An Ytterbium-Catalysed Intramolecular Aldehyde–Ene Reaction Approach to the Guaianolide and Pseudoguaianolide Diterpenoids: Synthesis of the Guaiane Skeleton

Philip C. Bulman Page,* Giovanni Gambera, Colin M. Hayman, Mark Edgar

Department of Chemistry, Loughborough University, Loughborough, Leicestershire LE11 3TU, UK
Fax +44(1509)223926; E-mail: p.c.b.page@lboro.ac.uk

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Abstract: A convergent approach to a functionalised guaiane ring system, the core of the guaianolide and pseudoguaianolide diterpenes, is described. The synthesis utilises an intramolecular aldehyde-ene reaction as the key step.

Key words: sesquiterpene lactone, guaianolide, pseudoguaianolide, perhydroazulene, intramolecular ene reaction

The sesquiterpene lactone guaianolide and pseudoguaianolide families of natural compounds include hundreds of molecules. They are characterised by the guaiane skeleton, a bicyclo[5.3.0]decane ring system (perhydroazulene framework). A γ-lactone moiety is always present between C6 and C12 or between C8 and C12 as a common feature. In addition, the pseudoguaianolides are characterised by the presence of a methyl group at C5 (Figure 1).[1]

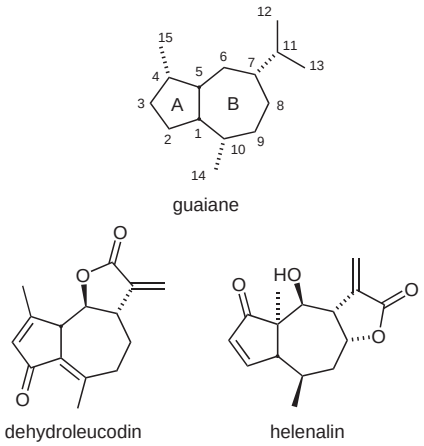

Figure 1 The guaiane skeleton and examples of guaianolides and pseudoguaianolides

Guaianolides and pseudoguaianolides have been extracted from several genera of *Compositae*,[1] including *Achillea*, *Arnica*, *Artemisia*, *Cichorium*, *Helenium*, *Lactuca*, *Matricaria*, and *Tanacetum*. Structure–activity relationship studies[2] have demonstrated the prime importance for biological activity of the presence in the ring system of the α,β-unsaturated carbonyl group and an α-methylene-γ-lactone group, and the influence of the stereochemistry of the molecule on the biological properties of these terpenoid compounds. The electrophilic unsaturated systems may act as Michael acceptors with nucleophilic cysteine residues of proteins or enzymes involved in important cellular activities. The result of such formation of a stable covalent bond is often the inactivation of the target, resulting in the biological effect.[3] It is probably in this way that guaianolides and pseudoguaianolides exert cytotoxicity[2b,4] (and therefore anitumour activity) and many other useful biological activities such as antiulcer,[2c,5] antifungal,[2e,6] antinflammatory,[7] growth plant regulator,[2d,8] antidiabetic,[9] and antibacterial[10] behavior. The pharmaceutical ramifications of such a wide range of biological properties are considerable: guaianolides and pseudoguaianolides can be used as research tools better to understand the biomolecular mechanism of pathologies; as lead structures for the design of new drugs; and in structure–activity relationship studies. These facts perhaps explain the synthetic effort made over the last thirty years to access these compounds.[11]

Our aim was to develop a versatile synthesis of guaianolides and pseudoguaianolides by using a pathway related to that which led us to the realisation of the core carbon skeletons of the tigliane and daphnane families of natural compounds.[12] In this way we would be able to access four different families of natural compounds with a unified approach. The strategy adopted would allow us to obtain, from the same precursors, both guaianolide and pseudoguaianolide skeletons with a *trans* configuration between the A and B rings.[13]

Retrosynthetic analysis suggested that an intramolecular aldehyde–ene reaction of a substrate obtained through convergent synthesis would provide access to the guaiane skeleton (Scheme 1),[14] which could subsequently be converted into a guaianolide or pseudoguaianolide structure. Intramolecular aldehyde–ene reactions have previously been used to obtain guaianolides and pseudoguaianolides.[11d–11f] Synthesis of specific natural compounds could then be achieved by proper functionalisation of the building blocks. We demonstrate herein the feasibility of this approach, in a synthesis of the guaiane skeleton using an intramolecular aldehyde–ene reaction.

We have reported the preparation of A-ring synthon **1**[12] by copper-catalysed conjugate addition of vinyl magnesium bromide to cyclopentenone in the presence of TMSCl and

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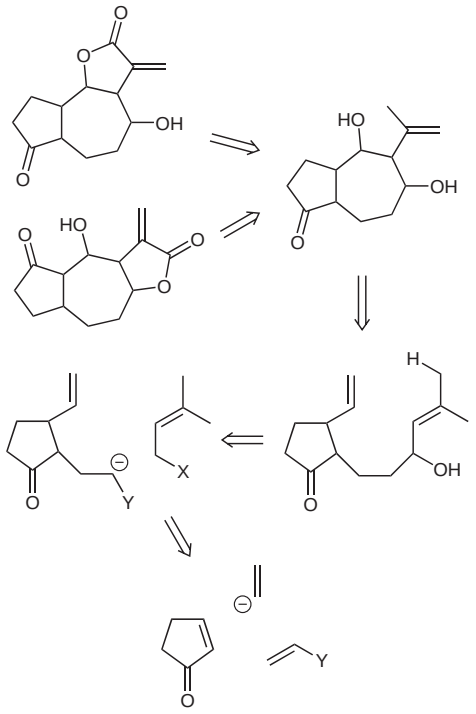
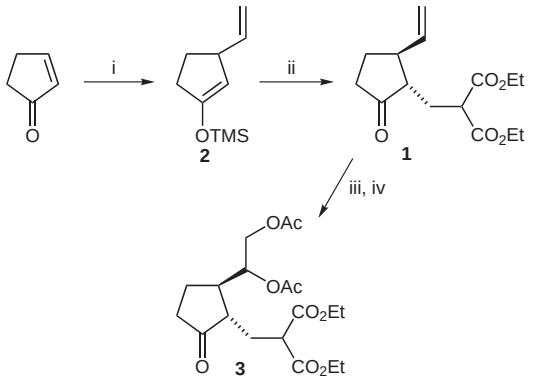


Scheme 1

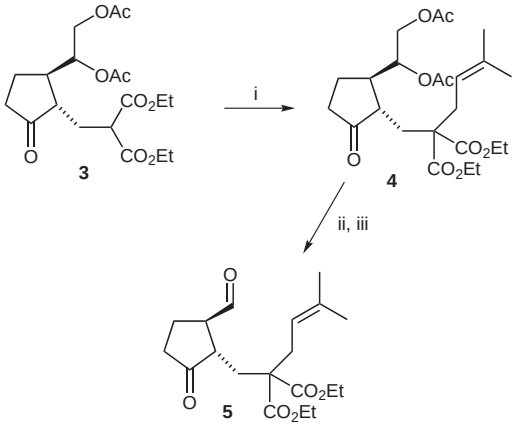
DMPU,[15] followed by $SnCl_4$-catalysed reaction of the resulting silyl enol ether **2** with diethyl methylidene malonate,[17] which was obtained by condensation of diethyl malonate and paraformaldehyde.[16]

Alkene **1** was converted into the pro-enophile component **3** by dihydroxylation of the vinyl group with $OsCl_3$/NMO[18] and acetylation of the resulting *gem*-diol in Ac_2O/pyridine with DMAP as the catalyst, in 75% yield over the two steps (Scheme 2).

The acidic malonate proton of **3** was removed with *n*-BuLi, and the resulting anion quenched with 3-methylbut-2-enyl bromide (prenyl bromide), to incorporate the ene component in product **4**. Compound **4** was deacetylated



Scheme 2 *Reagents and conditions*: (i) CH_2=CHMgBr/CuBr·DMS, Me_3SiCl, DMPU, Et_3N, anhyd THF, –78 °C; (ii) diethyl methylidene malonate, $SnCl_4$, CH_2Cl_2, –78 °C; (iii) $OsCl_3$/NMO, THF–H_2O; (iv) Ac_2O/pyridine, DMAP.



Scheme 3 *Reagents and conditions*: (i) *n*-BuLi, anhyd THF, –78 °C, 3-methylbut-2-enyl bromide, 57%; (ii) Amberlite 400 CI, MeOH, 56%; (iii) $NaIO_4$, THF–H_2O, 40%.

with Amberlite 400 CI (activated with KOH), and the resulting diol converted into aldehyde by oxidative cleavage with $NaIO_4$ to give the intramolecular aldehyde–ene substrate **5** in 40% yield as a colourless oil (Scheme 3).

The intramolecular aldehyde–ene reaction of **5** was investigated under a range of reaction conditions in order to find the optimum process for cyclisation. Lewis acids, including lanthanide catalysts,[19] are well known as mediators of carbonyl ene reactions, and indeed cycloheptanols have been prepared in this way.[20] We tested a number of Lewis acids, but only BF_3·OEt_2 and $Yb(OTf)_3$ were effective in catalysis of the cycloaddition of **5**. Use of microwave irradiation was unsuccessful.

Cyclisation of **5** under BF_3·OEt_2-catalysed conditions in anhyd THF at –78 °C followed by stirring at room temperature gave the *trans*-fused guaiane skeleton as a mixture of **6** and **7**, the *cis*-disubstituted isomers epimeric at C6 and C7 (Scheme 4).[21] The two isomers were separated by flash column chromatography to afford compound **6** in 41% yield and **7** in 10% yield. It is interesting that cyclisation of **5** with $Yb(OTf)_3$ at room temperature gave **6** in 46% yield as a single isolated isomer.[22]

The relative configurations of the two epimers were confirmed using high-resolution NMR spectroscopy: selective 1D NOESY, 2D NOESY, DQF-COSY and selective TOCSY experiments allowed the protons in the seven-membered ring to be assigned and their configurations to be determined. A *trans* configuration of substituents at C6 and C7 was considered, and dismissed because the NOE data was not consistent with such structures.[23]

We conjecture that this stereoselectivity arises through a concerted ene reaction and, preferentially, a chair transition state such as that shown in Figure 2, in which the protons at C5, C6, and C7 are positioned on the same face of the molecule. The large bulk of the Lewis acid presumably destabilises other transition states, and this effect is accentuated in the case of the lanthanide catalyst.

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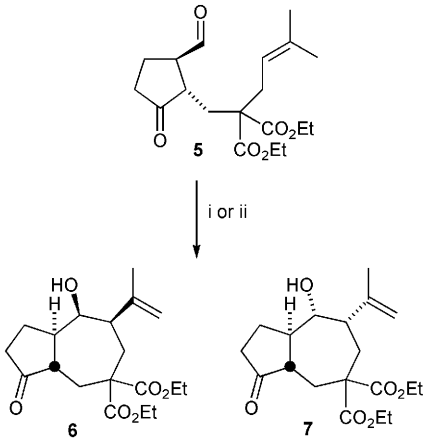

Scheme 4 *Reagents and conditions*: (i) $BF_3{\cdot}OEt_2$ (5 equiv), anhyd THF, –78 °C to r.t., 23 h, 51%; (ii) $Yb(OTf)_3$ (5 equiv), anhyd THF, r.t., 5 d, 46%.

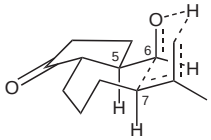

Figure 2

Acknowledgment

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References and Notes

(1) (a) Sorm, F.; Dolejs, L. In *Guaianolides and Germacranolides*; Hermann: Paris, **1965**. (b) Connolly, J. D.; Hill, R. A. *Dictionary of Terpenoids*, Vol. 1; Chapman and Hall: London, **1991**, 476–541.

(2) (a) Siedle, B.; Garcia-Pineres, A. J.; Murillo, R.; Sculte-Monting, J.; Castro, V.; Rungeler, P.; Klaas, C. A.; Da Costa, F. B.; Kisiel, W.; Merfort, I. *J. Med. Chem.* **2004**, *47*, 6042. (b) Kupchan, S. M.; Eakin, M. A.; Thomas, A. M. *J. Med. Chem.* **1971**, *14*, 1147. (c) Rodriguez, A. M.; Enriz, R. D.; Santagata, L. N.; Jaurengui, E. A.; Pestchanker, M. J.; Giordano, O. S. *J. Med. Chem.* **1997**, *40*, 1827. (d) Macias, F. A.; Velasco, R. F.; Castellano, D.; Galindo, J. C. G. *J. Agric. Food Chem.* **2005**, *53*, 3530. (e) Meng, J. C.; Hu, Y. F.; Chen, J. H.; Tan, R. X. *Phytochemistry* **2001**, *58*, 1141.

(3) (a) Garcia-Pineres, A. J.; Castro, V.; Mora, G.; Schmidt, T. J.; Strunck, E.; Pahl, H. L.; Merfort, I. *J. Biol. Chem.* **2001**, *276*, 39713. (b) Fardella, G.; Barbetti, P.; Grandolini, G.; Chiappini, I.; Ambrogi, V.; Scarcia, V.; Furlani Candiani, A. *Eur. J. Med. Chem.* **1999**, *34*, 515.

(4) (a) Treiman, M.; Caspersen, C.; Christensen, S. B. *Trends Pharmacol. Sci.* **1998**, *19*, 131. (b) Blanco, J. G.; Gil, R. R.; Alvarez, C. I.; Patrito, L. C.; Genti-Raimondi, S.; Flury, A. *FEBS Lett.* **1997**, *409*, 396. (c) Nielsen, S. F.; Thastrup, O.; Pedersen, R.; Olsen, C. E.; Christensen, S. B. *J. Med. Chem.* **1995**, *38*, 272. (d) Sims, D.; Lee, K.-H.; Wu, R.-Y.; Furukawa, H.; Itoigawa, M.; Yonaha, K. *J. Nat. Prod.* **1979**, *42*, 282. (e) Pettit, G. R.; Budzinski, J. C.; Cragg, G. M.; Brown, P.; Johnston, L. D. *J. Med. Chem.* **1974**, *17*, 1013. (f) Lee, K.-H.; Furukawa, H.; Huang, E.-S. *J. Med. Chem.* **1972**, *15*, 609.

(5) (a) Wendel, G. H.; Maria, A. O. M.; Mohamed, F.; Dominguez, S.; Scardapane, L.; Giordano, O. S.; Guerriero, E.; Guzman, J. A. *Pharmacol. Res.* **1999**, *40*, 339. (b) Guardia, T.; Guzman, J. A.; Pestchanker, M. J.; Guerreiro, E.; Giordano, O. S. *J. Nat. Prod.* **1994**, *57*, 507. (c) Giordano, O. S.; Guerreiro, E.; Pestchanker, M. J.; Guzman, J.; Guardia, T. *J. Nat. Prod.* **1990**, *53*, 803.

(6) Wedge, D. E.; Galindo, J. C. G.; Macìas, F. A. *Phytochemistry* **2000**, *53*, 747.

(7) (a) Jin, H. Z.; Lee, J. H.; Lee, D.; Hong, Y. S.; Kim, Y. H.; Lee, J. J. *Phytochemistry* **2004**, *65*, 2247. (b) Hilmi, F.; Gertsch, J.; Bremner, P.; Valovic, S.; Heinrich, M.; Sticher, O.; Heilmann, J. *Bioorg. Med. Chem.* **2003**, *11*, 3659. (c) Schorr, K.; Garcia-Pineres, A. J.; Siedle, B.; Merfort, I.; Da Costa, F. B. *Phytochemistry* **2002**, *60*, 733. (d) Siedle, B.; Gustavsson, L.; Johansson, S.; Murillo, R.; Castro, V.; Bohlin, L.; Merfort, I. *Biochem. Pharmacol.* **2003**, *65*, 897. (e) Yuuya, S.; Hagiwara, H.; Suzuki, T.; Ando, M.; Yamada, A.; Suda, K.; Kataoka, T.; Nagai, K. *J. Nat. Prod.* **1999**, *62*, 22.

(8) (a) Galindo, J. C. G.; De Luque, A. P.; Jorrin, J.; Macias, F. A. *J. Agric. Food Chem.* **2002**, *50*, 1911. (b) Macias, F. A.; Galindo, J. C. G.; Molinillo, J. M. G.; Castellano, D. *Phytochemistry* **2000**, *54*, 165.

(9) (a) Hou, C.-C.; Lin, S.-J.; Cheng, J.-T.; Hsu, F.-L. *J. Nat. Prod.* **2003**, *66*, 625. (b) Perez, R. M.; Perez, C.; Zavala, M. A.; Perez, S.; Hernandez, H.; Lagunes, F. *J. Ethnopharmacol.* **2000**, *71*, 391.

(10) Taylor, R. S. L.; Towers, G. H. N. *Phytochemistry* **1998**, *47*, 631.

(11) (a) Coquerel, Y.; Greene, A.; Depres, J.-P. *Org. Lett.* **2003**, *5*, 4453. (b) Cantrell, W. R.; Davies, H. M. L. *J. Org. Chem.* **1991**, *56*, 723. (c) Ando, M.; Kusaka, H.; Ohara, H.; Takase, K.; Yamaoka, H.; Yanagi, Y. *J. Org. Chem.* **1989**, *54*, 1952. (d) Hudlicky, T.; Govindam, S. V.; Frazier, J. O. *J. Org. Chem.* **1985**, *50*, 4166. (e) Semmelhack, M. F.; Yamashita, A.; Tomesch, J. C.; Hirotsu, K. *J. Am. Chem. Soc.* **1978**, *100*, 5565. (f) Kuroda, C.; Inoue, S.; Kato, S.; Satoh, J. Y. *J. Chem. Res., Synop.* **1993**, *2*, 62; *J. Chem. Res., Miniprint* **1993**, 458.

(12) (a) Page, P. C. B.; Hayman, C. M.; McFarland, H. L.; Willock, D. J.; Galea, N. M. *Synlett* **2002**, 583. (b) Page, P. C. B.; Jennens, D. C.; McFarland, H. *Tetrahedron Lett.* **1997**, *38*, 5395. (c) Page, P. C. B.; Jennens, D. C.; McFarland, H. *Tetrahedron Lett.* **1997**, *38*, 6913. (d) Page, P. C. B.; Jennens, D. C. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2587. (e) Page, P. C. B.; Jennens, D. C.; Porter, R. A.; Baldock, A. N. *Synlett* **1991**, 472.

(13) Hilmi, F.; Sticher, O.; Heilmann, J. *Phytochemistry* **2002**, *65*, 523.

(14) For leading references concerning the ene reaction, see: (a) Snider, B. B. In *Comprehensive Organic Chemistry*, Vol. 2; Trost, B. M.; Fleming, I., Eds.; Pergamon: Oxford, **1991**, 527–567. (b) Mikami, K.; Shimizu, M. *Chem. Rev.* **1992**, *92*, 1021.

(15) (a) Nakamura, E.; Horiguchi, Y.; Matsuzawa, S.; Kuwajima, I. *Tetrahedron* **1989**, *45*, 349. (b) Nakamura, E.; Horiguchi, Y.; Matsuzawa, S.; Kuwajima, I. *Tetrahedron Lett.* **1986**, *27*, 4025.

(16) (a) Mukaiyama, T.; Muratami, M. *Synthesis* **1987**, 1043. (b) Mukaiyama, T.; Kobayashi, S.; Tamura, M.; Sugawa, Y. *Chem. Lett.* **1987**, 491. (c) Mukaiyama, T.; Hara, R. *Chem. Lett.* **1989**, 1171.

(17) Bachmann, G. B.; Tanner, H. A. *J. Org. Chem.* **1939**, *4*, 493.

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(18) Raunkjr, M.; Olsen, C. E.; Wengel, J. *J. Chem Soc., Perkin Trans. 1* **1999**, 2543.
(19) De Bernardi, M.; Fronza, G.; Scilingo, A.; Vidari, G.; Vita-Finzi, P. *Tetrahedron* **1986**, *42*, 4277.
(20) (a) Marshall, J. A.; Andersen, N. H.; Johnson, P. C. *J. Org. Chem.* **1970**, *35*, 186. (b) Marshall, J. A.; Andersen, N. H.; Schlicher, J. W. *J. Org. Chem.* **1970**, *35*, 858.
(21) **(±)-(3a*S*,7*R*,8*R*,8a*R*)-8-Hydroxy-7-isopropenyl-3-oxooctahydroazulene-5,5-dicarboxylic Acid Diethyl Ester(6) and (±)-(3a*S*,7*S*,8*S*,8a*R*)-8-Hydroxy-7-isopropenyl-3-oxooctahydroazulene-5,5-dicarboxylic Acid Diethyl Ester (7).**
$BF_3{\cdot}OEt_2$ (0.86 mL, 7.0 mmol) was added to a stirred solution of **5** (490 mg, 1.4 mmol) in anhyd THF at –78 °C under a nitrogen atmosphere. After 1 h the solution was allowed to reach r.t. and stirred for further 22 h. The solution was diluted with EtOAc, washed with sat. aq $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4 and concentrated to dryness to give a colourless oil, which was purified by flash column chromatography on silica gel using 15–25% EtOAc–light PE as eluent to afford **6** (200 mg, 41%) and **7** (50 mg, 10%) as colorless oils. MS (EI): *m/z* calcd for $C_{19}H_{28}O_6$: 352.18859; found: 352.18226 [M^+]. Compound **6**: IR (neat): ν_{max} = 3542, 2978, 1730, 1645, 1245 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.17 (3 H, t, *J* = 7.1 Hz, CH_3CH_2O), 1.18 (3 H, t, *J* = 7.1 Hz, CH_3CH_2O), 1.76 (3 H, s, 11-H), 1.85–1.99 (4 H, m, 1-H_a, 1-H_b, 4-H_b, 8a-H), 2.06–2.17 (3 H, m, 1 of 6-H, 7-H, 1 of 2-H), 2.32–241 (2 H, m, 3a-H, 1 of 2-H), 2.43 (1 H, dd, *J* = 10.6, 15.0 Hz, 1 of 6-H), 2.61 (1 H, dd, *J* = 2.9, 15.2 Hz, 4-H_a), 3.82 (1 H, s, 8-H), 4.05–4.18 (4 H, m, 2 × CH_3CH_2O), 4.76 (1 H, s, 10-Ha), 4.87 (1 H, s, 10-Hb). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.8, 13.9 (2 × CH_3CH_2), 22.7 (1-C), 23.3 (11-C), 29.5 (6-C), 32.6 (4-C), 37.3 (2-C), 44.9 (3a-C), 47.0 (7-C), 50.1 (8a-C), 55.2 (5-C), 61.3, 61.4 (2 × CH_3CH_2), 67.8 (8-C), 111.7 (10-C), 148.7 (9-C), 172.3, 172.4 (2 × CO_2Et), 218.7 (3-C). Compound **7**: IR (neat): ν_{max} = 3533, 2979, 1737, 1731, 1646, 1255 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.22 (3 H, t, *J* = 7.1 Hz, CH_3CH_2O), 1.23 (3 H, t, *J* = 7.1 Hz, CH_3CH_2O), 1.49–1.60 (1 H, m, 1-Ha), 1.74 (1 H, dd, J_1 = 5.8 Hz, J_2 = 9.3 Hz, 8a-H), 1.76 (3 H, s, 11-H), 1.86 (1 H, dd, J_1 = 10.0, J_2 = 15.2 Hz, 6-Ha), 1.91 (1 H, dd, J_1 = 10.6, J_2 = 14.6 Hz, 1 of 4-H), 1.98 (1 H, dd, J_1 = 10.9 Hz, J_2 = 12.6 Hz, 3a-H), 2.13 (1 H, dd, J_1 = J_2 = 9.8 Hz, 7-H), 2.17 (1 H, dd, J_1 = 9.1 Hz, J_2 = 19.5 Hz, 2-Hb), 2.25 (1 H, d, *J* = 15.1 Hz, 6-Hb), 2.41 (1 H, dd, J_1 = 8.8 Hz, J_2 = 20.4 Hz, 2-Ha), 2.42–2.49 (1 H, m, 1-Hb), 2.71 (1 H, d, *J* = 14.2 Hz, 4-Hb), 3.35 (1 H, dd, J_1 = J_2 = 9.5 Hz, 8-H), 4.12–4.20 (4 H, m, 2 × CH_3CH_2O), 4.84 (1 H, s, 10-Ha), 4.95 (1 H, s, 10-Hb). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9, 14.0 (2 × CH_3CH_2O), 19.2 (11-C), 26.3 (1-C), 31.6 (4-C), 34.3 (6-C), 36.7 (2-C), 47.8 (3a-C), 49.4 (7-C), 51.7 (8a-C), 54.9 (5-C), 61.6, 61.7 (2 × CH_3CH_2O), 77.1 (8-C), 113.5 (10-C), 146.4 (9-C), 171.7, 172.7 (2 × CO_2Et), 217.3 (3-C).
(22) $Yb(OTf)_3$ (900 mg, 0.0014 mol) was added to a stirring solution of **5** (80 mg, 0.23 mmol) in anhyd THF (10 mL), at 0 °C under an atmosphere of nitrogen. The mixture was stirred at r.t. for 5 d, diluted with CH_2Cl_2, extracted with sat. aq $NaHCO_3$, dried over anhyd $MgSO_4$, and concentrated to dryness to give a colourless crude oil (120 mg). This was purified by flash column chromatography using 10–35% EtOAc–light PE as eluent to give **6** (37 mg, 46%) and starting material **5** (14 mg, 18%).
(23) NMR spectra were recorded using a Bruker Avance 400 MHz ultrashield spectrometer equipped with a shaped-pulse unit and employing a 5-mm auto-tune HX gradients probe.

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