Carbohydrates to Pyrano-Furanoids: New and Regioselective Palladium-Catalyzed Syntheses of Tetrasubstituted Furanoids from Carbohydrate Scaffolds

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A new strategy for the asymmetric syntheses of polysubstituted pyrano-furanoids using allylic sulfates derived from carbohydrate precursors and the dianion of diethoxycarbonyl acetone, catalyzed by Pd(0), is described.

Introduction

Furanoids are important targets either as a key entity itself or as a substructure that represents the framework of many biologically significant natural products [1]. Therefore, their access has attracted the interest of many groups [2]. Voelter et al. have described elegant strategies for the syntheses of furanoids using two different approaches, either mono or dianions derived from 1,3-dicarbonyl compounds as ambident nucleophiles and cis-oriented epoxy-triflate pyranosides as ambident electrophiles [2]. Others have reported the syntheses of furanoids fused to carbohydrate through free radical cyclization [3], Mitsunobo reaction [4], or a Pd-catalyzed process for ring closure [5].

Palladium-catalyzed reactions play a major role in the arsenal of synthetic chemistry [6]. Of particular interest is the Pd(0)-catalyzed alkylation of allylic carboxylate and/or sulfate derivatives by activated carbon nucleophiles [5, 6]. This reaction is widely applied in synthetic chemistry because the alkylation generally proceeds with high regio- and diastereoselectivity at the least hindered site of the allylic leaving residue [6, 7]. Previous studies of Pd-catalyzed alkylation in carbohydrate derivatives by different groups indicated that both steric and electronic factors played a role in controlling the regioselectivity of alkylation dihydropyran derivatives [7]. In the recent past, we have described the syntheses of bicyclopentanoids fused to carbohydrate precursors using Pd(0) catalyzed allylic alkylation with activated carbanions, followed by Co(CO)₈ catalyzed cyclization [8]. During the course of developing new synthetic strategies for the syntheses of cyclopentanoids such as IV (Scheme 2) derived from carbohydrates, it was anticipated that the dianion derived from diethoxycarbonyl acetone (4), would furnish IV when reacted with 2 in the presence of Pd(0). Instead, the pyrano-furanoid 3 is produced in a one-step reaction. In this report, we disclose our efforts for regioselective syntheses of polysubstituted and optically enriched furanoids using carbohydrate templates. It is worth mentioning that, to the best of our knowledge, this approach is not described before.

Discussion

Our strategy began with the carbohydrate scaffolds 2 and 6 synthesized according to procedures...
previously described by Voelter et al. [8,9]. Treatment of the allylic sulfate 2 (Scheme 1) with 1.5 equiv. of the dianion of diethoxycarbonyl acetone (4) (formed at 0 °C using 2.2 equiv. of NaH suspended in THF) in the presence of 5 mol-% of (Ph3P)4Pd and 10 mol-% of Ph3P, delivered furanoid 3 in 82% yield (Scheme 1). The 400 MHz 1H NMR spectrum of 3 indicated the presence of the enolether protons at 6.68 and 5.20 ppm. The coupling constants between 3-H and 4-H ($J = 7.3$ Hz, diequatorial) on one side, and 4-H and 5-H ($J = 11.0$ Hz, trans-diaxial) on the other side, establish the stereochemistry of 3. A salient feature of the 13C NMR spectrum of compound 3 is the downfield shift of the three methine carbons at 148.2, 98.2 and 76.0 ppm, assigned to C-1, C-2 and C-3, respectively. The formation of 3 is best explained with the mechanism proposed in Scheme 2. The allylic complex I is regioselectively alkylated by the dianion II from the same side in relation to the allylic leaving group (retention) to produce intermediate III with retention of configuration at C-4 and the ene position. At this glance, we anticipated that, if in intermediate III the oxo-anion is not coordinated to palladium, this would allow C-alkylation to take place to deliver the cyclopentanoid IV through 5-enolexo-exo-trig ring closure [10]. It seems that, stereoelectronic effects prevent such a cyclization (carbo-palladation leading to IV), in which the carbon cannot assume collinearity with the π-metal complex in III. Instead, oxo-palladation produces intermediate V, where Pd and the anomeric ethoxy residue are in cis relation. This preferential ring closure, through 5-endoendo-exo-trig leading to V (vide supra), might be due to the coordination between the oxo-anion and the Pd-complex. A retro-oxypalladation would reasonably complete the syntheses to arrive at compound 3 [11].

The same strategy was tested with compound 6 to deliver the tetrasubstituted furanoid 7 (Scheme 3) in 78% yield. The carbo-palladation of 6 proceeded selectively at C-4, leading to alkene migration. Oxo-palladation followed by reduction during work-up of the reaction delivered compound 7, due to the inability to undergo retro-palladation, since palladium and anomeric benzyl group are trans-oriented. An indicative feature of the 13C NMR spectrum of 7 assures the presence of four methylene and three methine carbon

![Scheme 2. Proposed mechanism for the formation of 3.](image-url)
atoms. Moreover, the 400 MHz \(^1\)H NMR spectrum of 7 confirms the stereochemistry for the proposed structure. (Experimental).

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\begin{array}{c}
\text{Scheme 3. i) NaI, AcOH, acetone; ii) POCl₃, pyridine;}
\text{iii) } \text{EtO}_2\text{C}CH_2\text{COCH}_2\text{COEt (4) (1.5 equiv.), NaH (2.2 equiv.), (Ph_3P)_4Pd (5 mol-%), Ph_3P (10 mol-%).}
\end{array}
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In conclusion, the described chemistry introduces a new application of palladium-catalyzed allylic alkylation, leading to enantiopure and polysubstituted furanoids. Further extension of the scope of this new methodology is underway in our laboratory.

**Experimental**

**General methods and materials:** NMR spectra were obtained with the indicated solvents, and chemical shifts are given in ppm on the \(\delta\) scale relative to internal TMS. The \(^{13}\)C NMR data were measured by applying Gated Spin Echo (GASPE) techniques. All reactions were monitored by tlc until the consumption of the starting material (~2 h). A saturated solution of NH₄Cl was added and the mixture was extracted with ethyl acetate, the solvent was evaporated, and the crude product was column chromatographed, eluting first with ethyl acetate/CH₂Cl₂ (5:95) followed by ethyl acetate/CH₂Cl₂ (10:90) to afford 3 (82%) or 7 (78%).

3: 82% yield, yellowish oil; [\(\alpha\)]\(_D\) = +47.0° (c = 0.48, CH₂Cl₂). – \(^1\)H NMR (CDCl₃, 400 MHz), \(\delta\) = 7.77 (d, J = 8.4 Hz, 2H, tosyl), 7.30 (d, J = 8.4 Hz, 2H, tosyl), 6.68 (d, J = 6.1 Hz, 1H, 1-H), 5.20 (dd, J = 5.2, 6.1 Hz, 1H, 2-H), 4.79 (ddd, J = 0.9, 5.2, 7.3 Hz, 1H, 3-H), 4.42 (dd, J = 2.0, 11.6 Hz, 1H, 6-H), 4.07 (dd, J = 1.5, 7.0 Hz, 1H, 6'-H), 3.70 (d, J = 16.5 Hz, 1H, 9-H), 3.66 (ddd, J = 2.1, 8.2, 11.0 Hz, 1H, 5-H), 3.45 (d, J = 16.5 Hz, 1H, 9'-H), 2.78 (dd, J = 7.3, 11.0 Hz, 1H, 4-H), 2.41 (s, 3H, CH₃Ph), 1.43 (s, 9H, C(CH₃)₃), 1.41 (s, 9H, C(CH₃)₃). – \(^{13}\)C NMR (GASPE, CDCl₃, 100 MHz), \(\delta\) = 166.8 (C-10), 166.4 (C-11), 164.2, 133.0, 129.9, 129.7 (tosyl), 148.6 (C-1), 144.6 (C-8), 106.7 (C-7), 98.2 (C-2), 81.7 (C(CH₃)₃), 81.0 (C(CH₃)₃), 76.0 (C-3), 74.5 (C-5), 70.2 (C-6), 35.9 (C-9), 28.2 (C(CH₃)₃), 28.1 (C(CH₃)₃), 21.5 (C(CH₃)₃). – MS (FD) \(m/z\) = 450.7 (M⁺). – Anal. C₂₂H₂₆O₈S (450.1355): Calculated C 58.33, H 6.12, O 28.73, S 7.76%. Found C 58.33, H 6.12, O 28.73, S 7.76%.

7: 78% yield, yellowish oil; [\(\alpha\)]\(_D\) = -11.5° (c = 0.37, CH₂Cl₂). – \(^1\)H NMR (CDCl₃, 400 MHz), \(\delta\) = 7.28–7.26 (m, 5H, Ph), 4.88 (m, 2H, H-1, 3-H), 4.75 (d, J = 12 Hz, 1H, OCH₂Ph), 4.44 (d, J = 12.0 Hz, 1H, OCH₂Ph), 3.89 (dd, J = 4.2, 12.0 Hz, 1H, 5-H), 3.67 (d, J = 16.5 Hz, 1H, 8-H), 3.65 (dd, J = 3.0, 9.1 Hz, 1H, 5'-H), 3.39 (d, J = 16.5 Hz, 1H, 8'-H), 3.08 (dt, J = 3.3, 9.9 Hz, 1H, 4-H), 2.35 (dt, J = 3.9, 15.2 Hz, 1H, 2-H), 1.87 (ddd, J = 3.7, 7.9, 15.2 Hz, 1H, 2'-H), 1.41 (s, 9H, C(CH₃)₃), 1.38 (s, 9H, C(CH₃)₃). – \(^{13}\)C NMR (GASPE, CDCl₃, 100 MHz), \(\delta\) = 167.3 (C-9), 164.4 (C-10), 163.7 (C-7), 107.9 (C-6), 137.8, 128.4, 127.8, 126.9 (Ph), 95.4 (C-1), 81.4 (C(CH₃)₃), 81.1 (C(CH₃)₃), 80.1 (C(CH₃)₃), 79.9 (C(CH₃)₃), 69.3 (OCH₂Ph), 60.2 (C-5), 40.8 (C-4), 35.5 (C-8), 30.6 (C-2), 29.6 (C(CH₃)₃), 28.8 (C(CH₃)₃). – MS (FD) \(m/z\) = 390.5 (M⁺). – Anal. C₂₁H₂₅O₇ (390.168): Calculated C 64.60, H 6.71, O 28.69. Found C 65.00, H 6.45, O 28.52%.

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