Enantioselective Total Synthesis of the Potent Anti-HIV Agent Neotripterifordin. Reassignment of Stereochemistry at C(16)

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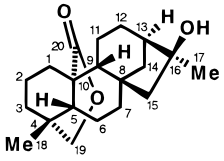
The Chinese medicinal plant *Tripterygium wilfordii* Hook (Celastraceae) has provided extracts with antitumor, antiinflammatory, and immunosuppressive activities[1,2] and a number of bioactive compounds, including the antitumor diterpenoids triptolide and tripdiolide[3] and the potent inhibitor of HIV replication, neotripterifordin (EC_{50} 25 nM).[4,5] Neotripterifordin, which had previously been assigned structure **1**,[5] is also of interest as a challenging target for synthesis because of the combined complexity of pentacyclic topology, stereochemistry, and functionality. In this paper, we describe an enantioselective total synthesis of neotripterifordin which dictates revision of structure from **1** to **2**. The absolute stereochemistry of the synthetic neotripterifordin was set in place by a combination of enantioselective catalytic epoxidation and oxirane-initiated cation−olefin polyannulation.



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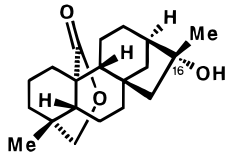

2

Wittig coupling of unsaturated ketone **3** with phosphonium ylide **4**[6] (1.1 equiv) in 20:1 THF−HMPA at −78 °C for 1 h and then at 23 °C for 5 h produced the *Z*-olefin **5** stereospecifically in 82% yield.[7] Conversion of **5** to the triene **6** was accomplished in 85% yield by the following sequence: (1) THP (tetrahydropyranyl) cleavage (0.1 equiv of pyridinium tosylate in ethanol at 55 °C for 4 h); (2) oxidation of the allylic alcohol (MnO_2 in hexane at 23 °C for 1 h); (3) Wittig methylenation ($Ph_3P{=}CH_2$ in THF at 23 °C); and (4) desilylation (Bu_4NF, THF, 23 °C, 4 h). Katsuki-Sharpless epoxidation[8] of the allylic alcohol subunit of **6** (0.09 equiv of (−)-diethyl tartrate, 0.075 equiv of Ti(O*i*-Pr)$_4$, 3 equiv of *t*-BuOOH, 4 Å molecular sieves, CH_2Cl_2, at −23 °C for 2 h and −12 °C for 15 h) gave the corresponding (*R*)-α,*β*-epoxy carbinol of 96% ee in 94% yield which was O-benzylated (1.15 equiv of NaH, 1.1 equiv of benzyl bromide, 0.1 equiv of *n*-Bu_4NI in THF at 23 °C for 6 h) to form the chiral epoxy diene ether **7** in 94% yield. Treatment of **7** with 1.2 equiv of $TiCl_4$ in CH_2Cl_2 at −94 °C for 10 min effected a remarkably clean and stereoselective double-annulation and afforded **8** as the exclusive product in 86% isolated yield. 2-D ^{1}H NMR studies (COSY-NOE) of the cyclization product fully confirmed the structure **8**. The efficiency of this process may be associated with bidentate coordination of the benzyloxy and oxirane oxygens with $TiCl_4$ and concerted oxirane C−O cleavage and cyclization, thus minimizing side reactions such as pinacol-type rearrangement and elimination. Replacement of the primary hydroxyl group of **8** by hydrogen (oxidation[9] and Wolff−Kishner reduction) followed by oxidative cleavage of the vinyl group afforded the aldehyde **9** (78% overall yield from **8**) which by Pd−C-catalyzed hydrogenation in acidic methanol provided the bridged ether **10** (98% yield). The aromatic bridged ether **10** was transformed into the α,*β*-enone **11** by Birch reduction and subsequent acid treatment (75%). Irradiation of the α,*β*-enone **11** (medium-pressure Hg lamp) in the presence of allene in hexane solution at −30 °C for 30 min afforded as major product the photoadduct **12** in 72% yield.[10]

Ozonolysis[11] of **12** in methanol containing $NaHCO_3$ at −78 °C for 10 min followed by treatment with Me_2S and stirring at 23 °C for 15 h effected cleavage of the exocyclic methylene group and methanolysis of the strained acylcyclobutanone unit to form a keto ester (88% yield) which was reduced to the corresponding hydroxy aldehyde **13** in 75% yield using diisobutylaluminum hydride (2 equiv, toluene, −78 °C, 3 h). Aldehyde **13** was transformed into the hydroxy acetylene **14** (94%) by reaction with 2.5 equiv of $CH_3COC(N_2)PO(OMe)_2$ and 3.4 equiv of K_2CO_3 in MeOH at 23 °C for 3 h.[12] The hydroxy acetylene **14** was converted to the corresponding xanthate ester (92%) by sequential treatment with sodium hydride (3.8 equiv)−imidazole (0.1 equiv) in THF at reflux for 3 h, then CS_2 (excess, 0.5 h) and CH_3I (excess, 0.5 h). Reaction of this xanthate with *n*-Bu_3SnH (2 equiv)−AIBN (cat.) in toluene at reflux for 10 min effected radical formation[13] and cyclization to form pentacycle **15** in 95% yield. Transformation of **15** to the target molecule **2** was accomplished by the following sequence: (1) epoxidation (2.1 equiv of *m*-chloroperoxybenzoic acid, 2.5 equiv of $NaHCO_3$ in CH_2Cl_2 at 0 °C for 30 min, 85%); (2) oxirane reduction (with 4.5 equiv of $LiAlH_4$ in ether, 23 °C, 30 min, 94%); (3) lactol ether cleavage (2:1 3 N HCl−THF, 40 °C, 2 h); and (4) Dess−Martin oxidation[9] of lactol to lactone at 23 °C for 4 h (80%). Synthetic **2** was compared with authentic neotripterifordin[14] by ^{1}H and ^{13}C NMR, IR, and mass spectroscopies and by optical rotation and thin-layer chromatography and was found to be identical.[14] In contrast, synthetic **1** (the C(16) diastereomer of **2**) and neotripterifordin were clearly distinguishable by each of the above comparisons. Synthetic **1** was prepared from **15** by the following sequence: (1) oxidative cleavage of the $C{=}CH_2$ group of **15** (O_3, CH_3OH, −78 °C, 10 min, 92%); (2) addition of MeMgI to the resulting ketone (ether, 23 °C, 1 h, 94%); (3) lactol ether cleavage (2:1 3 N HCl−THF, 40 °C, 2 h); and (4) Dess−Martin oxidation of lactol to lactone (80%).[15] Thus, it

(1) Kashiwada, Y.; Nishizawa, M.; Yamagishi, T.; Tanaka, T.; Nanaka, G. L.; Cosentino, L. M.; Snider, J. V.; Lee, K. H. *J. Nat. Prod.* **1995**, *58*, 392.

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(3) Kupchan, S. M.; Court, W. A.; Dailey, R. G.; Gilmore, J. C. J.; Bryan, R. F *J. Am. Chem. Soc.* **1972**, *94*, 7194.

(4) Chen, K.; Shi, Q.; Fujioka, T.; Zhang, D. C.; Hu, C. Q.; Jin, J. Q.; Kilkuskie, R. E.; Lee, K. H. *J. Nat. Prod.* **1992**, *55*, 88.

(5) Chen, K.; Shi, Q.; Fujioka, T.; Nakano, T.; Hu, C.-Q.; Jin, J.-Q; Kilkuskie, R. E.; Lee, K.-H. *Bioorg. Med. Chem.* **1995**, *3*, 1345.

(6) The Wittig reaction components **3** and **4** were prepared by standard methods using procedures described in the Supporting Information.

(7) For precedent, see: (a) Sreekumar, C.; Darst, K. P.; Still, W. C. *J. Org. Chem.* **1980**, *45*, 4260. (b) Inoue, S.; Honda, K.; Iwase, N.; Sato, K. *Bull. Soc. Chem. Jpn.* **1990**, *63*, 1629.

(8) Gao, Y.; Hanson, R. M.; Klunder, J. M; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765.

(9) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277.

(10) (a) Corey, E. J.; Bass, J. D.; Le Mahieu, R.; Mitra, R. B. *J. Am. Chem. Soc.* **1964**, *86*, 5570. (b) Crimmins, M. T.; Reinhold: T. L. *Org. React.* **1994**, *44*, 297. (c) In addition to **12**, the allene photoaddition reaction produced the diastereomeric α-cycloadduct in 24% yield.

(11) Schreiber, S. L.; Santini, C. *J. Am. Chem. Soc.* **1984**, *106*, 4038.

(12) (a) Muler, S.; Liepold, B.; Roth, G. T.; Bestmann, H. J. *Synlett* **1996**, 521. (b) Ohira, S. *Synth. Commun.* **1989**, *19*, 561.

(13) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574.

(14) We are grateful to Dr. Khozirah Shaari of the Forest Products Research Institute Malaysia (Kuala Lampur) and Drs. Ke Chen and K.-H. Lee of the University of North Carolina for providing authentic samples of neotripterifordin.

(15) Since it is clear that epoxidation of **15** must occur at the less sterically shielded *re* face of C(16), the stereochemistry in **2** follows unambiguously; a similar argument applies to the introduction of the C(16) stereocenter in **1**. See: Carman, R. M. *Aust. J. Chem.* **1981**, *34*, 923.

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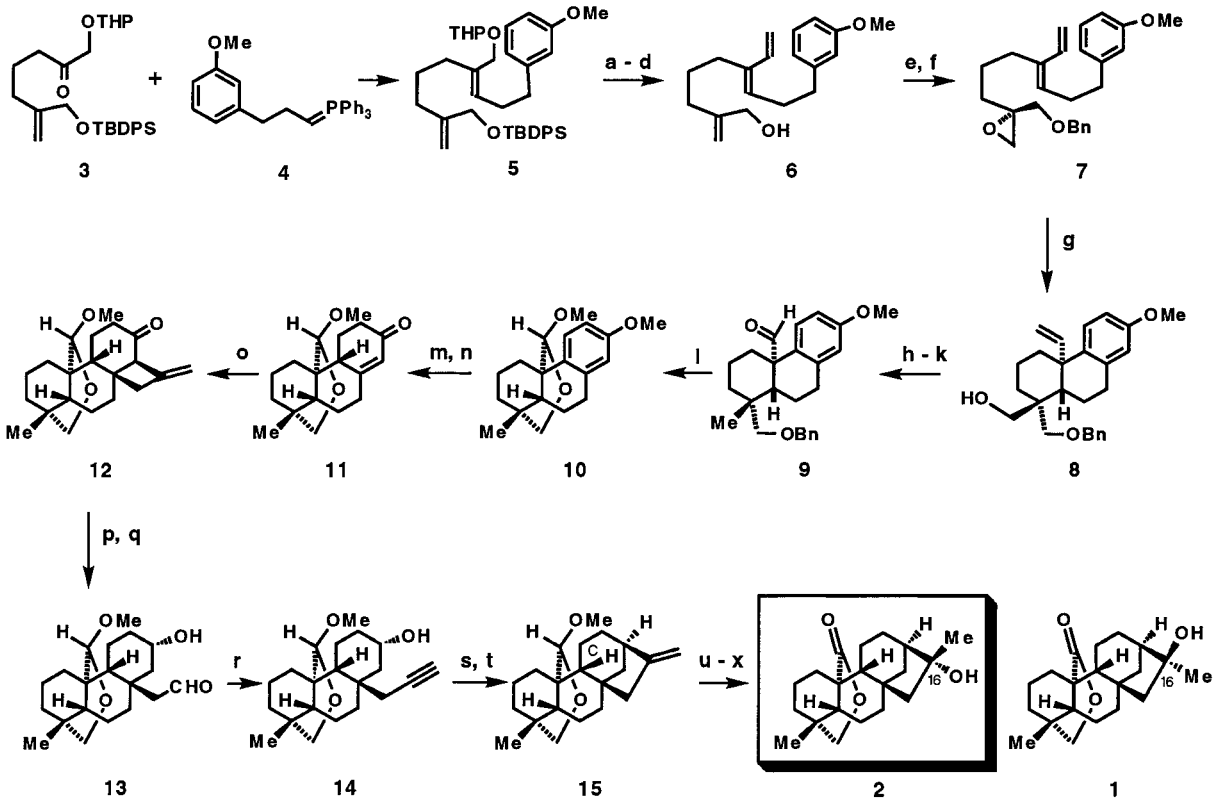
Scheme 1[a]



[a] Reagents: (a) pyridinium tosylate, EtOH, 55 °C, 4 h, 95%; (b) MnO_2, hexane, 99%; (c) $Ph_3P{=}CH_2$, THF, −78 to 23 °C, 95%; (d) Bu_4NF, THF, 95%; (e) (−)-diethyl tartrate (0.09 equiv), Ti(O-*i*-Pr)$_4$ (0.075 equiv), *t*-BuOOH (3.0 equiv), 4 Å molecular sieves, CH_2Cl_2, 94% yield, 96% ee; (f) NaH, benzyl bromide, *n*-Bu_4NI (cat.), THF, 94%; (g) $TiCl_4$ (1.2 equiv), CH_2Cl_2, −94 °C, 10 min, 86%; (h) Dess−Martin periodinane, CH_2Cl_2, 92%; (i) H_2NNH_2, K_2CO_3, bis(ethylene glycol), 210 °C, 94%; (j) OsO_4 (1.1 equiv), *t*-BuOH−H_2O; (k) $NaIO_4$, dioxane−H_2O, 90% (two steps); (l) H_2 (balloon), 10% Pd−C (cat.), AcOH (cat.), MeOH, 98%; (m) Li, NH_3; (*l*), THF-*t*-BuOH; (n) HCl, MeOH, 75% (two steps); (o) allene, *hν* (300−360 nm), hexane, −30 °C, 30 min, 72%; (p) O_3, $NaHCO_3$, MeOH, −78 °C; then Me_2S, 88%; (q) DIBAL-H (2.0 equiv), toluene, −78 °C, 75%; (r) $CH_3COC(N_2)PO(OMe)_2$, K_2CO_3, MeOH, 94%; (s) NaH, imidazole (cat.), THF, reflux, then CS_2, then MeI, 92%; (t) *n*-Bu_3SnH, azoisobutyronitrile, toluene, 110 °C, 10 min, 95%; (u) *m*-chloroperoxybenzoic acid, $NaHCO_3$, CH_2Cl_2, 85%; (v) $LiAlH_4$, Et_2O, 94%; (w) HCl, THF−H_2O; (x) Dess−Martin periodinane, 80% (two steps). Abbreviations: THP, tetrahydropyranyl; TBDPS, *tert*-butyldiphenylsilyl; Bn, benzyl.

is clear that the structure of neotripterifordin should be revised from **1**[4,5] to **2**.

This first synthesis of neotripterifordin is of special significance in view of its remarkable anti-HIV activity and its scarcity from natural sources. The process is ideal for the production of radiolabeled neotripterifordin which will be important for determining its biological target. Noteworthy features of the synthesis include the generally excellent yields, outstanding enantio- and stereocontrol, the completely stereoselective two-component coupling of **3** and **4**, the highly effective double-annulation of **7** to form **8**, the novel sequence for establishing the two-carbon bridge across ring C of **15**, and the resultant revision of stereochemistry at C(16).

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Supporting Information Available: Experimental procedures and spectroscopic data for synthetic intermediates (35 pages). See any current masthead page for ordering and Internet access instructions.

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