Tetrahedron: *Asymmetry* 20 (2009) 2267–2269

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

Stereoselective synthesis of (*R*)-10-methyltridecan-2-one, the sex pheromone of the southern corn rootworm, using (4*S*)-benzylthiazolidinethione as a chiral auxiliary

Cui-Fen Lu, Shou-Bo Zhang, Yan Li, Gui-Chun Yang, Zu-Xing Chen *

Ministry-of-Education Key Laboratory for the Synthesis and Application of Organic Functional Molecules and School of Chemistry and Chemical Engineering, Hubei University, Wuhan 430062, China

ARTICLE INFO

Article history:
Received 27 July 2009
Accepted 9 September 2009
Available online 14 October 2009

ABSTRACT

The stereoselective synthesis of (*R*)-10-methyltridecan-2-one, the sex pheromone of the southern corn rootworm, was carried out in 20.7% overall yield based on (4*S*)-benzylthiazolidinethione (five steps). In the crucial step, the stereogenic center was generated by an asymmetric Michael addition using enantiomerically pure (4*S*)-benzylthiazolidinethione as a chiral auxiliary.

1. Introduction

Chiral auxiliary-mediated asymmetric Michael addition reactions have been studied extensively and are now an important and general method for asymmetric carbon–carbon bond formation.[1] Organocopper reagents are amongst the most versatile reagents available for Michael addition reactions.[2] The addition of organocopper reagents to chiral alkenoate derivatives such as Evans' oxazolidinone has provided high diastereoselectivities.[3] Using thiazolidinethiones would be advantageous as they are more easily cleavable auxiliaries when compared to oxazolidinones or oxazolidinethiones.[4] Compared with the very popular oxazolidinones, thiazolidinethiones appear to be more efficient in aldol-type reactions. The aldol adducts of acylthiazolidinethiones are easily removed and can be directly converted to aldehydes as well as to other functional groups. In our previous research, we investigated the asymmetric Michael addition of organocopper reagents to acyloxazolidinones;[5] herein, we report Michael additions mediated by an acylthiazolidinethione.

(*R*)-10-Methyltridecan-2-one has been identified as the sex pheromone secreted by virgin females of the southern corn root worm.[6] Since effective and cost-efficient control of the insect populations can be foreseen with the aid of the sex pheromone, several total syntheses of the racemate and the (*R*)-enantiomer have been published.[7]

Recently, our group has undertaken a research program on the investigation of chiral auxiliaries and their application to synthesize the insect pheromones.[5,8] Herein, we have developed an efficient procedure to synthesize stereoselectively (*R*)-10-methyltridecan-2-one **1** through the key step of a Michael addition reaction using enantiomerically pure (4*S*)-benzylthiazolidinethione as a chiral auxiliary.

2. Results and discussion

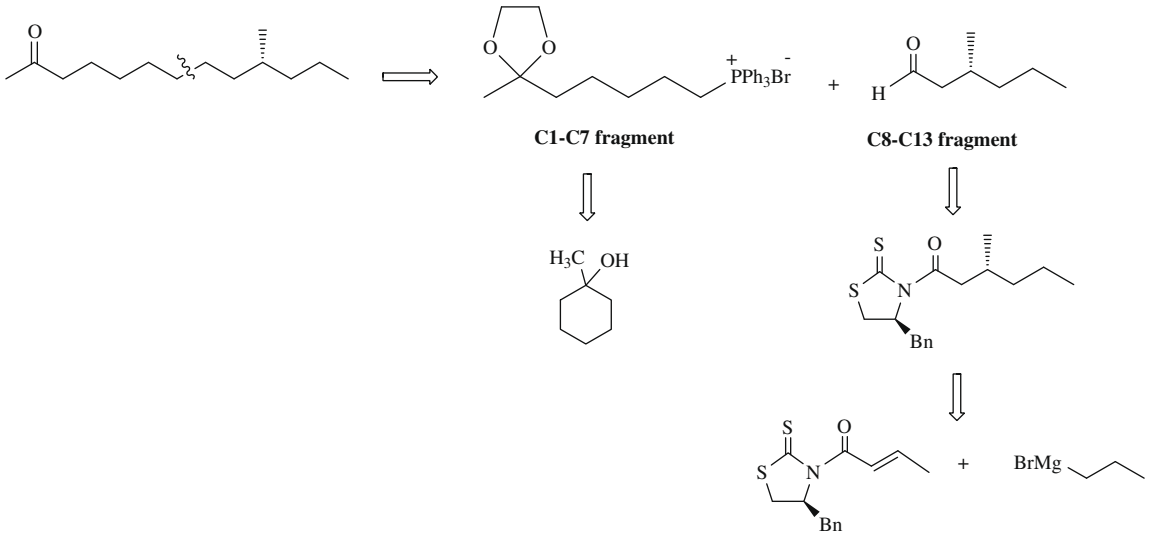
Our synthetic strategy is shown by the retrosynthetic analysis as outlined in Scheme 1. The target molecule can be divided into two fragments, the C1–C7 fragment, containing a ketone unit, and the C8–C13 fragment, containing a stereogenic center. The C1–C7 fragment can be prepared from 1-methylcyclohexanol according to the literature procedures.[9,7d,7f] For the synthesis of the C8–C13 fragment, we describe an efficient, scalable, and economical second-generation synthesis, utilizing a thiazolidinethione chiral auxiliary to control the stereochemistry at C10 by means of a key stereoselective Michael addition reaction.

The stereoselective synthesis of the C8–C13 fragment was carried out as shown in Scheme 2. The starting (4*S*)-benzylthiazolidinethione **3** was treated with crotonoyl chloride to give *N*-crotonyl (4*S*)-benzylthiazolidinethione **4** in 95.6% yield in the presence of Et_3N with DMAP as a catalyst. The Michael addition of the organocopper reagent to **4** afforded the product **5** in 91.3% yield after purification (de = 92% for the crude product). Non-destructive removal of the auxiliary group of **5** via the selective reduction with $(i\text{-}Bu)_2AlH$ gave (*R*)-3-methylhexanal **6** in 82.2% yield along with the recovery of **3** (92.6% yield).

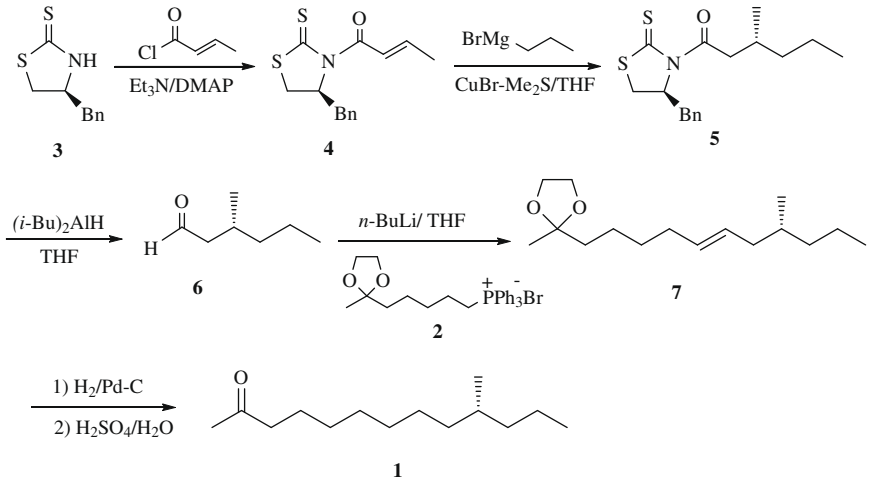
As illustrated in Scheme 2, (*R*)-3-methylhexanal **6** was subjected to a Wittig reaction with the phosphonium bromide **2** to yield olefin **7**. Catalytic hydrogenation of **7** with palladium on charcoal in methanol under hydrogen followed by hydrolysis under acidic conditions afforded (*R*)-10-methyltridecan-2-one **1** in 68.4% yield. Over the course of the synthesis, the stereocenter of the compounds was not touched and the spectroscopic data of **1** as well as its specific rotation values were in accordance with the literature.[7]

* Corresponding author. Tel.: +86 27 50865322; fax: +86 27 88663043.
E-mail address: chzux@hubu.edu.cn (Z.-X. Chen).

0957-4166/$ - see front matter
doi:10.1016/j.tetasy.2009.09.014



Scheme 1.



Scheme 2.

3. Conclusion

In conclusion, we have reported an effective procedure for the stereoselective synthesis of the sex pheromone (*R*)-10-methyltridecan-2-one **1** of the southern corn rootworm using enantiomerically pure (4*S*)-benzylthiazolidinethione as a chiral auxiliary. The key step in our approach was the regio- and stereocontrolled Michael addition reaction of an organocopper reagent to *N*-crotonyl (4*S*)-benzylthiazolidinethione **4**. All of the steps proceeded with excellent yields and full preservation of chirality, with **1** being obtained in 20.7% overall yield based on **3**. Further application of this methodology to the syntheses of other biologically active compounds is currently underway in our laboratory.

4. Experimental

4.1. General

All solvents were obtained from commercial sources and dried or purified by standard procedures before use. Separations by flash chromatography were performed on 300–400 mesh silica gel. Melting points were measured on a WRS-1A digital melting point apparatus and are uncorrected. Optical rotations were measured using a sodium D line on WZZ-2B Automatic Polarimeter. HPLC analyses were carried out on a Dionex chromatograph (Ultimate3000 pump, C8 reversed-phase chromatographic column) equipped with a diode-array UV detector. Mass spectra were recorded on Finnigan LCQ DUO MS system. IR spectra were recorded on an IR-spectrum one (PE) spectrometer. NMR spectra were recorded on Varian Unity Inova 600 spectrometer in $CDCl_3$ (^1H at 600 MHz and ^{13}C at 150 MHz) using TMS as the internal standard.

4.2. (*S*)-3-((*E*)-But-2-enoyl)-4-benzylthiazolidinethione 4

To a solution of (4*S*)-benzylthiazolidinethione **3** (5.0 g, 23.9 mmol), DMAP (0.58 g, 4.7 mmol), and Et_3N (3.8 mL, 27.2 mmol) in dry CH_2Cl_2 (100 mL) was added crotonyl chloride (2.8 mL, 29.2 mmol) dropwise and the solution was allowed to stir at rt for 2 h. The reaction was quenched with saturated aqueous NH_4Cl (10 mL), and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (25 mL × 3) and the organic layers were combined, washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated. The crude product was recrystallized from petroleum ether to give a yellow solid **4** (6.3 g, 95.6%). Mp 76.7–

77.5 °C; $[\alpha]_D^{25} = +97.8$ (*c* 0.9, $CHCl_3$); IR (NaCl, cm^{-1}): ν_{max} 3026, 1679, 1634; ^1H NMR (600 MHz, $CDCl_3$): δ 1.96 (dd, *J* = 1.5, 7.2 Hz, 3H), 2.92 (d, *J* = 11.4 Hz, 1H), 3.06 (dd, *J* = 10.8, 13.2 Hz, 1H), 3.34 (dd, *J* = 3.6, 13.2 Hz, 1H), 3.40 (dd, *J* = 9.6, 11.4 Hz, 1H), 5.18–5.21 (m, 1H), 7.05 (dq, *J* = 7.2, 15.0 Hz, 1H), 7.25–7.35 (m, 6H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 201.08, 166.34, 145.11, 136.62, 129.47, 128.91, 127.18, 124.55, 68.93, 36.68, 31.47, 18.52. MS: *m*/*z* = 278.10 ($M+H^+$).

4.3. (*S*)-3-((*R*)-3-Methylpropyl)-4-benzylthiazolidinethione 5

A three-necked flask was charged with a slurry of CuBr (8.2 g, 56.7 mmol) in ether (10 mL) and dimethyl sulfide (4.1 mL, 17.0 mmol) was added under argon. After cooling to −78 °C, *n*-propylmagnesium bromide (43.2 mmol) in ether (10 mL) was added dropwise to the mixture, followed by stirring for 10 min. Then a solution of **4** (6.0 g, 21.6 mmol) in THF (50 mL) was slowly added, and the mixture was stirred at −78 °C for 3 h. The mixture was warmed up to −20 °C and was kept stirring at −20 °C for 18 h. The reaction was quenched with saturated aqueous NH_4Cl (20 mL). After evaporation of the solvent, the aqueous layer was extracted with ethyl acetate. The organic layer was washed with saturated aqueous NH_4Cl, brine, dried over $MgSO_4$, and the solvent was removed in vacuo to afford a crude product as a mixture of diastereomers (92:8). Purification of the crude product by silica gel column chromatography (*n*-hexane/EtOAc, 16:1, V/V) gave a colorless oil **5** (6.3 g, 91.3%). $[\alpha]_D^{25} = +116.3$ (*c* 1.1, $CHCl_3$); IR (NaCl, cm^{-1}): ν_{max} 3021, 1692, 701; ^1H NMR (600 MHz, $CDCl_3$): δ 0.84–0.98 (m, 6H), 1.22–1.61 (m, 4H), 2.12 (s, 1H), 2.88 (dd, *J* = 4.2, 11.4 Hz, 2H), 3.02–3.07 (m, 2H), 3.22–3.39 (m, 2H), 5.34–5.38 (m, 1H), 7.26–7.35 (m, 5H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 201.04, 173.57, 136.56, 129.41, 128.84, 127.14, 68.65, 45.48, 39.01, 36.74, 31.89, 29.63, 20.02, 19.72, 14.23. MS: *m*/*z* = 322.15 ($M+H^+$).

4.4. (*R*)-3-Methylhexanal 6

To a solution of **5** (6.0 g, 18.7 mmol) in CH_2Cl_2 (15 mL) was added dropwise a solution of DIBALH (37.4 mL, 1 M in hexane) at −78 °C under argon and the mixture was stirred for 20 min. Then to the mixture was added saturated aqueous NH_4Cl (10 mL) and the mixture was warmed up to rt. After stirring for 20 min, the precipitated solid was filtered, and the filtrate was extracted with CH_2Cl_2 (15 mL × 3). The combined 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 **6** as a colorless oil (1.7 g, 82.2%). IR (NaCl, cm^{-1}): ν_{max} 3151, 1710; ^1H NMR (600 MHz, $CDCl_3$): δ 0.78–0.97 (m, 6H), 1.10–1.57 (m, 5H), 2.12–2.23 (m, 2H), 9.76 (d, *J* = 1.8 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 203.29, 51.01, 39.07, 27.83, 19.98, 19.93, 14.07. MS: *m*/*z* = 115.12 ($M+H^+$).

4.5. 2-Methyl-2-((*R*,*E*)-8-methylundec-5-enyl)-1,3-dioxolane 7

To a solution of **2** (3.0 g, 6.0 mmol) in dry THF (15 mL) was added *n*-BuLi in hexane (32 mL, 2.5 M) dropwise at 0 °C under argon and the mixture was stirred at 0 °C for 2 h. After cooling to −78 °C, a solution of **6** (0.7 g, 6.0 mmol) in dry THF (10 mL) was added dropwise, and the mixture was stirred at −78 °C for 1 h and then warmed up to rt. The stirring was continued for 2 h. The reaction was quenched with 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, 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 **7** (1.1 g, 72.6%). IR (NaCl, cm^{-1}): ν_{max} 3350, 3052; ^1H NMR (600 MHz, $CDCl_3$): δ 0.89–0.99 (m, 6H), 1.25 (s, 3H), 1.29–1.41 (m, 10H), 1.65 (m, 1H), 2.02–2.18 (m, 4H), 3.81–3.90 (m, 4H), 5.3 (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 131.24, 111.56, 65.68, 42.45, 40.18, 39.22, 37.52, 35.29, 32.11, 25.44, 22.75, 21.03, 15.15. MS: *m*/*z* = 255.25 ($M+H^+$).

4.6. (*R*)-10-Methyltridecan-2-one 1

To a solution of **7** (1.0 g, 3.9 mmol) in MeOH (15 mL) was added a catalytic amount of 10% Pd/C. The reaction mixture was stirred at rt under hydrogen for 2 h, then filtered through Celite, and the filtrate was concentrated under reduced pressure. The residue was dissolved in acetone (10 mL), after which 10% aqueous H_2SO_4 (2 mL) was added, and the mixture was stirred at rt for 1.5 h. After evaporation of the solvent, the residue was extracted with ether, and the organic layer was washed with saturated aqueous $NaHCO_3$, brine, dried over $MgSO_4$, filtered, and concentrated. Purification of the crude product by silica gel column chromatography (*n*-hexane/EtOAc, 14:1, V/V) gave a colorless oil **1** (0.5 g, 68.4%). $[\alpha]_D^{22} = -1.6$ (*c* 0.9, $CHCl_3$); {lit.[7d] $[\alpha]_D^{24} = -1.6$ (*c* 4.1, $CHCl_3$)} IR (NaCl, cm^{-1}): ν_{max} 1718; ^1H NMR (600 MHz, $CDCl_3$): δ 0.86–0.94 (m, 3H), 1.24–1.30 (m, 9H), 1.48–1.93 (m, 11H), 2.18 (s, 3H), 2.56 (t, *J* = 7.5 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 208.97, 43.56, 39.46, 37.35, 32.51, 29.86, 29.65, 29.33, 29.17, 27.21, 23.52, 20.62, 19.64, 14.96.

Acknowledgments

We gratefully acknowledge the National Natural Sciences Foundation of China (No. 20772026) and the Natural Sciences Foundation of Hubei province in China (No. 2008CDA078) for financial support.

References

1. (a) Suga, H.; Kitamura, T.; Kakehi, A.; Baba, T. *Chem. Commun.* **2002**, 1414–1415; (b) Kitajima, H.; Ito, K.; Katsuki, T. *Tetrahedron* **1997**, *53*, 17015–17028; (c) Krause, N.; Hoffmann-Roeder, A. *Synthesis* **2001**, 171–196.
2. (a) Nakamura, E.; Mori, S. *Angew. Chem., Int. Ed.* **2000**, *39*, 3750–3771; (b) Pollock, P.; Dambacher, J.; Anness, R.; Bergdahl, M. *Tetrahedron Lett.* **2002**, *43*, 3693–3697; (c) Dambacher, J.; Anness, R.; Pollock, P.; Bergdahl, M. *Tetrahedron* **2004**, *60*, 2097–2110; (d) Maezaki, N.; Sawamoto, H.; Suzuki, T.; Yoshigami, R.; Tanaka, T. *J. Org. Chem.* **2004**, *69*, 8387–8393.
3. (a) Pérez, L.; Bernès, S.; Quinteroa, L.; Parrodib, C. A. *Tetrahedron Lett.* **2005**, *46*, 8649–8652; (b) Liao, S.; Han, Y.; Qiu, W.; Bruck, M.; Hruby, V. J. *Tetrahedron Lett.* **1996**, *37*, 7917–7920; (c) Wipf, P.; Takahashi, H. *Chem. Commun.* **1996**, 2675–2676.
4. (a) Crimmins, M. T.; Chaudhary, K. *Org. Lett.* **2000**, *2*, 775–777; (b) Crimmins, M. T.; Caussanel, F. *J. Am. Chem. Soc.* **2006**, *128*, 3128–3129; (c) Crimmins, M. T.; Slade, D. J. *Org. Lett.* **2006**, *8*, 2192–2194.
5. Lu, C. F.; Li, D. L.; Wang, Q. Y.; Yang, G. C.; Chen, Z. X. *Eur. J. Org. Chem.* **2009**, 1078–1081.
6. Guss, P. L.; Tumlinson, J. H.; Sonnet, P. E.; McLaughlin, J. R. *J. Chem. Ecol.* **1983**, *9*, 1363–1375.
7. (a) Sharma, A.; Pawar, A.; Chattopadhyay, S.; Mamdapur, V. R. *Org. Prep. Proced. Int.* **1993**, *25*, 330–333; (b) Sonnet, P. E. *J. Org. Chem.* **1982**, *47*, 3793–3796; (c) Senda, S.; Mori, K. *Agric. Biol. Chem.* **1983**, *47*, 795–798; (d) Oppolzer, W.; Dudfield, P.; Stevenson, T.; Godel, T. *Helv. Chim. Acta* **1985**, *68*, 212–215; (e) Rossi, R.; Carpita, A.; Chini, M. *Tetrahedron* **1985**, *41*, 627–633; (f) Enders, D.; Jandeleit, B. *Liebigs Ann.* **1995**, 1173–1176; (g) Chow, S.; Kitching, W. *Tetrahedron: Asymmetry* **2002**, *13*, 779–793.
8. (a) Yang, J. H.; Yang, G. C.; Lu, C. F.; Chen, Z. X. *Tetrahedron: Asymmetry* **2008**, *19*, 2164–2166; (b) Lu, C. F.; Nie, J. Q.; Yang, G. C.; Chen, Z. X. *Can. J. Chem.* **2009**, *87*, 30–32; (c) Zhou, F. Y.; Li, D. L.; Zhang, G. S.; Chen, Z. X. *Hubei Daxue Xuebao, Ziran Kexueban* **2008**, *30*, 56–58.
9. Zhang, W. C.; Li, C. J. *J. Org. Chem.* **2005**, *65*, 5831–5833.