Pergamon

Tetrahedron Letters 43 (2002) 6505–6506

TETRAHEDRON LETTERS

Two-directional synthesis. Part 2: An expedient entry into the quinolizidine skeleton

Martin Rejzek and Robert A. Stockman*

School of Chemical Sciences, University of East Anglia, Norwich NR4 7TJ, UK

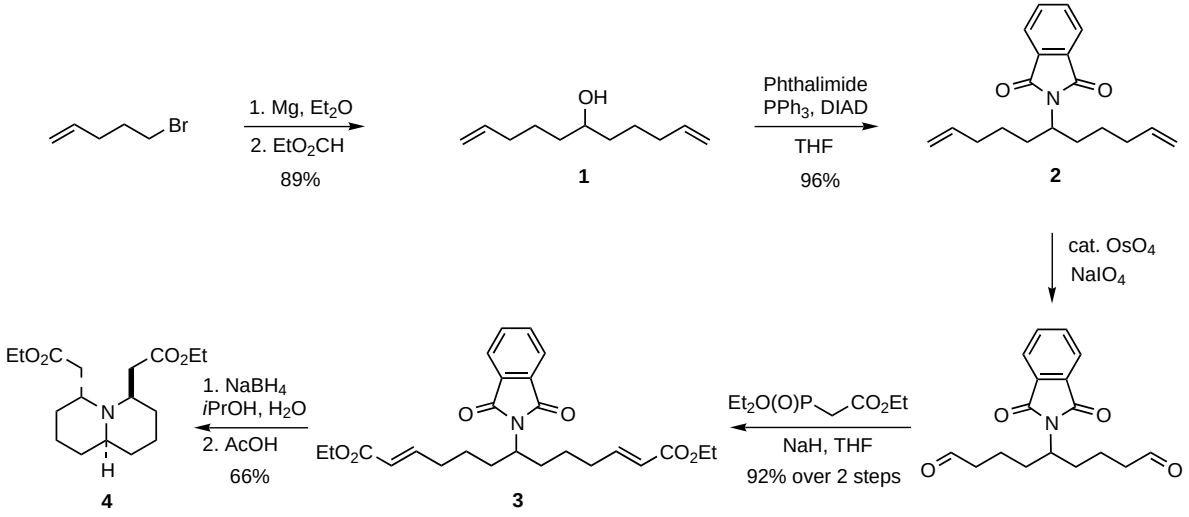
Received 18 June 2002; revised 5 July 2002; accepted 19 July 2002

Abstract—A two-directional synthesis strategy and a tandem deprotection/double intramolecular Michael addition provides a very direct route to the 4,6-disubstituted quinolizidine **4**. © 2002 Published by Elsevier Science Ltd.

Two-directional synthesis[1] and tandem reactions[2] offer the possibility of substantially reducing the number of chemical operations required to synthesise complex target molecules of biological and material interest. Recently we demonstrated the use of a two-directional strategy directed towards the synthesis of (±)-histrionicotoxin and (±)-histrionicotoxin 235A.[3] This formal synthesis[4] combined two-directional synthesis with a tandem Michael addition/cycloaddition, such that the skeleton of histrionicotoxin was formed in just six operations.

Herein we report the use of a two-directional strategy combined with a tandem deprotection/double intramolecular cycloaddition for the synthesis of the 4,6-disubstituted quinolizidine **4** (Scheme 1).

Ethyl formate was reacted with 2 equiv. of 4-pentenyl magnesium bromide in diethyl ether at room temperature for 12 hours,[5] to form symmetric alcohol **1** in 89% yield after distillation. Mitsunobu[6] substitution of the alcohol with phthalimide was then carried out by stirring a solution of phthalimide (2 equiv.) with alcohol **1**, di-*iso*propyl azodicarboxylate (2 equiv.) and triphenylphosphine (2 equiv.) in THF at room temperature for 12 hours, to give diene **2** in 96% yield after column chromatography. Oxidative cleavage of the terminal alkenes was carried out by treatment with



Scheme 1.

* Corresponding author. Tel.: +44 (0) 1603 593890; fax: +44 (0) 1603 592015; e-mail: r.stockman@uea.ac.uk

0040-4039/02/$ - see front matter © 2002 Published by Elsevier Science Ltd.
PII: S0040-4039(02)01494-6

sodium periodate (6 equiv.) and a catalytic amount of osmium tetroxide (2 mol%) in 3:1 THF/water, and the resulting dialdehyde was olefinated under standard Wadsworth–Emmons conditions[7] (using 2.1 equiv. of triethyl phosphonoacetate and 2.3 equiv. of sodium hydride in THF at 25°C for 2 days) to yield acyclic diester **3** in 92% yield over two steps from diene **2** as a single *E*,*E*-stereoisomer after purification over silica gel. *N*-Alkyl phthalimide **3** was then subjected to sodium borohydride (1.5 equiv.) in 6.2:1 *iso*-propanol/water mixture at 25°C for 24 hours.[8] After this time glacial acetic acid (30 equiv.) was added, and the reaction mixture was heated to 80°C (bath temperature) for a further 24 hours, producing quinolizidine **4** as a single (±)-*trans*-isomer[9] in 66% yield after purification by column chromatography over neutral alumina.[10]

In conclusion, we have further demonstrated the synthetic efficiency of combining two-directional synthesis with tandem reactions. Quinolizidine **4** was synthesised in just five steps and in 51.9% overall yield from ethyl formate. Study applying this approach to a range of natural products is ongoing in these laboratories.

Acknowledgements

The authors would like to thank the Leverhulme Trust for funding this research. They would also like to thank Pfizer for generous unrestricted funding of their research programme and the EPSRC Mass Spectrometry Service at the University of Wales, Swansea for carrying out high resolution mass spectra. The authors also acknowledge the use of the EPSRC's Chemical Database Service at Daresbury.[11]

References

1. Magnuson, S. R. *Tetrahedron* **1995**, *51*, 2167.
2. Bunce, R. A. *Tetrahedron* **1995**, *51*, 13103.
3. Stockman, R. A. *Tetrahedron Lett*. **2000**, *41*, 9163.
4. Williams, G. M.; Roughley, S. D.; Davies, J. E.; Holmes, A. B. *J. Am. Chem. Soc*. **1999**, *121*, 4900.
5. Kitching, W.; Lewis, J. A.; Perkins, M. V.; Drew, R.; Moore, C. J.; Schurig, V.; König, W. A.; Francke, W. *J. Org. Chem*. **1989**, *54*, 3893.
6. Mitsunobu, O. *Synthesis* **1981**, 1.
7. Wadsworth, W. S. *Org. React*. **1977**, *25*, 73.
8. Osby, O. J.; Martin, M. G.; Ganem, B. *Tetrahedron Lett*. **1984**, *25*, 2093.
9. The *trans* relative configuration of substituents at positions 4 and 6 of the quinolizidine **4** was determined from two-dimensional NMR spectra with reference to: Lebrun, B.; Braekman, J. C.; Daloze, D. *Magn. Reson. Chem*. **1999**, *37*, 60.
10. Analytical data for selected compounds are as follows. Compound **2**: ^{1}H NMR ($CDCl_3$, 400 MHz) 7.85–7.82 (2H, m), 7.73–7.70 (2H, m), 5.74 (2H, ddt, $J=16.8$, 10.0 and 6.8), 5.01–4.90 (4H, m), 4.26–4.18 (1H, m), 2.16–1.99 (6H, m), 1.78–1.69 (2H, m), 1.51–1.23 (4H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) 169.0 (s), 138.6 (d), 134.1 (d), 132.1 (s), 123.3 (d), 115.0 (t), 52.0 (d), 33.4 (t), 31.9 (t), 26.0 (t); IR (thin film, /cm^{-1}) 3076w, 3040m, 2927s, 2860m, 1772s, 1708s, 1641m, 1614w, 1468m, 1459m, 1441w, 1396s, 1372s, 1334s; HRMS calcd for $C_{19}H_{27}N_2O_2$ (M+NH_4): 315.2073. Found: 315.2072. Compound **3**: ^{1}H NMR ($CDCl_3$, 400 MHz) 7.86–7.84 (2H, m), 7.78–7.75 (2H, m), 6.90 (2H, dt, $J=15.6$ and 6.8), 5.79 (2H, d, $J=15.6$), 4.25–4.20 (1H, m), 4.18 (4H, q, $J=7.2$), 2.30–2.12 (6H, m), 1.80–1.72 (2H, m), 1.48–1.43 (4H, m), 1.27 (6H, t, $J=7.2$); ^{13}C NMR ($CDCl_3$, 100 MHz) 168.6 (s), 166.4 (s), 148.3 (d), 134.1 (d), 131.7 (s), 123.3 (d), 121.8 (d), 60.1 (t), 51.4 (d), 31.9 (t), 31.7 (t), 25.1 (t), 14.3 (q); IR (thin film, /cm^{-1}) 3462w, 3411w, 2980m, 2924s, 2852m, 1767w, 1705m, 1643m, 1607w, 1464m, 1444m, 1398w, 1367w; HRMS calcd for $C_{25}H_{32}NO_6$ (M+H): 442.2230. Found: 442.2227. Compound **4**: ^{1}H NMR (benzene-d_6, 400 MHz) 4.04–3.93 (4H, m), 3.83–3.80 (1H, m), 2.81 (1H, dd, $J=14.2$ and 4.4), 2.78–2.72 (1H, m), 2.65 (1H, dd, $J=$ 14.6 and 3.2), 2.41 (1H, dd, $J=14.6$ and 10.4), 2.29 (1H, dd, $J=14.2$ and 6.8), 1.98–1.92 (1H, m), 1.72–1.66 (3H, m), 1.47–1.36 (2H, m), 1.34–1.29 (4H, m), 1.24–1.04 (3H, m), 1.02–0.98 (6H, m); ^{13}C NMR (benzene-d_6, 75 MHz) 171.9 (s), 170.9 (s), 59.0 (t), 58.9 (t), 53.9 (d), 52.9 (d), 50.0 (d), 38.5 (t), 33.7 (t), 33.6 (t), 32.0 (t), 28.6 (t), 26.3 (t), 22.9 (t), 17.7 (t), 12.9 (q); IR (thin film, /cm^{-1}) 2980m, 2929s, 2853m, 1726s, 1465w, 1445w, 1368w, 1337w, 1301m, 1276m, 1163m, 1096m, 1030m; HRMS calcd for $C_{17}H_{30}NO_4$ (M+H): 312.2175. Found: 312.2171.
11. Fletcher, D. A.; McMeeking, R. F.; Parkin, D. *J. Chem. Inf. Comput. Sci*. **1996**, *36*, 746.