ORGANIC LETTERS

2001
Vol. 3, No. 12
1785−1788

First Enantioselective Syntheses of (+)- and (−)-Wilforonide by Using Chiral Auxiliaries Derived from the Same Chiral Source

Dan Yang* and Ming Xu

Department of Chemistry, The University of Hong Kong, Pokfulam Road, Hong Kong

yangdan@hku.hk

Received February 17, 2001

ABSTRACT

The first enantioselective syntheses of both (+)-wilforonide (>98% ee) and (−)-wilforonide (>98% ee) have been accomplished by employing chiral auxiliaries derived from the same chiral source, (*R*)-pulegone. The bicyclic skeleton of wilforonide was constructed by using Mn(III)-based oxidative radical cyclization reactions of chiral *β*-keto esters. The absolute configuration of natural wilforonide has been established to be (5a*R*,9a*R*).

Wilforonide, a terpenoid isolated from the Chinese medicinal herb *Triperygium wilfordii* Hook F (Lei Gong Teng),[1] was found to have significant antiinflammatory activity.[2] It was also effective in inhibiting T-cell proliferation and cytokine release.[2] As a potential probe molecule for investigating inflammation and immunosuppression processes, wilforonide became an important target for organic synthesis. The first synthesis of (±)-wilforonide, taking 10 steps starting from commercially available compounds, was synthesized by Coghlan and co-workers in 1998.[3] However, the absolute configuration of wilforonide was still unknown due to the minute quantities available from natural sources.[4] It is more challenging to complete the chiral syntheses of both enantiomers of wilforonide and examine the difference of their biological activities, which is essential for the development of more selective chiral wilforonide analogues. Recently, on the basis of the pioneering work by Snider and co-workers,[5] we developed an asymmetric Mn(III)-mediated oxidative radical cyclization method for the construction of polycyclic natural products by using chiral auxiliaries derived from the same chiral source, (*R*)-pulegone.[6] Here, we report the application of this method in the first enantioselective syntheses of both enantiomers of wilforonide and the establishment of the absolute configuration of natural wilforonide.

Our retrosynthetic scheme for racemic wilforonide is shown in Figure 1. The key steps involve (1) lactone

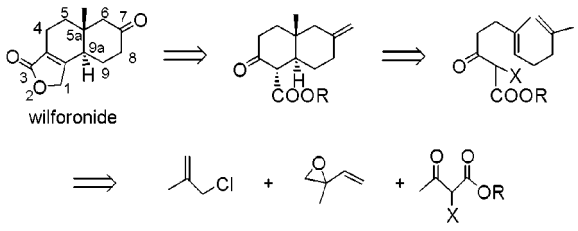
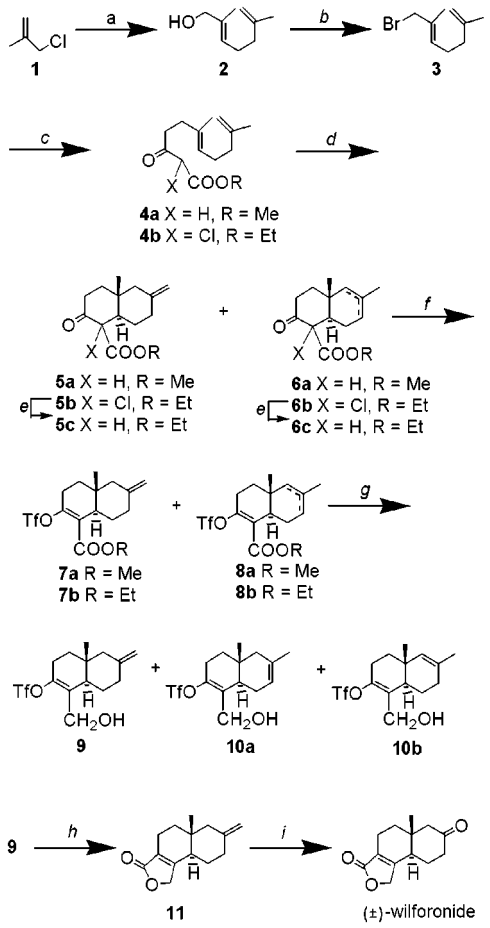


Figure 1.

(1) Chen, K.; Yang, R.; Wang, C. *Zhongcaoyao* **1986**, *17*, 242.
(2) (a) Lipsky, P. E.; Tao, X. L.; Cai, J.; Kovacs, W. J.; Olsen, N. J. U.S. Patent 5616458, 1997; *Chem. Abstr*. **1997**, *126*, 246818h. (b) Lipsky, P. E.; Tao, X. L.; Cai, J. U.S. Patent 5580562, 1996; *Chem. Abstr*. **1996**, *126*, 70141r.
(3) Schkeryantz, J. M.; Luly, J. R.; Coghlan, M. J. *Synlett* **1998**, 723.
(4) The absolute configuration of natural wilforonide was proposed to be (5a*R*,9a*R*) on the basis of similar CD absorption patterns of wilforonide and tripdiolide. See: Zhou, B. N.; Zhu, D. Y.; Deng, F. X.; Huang, C. G.; Kutney, J. P.; Roberts, M. *Planta Med.* **1988**, 330.

10.1021/ol015722p CCC: $20.00
Published on Web 05/12/2001

Scheme 1[a]



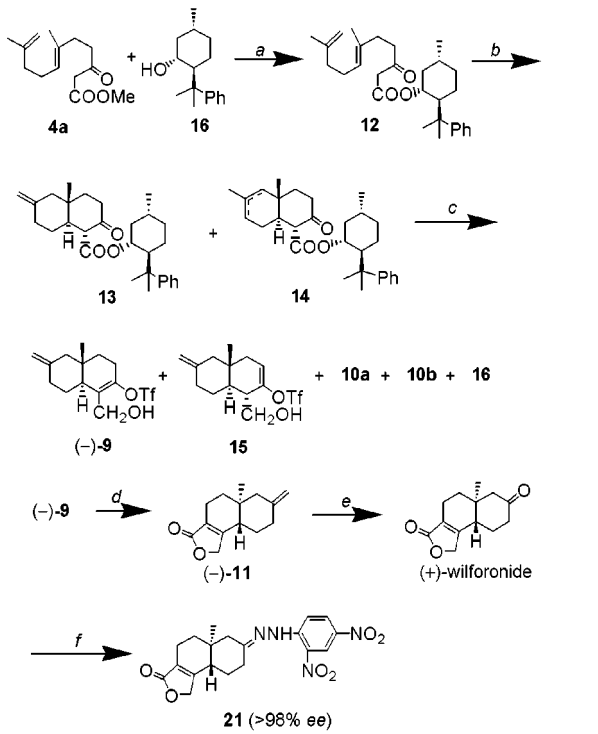
[a] Reagents and conditions: (a) Mg, THF, 0 to 25 °C, 15 h; CuI, 2-methyl-2-vinyloxirane, −20 °C, 1 h, 97% (*E*/*Z* ratio 13:1); (b) MsCl, Et_3N, CH_2Cl_2, −40 to −20 °C, 2 h; LiBr, THF, −20 to 25 °C, 3 h, 90%; (c) (i) $CH_3COCH_2COOCH_3$, NaH, *n*-BuLi, THF, 0 °C, 2 h, 82% of **4a**; (ii) $CH_3COCHClCOOCH_2CH_3$, LDA, THF, −10 °C, 2 h, 70% of **4b**; (d) (i) $Mn(OAc)_3 \cdot 2H_2O$, $Cu(OAc)_2$, HOAc, 25 °C, 24 h, 50% of **5a** and **6a** (ratio 2.5:1); (ii) $Mn(OAc)_3 \cdot 2H_2O$, $Cu(OAc)_2$, HOAc, 25 °C, 5 h, 70% of **5b** and **6b** (ratio 3.1:1); (e) Zn, HOAc, 25 °C, 5 h, 90% of **5c** and **6c** (ratio 3.1:1); (f) KHMDS, $PhNTf_2$, THF, −78 to 0 °C, 5 h; (g) DIBAL-H, CH_2Cl_2, −78 to −20 °C, 6 h, 56% in two steps (**9**: 74% based on the amount of **5a** or **5c** in the mixtures of **5a** and **6a** or **5c** and **6c**; (h) LiCl, Et_3N, $Pd(PPh_3)_4$, CO (1 atm), CH_3CN, 60 °C, 14 h, 94%; (i) $NaIO_4$, OsO_4, *t*-BuOH, H_2O, 85%.

formation, (2) radical cyclization, and (3) acyclic precursor construction.

As shown in Scheme 1, allylic alcohol **2** was prepared in 97% yield (*E*/*Z* = 13:1) by treating the Grignard reagent of 3-chloro-2-methyl-1-propene with 2-methyl-2-vinyloxriane in the presence of CuI.[7] Allylic alcohol **2** was converted to bromide **3**,[8] which upon treatment with the dianion of methyl acetoacetate or ethyl 2-chloroacetoacetate furnished acyclic precursor **4a** or **4b**, respectively.[9] Oxidative radical cyclization[10] of **4a** using $Mn(OAc)_3$ and $Cu(OAc)_2$ provided *trans*-ring junction compounds **5a** and **6a** (ratio 2.5:1) as major products (50% yield), along with a *cis*-ring junction product (18% yield). Meanwhile, cyclization of precursor **4b** with an α-chloro substituent afforded only the *trans*-ring junction products **5b** and **6b**, which were subsequently dechlorinated with Zn/HOAc[11] to give **5c** and **6c** (ratio 3.1:1) in 63% yield in two steps. Following the method developed by Crisp,[12] vinyl triflates **7a/b** and **8a/b** were obtained by treating the cyclization products **5a/c** and **6a/c** with KHMDS followed by $PhNTf_2$. DIBAL-H reduction of **7a/b** and **8a/b** in dichloromethane produced allylic alcohols **9** and **10**, which could be separated by using flash column chromatography. Subsequent Pd-catalyzed carbonylation of allylic alcohol **9** provided lactone **11** in 94% yield. Oxidative cleavage of **11** with $OsO_4/NaIO_4$[13] afforded (±)-wilforonide in 85% yield. Thus far, a concise total synthesis of (±)-wilforonide was accomplished in eight steps in 14.0% total yield or in nine steps in 16.4% total yield, which was about 10 times higher than the one reported in recent literature (1.5% total yield for 10 steps).[3]

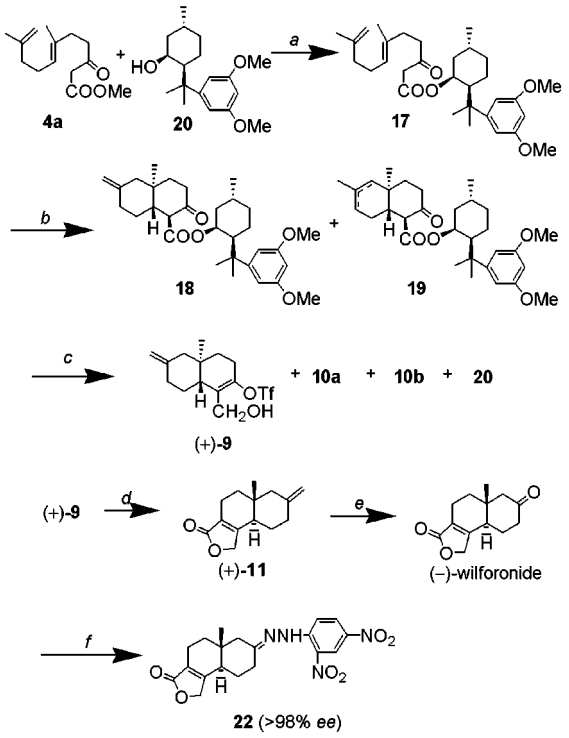
For the asymmetric syntheses of both enantiomers of wilforonide, chiral auxiliaries **16** and **20**,[6] derived from the same chiral source, (*R*)-pulegone,[14] were incorporated into chiral *β*-keto esters **12** (Scheme 2) and **17** (Scheme 3), respectively, by ester exchange with achiral precursor **4a**.[15] Cyclization of **12** with $Mn(OAc)_3$ and $Cu(OAc)_2$ in CF_3CH_2-OH at 0 °C[16] provided products **13** and **14** (ratio 1:1.2) in 50% yield. Because the α-protons of *β*-keto esters **13** and

Scheme 2[a]



[a] Reagents and conditions: (a) DMAP, toluene, reflux, 30 h, 95%; (b) $Mn(OAc)_3 \cdot 2H_2O$, $Cu(OAc)_2$, CF_3CH_2OH, 0 °C, 12 h, 51% of **13** and **14** (ratio 1:1.2); (c) (i) KHMDS, $PhNTf_2$, THF; (ii) DIBAL-H, CH_2Cl_2, 12% of (−)-**9**, 20% of **10**, 10% of **15**, and recovered 83% of **16** in two steps; (d) LiCl, Et_3N, $Pd(PPh_3)_4$, CO (1 atm), CH_3CN, 60 °C, 14 h, 94%; (e) $NaIO_4$, OsO_4, *t*-BuOH, H_2O, 85%; (f) 2,4-DNP, $EtOH/H^+$, 60%.

Scheme 3[a]



[a] Reagents and conditions: (a) DMAP, toluene, reflux, 30 h, 97%; (b) $Mn(OAc)_3 \cdot 2H_2O$, $Cu(OAc)_2$, $Yb(OTf)_3$, CF_3CH_2OH, −10 to 0 °C, 10 h, 50% of **18** and **19** (ratio 1.2:1); (c) (i) KHMDS, $PhNTf_2$, THF; (ii) DIBAL-H, CH_2Cl_2, 33% of (+)-**9**, 20% of **10**, and recovered 82% of **20** in two steps; (d) LiCl, Et_3N, $Pd(PPh_3)_4$, CO (1 atm), CH_3CN, 60 °C, 14 h, 94%; (e) $NaIO_4$, OsO_4, *t*-BuOH, H_2O, 85%; (f) 2,4-DNP, $EtOH/H^+$, 60%.

14 were shielded by the phenyl group of the auxiliary[17] and the angular methyl group of the cyclic skeleton (Figure 2), the deprotonation, followed by reduction with DIBAL, resulted in a low chemical yield of the desired product (−)-**9** (12% yield, 27% based on the amount of **13** in the mixture of **13** and **14**) along with a side product, **15**. With the chiral intermediate (−)-**9** in hand, we accomplished the first enantioselective synthesis of (+)-wilforonide ($[\alpha]_D$ +25.1° (*c* 0.18, CH_2Cl_2)) by following the same procedure shown in Scheme 1. While the direct determination of the enantiomeric purity of synthetic (+)-wilforonide failed, the HPLC analysis of its 2,4-DNP derivative **21**[18] showed more than 98% ee.

As shown in Scheme 3, cyclization of **17** with $Mn(OAc)_3$ (2.1 equiv) and $Cu(OAc)_2$ (0.5 equiv) in the presence of Yb-

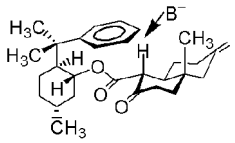


Figure 2.

$(OTf)_3$ (1.0 equiv)[6] in CF_3CH_2OH at −10 to 0 °C afforded a mixture of **18** and **19** (ratio 1.2:1). Because of less shielding of the α-protons of *β*-keto esters **18** and **19** by the aromatic group,[19] the deprotonation occurred smoothly with KHMDS, and the desired vinyl triflate (+)-**9** was obtained in 33% yield over two steps (61% yield based on the amount of **18** in the mixture of **18** and **19**). After the Pd-catalyzed carbonylation and the oxidative cleavage reaction, compound (+)-**9** was converted to (−)-wilforonide ($[\alpha]_D$ −26.6° (*c* 0.14, CH_2Cl_2)), which showed the same sign of the specific optical rotation as natural (−)-wilforonide ($[\alpha]_D$ −26.8° (*c* 0.045, CH_2Cl_2)).[20] HPLC analysis of the 2,4-DNP derivative **22** of synthetic (−)-wilforonide revealed that its ee value was also greater than 98%.

The assignments of stereochemistry for the cyclization products **13**/**14** and **18**/**19** were made by comparison to closely related systems in which the absolute stereochemistry was proved by conversion to compounds of known absolute configuration.[6c] As shown in Figure 3, in the cyclization of

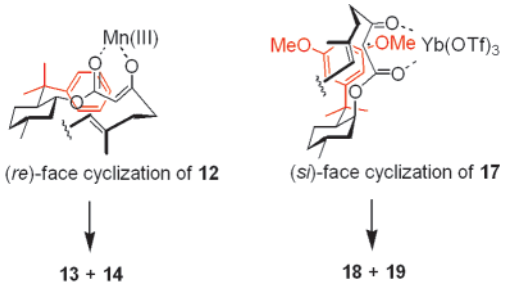


Figure 3.

12, the 8-phenyl group of the chiral auxiliary can effectively shield the (*si*)-face of the Mn(III)-enolate[21] and restrict the

(5) (a) Zhang, Q.-W.; Mohan, R. M.; Cook, L.; Kazanis, S.; Peisach, D.; Foxman, B. M.; Snider, B. B. *J. Org. Chem.* **1993**, *58*, 7640. (b) Snider, B. B.; Wan, B. Y.-F.; Buckman, B. O.; Foxman, B. M. *J. Org. Chem.* **1991**, *56*, 328. (c) Zoretic, P. A.; Weng, X.; Biggers, C. K.; Biggers, M. S.; Caspar, M. L.; Davis, D. G. *Tetrahedron Lett.* **1992**, *33*, 2637. (d) Garcia-Ruano, J. L.; Rumbero, A. *Tetrahedron: Asymmetry* **1999**, *10*, 4427.

(6) (a) Yang, D.; Ye, X.-Y.; Gu, S.; Xu, M. *J. Am. Chem. Soc.* **1999**, *121*, 5579. (b) Yang, D.; Ye, X.-Y.; Xu, M. *J. Org. Chem.* **2000**, *65*, 2208. (c) Yang, D.; Xu, M.; Bian, M.-Y. *Org. Lett.* **2001**, *3*, 111.

(7) (a) Baker, K. V.; Brown, J. M.; Hughes, N.; Skarnulis, A. J.; Sexton, A. *J. Org. Chem.* **1991**, *56*, 698. (b) Cahiez, C.; Alexakis, A.; Normant, J. F. *Synthesis* **1978**, 528.

(8) Corey, E. J.; Tius, M. A.; Das, J. *J. Am. Chem. Soc.* **1980**, *102*, 1742.

(9) (a) Axelrod, E. H.; Milne, G. M.; van Tamelen, E. E. *J. Am. Chem. Soc.* **1970**, *92*, 2139. (b) Huckin, S. N.; Weiler, L. *J. Am. Chem. Soc.* **1974**, *96*, 1082.

(10) For recent examples of Mn(III)-based oxidative free-radical cyclization reactions, see: (a) Pettus, T. R. R.; Inoue, M.; Chen, X.-T.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2000**, *122*, 6160. (b) Snider, B. B.; Kiselgof, J. Y.; Foxman, B. M. *J. Org. Chem.* **1998**, *63*, 7945. (c) Zoretic, P. A.; Fang, H.; Ribeiro, A. A. *J. Org. Chem.* **1998**, *63*, 4779. (d) Zoretic, P. A.; Zhang, Y.; Fang, H.; Ribeiro, A. A.; Dubay, G. *J. Org. Chem.* **1998**, *63*, 1162. (e) Jones, P.; Pattenden, G. *Synlett* **1997**, 398. For a review, see: (f) Snider, B. B. *Chem. Rev.* **1996**, *96*, 339.

(11) Corey, E. J.; Gross, A. W. *Tetrahedron Lett.* **1985**, *26*, 4291.

(12) Crisp, G. T.; Meyer, A. G. *J. Org. Chem.* **1992**, *57*, 6972.

(13) Pappo, R.; Allen, D. S., Jr.; Lemieux, R. U.; Johnson, W. S. *J. Org. Chem.* **1956**, *21*, 478.

cyclization to the (*re*)-face to give **13** and **14** as major products. However, in the case of **17**, the (*re*)-face of the α-radical is shielded and the (*si*)-face is more accessible, yielding **18** and **19** as the major products. Therefore, the absolute configuration of (−)-wilforonide was determined to be (5a*R*,9a*R*).

In summary, by using chiral auxiliaries derived from the same chiral source, (*R*)-pulegone, we have completed the first enantioselective syntheses of natural (−)-wilforonide in greater than 98% ee in 8.5% total yield (nine steps) and its enantiomer (+)-wilforonide in more than 98% ee. Our efficient synthetic schemes should allow rapid access to chiral wilforonide analogues for the development of novel antiinflammatory and immunosuppressive drugs.

Acknowledgment. This work was supported by The University of Hong Kong and Hong Kong Research Grants Council. We thank Professor Yuan-Chao Li of the Shanghai Institute of Materia Medica for providing the authentic sample of natural wilforonide.

Supporting Information Available: The experimental details; HPLC analysis of the 2,4-DNP derivatives of synthetic (+)-wilforonide and (−)-wilforonide; the CD spectra of (+)-wilforonide and (−)-wilforonide; and NMR spectra of compounds **4a**, **4b**, **5a**/**6a**, **5c**/**6c**, **9**−**14**, **17**−**19**, **21**, and wilforonide. This material is available free of charge via the Internet at http://pubs.acs.org.

OL015722P

(14) (a) Buschmann, H.; Scharf, H.-D. *Synthesis* **1988**, 827. (b) Corey, E. J.; Ensley, H. E.; Suggs, J. W. *J. Org. Chem.* **1976**, *41*, 380. (c) Corey, E. J.; Ensley, H. E. *J. Am. Chem. Soc.* **1975**, *97*, 6908.

(15) Taber, D. F.; Amedio. J. C., Jr.; Patel, Y. K. *J. Org. Chem.* **1985**, *50*, 3619.

(16) For the oxidative cyclization of substrate **12**, the addition of Lewis acid $Yb(OTf)_3$ resulted in a low chemical yield of the desired product.

(17) The chemical shifts of the α-protons of *β*-keto esters **13** and **14** were more upfield than 2.5 ppm whereas those of **5a** and **6a** were about 3.2 ppm.

(18) Behforouz, M.; Bolan, J. L.; Flynt, M. S. *J. Org. Chem.* **1985**, *50*, 1186.

(19) The chemical shifts of the α-protons of *β*-keto esters **18** and **19** were about 3.1 ppm.

(20) The authentic sample of natural (−)-wilforonide was obtained from the Shanghai Institute of Materia Medica, Chinese Academy of Sciences, P. R. China.

(21) Snider, B. B.; Patricia, J. J.; Kates, S. A. *J. Org. Chem.* **1988**, *53*, 2137.