Supplementary Material for:

Free Radical Allyl Transfers Utilizing Soluble Non-Cross-Linked Polystyrene and Carbohydrate Scaffold Supports

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Experimental Methods

General methods. Proton Nuclear Resonance (^{1}H NMR) spectra were recorded on a Varian Gemini-300 (300MHz) spectrometer. Carbon 13 spectra were recorded on a Varian Gemini-300 spectrometer at 75 MHz. The chemical shifts were recorded in ppm relative to tetramethylsilane in deuterated chloroform, which was used as an internal standard. The glassware used was oven dried and reactions were run under an inert atmosphere of argon. The yields reported were from isolated products determined to be pure from by thin layer chromatography and NMR spectroscopy. The solvents utilized were dried by established distillation methods under an inert atmosphere of argon from the appropriate drying reagents. Thin layer chromatography was completed using Aldrich Z12272-6 precoated silica plates (0.25 mm). Both a 254nm UV light and p-anisaldehyde in ethanol and acetic acid were used as indicators to visualize the plates. Column chromatography was preformed with Kieselgel silica gel 60 (2230-400 mesh). Analysis using gas chromatography was performed on a Varian 3500 capillary instrument using a J&W fused silica capillary column (DB5-30W; film thickness 0.25).

Polystyrene Supported Benzyl Chloride 3: The subsequent procedure was adapted from that of Narita.[1] A solution of styrene (13.6 g, 131 mmol), 4-vinylbenzylchloride (9.90 g, 65.4 mmol), and AIBN (210 mg, 1.30 mmol) was stirred in benzene (48 mL). The mixture was degassed with argon for 20 min and subsequently heated to reflux for a period of 40 h. The solution was slowly poured into methanol at -78^{o}C. A white precipitate was collected by filtration and dried under vacuum to give 19.4 g of **3** as a white solid: (33% reactive sites, 2.8 mmol/g, 83% yield) ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.3-6.2 (m, 14H), 4.4 (s, 2H), 2.2-1.2 (m, 18H).

Polystyrene Supported α-Bromoester 4: A mixture of the polystyrene supported benzyl chloride **3** (6.0 g, 16.2 mmol), potassium acetate (20.0 g, 204 mmol), and tetrabutylammonium bromide (6.0 g, 18.6 mmol) was stirred at reflux in 150 mL THF/H_2O (3:1) for a period of 8 h. Potassium hydroxide (17.3 g, 308 mmol) was then added and the solution continued to stir at reflux for 12 h. The milky white solution was slowly poured into methanol cooled to -78^{0}C, and the precipitate was collected through vacuum filtration to give 6.79 g of a white solid (polystyrene supported benzyl alcohol): (35% reactive sites, 2.5 mmol/g, 91% yield) ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.2-6.2 (m, 12H), 4.6-4.4 (s, 2H), 1.9-1.2 (m, 8.4H). A solution of the polystyrene supported benzyl alcohol (5.7 g, 15.7 mmol), dicyclohexylcarbodiimide (4.8 g, 23.5 mmol), and dimethylaminopyridine (700 mg, 6.3 mmol), was stirred at 0^{o}C in CH_2Cl_2 (30 mL). Bromoacetic acid (4.40 g, 31.3 mmol) dissolved in CH_2Cl_2 (10 mL) was then slowly added. The subsequent solution was allowed to warm to room temperature and stirred an additional 1.5 h. The yellow mixture was poured into methanol at -78^{o}C and the precipitate was collected by vacuum filtration and dried under vacuum to give 8.6 g of **4** as a yellow solid: (38% reactive sites, 2.4 mmol/g, 94% yield) ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.3-6.2 (m, 12H), 5.2-5.0 (s, 2H), 3.9-3.7 (s, 2H), 1.8-1.2 (m, 10.6H).

Polystyrene Supported 4-Pentenoic Ester 5: A solution of the α-bromoester **4** (2.0 g, 5.4 mmol), allyltributyltin (5.0 mL, 16.2 mmol), and AIBN (10 mg) was degassed with Argon for 10 min and stirred in freshly distilled benzene (30 mL) for 12 h. The solvent was then concentrated under reduced pressure with no heat, and was poured into cold methanol to induce precipitation. The yellow solid **5** weighing 2.07 g was recovered upon vacuum filtration and drying: (38% reactive sites, 2.5 mmol/g, 89% yield) ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.2-6.2 (m, 19.7H), 5.9-5.7 (s, 1H), 5.1-4.9 (m, 2H), 2.4-2.2 (s, 2H), 1.8-0.9 (m, 10.3H). Cleavage of 4-Pentenoic acid from the polymer backbone was completed as following: a mixture of the polystyrene supported 4-pentenoic ester **5** (1.1 g, 1.9 mmol), lithium hydroxide (1.0 g, 29.7 mmol), and tetrabutylammonium bromide (600 mg, 1.9 mmol) was stirred in THF/H_2O (3:1) at reflux for 12 h. The white solution was extracted with diethyl ether (2 X 30 mL), and the aqueous layer was acidified with 3M HCl until pH = 1 was attained. The aqueous layer was extracted with ethyl acetate four times and the organic extracts were concentrated under reduced pressure. An orange precipitate was purified through a slurry of silica gel and 10 drops of acetic acid giving 4-pentenoic acid as a pure yellow oil (157mg, 84% yield).

Polystyrene Supported 4-Methyl-4-Pentenoic Ester 6: Polystyrene supported α-bromoester **4** (3.0 g, 8.3 mmol) was added to solution of methallyltributyltin (3.6 g, 24.9 mmol) and AIBN (10 mg) in freshly distilled benzene (125 mL). The solution was degassed with Argon for 10 min and was stirred at reflux for 12 h. The solvent was concentrated under reduced pressure and poured into methanol at -78 °C. White precipitate was collected by vacuum filtration and dried under vacuum to give 2.8 g of **6**: (26% reactive sites, 2.0 mmol/g, 77% yield) ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.2-6.2 (m, 18H), 5.0 (s, 2H), 4.6 (d, 2H), 2.6-2.2 (m, 4H), 1.8-0.8 (m, 22H). Cleavage of 4-methyl-4-pentenoic acid from the polymer backbone was performed by adding polystyrene supported 4-methyl-4-pentenoic ester **6** (1.0 g, 1.8 mmol) to a solution of lithium hydroxide (1.0 g, 30 mmol), and tetrabutylammonium bromide (1.1 g, 30 mmol) in a mixture of THF/H_20 (50 mL). The mixture was stirred at reflux 12 h. The solvent was then concentrated under reduced pressure and extracted with ether. The aqueous layer was separated and acidified with 3M HCl until a pH = 1 was attained. The aqueous layer was re-extracted with ethyl acetate (4 x 30 mL) and then concentrated to give 4-methyl-4-penteniоc (143 mg, 70%) acid as a light yellow oil identical to that reported by Negishi and Coperet.[2]

(D)-Xylose α-bromoester 8: Sodium hydride (60% in mineral dispersion, 2.7g, 68.5 mmol) was placed in an oven dried 250 mL round bottom flask purged with argon. The sodium hydride was washed with pentane (3 X 20 mL) to remove the mineral oil coating and was diluted with THF (90 mL). Diol **7** (10.9 g, 57.0 mmol) was dissolved into THF (10 mL) and added slowly via syringe to the sodium hydride solution in THF which was cooled to -78°C. After H_2 gas liberation was complete in 10 min., tetrabutylammonium iodide (10.5 g, 28.5 mmol) was added to the stirring solution. Benzyl bromide (7.1 mL, 59.9 mmol) was then added to the solution by syringe, and the solution was allowed to warm to room temperature. The reaction was complete by TLC after 2.5 h. The reaction was extracted with ethyl acetate (3 X 30 mL), and the resultant organic layer was dried over magnesium sulfate. The filtered solution was concentrated under reduced pressure and purified by flash column chromatography to give 5-O-Benzyl-2,3-isopropylidene-(D)-xylofuranose: (8.8g, 61% yield) that was identical to that reported by Wong[3]. Next, DCC (4.42g, 21.4 mmol) was dissolved in freshly distilled methylene chloride (138 mL) in an oven dried 500 mL round bottom flask purged with argon. 2-Bromopropionoic acid (2.17 mL, 24.14 mmol) was added via syringe and then cooled to 0°C for 30 min. In a separate flask, 5-O-Benzyl-2,3-isopropylidene-(D)-xylofuranose (4.0 g, 14.2 mmol) was dissolved in freshly distilled methylene chloride (100 mL) with 4-DMAP (700 mg, 5.7 mmol). The solution of the sugar was added via syringe to the DCC solution at 0°C, and allowed to warm up to room temperature. The reaction was complete by TLC in 30 min. The solution was concentrated under reduced pressure and then redissolved in a 1:1 mixture of methyene chloride/hexane. The white precipitate was then separated by gravity filtration. The solvent was concentrated and the crude mixture was purified by flash chromatography to give compound **8** (5.8 g, 98% yield). R_f 2.0cm (35% THF/Hex); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.34 (m, 5H), 5.97 (d, J=3.8 Hz, 1H), 4.64 (d, J=3.8 Hz, 1H), 4.60 (center of AB q, J=2 Hz), 4.39 (complex m, 4H), 4.01 (d, J=3.3 Hz), 1.81 (dd, J=3.4,3.4 Hz, 3H), 1.5 (s, 3H), 1.33 (s,3H) ^{13}C NMR ($CDCl_3$, 300 MHz) δ 170.18, 137.25, 128.73, 128.61, 127.99, 112.12, 105.44, 82.24, 77.86, 72.16, 63.74, 39.93, 26.99, 21.75; IR(NaCl) 1742.7cm^{-1}, 1072.9 cm^{-1}, 732.1cm^{-1}. Anal. Calcd for $C_{18}H_{20}O_5$ C, 52.06; H, 5.58. Found: C, 52.36; H, 5.68.

Allylester 9: (D)-Xylose α-bromoester **8** (100 mg, 24.08 mmol) and zinc chloride (32.9 mg, 0.24 mmol) were dissolved in a mixture of freshly distilled 4:1 CH_2Cl_2/THF (0.5 mL) and the solution was cooled to -78°C. Allyltributyltin (370 mg, 1.20 mmol) and triethylborane (1M in hexane, 1.0 mL, 1.0 mmol) were added. Oxygen (5.0 mL) was added via syringe over 2 min. The reaction was kept at –78°C until judged to be complete by TLC (35% THF/Hex) after 2h. The reaction was extracted with ether (20 mL) and washed with brine (3 X 10 mL). The concentrate was dried over magnesium sulfate and finally purified by flash chromatography to give compound **9** (80 mg, 89% yield): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.32 (m, 5H), 5.96 (d, J=3.8 Hz, 1H), 5.73 (m, 1H), 5.01 (t, J=13.1 Hz, 1H), 4.64 (d, J=3.8 Hz, 1H), 4.59 (center of ab q, J=11.9 Hz, 2H), 4.39 (m, 3H), 3.99 (d, J=2.5 Hz, 1H), 2.49 (complex m, 2H), 2.19 (m, 1H), 1.49 (s, 3H), 1.36 (s, 3H), 1.15 (dd, J=1.9, 1.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 175.97, 137.32, 128.68, 128.17, 127.83, 117.13, 111.95, 105.34, 82.22, 81.79, 78.31, 76.27, 72.05, 62.24, 39.18, 39.09, 37.84, 26.94, 16.63; IR (NaCl) 3072.0cm^{-1}, 1736.9cm^{-1}, 1637.0cm^{-1}, 1078.7cm^{-1}. Anal. Calcd for $C_{21}H_{28}O_{6:}$ C, 67.00; H, 7.50. Found: C, 67.25; H, 7.62.

(D)-xylose polymer 10: To a mixture of Polymer **3** (2.3 g, 6.8 mmol) in DMA (12 mL) was added NaH (60% in mineral oil, 0.44g, 10.8 mmol) previously washed with pentane (2 X 3mL) in DMA (4 mL), and the solution was cooled to -30°C. A solution of **7** (2g, 10.6 mmol) in DMA (12 mL) was slowly transferred into the NaH suspension at –30°C with a syringe. After transfer was complete, the mixture was stirred for 30 min at room temperature to insure that no further hydrogen was released. The alkoxide solution was transferred into the polymer solution. The reaction was stirred for 10 h. This solution was poured into methanol (200 mL) at -78°C with agitation to obtain a white precipitate. It was filtered, washed with methanol, and dried by full vacuum pump to give 2.9 g of (D)-xylose polymer **10**. (27% reactive sites, 1.7 mmol/g, 85% yield): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.2-6.1 (m, 17H), 5.98 (s, 1H), 4.8-4.3 (m, 3H), 4.2 (s, 1H), 3.8 (m, 3H), 2.0-0.9 (m, 20H).

α-Bromoester polymer 11: (D)-xylose polymer **10** (1.7 mmol/g, 1.0 g, 1.7 mmol) and 4-DMAP (80 mg, 0.68 mmol) were dissolved in methylene chloride (10 mL). To a solution of DCC (63 mg, 3.1 mmol) in methylene chloride (16 mL) was added 2-bromopropionic acid (0.31g, 3.5 mmol) at –30°C. The mixture was stirred for 30 min. The prepared polymer solution was then added at -30°C. The mixture was stirred for 8 h at room temperature. The white urea precipitate was removed by filtration. The filtrate was poured into methanol at –78°C to obtain a white precipitate. The solid was filtered, washed with methanol and dried by full vacuum pump to give 1.2 g of α-Bromoester polymer **11** (1.4 mmol/g, 27% reactive sites, 98% yield) ^{1}H NMR ($CDCL_3$, 300 MHz) δ 7.2-6.1 (m, 17H), 5.98 (s, 1H), 4.8-4.5 (m, 3H), 4.2 (m, 4H), 3.9 (s, 1H), 1.8 (s, 3H), 1.6-0.9 (m, 14H).

Allyl polymer 13: To a solution of bromoester polymer **3** (1.38 mmol/g, 0.4g, 0.55 mmol) in benzene (8 mL) was added AIBN (0.28g, 1.7 mmol) and allyltributyltin (2 mL, 5.5 mmol). The solution was stirred at 80°C for 14 h. The solution was poured into –78°C methanol to precipitate the allylated polymer **4**. The white solid was filtered, washed with methanol and dried by full vacuum pump to give 0.35g of **13**. (14% reactive sites, 1 mmol/g, 93% yield) as determined by allyl functionality. (24% reactive sites, 1.4 mmol/g) as determined by the sugar auxiliary. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.2-6.1 (m, 20H), 5.98 (s, 1H), 5.70 (m, 1H), 5.0 (m, 2H), 4.5 (m, 6H), 3.9 (s, 1H), 2.58 (s, 1H), 2.38 (s, 1H), 2.15 (s, 1H), 1.8-0.9 (m, 16H), 1.1 (s, 3H).

R-(-)-2-Methyl-4-Pentenoic acid (14): Allyl polymer **13** (1.4 mmol/g, 350 mg, 0.50 mmol) was dissolved in THF:H_2O (9:1, 20 mL). To this solution was added H_2O_2 (30%, 1.2 mL, 12 mmol) followed by addition of LiOH solution (0.27 g in 2.0 mL of distilled water, 6.4 mmol). The mixture was stirred for 6-8 h at reflux. The two layers were separated and to the aqueous layer was added 6N HCl to pH = 1, followed by extraction with ethyl acetate. The organic extracts were dried with anhydrous $NaSO_4$, and concentrated to about 2 mL solution, then poured into methanol at -78°C to obtain a white precipitate. It was filtered, washed with methanol and dried by full vacuum pump to give 0.28g of recovered **10** with a remaining sugar content at 24% by ^{1}H NMR (1.57 mmol/g, 24% reactive sites, 92% yield recovery). The filtrate was evaporated, dried on anhydrous $NaSO_4$, and evaporated to give S-(+)-2-methyl-4-pentenoic acid **14** (30 mg, 80% yield) with a determined value of $[\alpha]_D$ = -10.2 (c, 1.0, $CHCl_3$). This was otherwise identical in all respects to the antipode reported by Silverstein and Riley $[\alpha]_D$ = +10.5 (c, 1.0, $CHCl_3$).[4]

References:

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