The Synthesis of (±)-Wilforonide

Jeffrey M. Schkeryantz, Jay R. Luly, Michael J. Coghlan*

Pharmaceutical Products Division, Abbott Laboratories, Dept. 4NB, Bldg. AP10, 100 Abbott Park Road, Abbott Park, IL 60064-3500, USA

Fax (847) 938-5034; Email: Michael.J.Coghlan@abbott.com

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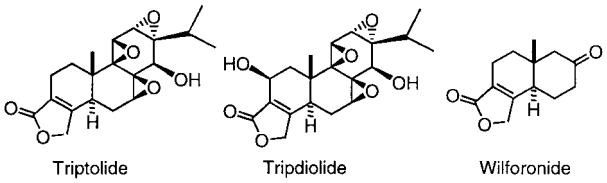
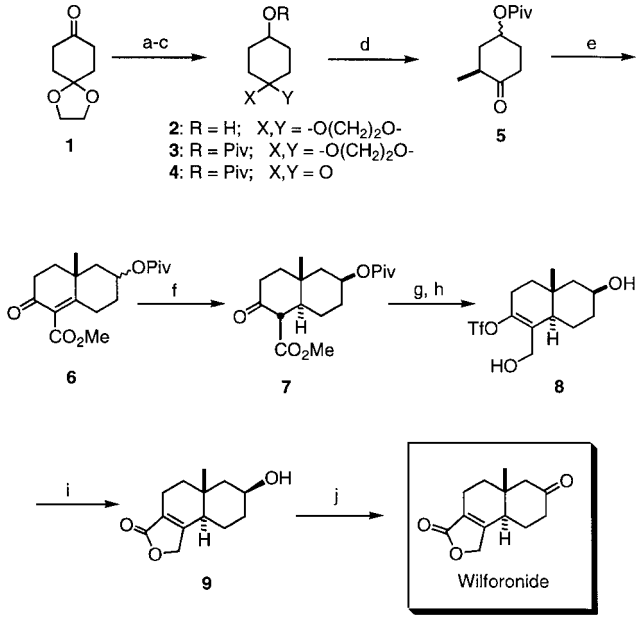
Abstract: The first synthesis of (±)-wilforonide has been completed in ten steps from commercially available starting materials. A high-yielding monomethylation of a reactive ketone enolate, a regioselective α-annulation of an unactivated α-substituted cyclohexanone, and a selective hydrogenation of the resulting unsaturated keto ester were key steps in the synthesis.

Extracts of the Chinese twinning vine *Tripterygium wilfordii* Hook F. have traditionally found a variety of uses in Asian folk medicine. Control of skin disorders, male fertility, and cancer are a few of the customary uses of this extract which contains a variety of natural products believed to be the therapeutic agents. Anti-inflammatory effects have also been reported, and the diterpene components of *T. wilfordii* have historically been the subject of considerable physiologic and synthetic efforts.[1-7] Cytotoxic and immunosuppressant agents such as triptolide and tripdiolide have been isolated and synthesized, [6,8] yet to date this class of compounds has shown considerable toxicity. More recently, the anti-inflammatory effects of these diterpenes have been associated with the modulation of the glucocorticoid receptor (GR), and isolates from *T. wilfordii* have been used as probes for anti-inflammatory agents lacking typical steroidal side effects.[9] More recently isolated butenolide natural products from *T. wilfordii* such as wilforonide have been patented as lead compounds for modulation of GR. [9]



As novel GR ligands, wilforonide or its analogs which interact with GR have potential as novel anti-inflammatory agents or modulators of other endogenous endocrine functions. Wilforonide is also a component of the *T. wilfordii* extract involved in GR-mediated anti-inflammatory processes, and wilforonide is effective as an inhibitor of proliferation and cytokine release in stimulated T cells.[9] Consequently the preparation of this pharmacophore would be useful for investigating the pervasive role of this class of natural products in human systems - especially those related to inflammation and immunosuppression. Despite the potential utility of wilforonide, the quantities isolated from *T. wilfordii* are so minute that the compound has not been fully characterized. Distinguishing data such as the optical rotation have yet to be reported. As a consequence of the scant quantities available from natural sources and its potential utility, we wish to report the first synthesis of wilforonide in pursuit of a fuller understanding the biological role of this molecule and an expedient entry to the preparation of analogs.

Commercially available ketone **1** was reduced with 0.33 equiv. of sodium borohydride in methanol at 0°C (Scheme 1). The resulting alcohol **2** was protected as its pivalate ester **3** using 1.2 equiv of pivaloyl chloride and 1.2 equiv of triethylamine in methylene chloride at room temperature. The remaining ketal was cleaved via hydrolysis in 10:1 acetone/water to provide keto ester **4** in 51% overall yield from **1**. Enolate alkylation of **4** via treatment with 1.1 equiv of lithium hexamethyldisilazide in tetrahydrofuran followed by addition of 1.1 equiv of iodomethane at -78°C afforded **5** as a 1:1 mixture of diastereomers in high yield. Remarkably, this transformation proceeded with no detectable quantity of polyalkylated product arising from sequential methylation of **5.**[10]



Scheme 1. Reagents and yields: a) $NaBH_4$, MeOH; b) PivCl, Et_3N, CH_2Cl_2; c) *p* -TsOH•H_2O, acetone, H_2O, 51% for three steps; d) LiHMDS, THF, MeI, 89%; e) *p*-TsOH•H_2O, CH_2=CHC(O)CH_2CO_2Et, benzene, 30%; f) H_2, $Pd/BaSO_4$, 71%; g) KHMDS, Tf_2NPh, THF, 50%; h) Dibal, THF, 62%; i) $Pd(PPh_3)_4$, CH_3CN, CO, Et_3N, 92%; j) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, 55%

Modified Robinson annulation of **5** with 3.0 equiv of the Nazarov reagent in refluxing benzene using *p*-toluenesulfonic acid monohydrate as catalyst furnished bicyclic ester **6.**[11] During the course of this study, several variants of the Nazarov reagent were also employed,[12-16] yet these delivered much lower yields of **6** under a wide variety of conditions. Although many reported annulations of α-substituted cyclic ketones proceed in good yield, these typically employ

2-alkyl-1,3-cycloalkyldiketones[11] as substrates whereas unactivated α-substituted cyclic ketones are apparently much less reactive. Transformation of **5** to **6** is notable since it proceeds regioselectively to the α position of an unactivated ketone. Investigation of the complete product profile from this reaction showed none of the possible regioisomeric cyclization product. The only isolable contaminants of these reactions were products arising from loss of the carboethoxy group following the desired ring closure.

The double bond in **6** was selectively reduced via hydrogenation at room temperature to provide keto diester **7** in 71% yield along with ~7% of the isomer with the *cis* ring juncture. This reaction thereby provided mostly the desired *trans* decalin ring fusion observed in the natural product.[17] Following the isolation of **7** via flash chromatography, the

enol triflate was prepared using 1.2 equiv of potassium hexamethyldisilazide and 1.2 equiv of N-phenyltrifluoromethanesulfonimide at -78°C.[18,19] The carboxylic esters were then reduced with 2.2 equiv of diisobutylaluminium hydride in tetrahydrofuran at -78°C to deliver diol **8**. Carbonylation of the triflate using 0.10 equiv of tetrakis(triphenylphosphine) palladium(0) with 10 equiv of triethylamine under an atmosphere of carbon monoxide in acetonitrile at room temperature provided the butenolide of **9** in high yield. [20, 21]

At this point all that remained was an apparently straightforward oxidation to complete the synthesis. A wide variety of oxidants were employed with varying degrees of success, [22] and of these, the Swern oxidation proved to be optimal. Alcohol **9** was thereby cleanly oxidized to provide synthetic (±) wilforonide. ^{1}H NMR and ^{13}C NMR spectra of the synthetic material were identical with those of the natural product. [23] Studies investigating the mode of immunosuppressant action, the GR-mediated effects, as well as structure-activity relationships of analogs will be published elsewhere.

References and Notes:

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(17) Spectral data for **7**: ^{1}H NMR (DMSO-d_6) 4.97 (m, 1H), 3.65 (s, 3H), 3.36 (d, J = 12.6 Hz, 1H), 2.65 (m, 1H), 2.20 (dq, J = 4.5, 15 Hz, 1H), 1.9-1.4 (series of m, 9H), 1.22 (s, 3H), 1.15 (s, 9H) ppm. ^{13}C NMR (DMSO-d_6) 205.4, 176.8, 169.9, 68.8, 59.2, 51.4, 45.6, 42.4, 39.3, 38.2, 36.9, 32.0, 29.2, 26.8(3C), 21.9, 17.2 ppm.

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(22) Ruthenium, sulfurane, and chromium-based oxidants returned or decomposed alcohol **9**. Swern conditions provided the natural product albeit in low yield.

(23) We are indebted to Prof. Peter Lipsky from the Department of Internal Medicine at the University of Texas Southwest Medical Center at Dallas for providing authentic ^{1}H NMR, IR, and ^{13}C NMR spectra of natural wilforonide. Spectra of the synthetic sample were also identical to those reported by Chen, K.; Yang, R.; Wang, C. *Zhongcaoyao* **1986**, *17*, 242.