas (Shin Yang Co.). Tetrahydrofuran was distilled from sodium metal (Lacaster) and benzophenone (Lacaster). Chloroform was distilled and filtered with neutral alumina (Merck, Aluminium oxide 90, active, 70-230 mesh). Anhydrous *N,N*-dimethylformamide was purchased from Aldrich. . Flash chromatography following the method of Still (Still *et al.*, 1978) employed Merck silica gel (Kieselgel 60, 200-400 mesh). Analytical thin-layer chromatography (TLC) was performed with commercial silica gel glass plates (Sigma-Aldrich, 250 m layer tickness, 5-17m particle size, 60 pore size, fluorescent indicator). Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Varian Gemini 2000 instrument (200 MHz). Chemical shifts are reported in parts per million (ppm) downfield from the internal standard, tetramethylsilane. Coupling constants are reported in hertz (Hz). Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a Varian Gemini 2000 instrument (50 MHz), fully decoupled and chemical shifts are reported in parts per million (ppm) dowmfield that are determined relative to the carbon signals of the solvent ($CDCl_3$, 77.0 ppm) Infrared(IR) spectra were recorded in 5mm path length potassium bromide cells or potassium bromide disk on JASCO FT/IR-430. All drawing chemical structures were generated by CS ChemDraw Pro™ Version 4.0.1.

Synthetic Procedures

5-Hydroxy-*N*-methoxy-*N*-methylpentamide (2)

To 1.95 g (20 mmol, 2 equiv.) of *N,O*-dimethylhydroxylamine hydrochloride (Aldrich) in 20 ml of chloroform was added very slowly 10 ml (20 mmol, 2 equiv.) of 2.0 M solution of trimethylaluminum in hexane (Aldrich) at -10°C. After the addition was completed, the reaction mixture was allowed to warm to 0 and was stirred for 1 h. To the aluminum amide reagent was added slowly 1.079 g (10 mmol, 1 equiv.) of δ-valerolactone (Aldrich) dissolved in 10 ml of chloroform. The solution was stirred for 20 h at 0°C. The reaction mixture was carefully quenched with a cold mixture of 5 ml of water and 100 ml of ethyl acetate at 0°C. The heterogeneous substance was removed with filtration. The organic layer was concentrated to 20 ml. After adding 5 g of Silica gel, the reaction mixture was stirred for 1 h. The reaction mixture was filtered and dried over anhydrous sodium sulfate and concentrated *in vacuo* to afford 1.323 g (90% yield) of product which was purified by flash silica gel chromatography (hexanes : ethyl acetate=1 : 1). Rf=0.125 (hexanes: ethyl acetate =1 : 1) IR (neat) cm^{-1}: 3418, 2940, 2868, 1649, 1462, 1385, 1323, 1180, 1117, 1062, 998, 941, 831. ^{1}H NMR (200 MHz, $CDCl_3$) : 3.64 (s, 3 H), 3.62 (t, J=6.2 Hz, 2 H), 3.14 (s, 3 H), 2.74 (s, 1 H), 2.43 (t, J=7 Hz, 2 H), 1.76-1.50 (m, 4 H). ^{13}C NMR (50 MHz, CD_3OD) δ: 172.6, 58.9, 58.2, 29.5, 28.8, 18.6.

7-(2'-Tetrahydropyranoxy)hepta-2-en-3-one (3)

To 1.472 g (10 mmol) of 5-Hydroxy-*N*-methoxy-*N*-methylpentamide(**1**) was added 19 mg (0.1 mmol, 0.01 equiv.) of *p*-toluenesulfonic acid (Shinyo Pure Chemicals) and 50 ml of dichloromethane at room temperature. To the solution was added 1.4 ml (15 mmol, 1.5 equiv.) of 3,4-dihydro-2*H*-pyran (Lancaster). This reaction mixture was allowed to stand at room temperature overnight. This reaction mixture was diluted with 100 ml of dichloromethane, and washed with 5 ml of saturated sodium bicarbonate solution. This aqueous layer was extracted with 2 × 5ml of dichloromethane. The combined organic layer was dried over anhydrous sodium sulfate. The solvent was evaporated *in vacuo* and the residues were purified by flash column chromatography on silica gel (hexanes : ethyl acetate=5 : 1) to yield 1.738 g (70.8%) of THP-protected amide as a clear oil. Rf=0.475 (hexanes : ethyl acetate=1 : 1) IR (neat) cm^{-1} : 3504, 2942, 2870, 1726, 1666, 1443, 1386, 1323, 1283, 1179, 1138, 1120, 1076, 1035, 999, 906, 869, 814, 434. ^{1}H NMR (200MHz, $CDCl_3$) δ : 4.57 (t, J=3.2 Hz, 1 H), 3.91-3.71 (m, 2 H), 3.68 (s, 3 H), 3.54-3.35 (m, 2 H), 3.17 (s, 3 H), 2.46 (t, J=7 Hz, 2 H), 1.83-1.68 (m, 6 H), 1.64-1.50 (m, 4 H) ^{13}C NMR (50 MHz,$CDCl_3$) : 172.7, 97.1, 65.6, 60.6, 59.5, 30.5, 29.1, 27.8, 23.8, 19.8, 17.9.

To 1.738 g (7.09 mmol) of THP-protected amide was added 35 ml of THF at 0°C. To the solution was added slowly 10.64 ml (10.64 mmol, 1.5equiv.) of vinylmag-

nesium bromide, 1.0 M solution in THF (Aldrich) at 0°C. The reaction mixture was stirred for 2 h at 0°C. This reaction mixture was diluted with 100 ml of diethyl ether and quenched with 10ml of water at 0°C. This mixture was washed with 100 ml of saturated sodium bicarbonate solution and washed with 100 ml of brine. The organic layer was dried over anhydrous sodium sulfate. The solvent was evaporated *in vacuo* and the residues were purified by flash column chromatography on silica gel (hexanes : ethyl acetate=10 : 1) to yield 848.8 mg (56.4%) of product as a clear oil. Rf=0.72 (hexanes: ethyl acetate=1 : 1) IR (neat) cm^{-1}: 3510, 2942, 2871, 1726, 1683, 1615, 1454, 1402, 1353, 1323, 1276, 1200, 1185, 1120, 1075, 1034, 989, 904, 869, 814, 744, 541, 428. ^1H NMR (200 MHz, $CDCl_3$) δ : 6.44-6.16 (m, 2 H), 5.85 and 5.80 (ABq, J_{AB}=.8 Hz, 1.8 Hz, 1 H), 4.57 (t, J=2.2 Hz, 1H), 3.92-3.69 (m, 2 H), 3.55-3.35 (m, 2 H), 2.64 (t, J=7 Hz, 2 H), 1.91-1.21 (m, 10 H). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 134.9, 126.3, 111.6, 97.2, 65.5, 60.7, 37.6, 29.1, 27.6, 23.8, 19.1, 18.0.

1-(4',5'-Dihydro-5'*H*-pyranyl)-7-(2'-tetrahydropyranoxy) heptan-3-one (4)

To a stirred solution of 3.65 ml (40 mmol, 10 equiv.) of 3,4-dihydro-2*H*-pyran (Lancaster) in 40 ml of THF was added dropwise 35.3 ml (60 mmol, 15equiv.) of 1.7 M solution of *t*-butyl lithium in pentane (Aldrich) at -78°C. The mixture was stirred at 0°C for 1h and re-cooled down to -78°C. The reaction mixture was added rapidly to a vigorously stirred suspension of 3.81g (20 mmol, 5 equiv.) of copper(I) iodide in 40 ml of THF at -78°C. To this reaction suspension was then added 2.91 ml (20 mmol, 5 equiv.) of isopropyl sulfide (Aldrich) and stirred for 1h at -78°C. 848.8mg (4 mmol, 1 equiv.) of 7-(2'-tetrahydropyranoxy)hepta-2-en-3-one (**3**) was diluted with 10 ml of THF at -78°C. This solution was added to the suspension of organocopper lithium complex at -78°C and the mixture allowed to warm slowly to room temperature and was stirred overnight at this temperature. The reaction mixture was diluted with 100 ml of dichlorolmethane and was quenched with saturated ammonium chloride solution containing 10% ammonium hydroxide and repeatedly extracted with dichloromethane. The organic phase was shaken several times with saturated ammonium chloride solution containing 10% ammonium hydroxide until the aqueous phase was no longer blue. The combined aqueous phase was again extracted with dichloromethane. The com-bined organic phases were washed with brine and then dried over anhydrous sodium sulfate. After removal of the solvent by evaporation *in vacuo,* the residues were purified by flash column chromatography on silica gel (hexanes : ethyl acetate=20 : 1) to yield 392.5 mg (33.1 %) of product as a clear oil. Rf=0.625 (hexanes : ethyl acetate=20 : 1). IR (neat) cm^{-1} : 2935, 2871, 1728, 1628, 1465, 1382, 1341, 1277, 1189, 1122, 1090, 911, 841, 770, 742, 507. ^1H NMR (200 MHz, $CDCl_3$) δ : 5.17 (t, J=7 Hz, 1 H), 4.21 (m, 1 H), 4.05 (m, 2 H), 3.72-3.64 (m, 4H), 2.25-2.05 (m, 6 H), 1.90-1.80 (m, 4 H), 1.75-1.52 (m, 10 H). ^{13}C NMR (50 MHz, $CDCl_3$) δ : 149.5, 108.0, 95.2, 71.2, 65.0, 64.6, 41.5, 35.3, 33.3, 33.0, 32.0, 30.5, 28.0, 27.7, 20.8, 19.0.

1-(4',5'-Dihydro-5*H*-pyranyl)-7-hydroxyheptan-3-one (5)

To 186.6 mg (0.63 mmol) of 1-(4',5'-Dihydro-5'*H*-pyranyl)-7(2'-tetra-hydropyranoxy)heptan-3-one (**4**) was added 20 ml of mixed solvent (acetic acid : tetrahydrofuran : water=4 : 2 : 1) at room temperature. The reaction mixture was allowed to warm to 45°C in the pre-heated silicon-oil bath and stirred for 3.5h. The reaction mixture was diluted with 100 ml of dichloromethane, washed with saturated sodium bicarbonate solution (50 ml), water (50 ml), brine (50 ml) and dried over anhydrous sodium sulfate. The solvent was evaporated *in vacuo* and the residues were purified by flash column chromatography on silica gel (hexanes : ethyl acetate=2 : 1) to yield 111.9 mg (83.7%) of product as a clear oil. Rf=0.325 (hexanes : ethyl acetate=1 : 1) IR (neat) cm^{-1}: 3428, 2935, 2868, 1680, 1625, 1446, 1385, 1348, 1286, 1237, 1175, 1059, 917, 782, 744. ^1H NMR (200 MHz, $CDCl_3$) : δ 5.98 (t, 7 Hz, 1 H), 4.23 (m, 1 H), 4.05 (t, J =7 Hz, 2 H), 3.62 (t, J=7 Hz, 2 H), 2.61 (t, J=9 Hz, 2 H), 2.20 (m, 4 H), 1.85-1.50 (m, 8 H). ^{13}C NMR (50 MHz, $CDCl_3$) : δ 195.3, 149.5, 108.0, 64.6, 60.8, 37.0, 35.3, 30.5, 30.4, 29.8, 25.5, 19.9.

1,2-Bis(1'-butoxytetrahydro-5'*H*-pyranyl)ethane (6)

To a stirred solution of 17.9 mg (0.084 mmol) of 1-(4',5'-Dihydro-5*H*-pyranyl)-7-hydroxyheptan-3-one(**5**) and 16 mg (0.084 mmol, 1 equiv.) of *p*-toluensulfonic acid in 10 ml of dichloromethane was added 16 μl (0.17 mmol, 2 equiv.) of *n*-butyl alcohol at room temperature. The reaction mixture was stirred for 2 h at room temperature. The reaction mixture was diluted with 50 ml of dichloro-methane, quenched with 50 ml of saturated sodium bicarbonate solution. The organic layer was washed with 50 ml of brine and dried over anhydrous sodium sulfate. The solvent was evaporated *in vacuo* and the residues were purified by flash column chromatography on silica gel (hexanes : ethyl acetate 20 : 1) to yield 10.09 mg (35.5%) of product as a clear oil. Rf=0.5 (hexane : ethyl acetate=20 : 1) IR (neat) cm^{-1} : 2928, 2859, 1731, 1600, 1580, 1463, 1380, 1274, 1122, 1072, 1039, 959, 742, 705, 652. ^1H NMR (200 MHz, $CDCl_3$) : δ 4.29(m, 4H), 4.20(m, 4H), 1.72~1.63(m, 4H), 1.49~1.26(m, 20H), 0.92(t, J=6Hz, 6H). ^{13}C NMR (50MHz, $CDCl_3$) δ: 98.0, 66.5, 63.5, 37.1, 35.5, 28.7, 28.0, 22.1, 17.0, 12.4.

1'-[1-(3'4'-Dihydro-5'*H*-pyranyl)-2-(tetrahydro-5'*H*-pyranylethanyl] Wang resin (7)

To 236 mg (0.5 mmole/g) of Wang resin (Novabiochem®, 100-200 mesh) and 22.6 mg (0.118 mmole, 1 equiv.) of *p*-toluenesulfonic acid in 5 ml of dichloromethane were added 1-(4',5'-Dihydro-5*H*-pyranyl)-7-hydroxyheptan-3-one (**5**) at room temperature. The reaction mixture was stirred for 48 h at room temperature. The mixture was filtered and washed with dichloromethane to remove the unreacted reagents and impurities. The filtered resin was dried over vacuum pump and 200 mg of yellow resin was produced. IR (KBr Disk) cm^{-1} : 3446, 3077, 3058, 3022, 2924, 2855, 1938, 1877, 1803, 1599, 1514, 1489, 1446, 1366, 1299, 1230, 1169, 1070, 1015, 911, 819, 751, 702, 542.

*Wang Resin IR (KBr Disk) cm^{-1}: 3575, 3444, 3083, 3059, 3022, 2922, 2849, 1945, 1938, 1871, 1809, 1748, 1602, 1507, 1452, 1372, 1305, 1225, 1170, 1114, 1010, 911, 868, 819, 744, 695, 535 cm^{-1}

1'-[1,2-Dis(tetrahydro-5'*H*-pyranyl)-1'-(1",2",3",4"-tetraacetyl-D-(+)-glucose- 6"-oxy)ethanyl] Wang resin (9)

To 340 mg (0.17 equiv.) of 1'-[1-(3'4'-Dihydro-5'*H*-pyranyl)-2-(tetrahydro-5'*H*-pyranyl)ethanyl] Wang resin (**7**) and 8.6 mg (0.034 mmol, 2 equiv.) of pyridinium *p*-toluenesulfonate (Aldrich) in 30 ml of dichloroethane was added 6 mg (0.017 mmol, 1 equiv.) of 1,2,3,4-tetraacetyl-D-(+)-glucose(**8**) (Corey and Venkateswarlu, 1972; Corey *et al.*, 1978) at room temperature. The reaction mixture was refluxed for 24 h. The mixture was filtered and washed with dichloromethane to remove the unreacted reagents and impurities. The filtered resin was dried over vacuum pump. 250 mg of resin was produced. IR (KBr Disk) cm^{-1} : 3421, 3083, 3059, 3028, 2922, 2849, 2363, 2338, 1754, 1606, 1493, 1452, 1372, 1224, 1175, 1114, 1034, 904, 757, 698, 548.

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