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STEREOSELECTIVE SYNTHESIS OF THE SEX PHEROMONE OF THE YELLOW MEALWORM USING (*S*)-4-BENZYLOXAZOLIDINONE AS CHIRAL AUXILIARY

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*(*R*)-4-Methyl-1-nonanol, the sex pheromone of the yellow mealworm (*Tenebrio molitor *L.), was synthesized with high stereoselectivity using (*S*)-4-benzyloxazolidinone as chiral auxiliary. The stereoselective synthesis was achieved by asymmetric Michael addition of organocopper reagent to* N*-crotoyloxazolidinone, and the target product was obtained in an overall yield of 41.8% over 7 steps.*

Keywords: (*S*)-4-benzyloxazolidinone, chiral auxiliaries, Michael addition, synthesis, sex pheromone.

The yellow mealworm (*Tenebrio molitor* L.) is known to cause serious losses in stored cereal grains throughout the world. Effective, cost-efficient grain weevil management can be accomplished by monitoring pest populations with pheromone-baited insect traps and applying control methods only when pest densities reach economic thresholds. Its common sex pheromone was firstly identified by Tanaka et al as 4-methyl-nonan-1-ol (**1**) in 1984 [1]. Bioassays of the two possible stereoisomers of **1** revealed that the (*R*) isomer was the active form of the pheromone and the (*S*) isomer had minimum activity [2]. Since 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 [3–6].

The Michael addition reaction of organometallics is an important method for carbon–carbon bond formation in organic synthesis [7–9]. Organocopper reagents are among the most versatile reagents available for Michael addition reactions [10–13]. The addition of organocopper reagents to chiral alkenoate derivatives such as Evans′ oxazolidinone has provided high diastereoselectivities [14–16].

Recently, our group has undertaken a research program on the preparation of chiral auxiliaries [17–19] and their application to the synthesis of insect pheromones [20, 21]. In this paper, we have developed an efficient procedure to prepare the sex pheromone of the yellow mealworm (*R*)-**1** through a key step of stereoselective Michael addition using (*S*)-4-benzyl-oxazolidinone as chiral auxiliary (Scheme 1).

The synthesis of (*R*)-4-methyl-1-nonanol ((*R*)-**1**) was carried out as shown in Scheme 1, and the stereoselective Michael addition of organocopper reagent to *N*-crotonyloxazolidinone was the key step. Firstly, crotonoyl chloride reacted with (*S*)-4-benzyloxazolidinone **2** to give *N*-crotonyloxazolidinone **3** in 83.8% yield in the presence of NaH. Then the diastereoisomeric mixture of (*S*)-3-(3-methyloctanoyl)-4-benzyloxazolidinone was obtained via Michael addition of organocopper reagent to *N*-crotonyloxazolidinone **3** in 98% yield, which was analyzed by HPLC. The diastereoisomeric mixture was separated by silica gel column chromatography, and the (*R*) isomer **4**, (*S*)-3-((*R*)-3-methyloctanoyl)-4-benzyloxazolidinone, was obtained in 86.5% yield. Nondestructive removal of the auxiliary group of the (*R*) isomer **4** gave (*R*)-3-methyloctan-1-ol **5** in 81.6% yield. The (*R*)-**5** was subjected to further manipulation by four steps of reaction to get the sex pheromone of yellow mealworm (*R*)-**1**. In these reactions, the stereocenter of the compounds was not touched, and spectral data of (*R*)-**1** were in accord with the literature, as well as the specific rotation value [4].

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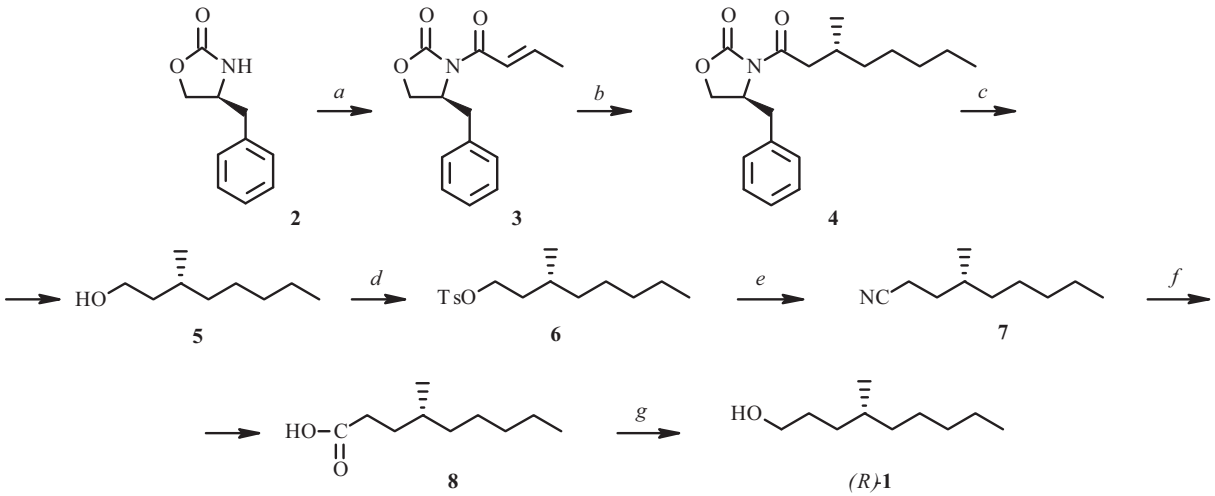

a. NaH/THF, crotonyl chloride; *b*. Me_2S/CuBr/THF, *n*-amylmagnesium bromide; *c*. $NaBH_4$/THF; *d*. TsCl/CH_2Cl_2; *e*. NaCN/DMF; *f*. NaOH/H_2O; *g*. $LiAlH_4$/THF

Scheme 1

In summary, an efficient synthesis (seven steps, 40.1% overall yield) of optically pure (*R*)-**1** was developed through a key step of stereoselective Michael addition using (*S*)-4-benzyloxazolidinone as chiral auxiliary. The method has the advantage of short routes, high yield, and high stereoselectivity.

EXPERIMENTAL

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). Melting points were measured on a WRS-1A digital melting point apparatus and uncorrected. Optical rotations were determined with a Perkin–Elmer Model 241 MC polarimeter. IR spectra were recorded on a PE Spectrum One spectrometer, ^{1}H NMR (600 MHz) and ^{13}C NMR (150 MHz) spectra were recorded on a Varian Unity INOVA 600 spectrometer in $CDCl_3$ using TMS as internal standard. Mass spectra were recorded on a Finnigan LCQ DUO MS system. The diastereoisomeric purity was determined by means of HPLC (Dionex, Ultimate 3000 pump) using solid-phase extraction in reversed phase mode (C8 phase) (70:30 water–methanol, 1 mL/min, 254 nm).

(*S*)-3-((*E*)-But-2-enoyl)-4-benzyloxazolidinone (3). To a solution of the (*S*)-4-benzyloxazolidinone (**2**) (5.0 g, 28.22 mmol) in dry THF (70 mL) was added NaH (0.35 g, 31.04 mmol) portionwise, and the mixture was stirred for 30 min at room temperature. Crotonyl chloride (1.7 mL, 33.86 mmol) was added dropwise to the mixture, and the solution was stirred for 5 h. The reaction mixture was quenched with H_2O (50 mL), and then THF in the resulting mixture was removed under reduced pressure. The aqueous layer was extracted with CH_2Cl_2 (50 mL × 3), and the organic layers were combined, washed with dilute HCl, aqueous saturated $NaHCO_3$, and brine, dried over $MgSO_4$, and concentrated. Purification of the crude product by silica gel column chromatography (*n*-hexane–EtOAc, 8:1, v/v) gave a white solid **3** (5.8 g, 83.8%). $[\alpha]_D^{20}$ +75.3° (*c* 2.00, $CHCl_3$), lit. [22] $[\alpha]_D^{20}$ +77.9° (*c* 2.00, $CHCl_3$), mp 84.8–85.1°C, lit. [22] 85.0–86.0°C. IR (NaCl, ν, cm^{-1}): 2953, 2914, 2847, 1769, 1677, 1630. ^{1}H NMR ($CDCl_3$, δ, ppm, J/Hz): 7.22–7.35 (7H, m, Ar-H, CH=CH), 4.7 (1H, m, CH), 4.19 (2H, m, OCH_2), 3.33 (1H, dd, J_1 = 3, J_2 = 13.2, $PhCH_2$), 2.80 (1H, dd, J_1 = 9.6, J_2 = 13.2, $PhCH_2$), 1.99 (3H, t, J_1 = 0.6, J_2 = 5.4, CH_3). ^{13}C NMR ($CDCl_3$, δ): 164.9, 153.4, 147.0, 135.3, 129.4, 128.9, 127.2, 121.7, 66.0, 55.2, 37.8, 18.6. MS *m/z*: 246.12 $[M + H]^+$.

(*S*)-3-((*R*)-3-Methyloctanoyl)-4-benzyloxazolidinone (4). A three-necked flask was charged with a slurry of CuBr (4.39 g, 30.71 mmol) in ether (10 mL), and methyl sulfide (7.4 mL, 30.71 mmol) was added under argon. After cooling to –78°C, *n*-amylmagnesium bromide (30.71 mmol) in ether (10 mL) was added dropwise, followed by stirring for 10 min. Then a solution of **3** (5.0 g, 20.39 mmol) in ether (50 mL) was slowly added, and the mixture was stirred at –78°C for 1 h. The mixture was warmed up to –20°C, and stirring was kept at –20°C for 18 h. The reaction was quenched by saturated aqueous NH_4Cl (20 mL). After evaporation of the solvent, the aqueous layer was extracted by ethyl acetate, and the organic layer was

washed with saturated aqueous NH_4Cl, brine, dried over $MgSO_4$, filtered, and concentrated. Purification of the crude product by silica gel column chromatography (*n*-hexane–EtOAc, 16:1, v/v) gave a colorless oil **4** (5.6 g, 86.5%). IR (NaCl, ν, cm^{-1}): 2925, 1784, 1698, 1631. ^1H NMR ($CDCl_3$, δ, ppm): 7.21–7.34 (5H, m, ArH), 4.69–4.67 (1H, m, NCH), 3.32–3.05 (1H, m, CHAr), 2.99–2.96 (1H, m, CHAr), 2.90–2.70 (2H, d, CH_2), 2.09–2.05 (1H, m, CH), 1.19–1.39 (8H, m, $4CH_2$), 1.01–0.96 (3H, d, CH_3), 0.87–0.90 (3H, t, CH_3). ^{13}C NMR ($CDCl_3$, δ): 172.8, 153.4, 135.3, 129.4, 128.9, 127.3, 66.0, 55.2, 42.5, 37.9, 36.4, 29.5, 29.1, 22.8, 19.7, 14.06. MS *m*/*z*: 318.25 $[M + H]^+$.

(*R*)-3-Methyloctan-1-ol (5). To a solution of **4** (4.1 g, 13.0 mmol) in THF (80 mL) was added dropwise a solution of $NaBH_4$ (0.75 g, 19.5 mmol) in ethanol (10 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 hydride reagent. After evaporation of the solvent, the aqueous layer was extracted with ethyl ether, and the organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated. Purification of the crude product by silica gel column chromatography (*n*-hexane–EtOAc, 6:1, v/v) gave **5** as a colorless oil (1.52 g, 81.6%). $[\alpha]_D^{20}$ +4.68° (*c* 0.60, hexene), lit. [4] $[\alpha]_D^{19.5}$ +4.78° (*c* 0.62, hexene). IR (NaCl, ν, cm^{-1}): 3337, 2926, 1455, 1382, 1065. ^1H NMR ($CDCl_3$, δ, ppm): 3.64–3.72 (2H, t, OCH_2), 1.12–1.62 (11H, m, CH_2, CH), 0.87–0.91 (6H, m, $2CH_3$). ^{13}C NMR ($CDCl_3$, δ): 63.4, 36.9, 32.9, 32.6, 32.2, 30.3, 26.7, 22.7, 14.1. MS *m*/*z*: 145.22 $[M + H]^+$.

(*R*)-3-Methyloctyl-4-methylbenzenesulfonate (6). To a solution of **5** (1.2 g, 8.32 mmol) in CH_2Cl_2 (30 mL) was added *p*-toluenesulfonate (1.9 g, 10.0 mmol) and Et_3N (1.36 mL, 10.0 mmol). 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, dried with $MgSO_4$, and concentrated. Purification of the crude product by silica gel column chromatography (*n*-hexane–EtOAc, 8:1, v/v) gave a colorless oil **6** (2.4 g, 96.5%). $[\alpha]_D^{20}$ +3.95° (*c* 0.72, MeOH). lit. [23] $[\alpha]_D^{19.5}$ +4.00° (*c* 0.72, MeOH). IR (NaCl, ν, cm^{-1}): 2985, 2865, 1601, 1350, 1175, 801. ^1H NMR ($CDCl_3$, δ, ppm): 7.30–7.89 (m, Ar), 3.98–4.14 (2H, m, CH_2-Ar), 2.45 (3H, s, CH_2, CH), 0.93–1.56 (11H, m, CH_2), 0.77–0.93 (6H, m, CH_3). ^{13}C NMR ($CDCl_3$, 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. MS *m*/*z*: 299.28 $[M + H]^+$.

(*R*)-4-Methylnonanenitrile (7). To a solution of **6** (2.0 g, 6.70 mmol) in dry dimethyl sulfoxide (40 mL) was added sodium cyanide (0.34 g, 7.38 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 (50 mL), and the resulting mixture was washed with dilute HCl, aqueous saturated $NaHCO_3$, and brine, dried over $MgSO_4$, filtered, and concentrated to give a colorless oil **7** (0.86 g, 83.7%). $[\alpha]_D^{20}$ +5.65° (*c* 0.93, Et_2O). lit. [23] $[\alpha]_D^{19.5}$ +5.76° (*c* 0.93, Et_2O). IR (NaCl, ν, cm^{-1}): 2911, 2247, 1215, 796. ^1H NMR ($CDCl_3$, δ, ppm, J/Hz): 2.26–2.42 (2H, m, CH_2-CN), 0.96–1.66 (11H, m, CH_2, CH), 0.70–0.94 (6H, d, J = 3.6, CH_3). ^{13}C NMR ($CDCl_3$, δ): 119.2, 37.6, 35.2, 32.8, 32.2, 30.5, 26.6, 24.5, 23.1, 15.3, 14.2. MS *m*/*z*: 154.12 $[M + H]^+$.

(*R*)-4-Methylnonanoic Acid (8). To a stirred solution of NaOH (2.0 g, 50 mmol) in water (40 mL) and ethanol (10 mL) was added **7** (0.70 g, 4.58 mmol), and the mixture was stirred at 50°C for 12 h. After evaporation of ethanol, the aqueous layer was acidified with conc. HCl to pH 2 and extracted with CH_2Cl_2 (50 mL × 3). The combined organic layer was washed with water and brine, dried over $MgSO_4$, filtered, and concentrated to give a colorless oil **8** (0.66 g, 83.9%). $[\alpha]_D^{20}$ +0.92° (*c* 0.79, Et_2O). lit. [23] $[\alpha]_D^{19.5}$ +0.96° (*c* 0.79, Et_2O). IR (NaCl, ν, cm^{-1}): 3520, 2911, 1711, 1420, 950, 720. ^1H NMR ($CDCl_3$, δ, ppm): 2.27–2.45 (2H, m, CH_2-COO), 0.90–1.74 (11H, m, CH_2, CH), 0.81–0.90 (6H, m, CH_3). ^{13}C NMR ($CDCl_3$, δ): 179.2, 37.2, 34.5, 32.2, 31.6, 30.9, 26.6, 22.5, 20.1, 14.2. MS *m*/*z*: 173.18 $[M + H]^+$.

(*R*)-4-Methylnonan-1-ol (1). To a solution of **8** (0.48 g, 2.78 mmol) in dry THF (20 mL) was added a suspension of $LiAlH_4$ (0.13 g, 3.34 mmol) in dry THF (5 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 hydride reagent. After evaporation of the solvent, the aqueous layer was extracted with CH_2Cl_2 (20 mL × 3), and the organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated. Purification of the crude product by silica gel column chromatography (*n*-hexane–EtOAc, 8:1, v/v) gave the compound (*R*)-**1** as a colorless oil (0.38 g, 88.0%). $[\alpha]_D^{20}$ +1.58° (*c* 0.72, $CHCl_3$), lit. [4] $[\alpha]_D^{18.5}$ +1.55° (*c* 0.72, $CHCl_3$). IR (NaCl, ν, cm^{-1}): 3337, 2926, 1382, 1050. ^1H NMR ($CDCl_3$, δ, ppm, J/Hz): 3.63 (2H, m, OCH_2), 2.18 (1H, s, OH), 1.24–1.62 (12H, m, CH_2, CH), 1.11–1.14 (3H, d, J = 5.7, CH_3), 0.87 (3H, m, CH_3). ^{13}C NMR ($CDCl_3$, δ): 63.4, 36.9, 32.9, 32.6, 32.1, 30.3, 26.7, 22.7, 20.3, 14.2. MS *m*/*z*: 159.12 $[M + H]^+$.

REFERENCES

1. Y. Tanaka, H. Honda, K. Ohsawa, and I. Yamamoto, *Nippon Noyaku Gakkaishi*, **11**, 49 (1986).
2. Y. Tanaka, H. Honda, K. Ohsawa, and I. Yamamoto, *Nippon Noyaku Gakkaishi*, **14**, 197 (1989).
3. V. N. Odinokov, G. Y. Ishmuratov, M. P. Yakovleva, R. R. Musiukhov, R. L. Safiullin, A. N. Volgarev, V. D. Komissarov, and G. A. Tolstikov, *Dokl. Akad. Nauk*, **326**, 842 (1992).
4. T. Kitahara and S. H. Kang, *Proc. Jpn. Acad., Ser. B,* **70**, 181 (1994).
5. G. Y. Ismuratov, M. P. Yakovleva, A. V. Galyautdinova, and G. A. Tolstikov, *Chem. Nat. Comp.*, **39**, 31 (2003).
6. A. Baeza, C. Najera, and J. M. Sansano, *Eur. J. Org. Chem.*, 1101 (2007).
7. H. Suga, T. Kitamura, A. Kakehi, and T. Baba, *Chem. Commun.,* 1414 (2002).
8. H. Kitajima, L. Katsuji, and T. Katsuki, *Tetrahedron*, **53**, 17015 (1997).
9. N. Krause and A. Hoffmann-Roeder, *Synthesis*, 171 (2001).
10. E. Nakamura and S. Mori, *Angew. Chem., Int. Ed*., **39,** 3750 (2000).
11. P. Pollock, J. Dambacher, R. Anness, and M. Bergdahl, *Tetrahedron Lett.,* **43**, 3693 (2002).
12. J. Dambacher, R. Anness, P. Pollock, and M. Bergdahl, *Tetrahedron*, **60**, 2097 (2004).
13. N. Maezaki, H. Sawamoto, T. Suzuki, R. Yoshigami, and T. Tanaka, *J. Org. Chem.*, **69**, 8387 (2004).
14. L. Perez, S. Bernes, L. Quinteroa, and C. A. Parrodib, *Tetrahedron Lett.*, **46**, 8649 (2005).
15. S. Liao, Y. Han, W. Qiu, M. Bruck, and V. J. Hruby, *Tetrahedron Lett.*, **37**, 7917 (1996).
16. P. Wipf and H. Takahashi, *Chem. Commun.*, 2675 (1996).
17. J. H. Yang, C. F. Lu, Z. X. Chen, and G. C. Yang, *Acta Crystallogr., Sect. E,* **64**, O228 (2008).
18. Y. D. Wan, Z. X. Chen, and G. C. Yang, *Chin. J. Org. Chem.*, **25**, 1039 (2005).
19. Y. D. Wan, Z. X. Chen, G. C. Yang, and C. F. Lu, *Faming Zhuanli Shenqing Gongkai Shuomingshu,* CN ZL 200610019140.9.
20. F. Y. Zhou, D. L. Li, G. S. Zhang, and Z. X. Chen, *Hubei Daxue Xuebao, Ziran Kexueban*, **30,** 56 (2008).
21. C. F. Lu, J. Q. Nie, G. C. Yang, and Z. X. Chen, *Can. J. Chem.*, **87**, 30 (2009).
22. D. A. Evans, K. T. Chapman, and J. Bisaha, *J. Am. Chem. Soc.,* **110**, 1238 (1988).
23. T. Kitahara and S.-H. Kang, *Proc. Jpn. Acad., Ser. B*, **70** (10), 181 (1994).