

ASYMMETRIC SYNTHESIS ON AN INSOLUBLE POLYMER SUPPORT

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The method of synthesizing polypeptides on polymer supports was first reported by Merrifield,¹ and this method has been extensively applied to the syntheses of oligo-nucleotides² and -succharides³ and others.⁴ In this paper we wish to report the first example of asymmetric synthesis of atrolactic acid 2 on the polymer containing 1,2-0-cyclohexylidene- α -D-xylofuranose⁵ 2 as the chiral groups.

The polymer-bound sugar 3 was synthesized according to the method similar to that described by Hayatsu and Khorana⁶ and Cramer *et al.*⁷ Thus a commercially available styrene-2% divinylbenzene copolymer (100-200 mesh, 20.0 g) was treated with benzoyl chloride (5.6 g) and AlCl₃ (5.6 g) in CS₂ to give the 20% benzo-ylated polymer (24.1 g), which was converted into the polymer 1 in almost quantitative yield by the reaction with phenylmagnesium bromide in tetrahydrofuran.⁸ The chlorination of 1 with acetyl chloride in refluxing benzene followed by treatment with 2 in benzene-pyridine afforded 3; the remaining chloride groups were treated with MeOH. The exhaustive hydrolysis of 3 (1 g) with HCl in dioxane-H₂O released approximately 0.9 mmol of 2, representing about 80% conversion of the polymer-bound trityl groups. The polymer 4 (0.74 mmol of the ester/g of the polymer), ν (KBr) 1740, 1691 cm⁻¹, was prepared by the reaction of 3 with phenylglyoxyl chloride⁹ in benzene-pyridine. The gain in weight of 4 indicated that approximately 90% of the polymer-bound sugars had been esterified. In the above preparation, out of every 100 styrene, about 16 were derivatized to the sugar functions, about 15 of which had the ester groups.

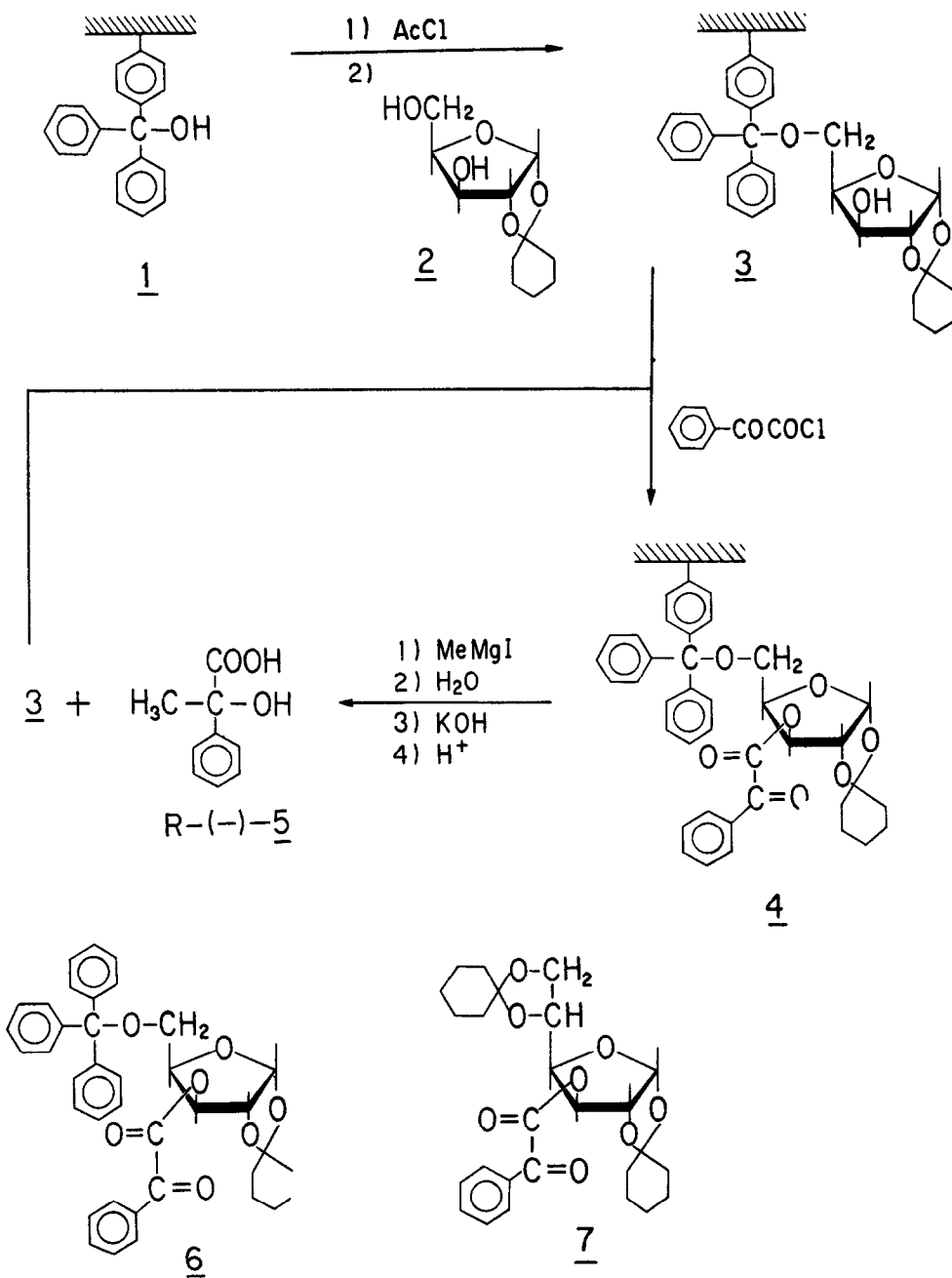
The polymer 4, thus obtained, was subjected to the Grignard asymmetric

reaction.¹⁰ To a suspension of 4 (3.0 g, 2.2 mmol of the ester) in benzene (18 ml) was added a solution of methylmagnesium iodide (6 mmol) in ether (18 ml) at 6-8° (bath) under N₂ atmosphere over a period of 35 min with stirring. After the addition had been complete, the mixture was stirred at room temperature for 1 hr and then treated with aqueous NH₄Cl-dioxane. The polymer was collected by filtration, washed successively with H₂O, dioxane, and MeOH, and then dried. The ir spectrum of the polymer showed the complete disappearance of the keto-carbonyl absorption. To a suspension of this polymer in dioxane (15 ml) was added a solution of KOH (600 mg) in MeOH-H₂O (9 ml, 2:1) at room temperature over a period of 15 min and the mixture was stirred for 6 hr. The polymer was collected by filtration, washed successively with H₂O-dioxane, H₂O, MeOH, and Et₂O, and then dried. The combined filtrate and washings were concentrated to give, upon acidification, 5 (280 mg), $[\alpha]_D^{25} -24.6^\circ$ (c 1, EtOH), in 77% chemical and 65% optical yields.¹¹ This product proved to be almost pure as judged by ir, nmr, and tlc. The ir spectrum of the polymer was identical with that of the intact specimen of 3.

Although some polymer beads broke down to fine grains during the reactions, the recovered polymer 3 was once again converted into 4, which could be used for the same asymmetric reaction. The chemical and optical yields of 5 from the used polymer were 73% and 58% respectively.

It is of interest to compare the optical yield of the reaction on the polymer with that of the reaction using an unit compound, 1,2-O-cyclohexylidene-3-O-phenylglyoxyl-5-O-trityl- α -D-xylofuranose 6, glasses,¹² ir (KBr) 1740, 1695 cm⁻¹, which was prepared from 1,2-O-cyclohexylidene-5-O-trityl- α -D-xylofuranose,¹³ mp 145-147°, $[\alpha]_D^{25} -28.3^\circ$ (c 1, EtOH), and phenylglyoxyl chloride in benzene-pyridine. Under the identical reaction conditions described above, except the use of MeOH instead of dioxane in the step of the hydrolysis of the ester, 6 gave 5, $[\alpha]_D^{25} -20.1^\circ$ (c 1, EtOH), in 68% chemical and 53% optical yields. Thus the optical yields of the reactions on the polymer were higher.

We reported previously that R-(-)-5 was obtained in 72% chemical and 38% optical yields on treatment of 1,2,5,6-di-O-cyclohexylidene-3-O-phenylglyoxyl- α -D-glucofuranose 7 with methylmagnesium iodide followed by the hydrolysis.¹⁴



It seems therefore that the steric bulkiness of the substituent on C-4 of the furane ring would play an important role in increasing the stereoselectivity of the Grignard reagent. In addition, the selectivity may slightly be enhanced by the conformational rigidity around the sugar and acid groups in the cross-linked polymer.^{3b,15}

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