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Stereoselective Synthesis of Sex Pheromone (*R*)-4-Methyl-1-Nonanol: Non-Cross-Linked Polystyrene Supported Oxazolidinone as a Chiral Auxiliary

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(*R*)-4-Methyl-1-nonanol, the sex pheromone of the yellow mealworm (*Tenebrio Molitor* L.), was synthesized by using non-cross-linked polystyrene supported oxazolidinone as a chiral auxiliary. The stereoselective synthesis was achieved by asymmetric Michael addition of an organocopper reagent to non-cross-linked polystyrene supported *N*-crotonoyoxazolidinone, and the target product was obtained in an overall yield of 41.8% over seven steps with a high enantiomeric excess of 98%.

Introduction

Since their first report by Evans in 1981,[1] oxazolidinone chiral auxiliaries have been widely utilized in, for example, alkylation, aldol, Diels–Alder, and Michael addition reactions.[2] However, in most cases, the chiral auxiliaries could not be recovered after the asymmetric reaction. In order to recycle the expensive material, oxazolidinones have been supported onto insoluble polymer supports.[3]

Insoluble polymer supports such as Merrifield resin and Wang resin were applied previously to simplify the procedure of separation and purification, but there were several disadvantages, including nonlinear kinetic behavior, unequal distribution or access to the chemical reaction, synthetic difficulties in transferring standard organic reactions to the solid phase, and the use of the recovered support does not always allow the results obtained in the first run to be reproduced. Then, chemists started to search for soluble polymers as supports.[4] This methodology has been demonstrated to be a very successful process that combines the superiorities of insoluble polymer supports with the advantages of classic liquid synthesis. In previous reports, our group has described some liquid-phase methods for the synthesis of small molecule libraries by using poly(ethylene glycol) (PEG) and non-cross-linked polystyrene (NCPS) as supports,[5] and grafting of the chiral auxiliary to a soluble polymer support has already been achieved by us[6] and other groups.[3e]

The yellow mealworm (*Tenebrio molitor* L) is known to cause serious losses of stored cereal grains throughout the world. Its common sex pheromone was first identified by Tanaka et al. as 4-methyl-nonan-1-ol (**1**; Figure 1) in 1984.[7] Bioassays of the two possible stereoisomers of **1** revealed the (*R*) enantiomer was the active form of the pheromone and that the (*S*) enantiomer had minimum activity.[8] Because effective and cost-efficient control of the yellow mealworm populations can be foreseen with the aid of the sex pheromone, several total syntheses of the racemate and (*R*)-**1** have been published.[7–9] In this paper, we describe a new synthetic route by applying our previously prepared non-cross-linked polystyrene supported oxazolidinone[6a] as a chiral auxiliary to stereoselectively synthesize (*R*)-**1** through a reaction sequence in which the key step is Michael addition (Scheme 1).

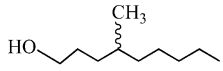

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Figure 1. Sex pheromone of the yellow mealworm.

Results and Discussion

NCPS-supported oxazolidinone chiral auxiliary **2** was prepared previously by copolymerizing (4*S*)-[4′-(4′′-vinylbenzyloxy)benzyl]oxazolidinone and styrene with a ratio of 1:1. The loading of the chiral auxiliary was analyzed by nitrogen elemental analysis.[6a] NCPS-supported *N*-crotonyloxazolidinone **3** was obtained smoothly by treating crotonoyl chloride with **2** in the presence of NaH.

The stereoselective Michael addition of an organocopper reagent to NCPS-supported *N*-crotonyloxazolidinone was the key step in the total synthesis of (*R*)-4-methyl-1-nonanol. Compound **4** was obtained by Michael addition of an organocopper reagent to NCPS-supported *N*-crotonyloxazolidinone **3**. Nondestructive removal of the auxiliary group

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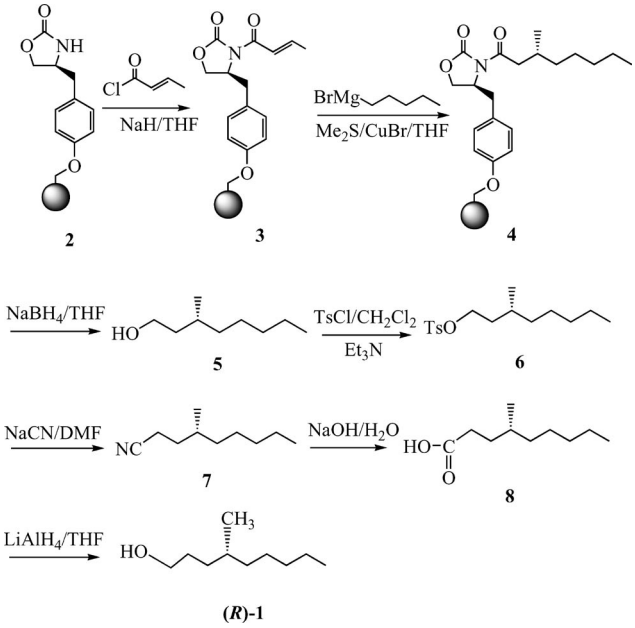

Scheme 1.

of **4** gave (*R*)-3-methyloctan-1-ol (**5**) in high optical purity (98%*ee*), which was analyzed by HPLC, and NCPS-supported chiral auxiliary **2** was recovered by simple filtration. Recovered **2** was reused, and the result obtained by running a second Michael addition on newly functionalized **3** starting from recovered **2** was similar to the first run (in terms of both reactions yields and induced stereoselectivities). The reactions on the polymer support were monitored by nitrogen elemental analysis, and all these three reactions were confirmed to go to completion. A higher yield in the Michael addition step was observed by using soluble polymer **3** instead of Merrifield resin,[3a] whereas the observed stereoselectivity was more similar to those reported for model substrate **5** under classical solution conditions.[9b] Substrate (*R*)-**5** was then subjected to further manipulation over four reaction steps to obtain the sex pheromone of the yellow mealworm, (*R*)-**1**. In these reactions, the stereocenter of the compound was not touched and the optical yield of (*R*)-**1** remained as 98%*ee*.

The use of non-cross-linked polystyrene as a polymer support instead of cross-linked ones (Merrifield resin) allowed higher loading, easier characterization of the intermediates, and easier interaction between the metal cations and the coordinating substrates. Thus, some of the intrinsic disadvantages of solid-phase chemistry were avoided.

Conclusions

In summary, a new method for the synthesis of (*R*)-4-methyl-1-nonanol was developed, in which the key step was a stereoselective Michael addition reaction performed with the use of non-cross-linked polystyrene supported oxazolidinone as a chiral auxiliary. The final product was obtained in an overall yield of 41.8% over seven steps in 98%*ee*. The method was efficient and the chiral auxiliary can be recovered by simple filtration.

Experimental Section

General: All organic solvents were dried by standard methods. TLCs were performed on precoated plates of silica gel HF254 (0.5 mm, Yantai, China). Flash column chromatography was performed on silica gel H (Yantai, China). Optical rotations were determined with a Perkin–Elmer Model 241 MC polarimeter. IR spectra were recorded with an IR-spectrum one (PE) spectrometer. ^{1}H NMR (600 MHz) and ^{13}C NMR (150 MHz) spectra were recorded with a Varian Unity INOVA 600 spectrometer in $CDCl_3$ by using TMS as an internal standard. Mass spectra were recorded with a Finnigan LCQ DUO MS system. Elemental analysis was determined with a Vario EL III (Germany) analyzer. Optical purity was estimated by HPLC (Chiracel OD-H; hexane/2-propanol, 70:30; flow rate 1.0 mL min^{-1}; ELSD PL-ELS2100).

3: To a solution of NCPS-supported oxazolidinone **2** (5.10 g, 12.29 mmol functional group) in dry THF (100 mL) was added NaH (0.32 g, 13.52 mmol) portionwise, and the mixture was stirred for 30 min at room temperature. Crotonyl chloride (1.4 mL, 14.96 mmol) was added dropwise to the mixture, and the solution was stirred for 5 h. The reaction mixture was quenched by the addition of H_2O (50 mL), and THF in the resulting mixture was then removed under reduced pressure. The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL), and the combined organic layer was washed with dilute HCl, aqueous saturated $NaHCO_3$, and brine and dried with $MgSO_4$. After filtration, most of the solvent was removed under reduced pressure. The viscous solution was dropped into cold ethanol (200 mL), and the precipitated solid was filtered, washed with cold ethanol, and dried to afford polymer **3** (5.54 g, 93.3%). IR (NaCl): $\tilde{\nu}$ = 1769, 1677, 1630, 1511, 1403, 820, 760, 700 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.65–6.25 (m, broad signal due to the polymer resonance), 4.98 (s, 2 H, OCH_2Ar), 4.75 (s, 1 H, CHN), 4.16 (s, 2 H, CH_2-OCO), 3.12 (s, 1 H, CH_2Ar), 2.78 (s, 1 H, CH_2Ar), 1.92 (s, 3 H, CH_3), 1.90–1.25 (m, broad signal due to the polymer resonance) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 164.9, 158.2, 153.5, 146.9, 145.1, 130.4, 127.9–127.6, 125.6, 121.8, 115.1, 66.1, 60.3, 55.3, 53.4, 50.8, 42.7, 40.3, 36.9, 18.5, 14.1 ppm. $C_{31}H_{31}NO_4$ (481.58): C 77.31, H 6.49, N 2.91; found C 77.35, H 6.46, N 2.89.

4: A three-necked flask was charged with a slurry of CuBr (2.24 g, 15.67 mmol) in THF (30 mL). Methyl sulfide (3.8 mL, 15.67 mmol) was then added to the flask under an atmosphere of argon. After being cooled to –78 °C, *n*-amylmagnesium bromide (15.67 mmol) in THF was added dropwise, followed by stirring for 10 min. Then, the solution of polymer **3** (5.0 g, 10.39 mmol functional group) in THF (10 mL) was slowly added, and the mixture was stirred at –78 °C for 1 h. The mixture was warmed up to –20 °C and kept at this temperature for 18 h. The reaction was quenched by the addition of saturated aqueous NH_4Cl (20 mL). After evaporation of the solvent, the aqueous layer was extracted with ethyl acetate, and the organic layer was washed with saturated aqueous NH_4Cl and brine and dried with $MgSO_4$. After filtration, the filtrate was concentrated. The obtained viscous solution was dropped into cold ethanol (100 mL), and the precipitated solid was filtered, washed with cold ethanol, and dried to afford polymer **4** (5.17 g, 90.0%). IR (NaCl): $\tilde{\nu}$ = 1784, 1698, 1631, 1512, 1402, 821, 758, 699 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.65–6.25 (m, broad signal due to the polymer resonance), 4.98 (s, 2 H, OCH_2Ar), 4.75 (s, 1 H,

CHN), 4.16 (s, 2 H, CH_2-OCO), 3.12 (s, 1 H, CH_2Ar), 2.81 (s, 1 H, CH_2Ar), 2.15 (s, 2 H, $COCH_2$), 1.90–1.25 (m, broad signal due to the polymer resonance), 0.98 (s, 6 H, $2CH_3$) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 164.9, 158.2, 153.5, 146.9, 145.1, 130.5, 127.9, 127.6, 115.1, 70.0, 67.9, 66.1, 55.3, 42.7, 40.3, 36.9, 25.6, 23.1, 18.6, 14.0 ppm. $C_{36}H_{43}NO_4$ (553.71): C 78.09, H 7.83, N 2.53, found C 78.12, H 7.79, N 2.51.

5: To a solution of polymer **4** (4.8 g, 8.67 mmol functional group) in THF (70 mL) was added dropwise a solution of $NaBH_4$ (0.50 g, 13.00 mmol) in ethanol (5 mL) at 0 °C. The ice bath was removed, and the mixture was stirred at room temperature for 2 h. The mixture was then recooled to 0 °C and dilute HCl was added carefully to quench the excess amount of $NaBH_4$. After evaporation of the solvent, the aqueous layer was extracted with ethyl ether, and the organic layer was washed with brine and dried with $MgSO_4$. After filtration, the filtrate was concentrated. The obtained viscous solution was dropped into cold ethanol (100 mL), and the precipitated solid was filtered and washed with cold ethanol to recover supported chiral auxiliary **2** (3.3 g, 91.6%). The combined filtrate was evaporated and purified by silica gel column chromatography (*n*-hexane/EtOAc, 6:1) to give **5** as a colorless oil (0.94 g, 75.2%). $[a]_D^{20}$ = +4.68 (*c* = 0.60, hexane), ref.[9b] $[a]_D^{19.5}$ = +4.78 (*c* = 0.62, hexane). IR (NaCl): $\tilde{\nu}$ = 3337, 2926, 1455, 1382, 1065 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ = 3.64–3.72 (t, 2 H, OCH_2), 1.12–1.62 (m, 11 H, CH_2, CH), 0.87–0.91 (m, 6 H, $2CH_3$) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 63.4, 36.9, 32.9, 32.6, 32.2, 30.3, 26.7, 22.7, 14.1 ppm. MS: *m*/*z* = 145.22 $[M + H]^+$.

6: To a solution of **5** (0.6 g, 4.16 mmol) in CH_2Cl_2 (20 mL) was added *p*-toluenesulfonyl chloride (0.95 g, 5.0 mmol) and Et_3N (0.68 mL, 5.0 mmol) at room temperature. After stirring at room temperature for 3.5 h, the mixture was poured into cold 1 M HCl. The resulting mixture was extracted with diethyl ether. The organic phase was washed with saturated aqueous $NaHCO_3$ and brine and dried with $MgSO_4$. After filtration, the filtrate was concentrated. Purification of the crude product by silica gel column chromatography (*n*-hexane/EtOAc, 8:1) gave colorless oil **6** (1.20 g, 96.5%). IR (NaCl): $\tilde{\nu}$ = 2985, 2865, 1601, 1350, 1175, 801 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ = 7.30–7.89 (m, Ar), 3.98–4.14 (m, 2 H, CH_2-Ar), 2.45 (s, 3 H, CH_2, CH), 0.93–1.56 (m, 11 H, CH_2), 0.77–0.93 (m, 6 H, CH_3) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 145.6, 139.8, 131.5, 130.8, 68.6, 37.2, 34.9, 33.2, 32.1, 30.4, 26.7, 24.5, 22.9, 14.3 ppm. MS: *m*/*z* = 299.28 $[M + H]^+$.

7: To a solution of **6** (1.0 g, 3.35 mmol) in dry dimethyl sulfoxide (20 mL) was added sodium cyanide (0.17 g, 3.69 mmol), and the mixture was stirred at 90 °C for 5 h. After evaporation of the solvent under reduced pressure, the residue was dissolved in CH_2Cl_2 (20 mL), and the resulting mixture was washed with dilute HCl, aqueous saturated $NaHCO_3$, and brine and then dried with $MgSO_4$. After filtration, the filtrate was concentrated to give crude **7** (0.43 g, 83.7%). IR (NaCl): $\tilde{\nu}$ = 2911, 2247, 1215, 796 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ = 2.26–2.42 (m, 2 H, CH_2-CN), 0.96–1.66 (m, 11 H, CH_2, CH), 0.70–0.94 (d, 6 H, CH_3) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 119.2, 37.6, 35.2, 32.8, 32.2, 30.5, 26.6, 24.5, 23.1, 15.3, 14.2 ppm. MS: *m*/*z* = 154.12 $[M + H]^+$.

8: To a stirred solution of NaOH (1.0 g, 25 mmol) in water (20 mL) and ethanol (5 mL) was added **7** (0.35 g, 2.29 mmol), and the mixture was stirred at 50 °C for 12 h. After evaporation of ethanol, the aqueous layer was acidified with concentrated HCl to pH 2 and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layer was washed with water and brine and dried with $MgSO_4$. After filtration, the filtrate was concentrated to give crude **8** (0.33 g, 83.9%). IR (NaCl): $\tilde{\nu}$ = 3520, 2911, 1711, 1420, 950, 720 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ = 2.27–2.45 (m, 2 H, CH_2-COO), 0.90–1.74 (m, 11 H, CH_2, CH), 0.81–0.90 (m, 6 H,CH_3) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 179.2, 37.2, 34.5, 32.2, 31.6, 30.9, 26.6, 22.5, 20.1, 14.2 ppm. MS: *m*/*z* = 173.18 $[M + H]^+$.

1: To a solution of **8** (0.24 g, 1.39 mmol) in dry THF (10 mL) was added a suspension of $LiAlH_4$ (0.064 g, 1.67 mmol) in dry THF (2 mL) over a period of 5 min at 0 °C. The ice bath was removed and the mixture was stirred at room temperature for 3 h. The mixture was then recooled to 0 °C and dilute HCl was added carefully to quench the excess amount of $LiAlH_4$. After evaporation of the solvent, the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL), and the organic layer was washed with brine and dried with $MgSO_4$. After filtration, the filtrate was concentrated. Purification of the crude product by silica gel column chromatography (*n*-hexane/EtOAc, 8:1) gave (*R*)-**1** as a colorless oil (0.19 g, 88.0%). $[a]_D^{20}$ = +1.58 (*c* = 0.72, $CHCl_3$), ref.[9b] $[a]_D^{18.5}$= +1.55 (*c* = 0.72, $CHCl_3$). IR (NaCl): $\tilde{\nu}$ = 3337, 2926, 1382, 1050 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ = 3.63 (m, 2 H, OCH_2), 2.18 (s, 1 H, OH), 1.24–1.62 (m, 12 H, CH_2, CH), 1.11–1.14 (d, 3 H, CH_3), 0.87 (m, 3 H, CH_3) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 63.4, 36.9, 32.9, 32.6, 32.1, 30.3, 26.7, 22.7, 20.3, 14.2 ppm. MS: *m*/*z* = 159.12 $[M + H]^+$.

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