Tetrahedron Letters 51 (2010) 5291–5293

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Enantiospecific synthesis of sex pheromone of the obscure mealybug from pantolactone via tandem conjugate addition/cyclization

Atul K. Hajare, Laxmikant S. Datrange, Samir Vyas, Debnath Bhuniya, D. Srinivasa Reddy *

Discovery Chemistry, Advinus Therapeutics Pvt. Ltd, Quantum Towers, Plot No. 9, Rajiv Gandhi Infotech Park, Phase-I, Hinjewadi, Pune 411057, India

ARTICLE INFO

Article history:
Received 29 June 2010
Revised 27 July 2010
Accepted 29 July 2010
Available online 5 August 2010

Keywords:
Pheromone
Enantiospecific synthesis
Tandem reaction
Pantolactone

ABSTRACT

An efficient synthesis of an enantiomer of insect's natural pheromone is reported starting from chiral pool D-(−)-pantolactone. Highly stereoselective tandem conjugate addition/cyclization sequence and hydrogenation of exocyclic double bond are the key steps in the present synthesis.

Synthesis of pheromones is an important and exciting area in organic chemistry which helps in establishing their stereochemical assignments. The synthesis also provides sufficient quantities to carry out extensive biological tests, as pheromones are available in limited quantities from nature (usually in microgram). While constructing such low molecular weight pheromones, several stereoselective methods have been reported in the literature.[1] Recently, pioneering work from Millar's group led to the identification,[2] the diastereoselective racemic synthesis,[3] and the determination of absolute configuration using vibrational circular dichroism (VCD)[4] of 1*S*,2*S*,3*R*-1-acetoxymethyl-2,3,4,4-tetramethylcyclopentane (+)-**1** (Fig. 1). This powerful sex pheromone (+)-**1** was isolated from the female mealybug, *Pseudococcus viburni* (Homoptera: Pseudoccidae), a common and widely distributed pest that damages a range of economically important plants like grape vines, glasshouse crops, and ornamental plants. Soon after Millar's synthesis, the first and unique enantioselective synthesis of (+)-**1** was reported by Kuwahara's group.[5] The interesting chemical structure of **1** and its potential use in pest management prompted our efforts toward its synthesis. Herein, we disclose the first enantiospecific synthesis of (−)-**1** starting from an inexpensive and commercially available D-(−)-pantolactone.[6]

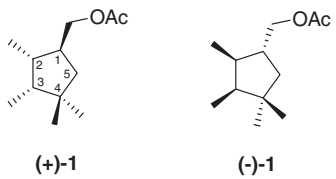
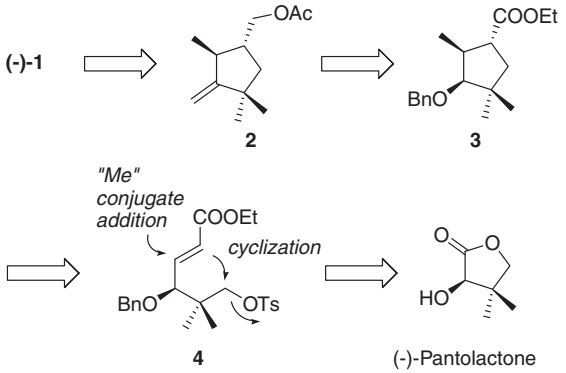


Figure 1. Structures of both enantiomers of sex pheromone.

We set out to synthesize the sex pheromone (−)-**1** as a means of developing chemistry that might be useful for more complex natural products. Retrosynthetically, the pheromone (−)-**1** could be prepared from the final precursor **2** through stereoselective hydrogenation of the exocyclic double bond which in turn can be obtained from **3**. The intermediate **3** could be derived from an acyclic intermediate **4** through a tandem intermolecular conjugate addition followed by intramolecular cyclization. The intermediate



Scheme 1.

* Corresponding author. Tel.: +91 20 66539600; fax: +91 20 66539620.
E-mail addresses: dsrinivas.reddy@advinus.com, dsreddy88@yahoo.com (D.S. Reddy).

0040-4039/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2010.07.166

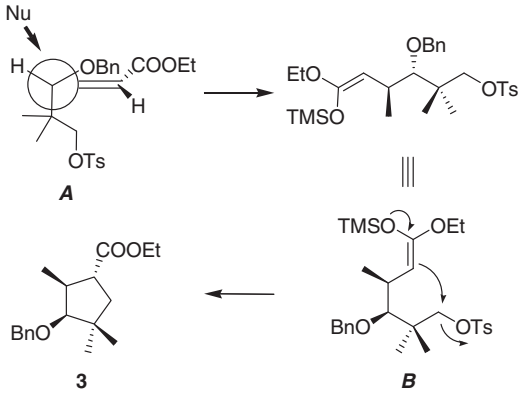
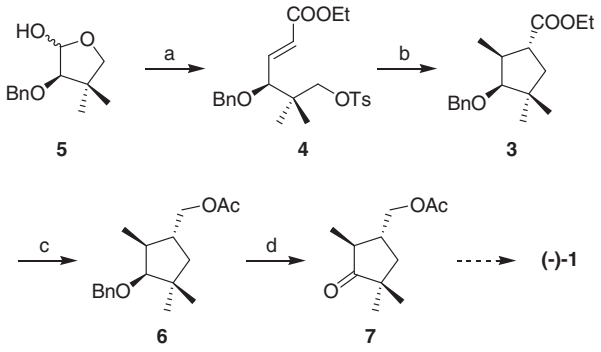


Figure 2. Plausible explanation for the observed stereoselectivity.

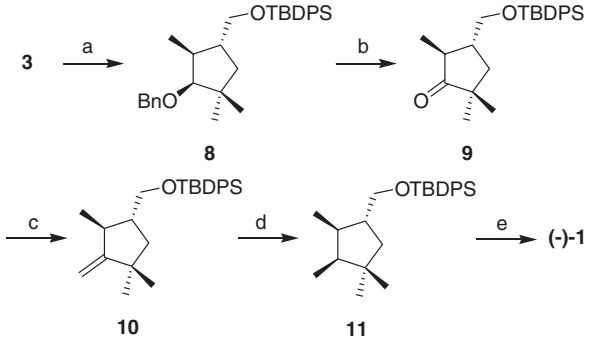


Scheme 2. *Reagents and conditions*: (a) (i) Ph_3P = CHCOOEt, toluene, reflux, 8 h, 75%; (ii) TsCl, py, DMAP, rt, 24 h, 88%; (b) Me_2CuLi, TMSCl, −78 °C to rt, THF, 24 h, 94%; (c) (i) $LiAlH_4$, THF, 0 °C, 0.5 h, 95%; (ii) Ac_2O, DMAP, py, DCM, rt, 92%; (d) (i) 10% Pd/C, H_2, MeOH, 24 h, 96%; (ii) Dess–Martin periodinane, DCM, 0 °C, 1 h, 93%.

4 could be prepared from commercially available D-(−)-pantolactone using routine functional group transformations (Scheme 1).

Our synthesis commenced from the benzyl-protected lactol **5** obtained from commercially available D-(−)-pantolactone.[7] The lactol **5** was transformed into an acyclic α,β-unsaturated ester **4** (pure *E*-isomer) using Horner–Wittig olefination followed by tosylation of resulting primary alcohol. Having **4** in hand, the desired conjugate addition followed by cyclization was carried out using Me_2CuLi/TMSCl to furnish the cyclopentane derivative **3** in excellent yield.[5,8–10] The cyclic compound **3** was characterized by NOE and ^1H–^1H COSY NMR experiments. The stereoselectivity obtained during the conjugate addition could be explained by the modified Felkin–Anh model.[8c] The transition state/intermediate is proposed as shown in Figure 2, where the attack of a nucleophile (cuprate) results in an *anti* (or in our cyclic case, *syn*) relationship between benzyloxy and the newly formed adjacent stereocenter. In the case of cyclization, simple thermodynamic stability may be providing the desired selectivity and probably the Thorpe–Ingold effect (*gem*-dimethyl effect on cyclization) driving the reaction.[12] The pleasing outcome from this reaction is the very high diastereoselectivity during both carbon–carbon bond-forming reactions, which installed two required chiral centers in one-pot for the synthesis of (−)-**1**.[11] The similar observations were made by Kuwahara's group, however, it was derived in two independent steps on related substrates.[5]

The primary alcohol obtained by LAH reduction of ester **3** was acetylated to provide compound **6**. Debenzylation (10% Pd/C, H_2) followed by oxidation using Dess–Martin's reagent resulted in ketone **7** in very high yield (Scheme 2). Olefination of ketone **7** followed by reduction of the double bond would have provided the final compound (−)-**1**, however, despite several attempts this



Scheme 3. *Reagents and conditions*: (a) (i) $LiAlH_4$, THF, 0 °C, 0.5 h, 95%; (ii) TBDPSCl, imidazole, py, rt, 93%; (b) (i) 10% Pd/C, H_2, MeOH, 91%; (ii) Dess–Martin periodinane, DCM, 0 °C, 1 h, 89%; (c) Tebbe's reagent, THF, 0 °C, 45 min, 89%; (d) $Rh(PPh_3)_3Cl$, H_2, THF-^{t}BuOH (1:1), rt; 85%; (e) (i) TBAF, THF, 60 °C, 1 h; 86%; (ii) Ac_2O, py, DMAP, DCM, rt, 1 h, 87%.

was not possible in our hands. The formation of desired olefin **2** was observed using Tebbe's reagent, however, we could not isolate it in pure form due to its volatile nature.

To circumvent this problem, we have protected the primary alcohol obtained from **3** with bulky TBDPS group to provide **8**. Deprotection of benzyl group followed by oxidation resulted in ketone **9**, which was subjected to Tebbe's olefination to furnish the compound **10**. After several attempts,[13] it was found that hydrogenation of the exocyclic double bond using Wilkinson's catalyst furnished the desired stereoisomer **11** in a highly diastereoselective fashion (>95% *de*, judged by NMR).[14] Removal of TBDPS group in **11** using TBAF and acetylation of resulting primary alcohol furnished the target compound pheromone (−)-**1** (Scheme 3). The spectral data (^1H and ^{13}C NMR) of the synthetic pheromone (−)-**1** from our lab were compared with that of synthetic (+)-**1** from Kuwahara's group[5] and both were found identical. Specific rotation of our sample (−)-**1** showed $[\alpha]_D^{24.5}$ −8.96 (*c* 0.50, $CDCl_3$) compared to that of natural enantiomer $[\alpha]_D^{23.3}$ +9.1 (*c* 0.4, $CDCl_3$)[4] and $[\alpha]_D^{27}$ +15.1 (*c* 1.50, $CDCl_3$).[5] The natural enantiomer (+)-**1** can be synthesized starting from corresponding L-(+)-pantolactone in a similar manner.

In short, we have achieved the enantiospecific synthesis of (−)-**1**, an isomer of insect's natural sex pheromone starting from readily available D-(−)-pantolactone chiral pool. An unprecedented tandem sequence of conjugate addition followed by cyclization using Me_2CuLi and a stereoselective reduction of exocyclic olefin are the key steps in our synthesis. This diastereoselective tandem sequence can be applied to the synthesis of more complex natural products.

Acknowledgments

We are grateful to Drs. Rashmi Barbhaiya, Kasim Mookhtiar, and Venkata P. Palle for their support and encouragement.

Supplementary data

Supplementary data (general methods, experimental details and analytical data for compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.07.166.

References and notes

1. (a) Mori, K.; Tashiro, T. *Curr. Org. Synth.* **2004**, *1*, 11; (b) Mori, K. *Acc. Chem. Res.* **2000**, *33*, 102; (c) Mori, K. *Tetrahedron* **1989**, *45*, 3233; (d) Mori, K. In *Chirality in Natural and Applied Science*; Lough, W. J., Wainer, J. W., Eds.; Blackwell: Oxford, 2002; pp 241–259; (e) Mori, K. *Chirality* **1998**, *10*, 578; (f) Mori, K. *Chem. Commun.* **1997**, 1153; (g) Mori, K. *Biosci. Biotechnol. Biochem.* **1996**, *60*, 1925; (h) Mori, K.. In *The Total Synthesis of Natural Products*; ApSimon, J., Ed.; John Wiley:

New York, 1992; pp 1–532; (i) Miller, J. G.; Daane, K. M.; Mcelfresh, J. S.; Mreira, J. A.; Bentley, W. J. Chemistry and Applications of Mealybug Sex Pheromones. In *ACS Symposium Series # 906, Semiochemicals in Pest Management and Alternative Agriculture*, Petroski, R., Ed.; American Chemical Society: Washington, DC, 2005; pp 11–27.; (j) Mori, K.. In *The Total Synthesis of Natural Products*; ApSimon, J., Ed.; John Wiley: New York, 1981; Vol. 4, pp 1–183; (k) Abbasipour, H.; Taghavi, A.; Askarianzadeh, A. *Entomol. Res.* **2007**, *37*, A120.

2. Millar, J. G.; Midland, S. L.; McElfresh, J. S.; Daane, K. M. *J. Chem. Ecol.* **2005**, *31*, 2999.
3. Millar, J. G.; Midland, S. L. *Tetrahedron Lett.* **2007**, *48*, 6377.
4. Figadère, B.; Devlin, F. J.; Millar, J. G.; Stephens, P. *J. Chem. Commun.* **2008**, 1106.
5. Hashimoto, K.; Morita, A.; Kuwahara, S. *J. Org. Chem.* **2008**, *73*, 6913.
6. Reddy, D. S.; Srinivas, G.; Rajesh, B. M.; Kannan, M.; Rajale, T. V.; Iqbal, J. *Tetrahedron Lett.* **2006**, *47*, 6373.
7. Mandel, A. L.; La Clair, J. J.; Burkart, M. D. *Org. Lett.* **2004**, *6*, 4803.
8. (a) Asao, N.; Lee, S.; Yamamoto, Y. *Tetrahedron Lett.* **2003**, *44*, 4265; (b) Chounan, Y.; Ono, Y.; Nishii, S.; Kitahara, H.; Ito, S.; Yamamoto, Y. *Tetrahedron* **2000**, *56*, 2821; (c) Yamamoto, Y.; Nishii, S.; Ibuka, T. *J. Chem. Soc., Chem. Commun.* **1987**, 1572; (d) Reetz, M. T. *Pure Appl. Chem.* **1992**, *64*, 351; (e) Lopez, F.; Harutyunyan, S. R.; Meetsma, A.; Minnaard, A. J.; Feringa, B. L. *Angew. Chem., Int. Ed.* **2005**, *44*, 2752.
9. See related tandem cyclization (a) Hassner, A.; Ghera, E.; Yechezkel, T.; Kleiman, V.; Balasubramanian, T.; Ostercamp, D. *Pure Appl. Chem.* **2000**, *72*, 1671; (b) Davies, S. G.; Mujtaba, N.; Roberts, P. M.; Smith, A. D.; Thomson, J. E. *Org. Lett.* **2009**, *11*, 1959; (c) Jeffery, D. W.; Perkins, M. V. *Tetrahedron Lett.* **2004**, *45*, 8667; (d) Ihara, M.; Fukumoto, K. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1010; (f) Wang, L.-C.; Luiz, A.-L.; Agpiou, K.; Jang, H.-Y.; Krische, M. J. *J. Am. Chem. Soc.* **2002**, *124*, 2402; (g) Agpiou, K.; Krische, M. J. *Org. Lett.* **2003**, *5*, 1737; (h) Jellerichs, B. G.; Kong, J.-R.; Krische, M. J. *J. Am. Chem. Soc.* **2003**, *125*, 7758; (i) Li, K.; Alexakis, A. *Tetrahedron Lett.* **2004**, *46*, 8019. and refs. cited therein.
10. Procedure for the key tandem reaction: *(1R,2S,3S)-3-benzyloxy-2,4,4-trimethyl-cyclopentanecarboxylic acid ethyl ester* (**3**). To a stirred suspension of CuI (6.4 g, 33.6 mmol) in THF (50 ml) was added methyl lithium (5% in diethyl ether, 20 ml, 44.8 mmol) at −78 °C, and the resulting mixture was stirred for 1 h. Then added chlorotrimethylsilane (4.3 ml, 33.6 mmol) and a solution of (*E*)-(*S*)-4-benzyloxy-5,5-dimethyl-6-(toluene-4-sulfonyloxy)-hex-2-enoic acid ethyl ester **4** (1.0 g, 2.2 mmol) in THF (10 ml). The mixture was gradually brought to room temperature and stirred for 24 h. The reaction was quenched with a mixture of saturated aq ammonium chloride and ~30% aq ammonia (1:1), filtered through Celite bed and extracted with ethyl acetate (2 × 30 ml). The combined extracts were washed with water, brine, dried over sodium sulfate, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (1% EtOAc in hexane) to give 0.61 g (94%) of (1*R*,2*S*,3*S*)-3-benzyloxy-2,4,4-trimethyl-cyclopentanecarboxylic acid ethyl ester **3** as a colorless oil. $[\alpha]_D^{24.3}$ −12.8 (*c* 0.60, $CHCl_3$); IR ($CHCl_3$) 1730 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.04 (s, 3H), 1.07 (s, 3H), 1.10 (d, *J* = 6.8 Hz, 3H), 1.25 (t, *J* = 7.2 Hz, 3H), 1.62 (dd, *J* = 7.6, 13.2 Hz, 1H), 1.88 (dd, *J* = 9.6, 13.2 Hz, 1H), 2.50–2.69 (m, 2H), 3.34 (d, *J* = 5.6 Hz, 1H), 4.12 (d q, *J* = 1.2, 6.8 Hz, 2H), 4.55 (s, 2H), 7.28–7.37 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.4, 14.8, 23.8, 29.2, 41.4, 42.1, 43.5, 49.1, 60.3, 74.2, 91.0, 127.5, 127.7, 128.3, 139.1, 176.6; LCMS = 291.3 (M+1); HRMS (ESI): *m*/*z* calculated for $C_{18}H_{27}O_3[M+H]^+$ 291.1960, found 291.1965. See Supplementary data for other experimental procedures.
11. See Supplementary data for details and copies of NMR spectra.
12. Jung, M. E.; Gervay, J. *J. Am. Chem. Soc.* **1991**, *113*, 224.
13. Hydrogenation using Adam's catalyst (PtO_2) gave 60:40 diastereoselectivty.
14. The olefin was hydrogenated using 10 mol % of chlorotris(triphenylphosphine)-rhodium(I) catalyst in 1:1 mixture of THF:^{t}BuOH under hydrogen-balloon pressure.