Stereoselective Synthesis of (4S,6S)-6-Hydroxy-4-undecanolide: A Pheromone of the Giant White Butterfly Idea leuconoe

Jhllu Singh Yadav,*a,b Poli Adi Narayana Reddy,a Hissana Ather,a Alleni Suman Kumar,a Attaluri R. Prasad,a Basi V. Subba Reddy,a Ahmad Al Khazimb

a Pheromone Group, Natural product Chemistry Division, CSIR-Indian Institute of Chemical Technology, Hyderabad 500007, India
Fax +91(40)27160512; E-mail: yadavpub@iict.res.in
b Engineer Abdullah Baqshan for Bee Research, King Saudi University, Saudi Arabia

Received 11 October 2011; revised 6 December 2011

SYNTHESIS 2012, 44, 579–584
Advanced online publication: 16.01.2012
DOI: 10.1055/s-0031-1289671; Art ID: Z97011SS
© Georg Thieme Verlag Stuttgart · New York

Abstract: The stereoselective synthesis of (4S,6S)-6-hydroxy-4-undecanolide, a major pheromone component in the secretion of Idea leuconoe has been accomplished employing Prins cyclization to produce anti-1,3-diols and hydroboration/oxidation of terminal olefin to introduce primary alcohol as the key steps.

Key words: pheromones, Prins cyclization, Mitsunobu inversion, anti-1,3-diol, chemoselective oxidation of 1,4-diols

The males of the giant white butterfly Idea leuconoe possess hairpencils on the end of their abdomen, which release a mixture of compounds, namely, alkaloids, aromatics, terpenoids, hydrocarbons, and lactones, to act as courtship pheromones.1 The lactones, which are isolated from the hairpencil extract, are hydroxyalkanolides with two chiral centers. The lactone ring size differs from four- to six-membered and the chain lengths vary from C10 to C13.2 Of these lactones, the major components of the hairpencil secretion are the g-lactones, 6-hydroxy-4-alkanolides 1a–c, which are accompanied by trace amounts of the respective b-lactones 2a (Figure 1). The first synthesis of a 6-hydroxy-4-alkanolide has been reported by Schulz et al. involving enantioselective hydrogenation of 4,6-diketo esters using a ruthenium–BINAP catalyst.3

Scheme 1

The synthetic approach (route A, Scheme 2) commenced from a chiral homoallylic alcohol 3, which was prepared via the copper-mediated regioselective opening of (S)-benzylglycylidyl ether (obtained via the Jacobsen’s HKR methodology)2 with vinylmagnesium bromide (formed in situ from vinyl bromide and Mg metal in THF) followed by debenzylolation with sodium in liquid ammonia (overall yield for two steps 69%). Prins cyclization of the homoallylic alcohol 3 with n-hexanal in the presence of trifluoroacetic acid followed by hydrolysis of the resulting trifluoroacetate gave the trisubstituted tetrahydropyran ring followed by hydroboration/oxidation of the terminal olefin. The pyran derivative 7 could in turn be prepared via the Prins cyclization of a homoallylic alcohol 3 and hexanal. The chemoselective oxidation of 1,4-diol 11 using 2,2,6,6-tetramethylpiperidinoxy (TEMPO) and (diacetoxyiodo)benzene would give the g-lactone 1b. In another strategy, 1,4-diol 11 could be alternatively prepared from compound 15 by ozonolytic oxidative cleavage of the olefin 15 followed by alkynylation of the resulting aldehyde and subsequent hydrogenation.

SYNTHESIS 2012, 44, 579–584
Advanced online publication: 16.01.2012
DOI: 10.1055/s-0031-1289671; Art ID: Z97011SS
© Georg Thieme Verlag Stuttgart · New York

Figure 1 Lactones 1a–c and 2a

In continuation of our research on the use of Prins cyclization in total synthesis of biologically active natural products,4 we herein report an efficient approach for the synthesis of (4S,6S)-6-hydroxy-4-undecanolide (1b), a pheromone of the giant white butterfly Idea leuconoe.

In the retrosynthetic analysis (Scheme 1), we envisaged that the target molecule could be prepared from compound 7 via the reductive opening of iodomethyl-substituted tetrahydropyran ring followed by hydroboration/oxidation of the terminal olefin. The pyran derivative 7 could in turn be prepared via the Prins cyclization of a homoallylic alcohol 3 and hexanal. The chemoselective oxidation of 1,4-diol 11 using 2,2,6,6-tetramethylpiperidinoxy (TEMPO) and (diacetoxyiodo)benzene would give the g-lactone 1b. In another strategy, 1,4-diol 11 could be alternatively prepared from compound 15 by ozonolytic oxidative cleavage of the olefin 15 followed by alkynylation of the resulting aldehyde and subsequent hydrogenation.
The stereochemistry was assumed to be in accordance with the literature as it was well examined and established previously. Moreover, the assumption was confirmed when compound 4 was elaborated to synthesize the target molecule 1b (overall yield 15%), which in all respects was identical to the reported data. TOSylation of the compound 4 with 1.2 equivalents of tosyl chloride in the presence of triethylamine in dichloromethane gave the corresponding primary tosylate 5 (95%). Protection of the secondary alcohol as a silyl ether in the presence of tert-butyldimethylsilyl chloride and imidazole in dichloromethane gave the compound 6 (97%). Treatment of tosylate 6 with sodium iodide in refluxing acetone gave the corresponding iodo derivative 7 (95%). Deprotection of the iodo derivative 7 with activated zinc in refluxing ethanol furnished the compound 8 (92%). The secondary alcohol of compound 8 was protected as its methoxymethyl ether 9 (98%) in the presence of N-disopropylethylamine and methoxymethyl chloride in dichloromethane. Upon exposure of compound 9 to dicyclohexylborane and 30% hydrogen peroxide afforded the primary alcohol 10 (77%). Subsequent removal of the silyl group from compound 10 using tetra-n-butylammonium fluoride in THF gave the lactone 11 (97%), which was readily converted into lactone 12 (87%) by chemoselective oxidation using TEMPO and (diacetoxyiodo)benzene in dichloromethane.

Deprotection of methoxymethyl ether 12 using trifluoroacetic acid in dichloromethane (1:4) gave the final product 1b (97%), which in all respects was identical to the reported structure.

The alternative synthetic approach (route B, Scheme 3) commenced from 13, which was converted into 14 according to a reported procedure in three steps (overall yield 30%). Compound 14 was protected as its methoxymethyl ether gave 15 (98%). Ozonolytic oxidative cleavage of 15 gave the aldehyde 16 (85%), which was then treated with O-benzylpropargyl alcohol in the presence of n-butyllithium in tetrahydrofuran at −78 °C. The resulting propargyl alcohol was obtained as a mixture of syn-17a and anti-17b in a 1:1 ratio. To assign the stereochemistry, both the isomers were converted into the corresponding acetones 18a and 18b in a three-step sequence. Upon exposure of both the isomers 17a/17b to 10% Pd/C in methanol resulted in the reduction of triple bond with concomitant removal of benzyl group to furnish the diols, which were then treated with aqueous 3 M hydrochloric acid in tetrahydrofuran to give the triols (structures not shown). Upon treatment of the triols with 2,2-DMP in acetone the acetones 18a and 18b were obtained. The stereochemistry of the diastereomers could be established by 13C NMR analysis. In 18a, the two methyl groups resonate at δ = 19.8 and 30.5 ppm and quaternary carbon shows a peak at δ = 98.5 ppm representing the 1,3-syn orientation of two hydroxy groups. However, the two methyl groups and quaternary carbon resonate at δ = 24.7, 24.9, and 100.3 ppm, respectively, indicating the 1,3-anti-orientation of the two hydroxy groups in 18b. The undesired isomer 17a was converted into 17b (overall yield 70%) under standard Mitsunobu condition. Reduction of the triple bond with a concomitant debenzylation of compound 17b was achieved using Pd/C in methanol to give the key fragment 1,4-diol 11 (97%). The chemoselective oxidation of 1,4-diol 11 using TEMPO and (diacetoxyiodo)benzene in dichloromethane gave the lactone 12 (87%). Deprotection of the methoxymethyl ether 12 us-

Scheme 2  Route A. Reagents and conditions: (a) n-hexanal, TFA, CHCl₃, 3 h; then K₂CO₃, MeOH, 25 °C, 0.5 h, 52%; (b) Et₃N, TsCl, CH₂Cl₂, 0–25 °C, 3 h, 95%; (c) TBSCI, imidazole, DMAP, CH₂Cl₂, 0 to 25 °C, 3 h, 97%; (d) NaI, acetone, reflux, 24 h, 95%; (e) Zn, EtOH, reflux, 2 h, 92%; (f) MOMCl, DIPEA, DMAP, CH₂Cl₂, 0–25 °C, 3 h, 98%; (g) C₂H₂B₃H₁₁, THF, 30% H₂O₂, NaOH, 77%; (h) TBAF, THF, 0–25 °C, 4 h, 97%; (i) TEMPO, Ph(dict bonded to OAc)₂, CH₂Cl₂, 25 °C, 4 h, 87%; (j) TFA, CH₂Cl₂ (1:4), 0–25 °C, 2 h, 97%.

Synthesis 2012, 44, 579–584 © Thieme Stuttgart · New York
In summary, we have described a stereoselective formal membered-ring lactones.

would be very useful to generate a wide variety of five-membered lactones employing two alternative strategies. These methods were separated and the aqueous layer was extracted with CH$_2$Cl$_2$.

CDCl$_3$. Mass spectra were recorded on Micromass VG-7070H for Bruker Avance 300 MHz, Varian Unity 400 MHz, or Varian TMS as an internal standard in MHz.

were dried and purified by conventional methods prior to use. The progress of the reaction was monitored by TLC using glass plates precoated with silica gel 60 F254 to a thickness of 0.5 mm (Merck).

All reactions were carried out under inert atmosphere. Solvents were dried and purified by conventional methods prior to use. The progress of the reaction was monitored by TLC using glass plates precoated with silica gel 60 F254 to a thickness of 0.5 mm (Merck).

Using the above two synthetic approaches, optically active 1a and 1c should be accessed readily.

was removed under reduced pressure. The trifluoroacetate obtained in this reaction was directly used in the next step without purification. The residue was dissolved in MeOH (40 mL) and stirred with K$_2$CO$_3$ (6.0 g) for 0.5 h. The mixture was extracted with CH$_2$Cl$_2$ (3 × 30 mL) and the combined organic layers were washed with sat. aq NaHCO$_3$ (15 mL), followed by H$_2$O (15 mL). The combined organic layers were washed with sat. aq NaHCO$_3$ (15 mL), followed by H$_2$O (15 mL). The combined organic phases were dried (Na$_2$SO$_4$) and concentrated under reduced pressure. Flash chromatography of the crude product afforded tosylate 5 (4.18 g, 95%) as a gummy liquid; [\(\delta_{1}^{1}J_{20} + 2.4\) (c 2.8, CHCl$_3$)].

IR (neat): 3380, 2930, 2859, 1722, 1651, 1458, 1373, 1025 cm$^{-1}$.

HRMS (ESI): mlz calcd for C$_{11}$H$_{22}$O$_3$ + Na: 225.1466; found: 225.1471.

[(2S,4R,6S)-4-6-Pentyltetrahydro-2H-pyran-2-yl]methyl 4-Methylbenzenesulfonate (5)

To stirred solution of diol 4 (2.5 g, 12.3 mmol) in anhyd CH$_2$Cl$_2$ (25 mL) was added Et$_2$N (8.68 mL, 61.88 mmol) at 0 °C, and then TsCl (2.82 g, 14.8 mmol) was added over 2 h. The reaction mixture was allowed to warm to 25 °C and then allowed to stir for 3 h. The mixture was then treated with aq 1 M HCl (10 mL) and extracted with CH$_2$Cl$_2$ (3 × 30 mL). The combined organic phases were washed with sat. aq NaHCO$_3$ (15 mL), followed by H$_2$O (15 mL). The combined organic phases were washed with sat. aq NaHCO$_3$ (15 mL), followed by H$_2$O (15 mL). The combined organic phases were washed with sat. aq NaHCO$_3$ (15 mL), followed by H$_2$O (15 mL). The combined organic phases were washed with sat. aq NaHCO$_3$ (15 mL), followed by H$_2$O (15 mL). The combined organic phases were washed with sat. aq NaHCO$_3$ (15 mL), followed by H$_2$O (15 mL). The combined organic phases were washed with sat. aq NaHCO$_3$ (15 mL), followed by H$_2$O (15 mL). The combined organic phases were washed with sat. aq NaHCO$_3$ (15 mL), followed by H$_2$O (15 mL). The combined organic phases were washed with sat. aq NaHCO$_3$ (15 mL), followed by H$_2$O (15 mL). The combined organic phases were washed with sat. aq NaHCO$_3$ (15 mL), followed by H$_2$O (15 mL). The combined organic phases were washed with sat. aq NaHCO$_3$ (15 mL), followed by H$_2$O (15 mL). The combined organic phases were washed with sat. aq NaHCO$_3$ (15 mL), followed by H$_2$O (15 mL). The combined organic phases were washed with sat. aq NaHCO$_3$ (15 mL), followed by H$_2$O (15 mL). The combined organic phases were washed with sat. aq NaHCO$_3$ (15 mL), followed by H$_2$O (15 mL). The combined organic phases were washed with sat. aq NaHCO$_3$ (15 mL), followed by H$_2$O (15 mL). The combined organic phases were washed with sat. aq NaHCO$_3$ (15 mL), followed by H$_2$O (15 mL). The combined organic phases were washed with sat. aq NaHCO$_3$ (15 mL), followed by H$_2$O (15 mL). The combined organic phases were washed with sat. aq NaHCO$_3$ (15 mL), followed by H$_2$O (15 mL). The combined organic phases were washed with sat. aq NaHCO$_3$ (15 mL), followed by H$_2$O (15 mL). The combined organic phases were washed with sat. aq NaHCO$_3$ (15 mL), followed by H$_2$O (15 mL). The combined organic phases were washed with sat. aq NaHCO$_3$ (15 mL), followed by H$_2$O (15 mL). The combined organic phases were washed with sat. aq NaHCO$_3$ (15 mL), followed by H$_2$O (15 mL). The combined organic phases were washed with sat. aq NaHCO$_3$ (15 mL), followed by H$_2$O (15 mL). The combined organic phases were washed with sat. aq NaHCO$_3$ (15 mL), followed by H$_2$O (15 mL). The combined organic phases were washed with sat. aq NaHCO$_3$ (15 mL), followed by H$_2$O (15 mL). The combined organic phases were washed with sat. aq NaHCO$_3$ (15 mL), followed by H$_2$O (15 mL). The combined organic phases were washed with sat. aq NaHCO$_3$ (15 mL), followed by H$_2$O (15 mL). The combined organic phases were washed with sat. aq NaHCO$_3$ (15 mL), followed by H$_2$O (15 mL). The combined organic phases were washed with sat. aq NaHCO$_3$ (15 mL), followed by H$_2$O (15 mL). The combined organic phases were washed with sat. aq NaHCO$_3$ (15 mL), followed by H$_2$O (15 mL). The combined organic phases were washed with sat. aq NaHCO$_3$ (15 mL), followed by H$_2$O (15 mL). The combined organic phases were washed with sat. aq NaHCO$_3$ (15 mL), followed by H$_2$O (15 mL). The combined organic phases were washed with sat. aq NaHCO$_3$ (15 mL), followed by H$_2$O (15 mL). The combined organic phases were washed with sat. aq NaHCO$_3$ (15 mL), followed by H$_2$O (15 mL). The combined organic phases were washed with sat. aq NaHCO$_3$ (15 mL), followed by H$_2$O (15 mL). The combined organic phases were washed with sat. aq NaHCO$_3$ (15 mL), followed by H$_2$O (15 mL). The combined organic phases were washed with sat. aq NaHCO$_3$ (15 mL), followed by H$_2$O (15 mL). The combined organic phases were washed with sat. aq NaHCO$_3$ (15 mL), followed by H$_2$O (15 mL). The combined organic phases were washed with
A stirred solution of alcohol 5 (3.8 g, 10.67 mmol) in anhydrous CH₂Cl₂ (30 mL) at 0 °C was added TBSCl (1.93 g, 12.8 mmol), DMAP (cat.), and imidazole (2.9 g, 42.6 mmol). The mixture was stirred for 3 h at 25 °C, quenched with H₂O (10 mL), and extracted with CH₂Cl₂ (3 × 20 mL). The combined organic extracts were washed with brine (10 mL) and dried (Na₂SO₄). Removal of the solvent followed by purification by column chromatography afforded the pure product 6 (4.86 g, 97%) as a colorless liquid; [α]D₂⁰ = –4.6, –4.1, 13.9, 18.0, 22.5, 24.0, 24.5, 25.8, 31.8, 42.3, 42.6, 55.4, 69.2, 75.7, 95.8, 116.9, 134.7. HRMS (ESI): m/z calc for C₁₇H₃₆O₂Si + Na: 323.2382; found: 323.2389.

To a stirred solution of alcohol 8 (1.8 g, 6 mmol) in anhydrous CH₂Cl₂ (15 mL) at 0 °C were added successively DIPEA (3.10 mL, 17.95 mmol), DMAP (cat.), and MOMCl (0.96 g, 11.99 mmol). The mixture was stirred for 3 h at 25 °C, quenched with H₂O (10 mL), and extracted with CH₂Cl₂ (2 × 20 mL). The combined organic extracts were washed with brine (10 mL), dried (Na₂SO₄), and concentrated under reduced pressure. The resulting residue was purified by column chromatography to afford the pure product 9 (2.02 g, 98%) as a colorless liquid; [α]D₂⁰ = 0.7 (silica gel, 10% EtOAc in hexane); [α]D₂⁰ +19.0 (c 1.5, CHCl₃).

IR (neat): 3076, 2953, 2930, 1640, 1466, 1379, 1253, 1150, 1041, 919, 835 cm⁻¹.

HRMS (ESI): m/z calc for C₁₉H₄₀O₃Si + Na: 367.2644; found: 367.2631.

To an ice cold solution of silyl ether 10 (300 mg, 1.31 mmol) in anhydrous CH₂Cl₂ (10 mL) was added Me₂S·BH₃ (1.22 mL, 13 mmol) at 0 °C. The aqueous phase was extracted with CH₂Cl₂ (2 × 20 mL). The combined organic extracts were washed with brine (10 mL), dried (Na₂SO₄), and concentrated under reduced pressure. The residue was purified by column chromatography to afford the alcohol 11 (2.12 g, 77%) as a colorless liquid; [α]D₂⁰ = 0.3 (silica gel, 20% EtOAc in hexane); [α]D₂⁰ +41.5 (c 1.2, CHCl₃).

IR (neat): 3417, 2931, 2858, 1466, 1380, 1253, 1212, 1150, 1041, 919, 835 cm⁻¹.

HRMS (ESI): m/z calc for C₁₇H₃₆O₂Si + Na: 449.1348; found: 449.1365.
extracted with EtOAc (3 × 10 mL). The combined organic layers were dried (Na₂SO₄) and concentrated in vacuo. The residue was purified by column chromatography to afford the alcohol 11 (0.49 mg, 97%) as a colorless gummy liquid; Rf = 0.2 (silica gel, 20% EtOAc in hexane); [α]D = -17.1 (c 1.2, CHCl₃).

IR (neat): 3019, 2932, 1724, 1215, 1036, 758 cm⁻¹.

1H NMR (300 MHz, CDCl₃): δ = 0.83 (t, J = 6.7 Hz, 3 H), 1.12–1.28 (m, 6 H), 1.43–1.71 (m, 8 H), 2.74 (br, OH), 3.35 (s, 3 H), 3.56–3.66 (m, 2 H), 3.70–3.91 (m, 2 H), 4.58–4.68 (m, 2 H).

13C NMR (75 MHz, CDCl₃): δ = 13.9, 22.5, 24.9, 31.8, 34.5, 34.7, 41.2, 55.7, 62.7, 67.7, 76.1, 96.2.


(4S)-4-(Methoxymethoxy)non-1-ene (15)

To a solution of alcohol 14 (5.0 g, 35.2 mmol) in anhyd CH₂Cl₂ (25 mL) at 0 °C were added successively Dipea (12.13 mL, 70.4 mmol), DMAP (20 mg, cat.), and MOMCl (8.02 mL, 105.5 mmol). The mixture was stirred for 3 h at 25 °C, quenched with H₂O (25 mL), and extracted with CH₂Cl₂ (3 × 20 mL). The combined organic extracts were washed with brine (25 mL), dried (Na₂SO₄), and concentrated under reduced pressure. The residue was purified by column chromatography to afford the pure product 15 (6.35 g, 97%) as a colorless liquid; Rf = 0.8 (silica gel, 10% EtOAc in hexane); [α]D = -17.8 (c 1.5, CHCl₃).

IR (neat): 3367, 3019, 1215, 1096, 1038 cm⁻¹.

1H NMR (300 MHz, CDCl₃): [D]-4-(Methoxymethoxy)non-1-ene (15)

IR (neat): 34.7, 41.2, 55.7, 62.7, 67.7, 76.1, 96.2.

The combined organic extracts were washed with brine (6 mL) and concentrated in vacuo. The residue was purified by column chromatography to afford the pure alcohol \( \text{Ib}\) (0.103 g, 97%) as a colorless oil; \( R_f = 0.3 \) (silica gel, 40% EtOAc in hexane); \( [\alpha]_D^{20} +59.6 \) (c 1.2, EtOH).

IR (neat): 3445, 2929, 2859, 1767, 1460, 1420, 1359, 1185, 1036, 917, 766, 653 cm\(^{-1}\).

\(^1\)H NMR (300 MHz, CDCl\(_3\)): \( \delta = 0.83 \) (t, \( J = 6.6 \) Hz, 3 H), 1.18–1.46 (m, 8 H), 1.69 (dd, \( J = 3.5 \), 9.8, 14.3 Hz, 1 H), 1.78 (dd, \( J = 2.8 \), 9.2 Hz, 1 H), 1.90 (ddt, \( J = 8.4 \), 9.4, 12.6 Hz, 1 H), 2.13 (br, OH), 2.25–2.36 (m, 1 H), 2.45–2.51 (m, 2 H), 3.76–3.85 (m, 1 H), 4.70–4.78 (m, 1 H).

\(^1^\)C NMR (75 MHz, CDCl\(_3\)): \( \delta = 13.9, 22.5, 25.0, 28.4, 28.8, 31.6, 37.9, 43.1, 63.8, 78.1, 177.2 \).

HRMS (ESI): m/z calcd for C\(_{11}\)H\(_{23}\)O\(_3\) + Na: 223.1310; found: 223.1336.

Acknowledgment

P.A.N.R. and H.A. thank CSIR, New Delhi for the award of fellowships. The correspondence author acknowledges the partial support by King Saud University for Global Research Network for Organic Synthesis (GRNOS).

References