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Convergent and enantioselective syntheses of both enantiomers of (5*Z*)-tetradecen-4-olide, scarab beetle pheromones

Alcindo A. Dos Santos[a,b,*] and Wittko Francke[b]

[a]*Departamento de Química, Universidade Federal de São Carlos, Rod. Washington Luiz, Km 235, CP 676, CEP 13565-905, São Carlos, SP, Brazil*
[b]*Institut für Organische Chemie, Universität Hamburg, Martin-Luther-King-Platz 6, 20146 Hamburg, Germany*

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Abstract—Japonilure and its enantiomer, that is, (*R*)-(−)- and (*S*)-(+)-(5*Z*)-tetradecen-4-olide, have been synthesised in satisfactory overall yields using a highly convergent procedure. In situ prepared 1-decynylethylzinc was enantioselectively coupled to isopropyl 4-oxobutanoate in the presence of (*S*)- or (*R*)-BINOL. The alkoxy-ester intermediates obtained were cyclised to the corresponding substituted γ-lactones, carrying a triple bond in the side chain. Lindlar-hydrogenation of the latter yielded the target compounds.

1. Introduction

Japonilure (*R*)-**1** is the sex pheromone of females of the Japanese Beetle, *Popillia japonica*.[1] While the (*R*)-isomer exhibits strong pheromone activity, its enantiomer is highly inhibitory. Accordingly, the racemic mixture is inactive, and even a sample with 90% ee of the (*R*)-isomer was only 1/3 as active as the pure enantiomer. On the other hand, (*S*)-**1** is the pheromone of the Osaka Beetle, *Anomala osakana*, which shares a common habitat with the Japanese Beetle (Fig. 1).[2] In these two scarab beetle species, a single binding protein binds both enantiomers, and two enantiospecific olfactory receptor neurons distinguish between the attractive enantiomer and the repellent.[3]

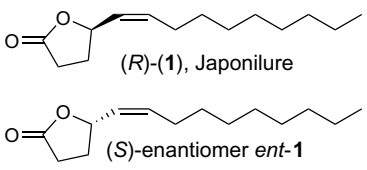

Figure 1. (*R*)-**1**: Japonilure, sex pheromone of the Japanese Beetle.

Earlier syntheses of the enantiomers of **1** have been compiled by Mori,[4,5] while some more recent syntheses including enzymatic approaches are summarised by Francke and Dettner.[6] Noyori's synthesis of (*R*)-**1** involved the enantioselective reduction of methyl 4-oxotetradec-5-ynoate with BINAL-H, which yielded the corresponding propargylic ester-alcohol with 73% ee.[7] We now aimed at a stereoselective synthesis of a similar intermediate by starting from an alkyl 4-oxobutanoate.

The chemoselective addition of an alkynyl Grignard reagent to ethyl 4-oxobutanoate producing a racemic mixture of the corresponding lactone, a 5-(1-alkynyl) tetrahydrofuran-2-one, was first reported in 1982.[8] Later, Soai and co-workers described the asymmetric synthesis of 4-alkyl-γ-butyrolactones and 5-alkyl-δ-valerolactones by reacting 4-oxobutanoate and 5-oxopentanoate esters, respectively, with diethyl- and dimethyl-zinc reagents catalysed by *N*,*N*-dibutylnorephedrine.[9] It is now well-documented that organozinc reagents add enantioselectively to aldehydes in the presence of optically active reagents such as (chiral) amino-alcohols and other derivatives of amines, oxazolines, diselenides and 1,1′-binaphthyl ligands.[10–12] Recently, a convenient protocol described the enantioselective addition of terminal alkynes to aliphatic and aromatic aldehydes upon reaction with $Zn(OTf)_2$ in the presence of *N*-methylephedrine to give the corresponding optically active propargyl alcohols in up to 99% ee.[13]

In the present study, we describe the convergent and enantioselective syntheses of (*R*)-(−)- and (*S*)-(+)-(5*Z*)-tetradecen-4-olide **1** involving the doubly chemoselective reaction of 1-decynylethylzinc (generated in situ) with isopropyl

* Corresponding author. Tel.: +55 016 33518213; e-mail: alcindo@dq.uf5CAR.BR

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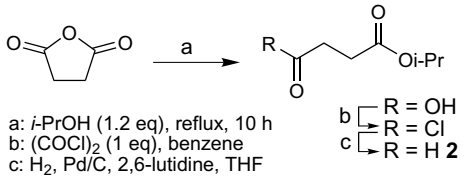
4-oxobutanoate **2** in the presence of (*S*)-(−)- or (*R*)-(+)-BINOL, followed by lactonisation and stereoselective hydrogenation of the triple bond.

2. Results and discussion

Using a modification of the protocol described by Cason,[14] isopropyl 4-oxobutanoate **2** was prepared in an overall yield of 70% from succinic anhydride (Scheme 1).

Ester-aldehyde **2** was subjected to a chemoselective 1,2-addition reaction (Scheme 2), involving the BINOL-assisted enantioselective addition of the mixed diorganylzinc reagent **3** to the aldehyde moiety of **2**. This was followed by an intramolecular nucleophilic addition of the chiral alkoxide functionality to the ester group of the intermediate **4**, to form the desired γ-lactone.

The diorganylzinc reagent was prepared by refluxing stoichiometric amounts of 1-decyne and diethylzinc at 100 °C in toluene for 12 h yielding a white solid that was assumed to be 1-decynylethylzinc. In accordance with the observation of Pu,[15] high chemoselectivity in the addition reaction of the alkynylzinc reagent to the aldehyde moiety of **2** was observed when diethylzinc was used in the formation of the mixed diorganylzinc compound. In contrast, when dimethylzinc was used instead, low yields of the desired lactone **5** were obtained. In this case, the methyl group of the mixed diorganylzinc reagent obviously competed with the decynyl substituent in the reaction with the aldehyde moiety of **2** producing the volatile and rather water soluble γ-valerolactone. In fact, the chemoselectivity of this catalysed addition reaction is highly dependent on the reaction time and temperature of the step involving the formation of the mixed diorganylzinc reagent. Under the conditions used, both (*R*)- and (*S*)-lactones **5** were produced in overall yields of 81%. Finally, (*R*)-**5** and (*S*)-**5** were submitted to hydrogenation at 0 °C with Lindlar catalyst in pentane in the presence of quinoline, giving (*R*)-japonilure and its antipode, (*S*)-**1**, in 90% yield and enantiomeric purities of 87% ee and 86% ee, respectively (by enantioselective GC).



Scheme 1. Preparation of aldehyde **2**.

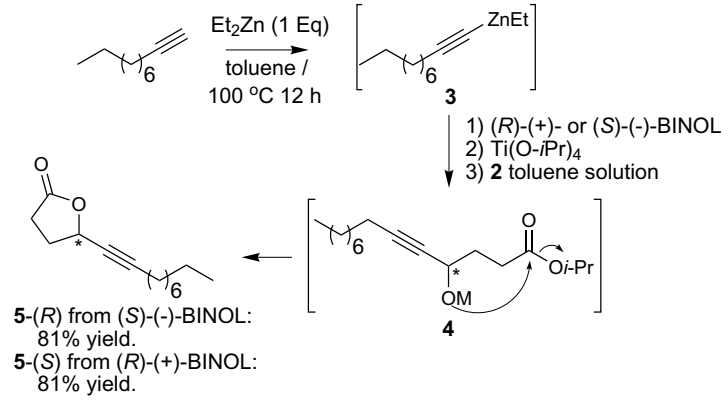
3. Experimental

3.1. General

All reagents and solvents used were purified and dried according to standard procedures.[16] THF was distilled under nitrogen from sodium/benzophenone immediately before use. NMR spectra (400 MHz for ^{1}H and 100 MHz for ^{13}C) were recorded in $CDCl_3$ solution with a Bruker AMX-400 spectrometer (Bruker, Karlsruhe, Germany) using TMS or the central peak of the $CDCl_3$ signal as internal standard. A Fisons GC8000/MD800 (Fisons Instruments, Mainz, Germany) coupled gas chromatograph/quadrupole mass spectrometer was used to obtain 70 eV spectra. Optical rotations were determined on a Jasco, DIP 370 digital polarimeter. Separation of the enantiomers of **1** was achieved with a tailor-made modified cyclodextrin as the stationary phase. By using a 25 m, 0.25 mm id fused silica capillary column coated with octakis-(6-*O*-methyl-2,3-di-*O*-pentyl)-γ-cyclodextrin, which was operated under a temperature program (5 min 60 °C, then programmed to 200 °C at a rate of 5 °C/min), base line separation was achieved [α-value = 1.085 = rt (*S*)-:rt (*R*)-].

3.2. Preparation of isopropyl 4-oxobutanoate 2

Succinic anhydride (4 g, 40 mmol) and isopropyl alcohol (3.67 mL, 48 mmol) were refluxed for 10 h in a 250 mL two-necked flask, and the excess of isopropyl alcohol was removed under reduced pressure. The resulting solid was dissolved in dry benzene (40 mL), cooled to 5 °C and oxalyl chloride (3.48 mL, 40 mmol) as well as dimethylformamide (two drops) were added. After warming to room temperature, the mixture was stirred for 6 h, followed by removal of the solvent under reduced pressure. The slurry was diluted with dry benzene (10 mL), stirred with charcoal



Scheme 2. Sequential 1,2-addition reactions.

(0.5 g) for 30 min, filtered and concentrated under reduced pressure. The resulting oil was diluted with anhydrous THF (100 mL), and freshly redistilled 2,6-lutidine (4.68 mL, 40.18 mmol) was added. The flask was purged with argon, and the mixture was stirred vigorously for 20 min. Lindlar catalyst (2 g, 10% Pd on carbon) was then added to the reaction mixture, and stirring was continued for 30 min, followed by further stirring for 12 h under an atmosphere of dry hydrogen. The mixture was filtered, the solvent removed under reduced pressure and the residue diluted with diethyl ether (50 mL). The resulting solution was sequentially washed with hydrochloric acid (3×10 mL, 1 mol/L), aqueous sodium bicarbonate (10 mL, 5% m/v) and brine (10 mL). The organic layer was dried over magnesium sulfate and filtered. The solvent was removed under reduced pressure, and the residue was distilled under vacuum (bp 58–59 °C, 0.4 mmHg) to yield 4.03 g (70%) of **2** as a pale oil. CAS 61720-57-8. ^{1}H NMR ($CDCl_3$) δ 1.2 (6H, d, $J = 6.4$ Hz), 2.56 (2H, t, $J = 6.6$ Hz), 2.78 (2H, t, $J = 6.9$ Hz), 4.98 (1H, hept, $J = 6.1$ Hz), 9.78 (1H, s). ^{13}C NMR (DEPT 135, $CDCl_3$) δ 22.2, 27.4, 30.0, 39.0, 68.6, 200.5. MS (70 eV) *m*/*z* (rel int.) 85 (44), 74 (16), 57 (12), 55 (10), 43 (100), 41 (66).

3.3. Preparation of (*S*)-(+)-5-(dec-1-ynyl)-tetrahydrofuran-2-one 5

Under an atmosphere of argon, 1-decyne (4.65 mL, 25.86 mmol), toluene (13 mL) and neat diethylzinc (2.65 mL, 25.86 mmol) were introduced sequentially into a 250 mL two-necked flask. The mixture was heated for 12 h at reflux and the resulting white slurry cooled to room temperature. (*R*)-(+)-BINOL (0.71 g, 2.48 mmol, 10 mol %), diethyl ether (100 mL) and Ti(O–*i*Pr)$_4$ (1.93 mL, 6.46 mmol) were added sequentially. After stirring for an additional 30 min at room temperature, a solution of isopropyl 4-oxobutanoate (**2**, 0.75 g, 6.46 mmol) in toluene (20 mL) was added dropwise by means of a syringe pump over a period of 2 h. The solution was stirred at room temperature for 10 h, Celite® (~3 g) was added and the mixture was stirred for an additional 30 min. The slurry was filtered on a Büchner funnel, and the residue was extracted with diethyl ether (3×50 mL). The resulting solution was sequentially washed with hydrochloric acid (10 mL, 0.5 mol/L), aqueous sodium bicarbonate (10 mL, 10% m/v) and brine (10 mL). The organic layer was dried over magnesium sulfate, filtered and the solvent was removed under reduced pressure. The crude material was purified by flash chromatography [Merck, silica 60, 240–400 mesh; dichloromethane/hexane/ethyl acetate 20:5:1]; affording 1.17 g of (*S*)-**5** (81% yield) as a colourless oil. CAS 72151-70-3. $[\alpha]_D^{23} = +6.0$ (*c* 4.64, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 0.84 (3H, t, $J = 6.8$ Hz), 1.24–1.36 (11H, m), 1.47 (2H, quint, $J = 7.5$ Hz), 2.12 (3H, td, $J = 7.1$, 2.3 Hz), 2.23 (1H, td, $J = 7.1$, 2.3 Hz), 2.41–2.50 (2H, m), 2.55–2.67 (1H, m), 5.10 (1H, ddt, $J = 7.4$, 5.6, 1.9 Hz). ^{13}C NMR ($CDCl_3$) δ 14.3, 18.9, 22.8, 28.1, 28.4, 29.0, 29.2, 29.3, 30.3, 31.9, 69.9, 76.7, 89.0, 176.4. MS (70 eV) *m*/*z* (rel int.) 223 M+1$^+$ (1.7), 222 M$^+$ (1.2), 221 (2.4), 165 (3), 163 (5), 142 (20), 137 (17), 124 (58), 116 (17), 111 (10), 109 (15), 107 (15), 97 (11), 96 (24), 95 (30), 93 (17), 91 (16), 85 (27), 83 (20), 81 (48), 79 (47), 74 (83), 73 (57), 69 (22), 67 (48), 55 (59), 45 (18), 43 (100), 41 (80).

3.4. Preparation of (*R*)-(−)-5-(dec-1-ynyl)-tetrahydrofuran-2-one 5

The procedure was the same as described in Section 3.3. but employing (*S*)-(−)-BINOL to afford 1.17 g (81% yield) of (*R*)-**5** as a colourless oil. CAS 72151-69-0. $[\alpha]_D^{23} = -6.0$ (*c* 2.6, $CHCl_3$) (lit.:[17] $[\alpha]_D^{21} = -6.5$ (*c* 5.5, $CHCl_3$)). Spectroscopic data were the same as for (*S*)-**5**.

3.5. Preparation of (*S*)-(+)-5-(*Z*)-(dec-1-enyl)-tetrahydrofuran-2-one 1

Under an argon atmosphere, (*S*)-(+)-5-(dec-1-ynyl)-tetrahydrofuran-2-one (**5**, 0.8 g, 3.6 mmol), pentane (50 mL) and freshly distilled quinoline (0.17 mL) were introduced sequentially into a 100 mL round-bottomed flask, and the mixture was cooled to 0 °C. Lindlar catalyst (0.177 g, 5% Pd on calcium carbonate poisoned with lead acetate) was added to the solution, and the mixture was stirred at 0 °C for 5 h under a hydrogen atmosphere followed by removal of the solvent. Celite (~1 g) was added to the mixture and stirring maintained for an additional 20 min at 0 °C. The mixture was filtered, the residue was extracted with pentane (2×5 mL) and the resulting solution was sequentially washed with hydrochloric acid (2×10 mL) and brine (10 mL). The organic layer was dried over magnesium sulfate and filtered under reduced pressure. The crude material was purified by flash chromatography [Merck, silica 60, 240–400 mesh; hexane/ethyl ether 7:3] affording 0.68 g of (*S*)-**1** (89% yield) as a colourless oil. CAS 64726-93-8. $[\alpha]_D^{23} = +60.0$ (*c* 2.0, $CHCl_3$) (lit.:[1] $[\alpha]_D^{26} = +70.5$ (*c* 5.5 $CHCl_3$)). ^{1}H NMR ($CDCl_3$) δ 0.85 (3H, t, $J = 6.8$ Hz), 1.20–1.30 (12H, m), 2.02–2.14 (2H, m), 2.31–2.39 (1H, m), 2.49–2.56 (2H, m), 5.22 (1H, tdd, $J = 8.3$, 6.6, 1.0 Hz), 5.42 (1H, ddt, $J = 10.7$, 8.6, 1.5 Hz), 5.64 (1H, dtd, $J = 10.9$, 7.7, 1.0 Hz). ^{13}C NMR ($CDCl_3$) δ 14.48, 23.05, 28.23, 29.41, 29.60, 29.63, 29.71, 29.80, 29.82, 32.26, 76.83, 127.64, 136.25, 177.52. MS (70 eV) *m*/*z* (rel int.) 224 M$^+$ (1), 126 (22), 125 (16), 111 (100), 98 (19), 95 (22), 81 (49), 67 (42), 55 (62), 43 (43), 41 (100).

3.6. Preparation of (*R*)-(−)-(5*Z*)-(dec-1-enyl)-tetrahydrofuran-2-one 1

The procedure as described in Section 3.5. was used but employing (*R*)-(−)-5-(dec-1-ynyl)-dihydrofuran-2(3*H*)-one **5** to afford 0.73 g (91% yield) of (*R*)-**1** as a colourless oil. CAS 64726-91-6. $[\alpha]_D^{23} = -61.1$ (*c* 1.5 $CHCl_3$); (lit.:[1] $[\alpha]_D^{26} = -69.6$ (*c* 5.0, $CHCl_3$)). Spectroscopic data were the same as for the (*S*)-(+)-enantiomer.

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References

1. Tumlinson, J. H.; Klein, M. G.; Doolittle, R. E.; Ladd, T. L.; Proveaux, A. T.. *Science* **1977**, *197*, 789–792.
2. Leal, W. S. *Proc. Natl. Acad. Sci. U.S.A.* **1996**, *93*, 12112–12115.
3. Wojtasek, B. S.; Hansson, B. S.; Leal, W. S. *Biochem. Biophys. Res. Commun.* **1998**, *250*, 217–222.
4. Mori, K. In *The Total Synthesis of Natural Products*; Ap Simon, J., Ed.; John Wiley & Sons: New York, 1981; Vol. 4, pp 1–183.
5. Mori, K. In *The Total Synthesis of Natural Products*; Ap Simon, J., Ed.; John Wiley & Sons: New York, 1992; Vol. 9, pp 1–534.
6. Francke, W.; Dettner, K. *Top. Curr. Chem.* **2005**, *240*, 85–166.
7. Noyori, R.; Tomino, I.; Yamada, M.; Nishizawa, M. *J. Am. Chem. Soc.* **1984**, *106*, 6717–6725.
8. Maurer, B.; Hauser, A. *Helv. Chim. Acta* **1982**, *65*, 462–476.
9. Soai, K.; Yokoyama, S.; Hayasaka, T.; Ebihara, K. *Chem. Lett.* **1988**, 843–846.
10. Soai, K.; Niwa, S. *Chem. Rev.* **1992**, *92*, 833–856.
11. Pu, L.; Yu, H-B. *Chem. Rev.* **2001**, *101*, 757–782.
12. Pu, L. *Tetrahedron* **2003**, *59*, 9873–9886.
13. Bode, J. W.; Carreira, E. M. *J. Am. Chem. Soc.* **2001**, *123*, 3611–3612, and references cited therein.
14. Cason, J. *Org. Synth.* **1945**, *25*, 19–24.
15. Moore, D.; Pu, L. *Org. Lett.* **2002**, *11*, 1855–1857.
16. Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals*; Pergamon: Oxford, 1980.
17. Baker, R.; Rao, V. B. *J. Chem. Soc., Perkin Trans. 1* **1982**, 60–61.