Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 48 (2007) 7279–7282

A stereoselective total synthesis of (−)-andrachcinidine via an olefin cross-metathesis protocol

Palakodety Radha Krishna* and G. Dayaker

D-206/B, Discovery Laboratory, Organic Chemistry Division-III, Indian Institute of Chemical Technology, Hyderabad 500 007, India

Received 11 July 2007; revised 8 August 2007; accepted 13 August 2007
Available online 16 August 2007

Abstract—A stereoselective total synthesis of 1-(2*S*,6*R*)-6-[(2*S*)-2-hydroxypentyl]-hexahydro-2-pyridinylacetone, (−)-andrachcinidine is reported. The strategy utilizes olefin cross-metathesis and intramolecular S_N2 cyclization as the key steps.

The piperidine ring is a common structural feature of numerous naturally occurring alkaloids and can be frequently recognized in the structure of drug candidates.[1] Substituted five- or six-membered N-heterocycles are found in numerous natural products and pharmaceutical compounds and they continue to attract considerable attention, due to their broad and important biological activities. It is interesting to note that over 12,000 piperidine derivatives have been reported in clinical or preclinical studies in the last decade.[2]

The plant *Andrachne aspera* spreng is a small perennial undershrub commonly found in Karachi and is used in the local system of medicine for the treatment of eye sores and eye sight improvement. The crude alkaloidal mixture was found to be biologically potent with predominantly antibacterial activity.[3] *A. aspera* spreng was previously shown to contain the piperidine alkaloids andrachamine and andrachcine.[3,4] Recently, two new 2,6-disubstituted piperidine alkaloids, namely, andrachcinine and (−)-andrachcinidine **1** have been isolated from *A. aspera* spreng.[5]

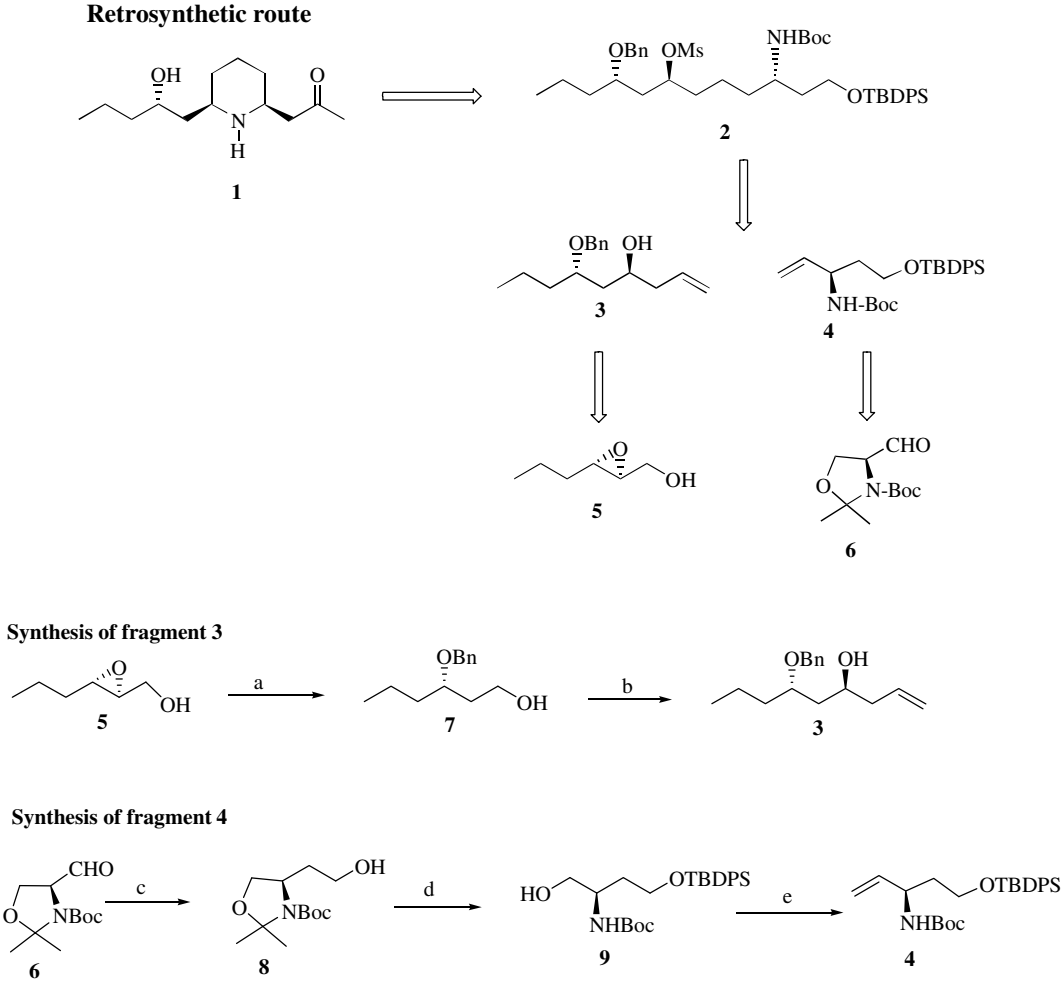
The development of new methods for the synthesis of pyrrolidine- or piperidine-based compounds is of considerable importance, particularly approaches leading to chiral derivatives. Lanny and Chutian[6] reported the first synthesis of **1** using chiral auxiliary-induced pseudo-desymmetrization in the presence of molybdenum complexes. In continuation of our interest in the synthesis of piperidine-containing bioactive natural products,[7] we report herein the stereoselective total synthesis of **1** using olefin cross-metathesis to prepare the requisite carbon chain with correctly disposed stereogenic centers and functional groups and an intramolecular nucleophilic cyclization to construct the piperidine ring system as the key step.

Retrosynthetic analysis suggested that **1** could be obtained from **2** by intramolecular S_N2 cyclization and functional group transformations. Compound **2** in turn could be formed from **3** and **4** by olefin cross-metathesis, hydrogenation, and mesylation reactions. Fragment **3** can be visualized from **5** by a regioselective ring opening reaction of an epoxide and 1,3-*anti* chiral allylation. Alkene **4** was conceived from Garner's aldehyde by Wittig olefination and hydroboration reactions.

The synthesis of fragment **3** began from known epoxide **5** (Scheme 1), which was readily obtained from *trans*-2-hexenol.[8] Regioselective ring-opening of **5** with Red-Al in dry THF gave the corresponding 1,3-diol[9] (80%), which was converted into a benzylidene derivative with benzaldehyde dimethyl acetal in CH_2Cl_2 using PTSA (cat) to afford an acetal (95%), selective opening of which with LAH–$AlCl_3$ furnished benzyl protected primary alcohol **7** (90%). Alcohol **7** was oxidized under Swern conditions and then allylated[10] ($TiCl_4$/allyltrimethylsilane) to afford fragment **3** (de 90%, 80% yield over the two steps) in favor of the 1,3-*anti* isomer.

Keywords: Garner's aldehyde; Hydroboration; 1,3-*anti* Chiral allylation; Sharpless asymmetric epoxidation; Grubbs' catalyst; Olefin cross-metathesis; Intramolecular S_N2 cyclization.
* Corresponding author. Tel.: +91 40 27160123x2651; fax: +91 40 27160387; e-mail: prkgenius@iict.res.in

0040-4039/$ - see front matter © 2007 Published by Elsevier Ltd.
doi:10.1016/j.tetlet.2007.08.053



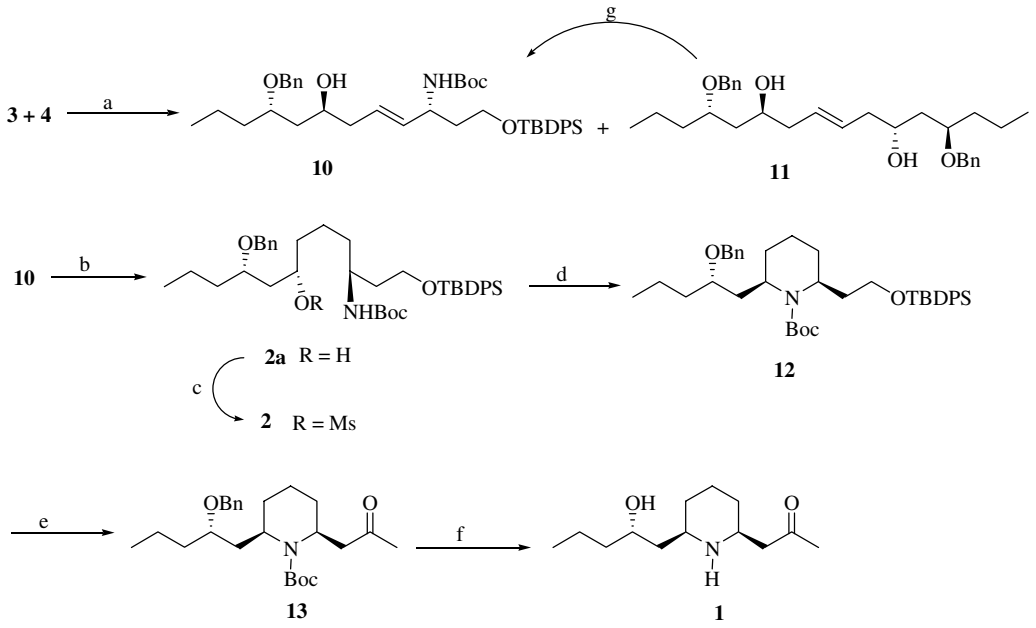
Scheme 1. Reagents and conditions: (a) (i) Red-Al, THF, 0 °C to rt, 80%, (ii) $PhCH(OMe)_2$, CH_2Cl_2, PTSA (cat), rt, 95%, (iii) LAH–$AlCl_3$, ether, 0 °C, 90%; (b) (i) $(COCl)_2$, DMSO, Et_3N, −78 °C, (ii) $TiCl_4$, allyltrimethylsilane, CH_2Cl_2, −78 °C, (80% over two steps); (c) (i) $CH_3{}^+PPh_3I^-$, KO^{t}Bu, THF, 0 °C, 78%, (ii) $(Cy)_2BH$, THF, 0 °C, 95%; (d) (i) TBDPSCl, imidazole, CH_2Cl_2, rt, 95%, (ii) $CuCl_2{\cdot}2H_2O$, CH_3CN, 90%; (e) (i) $(COCl)_2$, DMSO, Et_3N, −78 °C, 95%, (ii) $CH_3{}^+PPh_3I^-$, KO^{t}Bu, THF, 0 °C, THF, 0 °C, 66%.

The synthesis of fragment **4** started from Garner's aldehyde[11] **6**, which on Wittig olefination and hydroboration with dicyclohexylborane [$(Cy)_2BH$] afforded homologated primary alcohol **8** (95%) as the exclusive product. Next, alcohol **8** was silylated (TBDPSCl/imidazole/CH_2Cl_2/rt) and then exposed to $CuCl_2{\cdot}2H_2O$[12] in acetonitrile to give the free alcohol **9** (90%). Oxidation of **9** under Swern conditions followed by Wittig olefination furnished fragment **4**.

In order to access intermediate **10** (Scheme 2) we adopted the olefin cross-metathesis strategy through the coupling of fragments **3** and **4** using Grubbs' catalyst.[13] Initially we attempted the reaction in CH_2Cl_2 or toluene as the solvent in combination with Grubbs' 1st generation (**A**) or 2nd generation (**B**) catalysts. The best yield of **10** (60%), was obtained when olefin cross-metathesis was performed using **3** and **4** in 1:2 ratio with Grubbs' 2nd generation catalyst in toluene (Table 1, entry 5). All the other results are tabulated.

During the cross-metathesis reaction we observed the formation of homo-coupled **11** in yields ranging from 15% to 80% (Table 1, Scheme 2). However, **11** could be recycled effectively to the desired olefin **10** (75%) by utilizing a cross-metathesis reaction with **4** under standardized reaction conditions (**4**:**11** in a 2:1 ratio, Grubbs' 2nd generation catalyst). Hydrogenation of **10** (PtO_2–$NaHCO_3$/H_2) and subsequent mesylation of resulting **2a** [MsCl/Et_3N/DMAP (cat)/−15 to 0 °C] afforded mesylate **2** in 80% yield. Boc deprotection (TFA/CH_2Cl_2/0 °C to rt) of **2** followed by intramolecular S_N2 cyclization[14] (K_2CO_3/CH_3CN/rt) and Boc protection of the ensuing secondary amine [$(Boc)_2O$/Et_3N/CH_2Cl_2/0 °C to rt] afforded 2,6-disubstituted piperidine derivative **12**.

Silyl deprotection of **12** (TBAF/THF/0 °C to rt) and Dess–Martin periodinane oxidation (DMP/CH_2Cl_2/0 °C to rt) followed by Grignard reaction (MeMgI/ether) gave the corresponding secondary alcohol, which on further oxidation with Dess–Martin periodinane gave methyl ketone[15] **13** (80%). Hydrogenation (10% Pd–C/MeOH) of **13** and Boc deprotection (TFA/CH_2Cl_2/0 °C to rt) gave target compound **1** (50%), $[\alpha]_D^{25}$ −23.0 (*c* 0.25, $CHCl_3$) {natural **1**; $[\alpha]_D^{25}$ −20.0 (*c*



Scheme 2. Reagents and conditions: (a) Grubbs' 2nd generation catalyst (**B**, 10 mol %), toluene, 110 °C, 18 h, 60%; (b) PtO_2–$NaHCO_3/H_2$, EtOAc, rt, 95%; (c) Et_3N, MsCl, DMAP (cat), −15 to 0 °C, 80%; (d) (i) TFA, CH_2Cl_2, 0 °C to rt, 2M K_2CO_3, (ii) K_2CO_3, CH_3CN, rt, (iii) Et_3N, $(Boc)_2O$, CH_2Cl_2, 0 °C to rt; (e) (i) TBAF, THF, 0 °C to rt, 80%, (ii) DMP, CH_2Cl_2, 0 °C to rt, 80%, (iii) CH_3MgI, ether, 0 °C to rt, 60%, (iv) DMP, CH_2Cl_2, 0 °C to rt, 80%; (f) (i) 10% Pd–C/H_2, MeOH, rt, 90%, (ii) TFA, 0 °C to rt, CH_2Cl_2, 2M K_2CO_3, 50%; (g) **4**, Grubbs' 2nd generation catalyst (**B**, 10 mol %), toluene, 110 °C, 24 h, 75%.

Table 1. Study of the olefin cross-metathesis reaction of **3** and **4** under various reaction conditions

Entry	**3**:**4** (equiv)	Catalyst (10 mol %)	Solvent	Time (h)	Yield (%)	
					10	**11**
1	2:1	**A**	CH_2Cl_2	24	5	80
2	1:1	**A**	CH_2Cl_2	24	10	70
3	1:2	**A**	CH_2Cl_2	24	10	70
4	1:2	**B**	CH_2Cl_2	24	20	50
5	1:2	**B**	Toluene	18	60	15

1.6, $CHCl_3$)}.[5] The physical and spectroscopic data of synthetic sample **1**[16] were identical to those of the natural product.[5]

In conclusion, the stereoselective synthesis of **1** has been accomplished by an olefin cross-metathesis approach to access the requisite cyclization precursor, which was elaborated to the target compound. The synthesis reported herein is general and could be adopted for accessing related natural products.

Acknowledgment

One of the authors (G.D.) thanks the UGC, New Delhi, for financial support in the form of a fellowship.

References and notes

1. Lebrum, S.; Couture, A.; Deniau, E.; Grandclaydon, P. *Org. Lett.* **2007**, *9*, 2473–2476.
2. Felpin, F.-X.; Lebreton, J. *Curr. Org. Synth.* **2004**, *1*, 83–109.
3. Ahmed, V. Q.; Nasir, M. A. *Phytochemistry* **1986**, *24*, 2841–2844.
4. Ahmed, V. Q.; Nasir, M. A. *Phytochemistry* **1987**, *26*, 585–586.
5. Mill, S.; Hootelé, C. *J. Nat. Prod.* **2000**, *63*, 762–764.
6. Chutian, S.; Lanny, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 2878–2879.
7. (a) Radha Krishna, P.; Krishnarao, L. *Synlett* **2007**, 1742–1745; (b) Radha Krishna, P.; Sreeshailam, A. *Tetrahedron Lett*. **2007** *48*, in press.
8. (a) Gao, Y.; Hanson, R. M.; Kluder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765–5780; (b) Brunner, H.; Sicheneder, A. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 718–719.
9. Steven, M. V. *Tetrahedron Lett.* **1982**, *23*, 4541–4544.
10. Reetz, M. T.; Jung, A. *J. Am. Chem. Soc.* **1983**, *105*, 4833–4835.
11. Garner, P.; Ramakanth, S. *J. Org. Chem.* **1986**, *51*, 2609–2912.
12. Chandrasekhar, M.; Chandra, K. L.; Singh, V. K. *J. Org. Chem.* **2003**, *68*, 4039–4045.
13. (a) Grubbs, R. H. *Tetrahedron* **2004**, *60*, 7117–7140; (b) Nolen, E. G.; Kurish, A. J.; Wong, K. A.; Orlando, M. D. *Tetrahedron Lett.* **2003**, *44*, 2449–2453.
14. Takashi, L. S.; Gerwick, H. *Org. Lett.* **2006**, *8*, 4541–4543.
15. Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277–7278.
16. *Spectral data for selected compounds.* Compound **3**: light yellow liquid; $[\alpha]_D^{25}$ +52.89 (*c* 0.55, $CHCl_3$): ^1H NMR (200 MHz, $CDCl_3$): δ 7.35–7.20 (m, 5H, Ar-H), 5.91–5.66 (m, 1H, CH), 5.03 (d, 2H, $J = 13.2$ Hz, CH_2), 4.52 (d, 2H, $J = 2.3$ Hz, CH_2–Ph), 3.98–3.82 (m, 1H, CH), 3.75–3.60 (m, 1H, CH), 2.58 (br s, 1H, OH), 2.18 (t, 2H, $J = 6.2$ Hz, CH_2), 1.76–1.25 (m, 6H, $3 \times CH_2$), 0.92 (t, 3H, $J = 7.8$ Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.3, 134.8, 128.3,

127.8, 127.6, 117.3, 76.8, 71.1, 67.7, 42.1, 39.3, 35.7, 18.6, 14.1; IR (neat) 3400, 3050, 2950, 1590 cm^{-1}; ESI-MS; 271 $[M+Na]^+$, 249 $[M+H]^+$. Anal. Calcd for $C_{16}H_{24}O_2$: C, 77.38; H, 9.74. Found: C, 77.33; H, 9.78. Compound **4**: light yellow liquid; $[\alpha]_D^{25}$ +8.13 (*c* 0.30, $CHCl_3$): ^1H NMR (200 MHz, $CDCl_3$): δ 7.69–7.57 (m, 4H, Ar-H), 7.38–7.29 (m, 6H, Ar-H), 5.84–5.65 (m, 1H, CH), 5.50–5.37 (m, 1H, NH–Boc), 5.31–5.05 (m, 2H, CH_2), 4.39–4.23 (m, 1H, CH), 3.86–3.58 (m, 2H, CH_2), 1.99–1.79 (m, 1H, CH), 1.72–1.51 (m, 1H, CH), 1.43 (s, 9H), 1.05 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.4, 138.3, 135.6, 134.7, 133.2, 129.6, 127.5, 114.3, 61.0, 51.3, 28.3, 26.7, 26.5, 19.0; IR (neat) 3300, 3015, 2900, 1690, 1580 cm^{-1}; ESI-MS; 440 $[M+H]^+$. Anal. Calcd for $C_{26}H_{37}NO_3Si$: C, 71.03; H, 8.48; N, 3.19. Found: C, 71.10; H, 8.44; N, 3.23. Compound **2a**: Syrupy liquid; $[\alpha]_D^{25}$ +32.53 (*c* 0.30, $CHCl_3$): ^1H NMR (300 MHz, $CDCl_3$): δ 7.64–7.59 (m, 4H, Ar-H), 7.41–7.20 (m, 11H, Ar-H), 4.97 (t, 1H, $J = 9.8$ Hz, NH–Boc), 4.52 (d, 2H, $J = 2.2$ Hz, CH_2–Ph), 3.89–3.63 (m, 5H), 1.86–1.74 (m, 1H), 1.56–1.28 (m, 22H), 1.04 (s, 9H), 0.92 (t, 3H, $J = 6.7$ Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.7, 138.4, 135.5, 133.4, 129.6, 128.3, 127.8, 127.6, 78.63, 71.1, 68.3, 61.2, 48.8, 39.9, 39.6, 37.6, 35.7, 28.4, 26.8, 22.0, 21.8, 19.0, 18.7, 14.1; IR (neat) 3400, 3015, 2940, 1670, 1550 cm^{-1}; ESI-MS; 684 $[M+Na]^+$, 662 $[M+H]^+$. Anal. Calcd for $C_{40}H_{59}NO_5Si$: C, 72.57; H, 8.98; N, 2.12. Found: C, 72.54; H, 9.00; N, 2.14. Compound **13**: Colorless syrupy liquid;$[\alpha]_D^{25}$ −4.56 (*c* 0.66, $CHCl_3$): ^1H NMR (300 MHz, $CDCl_3$): δ 7.39–7.22 (m, 5H, Ar-H), 4.54 (dd, 2H, $J = 11.7$, 19.2 Hz, CH_2–Ph), 4.19–4.09 (m, 1H, CH), 4.09–3.99 (m, 1H, CH), 3.46 (p, 1H, $J = 5.8$ Hz, CH), 3.04 (dd, 1H, $J = 5.2$, 16.6 Hz, CH), 2.62 (dd, 1H, $J = 8.4$, 16.6 Hz, CH), 2.14 (s, 3H, CH_3), 2.06 (dd, 1H, $J = 7.1$, 16.0 Hz, CH), 1.73–1.49 (m, 8H), 1.43 (s + m, 12H), 0.91 (t, 3H, $J = 7.3$ Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 206.9, 155.3, 139.1, 128.1, 127.6, 127.2, 79.3, 76.4, 70.5, 49.9, 48.2, 47.9, 36.7, 35.9, 30.1, 28.4, 27.0, 26.0, 18.5, 16.6, 14.2; IR (neat) 3030, 2900, 1740, 1580 cm^{-1}; ESI-MS; 440 $[M+Na]^+$, 418 $[M+H]^+$. Anal. Calcd for $C_{25}H_{39}NO_4$: C, 71.91; H, 9.41; N, 3.35. Found: C, 71.93; H, 9.39; N, 3.31. Compound **1**: Yellow oil; $[\alpha]_D^{25}$ −23.0 (*c* 0.25, $CHCl_3$): ^1H NMR (400 MHz, $CDCl_3$): δ 3.84–3.80 (m, 1H, CH), 3.18–3.11 (m, 2H, CH and NH), 3.07–2.99 (m, 1H, CH), 2.65 (m, 1H, CH), 2.19 (s + m, 4H, CH_3 and CH), 1.90–1.00 (m, 13H), 0.91 (t, 3H, $J = 6.7$ Hz, CH_3);^{13}C NMR (150 MHz, $CDCl_3$): δ 207.0, 72.9, 58.9, 53.0, 49.0, 43.5, 39.7, 33.4, 32.2, 30.0, 24.0, 18.6, 14.0; IR (neat) 3300, 2900, 1740 cm^{-1}; ESI-MS; 228 $[M+H]^+$. Anal. Calcd for $C_{13}H_{25}NO_2$: C, 68.68; H, 11.08; N, 6.16. Found: C, 68.63; H, 11.12; N, 6.15.