Tetrahedron Letters 53 (2012) 1119–1121

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

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

Asymmetric synthesis of (−)-(*S*,*S*)-homaline

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ARTICLE INFO

Article history:
Received 6 December 2011
Accepted 20 December 2011
Available online 30 December 2011

Keywords:
(−)-(*S*,*S*)-Homaline
Homalium alkaloids
Lithium amide
Conjugate addition
Asymmetric synthesis

ABSTRACT

The asymmetric synthesis of (−)-(*S*,*S*)-homaline was achieved in 8 steps from commercially available starting materials using the diastereoselective conjugate addition of the novel lithium amide reagent lithium (*R*)-*N*-(3-chloropropyl)-*N*-(α-methyl-*p*-methoxybenzyl)amide to methyl cinnamate to install the correct stereochemistry. Subsequent functional group manipulation of the resultant β-amino ester and $Sb(OEt)_3$-mediated macrolactamisation was followed by homodimerisation to give (−)-(*S*,*S*)-homaline in 18% overall yield, representing the first asymmetric, and by far the most efficient synthesis of this natural product reported to date.

The family of homalium alkaloids **1**–**4** was isolated from the leaves of an African *Homalium* species and *Homalium pronyense* Guillaum (a member of the Flacourtiacae family) found in the forests of New Caledonia (Fig. 1). They were first isolated in the early 1970s by Païs et al. and found to correspond to a combination of two α,β-unsaturated carboxylic acid residues with a spermine backbone.[1] (−)-(*S*,*S*)-Homaline **1** is the only symmetrical member of this family of alkaloids and has therefore received the most interest from synthetic chemists,[2] although no asymmetric syntheses of (−)-(*S*,*S*)-homaline **1** have been reported to date. In 1982 Wasserman and Berger focussed on the exploitation of β-lactams and their subsequent transamidations for the synthesis of homaline **1**.[3,4] In this ground breaking synthesis methyl (*R*,*S*)-3-amino-3-phenylpropanoate was resolved by recrystallisation of its L-tartrate salt[5] and after a further 14 steps enantiopure (−)-(*S*,*S*)-homaline **1** was isolated in 0.07% overall yield. In 1983 Crombie et al. first reported their enantiospecific synthesis of (−)-(*S*,*S*)-homaline **1** which proceeded via an Arndt-Eistert homologation of (*R*)-phenylglycine.[6] Ten years later they reported their full investigations within this area, which revealed that (−)-(*S*,*S*)-homaline **1** was produced in 10 steps and 1.4% overall yield from (*R*)-phenylglycine.[7] Several other methods for the synthesis of the homalium alkaloids have also been investigated, although inseparable mixtures of stereoisomers were formed in each case.[8–10] In 2002, Ensch and Hesse reported an enantiospecific synthesis of (−)-(*R*,*R*)-hopromine **2** from L-aspartic acid,[11,12] and comparison of the specific rotation of the synthetic sample with that of the sample isolated from the natural source established the absolute configuration within (−)-(*R*,*R*)-hopromine **2**.[11] The relative and absolute configurations within hoprominol **3** and hopromalinol **4**, to date, remain unknown.

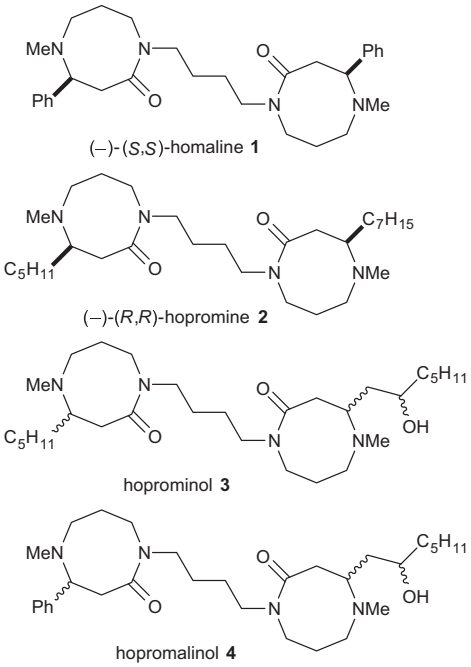

Figure 1. The homalium alkaloids **1**–**4**.

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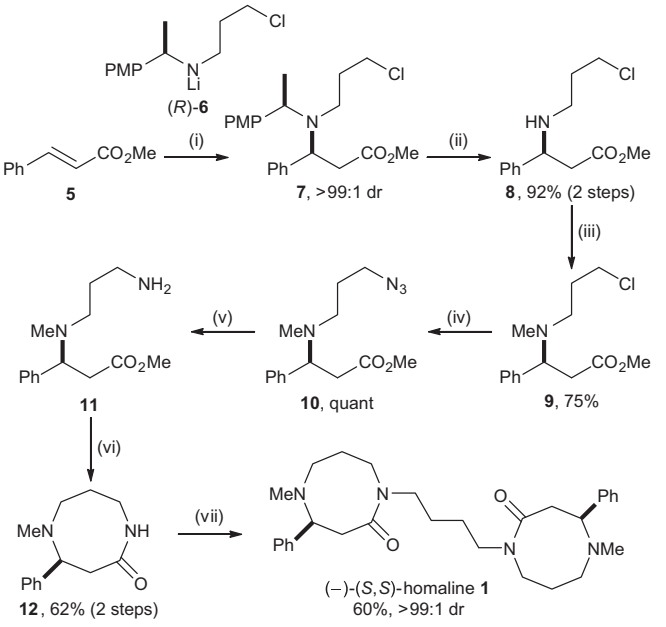
doi:10.1016/j.tetlet.2011.12.088

Previous investigations from our laboratory have demonstrated that the conjugate addition of numerous enantiopure secondary lithium amides (derived from α-methylbenzylamines) to α,β-unsaturated esters represents a general and efficient synthetic protocol for the synthesis of β-amino esters and their derivatives.[13] This methodology has found numerous applications, including the total syntheses of natural products,[14] molecular recognition phenomena[15] and resolution protocols,[16] and has been reviewed.[17] As part of our ongoing research programme in this area we became interested in the application of this methodology for the preparation of the homalium alkaloids and envisaged that the conjugate addition of a functionalised lithium amide such as (*R*)-**6** to methyl cinnamate **5** could be used to install the required configuration within the azalactam units of homaline **1**. It was then anticipated that a homodimerisation strategy could then be employed to exploit the symmetry within this natural product target. Thus, the conjugate addition of lithium (*R*)-*N*-(3-chloropropyl)-*N*-(α-methyl-*p*-methoxybenzyl)amide (*R*)-**6**[18] to methyl cinnamate **5** proceeded to full conversion and gave β-amino ester **7** as a single diastereoisomer (>99:1 dr). The stereochemical outcome of this transformation was initially assigned by reference to the well established transition state mnemonic developed by us to rationalise the diastereoselectivity observed upon conjugate addition of lithium amides derived from α-methylbenzylamine.[19] Subsequent removal of the *N*-α-methyl-*p*-methoxybenzyl group within **7** upon treatment with TFA gave **8** in 92% yield (from **5**), which was followed by reductive methylation of **8** to give **9** in 75% isolated yield. Displacement of the primary chloride functionality within **9** with NaN_3 (in the presence of NaI) gave **10** in quantitative yield, then Staudinger reduction of **10** followed by $Sb(OEt)_3$-mediated cyclisation[11,12] of **11** gave the known azalactam **12** in 62% yield over the two steps. Comparison of the specific rotation value for this sample of **12** with that of the previously reported[10] sample confirmed unambiguously the absolute configuration within (*S*)-**12**, as well as the absolute configurations within **7**–**11**. The synthesis of (−)-(*S*,*S*)-homaline **1** was then completed upon treatment of **12** with 1,4-dibromobutane and KOH in DMSO which gave, after chromatographic purification of the crude reaction mixture, (−)-(*S*,*S*)-homaline **1** in 60% yield and >99:1 dr (Scheme 1).



Scheme 1. Reagents and conditions: (i) (*R*)-**6**, THF, −78 °C, 2 h; (ii) TFA, 60 °C, 2.5 h; (iii) $(CH_2O)_n$, MeOH, $NaBH_3CN$, rt, 18 h; (iv) NaN_3, NaI, DMSO, 50 °C, 24 h; (v) PPh_3, THF/H_2O (v/v 7:3), 50 °C, 2 h; (vi) $Sb(OEt)_3$, PhMe, reflux, 18 h; (vii) $Br(CH_2)_4Br$, KOH, DMSO, rt, 4 d. [PMP = *p*-methoxyphenyl].

The spectroscopic data obtained for this sample[20] of (−)-(*S*,*S*)-homaline **1** were in excellent agreement with those for the sample isolated from the natural source {$[\alpha]_D^{21}$ −28.1 (*c* 1.0 in $CHCl_3$); Lit.[1f] $[\alpha]_D^{20}$ −34 (*c* 1.0 in $CHCl_3$)}, and other samples obtained by total synthesis.[21] This synthesis of (−)-(*S*,*S*)-homaline **1** was completed in 8 steps and 18% overall yield from commercially available starting materials, representing the first asymmetric, and by far the most efficient, synthesis of this natural product reported to date. The application of this methodology in the synthesis of the unsymmetrical homalium alkaloids hopromine **2**, hopromінol **3** and hopromalinol **4** is ongoing within our laboratories.

Acknowledgment

The authors would like to thank the EPSRC–Pharma Synthesis Network for a CASE award (J.A.L.).

References and notes

1. (a) Païs, M.; Rattle, G.; Sarfati, R.; Jarreau, F.-X. *C. R. Seances Acad. Sci., Ser. C* **1968**, *266*, 37; (b) Païs, M.; Rattle, G.; Sarfati, R.; Jarreau, F.-X. *C. R. Seances Acad. Sci., Ser. C* **1968**, *267*, 82; (c) Païs, M.; Sarfati, R.; Jarreau, F.-X.; Goutarel, R. *C. R. Seances Acad. Sci., Ser. C* **1971**, *272*, 1728; (d) Sarfati, R.; Païs, M.; Jarreau, F.-X. *Bull. Soc. Chim. Fr.* **1971**, 255; (e) Païs, M.; Sarfati, R.; Jarreau, F.-X. *Bull. Soc. Chim. Fr.* **1973**, 331; (f) Païs, M.; Sarfati, R.; Jarreau, F.-X.; Goutarel, R. *Tetrahedron* **1973**, *29*, 1001.
2. (*S*,*S*)-Homaline **1** is the only member of this family of alkaloids whose structure has been confirmed unambiguously by single crystal X-ray diffraction analysis, see: Lefebvre-Soubeyran, O. *Acta Crystallogr. B* **1976**, *32*, 1305.
3. Wasserman, H. H.; Berger, G. D.; Cho, K. R. *Tetrahedron Lett.* **1982**, *23*, 465.
4. Wasserman, H. H.; Berger, G. D. *Tetrahedron* **1983**, *39*, 2459.
5. Pietsch, H. *Tetrahedron Lett.* **1972**, *13*, 2789.
6. Crombie, L.; Jones, R. C. F.; Mat-Zin, A. R.; Osborne, S. *J. Chem. Soc., Chem. Commun.* **1983**, 960.
7. Crombie, L.; Haigh, D.; Jones, R. C. F.; Mat-Zin, A. R. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2047.
8. Crombie, L.; Jones, R. C. F.; Haigh, D. *Tetrahedron Lett.* **1986**, *27*, 5147.
9. Crombie, L.; Haigh, D.; Jones, R. C. F.; Mat-Zin, A. R. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2055.
10. Itoh, N.; Matsuyama, H.; Yoshida, M.; Kamigata, N.; Iyoda, M. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 3121.
11. Ensch, C.; Hesse, M. *Helv. Chim. Acta* **2002**, *85*, 1659.
12. Ensch, C.; Hesse, M. *Helv. Chim. Acta* **2003**, *86*, 233.
13. (a) Davies, S. G.; Ichihara, O. *Tetrahedron: Asymmetry* **1991**, *2*, 183; (b) Davies, S. G.; Garrido, N. M.; Kruchinin, D.; Ichihara, O.; Kotchie, L. J.; Price, P. D.; Price Mortimer, A. J.; Russell, A. J.; Smith, A. D. *Tetrahedron: Asymmetry* **2006**, *17*, 1793; (c) Davies, S. G.; Nicholson, R. L.; Price, P. D.; Roberts, P. M.; Russell, A. J.; Savory, E. D.; Smith, A. D.; Thomson, J. E. *Tetrahedron: Asymmetry* **2009**, *20*, 758; (d) Davies, S. G.; Garner, A. C.; Nicholson, R. L.; Osborne, J.; Roberts, P. M.; Savory, E. D.; Smith, A. D.; Thomson, J. E. *Org. Biomol. Chem.* **2009**, *7*, 2604; (e) Davies, S. G.; Mujtaba, N.; Roberts, P. M.; Smith, A. D.; Thomson, J. E. *Org. Lett.* **2009**, *11*, 1959; (f) Bentley, S. A.; Davies, S. G.; Lee, J. A.; Roberts, P. M.; Russell, A. J.; Thomson, J. E.; Toms, S. M. *Tetrahedron* **2010**, *66*, 4604; (g) Abraham, E.; Bailey, C. W.; Claridge, T. D. W.; Davies, S. G.; Ling, K. B.; Odell, B.; Rees, T. L.; Roberts, P. M.; Russell, A. J.; Smith, A. D.; Smith, L. J.; Storr, H. R.; Sweet, M. J.; Thompson, A. L.; Thomson, J. E.; Tranter, G. E.; Watkin, D. J. *Tetrahedron: Asymmetry* **2010**, *21*, 1797; (h) Abraham, E.; Claridge, T. D. W.; Davies, S. G.; Odell, B.; Roberts, P. M.; Russell, A. J.; Smith, A. D.; Smith, L. J.; Storr, H. R.; Sweet, M. J.; Thompson, A. L.; Thomson, J. E.; Tranter, G. E.; Watkin, D. J. *Tetrahedron: Asymmetry* **2011**, *22*, 69; (i) Brock, E. A.; Davies, S. G.; Lee, J. A.; Roberts, P. M.; Thomson, J. E. *Org. Lett.* **2011**, *13*, 1594; (j) Bagal, S. K.; Davies, S. G.; Fletcher, A. M.; Lee, J. A.; Roberts, P. M.; Scott, P. M.; Thomson, J. E. *Tetrahedron Lett.* **2011**, *52*, 2216.
14. For selected examples from this laboratory, see: (a) Davies, S. G.; Iwamoto, K.; Smethurst, C. A. P.; Smith, A. D.; Rodriguez-Solla, H. *Synlett* **2002**, 1146; (b) Davies, S. G.; Kelly, R. J.; Price Mortimer, A. J. *Chem. Commun.* **2003**, 2132; (c) Davies, S. G.; Burke, A. J.; Garner, A. C.; McCarthy, T. D.; Roberts, P. M.; Smith, A. D.; Rodriguez-Solla, H.; Vickers, R. J. *Org. Biomol. Chem.* **2004**, *2*, 1387; (d) Davies, S. G.; Haggitt, J. R.; Ichihara, O.; Kelly, R. J.; Leech, M. A.; Price Mortimer, A. J.; Roberts, P. M.; Smith, A. D. *Org. Biomol. Chem.* **2004**, *2*, 2630; (e) Abraham, E.; Candela-Lena, J. I.; Davies, S. G.; Georgiou, M.; Nicholson, R. L.; Roberts, P. M.; Russell, A. J.; Sánchez-Fernández, E. M.; Smith, A. D.; Thomson, J. E. *Tetrahedron: Asymmetry* **2007**, *18*, 2510; (f) Abraham, E.; Davies, S. G.; Millican, N. L.; Nicholson, R. L.; Roberts, P. M.; Smith, A. D. *Org. Biomol. Chem.* **2008**, *6*, 1655; (g) Abraham, E.; Brock, E. A.; Candela-Lena, J. I.; Davies, S. G.; Georgiou, M.; Nicholson, R. L.; Perkins, J. H.; Roberts, P. M.; Russell, A. J.; Sánchez-Fernández, E. M.; Scott, P. M.; Smith, A. D.; Thomson, J. E. *Org. Biomol. Chem.* **2008**, *6*, 1665; (h) Davies, S. G.; Fletcher, A. M.; Roberts, P. M.; Smith, A. D.

Tetrahedron **2009**, *65*, 10192; (i) Bentley, S. A.; Davies, S. G.; Lee, J. A.; Roberts, P. M.; Thomson, J. E. *Org. Lett.* **2011**, *13*, 2544; (j) Davies, S. G.; Ichihara, O.; Roberts, P. M.; Thomson, J. E. *Tetrahedron* **2011**, *67*, 216; (k) Davies, S. G.; Fletcher, A. M.; Hughes, D. G.; Lee, J. A.; Price, P. D.; Roberts, P. M.; Russell, A. J.; Smith, A. D.; Thomson, J. E.; Williams, O. M. H. *Tetrahedron* **2011**, *67*, 9975; (l) Davies, S. G.; Lee, J. A.; Roberts, P. M.; Thomson, J. E.; West, C. J. *Tetrahedron Lett.* **2011**, *52*, 6477.

15. For selected examples from this laboratory, see: (a) Cailleau, T.; Cooke, J. W. B.; Davies, S. G.; Ling, K. B.; Naylor, A.; Nicholson, R. L.; Price, P. D.; Roberts, P. M.; Russell, A. J.; Smith, A. D.; Thomson, J. E. *Org. Biomol. Chem.* **2007**, *5*, 3922; (b) Davies, S. G.; Durbin, M. J.; Goddard, E. C.; Kelly, P. M.; Kurosawa, W.; Lee, J. A.; Nicholson, R. L.; Price, P. D.; Roberts, P. M.; Russell, A. J.; Scott, P. M.; Smith, A. D. *Org. Biomol. Chem.* **2009**, *7*, 761.
16. For selected examples from this laboratory, see: (a) Davies, S. G.; Garner, A. C.; Long, M. J. C.; Morrison, R. M.; Roberts, P. M.; Smith, A. D.; Sweet, M. J.; Withey, J. M. *Org. Biomol. Chem.* **2005**, *3*, 2762; (b) Aye, Y.; Davies, S. G.; Garner, A. C.; Roberts, P. M.; Smith, A. D.; Thomson, J. E. *Org. Biomol. Chem.* **2008**, *6*, 2195; (c) Abraham, E.; Davies, S. G.; Docherty, A. J.; Ling, K. B.; Roberts, P. M.; Russell, A. J.; Thomson, J. E.; Toms, S. M. *Tetrahedron: Asymmetry* **2008**, *19*, 1356; (d) Davies, S. G.; Durbin, M. J.; Hartman, S. J. S.; Matsuno, A.; Roberts, P. M.; Russell, A. J.; Smith, A. D.; Thomson, J. E.; Toms, S. M. *Tetrahedron: Asymmetry* **2008**, *19*, 2870.
17. Davies, S. G.; Smith, A. D.; Price, P. D. *Tetrahedron: Asymmetry* **2005**, *16*, 2833.
18. Enantiopure (*R*)-α-methyl-*p*-methoxybenzylamine (99% ee) is commercially available. Alkylation of (*R*)-α-methyl-*p*-methoxybenzylamine upon treatment with 1-bromo-3-chloropropane gave (*R*)-(3-chloropropyl)-*N*-(α-methyl-*p*-methoxybenzyl)amine in 70% yield; subsequent deprotonation with BuLi in THF generated a yellow solution of lithium (*R*)-*N*-(3-chloropropyl)-*N*-(α-methyl-*p*-methoxybenzyl)amide (*R*)-**6**.
19. Costello, J. F.; Davies, S. G.; Ichihara, O. *Tetrahedron: Asymmetry* **1999**, *1994*, 10.
20. (*S*,*S*)-1,4-Di-[2′-oxo-4′-phenyl-*N*(5′)-methyl-1′,5′-diazocan-*N*(1′)-yl]butane [(−)-(*S*,*S*)-homaline] **1**: mp 115–117 °C; $[\alpha]_D^{21}$ −28.1 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 1630 (C=O); δ_H (400 MHz, $CDCl_3$) 1.57–1.67 (6H, m, C(2)H_2, C(3)H_2, 2 × C(7′)H_A), 1.76–1.87 (2H, m, 2 × C(7′)H_B), 2.26 (6H, s, 2 × N*Me*), 2.47–2.55 (4H, m, 2 × C(3′)H_A, 2 × C(6′)H_A), 2.93–3.08 (4H, m, C(1)H_A, C(4)H_A 2 × C(6′)H_B), 3.16 (2H, app t, *J* 12.1, 2 × C(3′)H_B), 3.32 (2H, app dt, *J* 15.4, 3.5, 2 × C(8′)H_A), 3.77–3.90 (4H, m, C(1)H_B, C(4)H_B, 2 × C(8′)H_B), 4.00 (2H, dd, *J* 11.6, 3.0, 2 × C(4′)*H*), 7.23–7.34 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 25.4 (*C*(2), *C*(3)), 29.9 (2 × *C*(7′)), 41.2 (2 × *C*(3′)), 43.7 (2 × N*Me*), 45.7 (*C*(1), *C*(4)), 47.9 (2 × *C*(8′)), 51.0 (2 × *C*(6′)), 68.1 (2 × *C*(4′)), 127.1, 127.5, 128.3 (*o*,*m*,*p*-*Ph*), 142.0 (*i*-*Ph*), 173.5 (2 × *C*(1′)); *m*/*z* (ESI^+) 982 ($[2M+H]^+$, 43%), 513 ($[M+Na]^+$, 100%), 491 ($[M+H]^+$, 96%); HRMS (ESI^+) $C_{30}H_{43}N_4O_2^+$ ($[M+H]^+$) requires 491.3381; found 491.3389.
21. See; Ref. 3: $[\alpha]_D^{24}$ −30 (*c* 0.43 in $CHCl_3$); Ref. 4: $[\alpha]_D^{24}$ −35 (*c* 0.92 in $CHCl_3$); Ref. 6: $[\alpha]_D^{22}$ −32 (*c* 0.95 in $CHCl_3$); Ref. 7: $[\alpha]_D^{22}$ −32 (*c* 0.95 in $CHCl_3$).