Total Synthesis of the Spiro-*o*-benzoquinonefuran (–)-Stypoldione[1]

J. R. Falck,* S. Chandrasekhar, Sukumar Manna, and Ching-Chen S. Chiu

Departments of Molecular Genetics and Pharmacology, University of Texas Southwestern Medical Center, Dallas, Texas 75235

Charles Mioskowski* and Isabelle Wetzel

Laboratoire de Chimie Bio-Organique Associé au CNRS, Université Louis Pasteur F-67401 Illkirch, France

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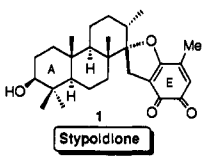
Stypoldione (**1**) is the most prominent member of a rare class of pentacyclic marine diterpenoids characterized by an unusual spiro-*o*-benzoquinonefuran moiety.[2,3] In addition to pronounced



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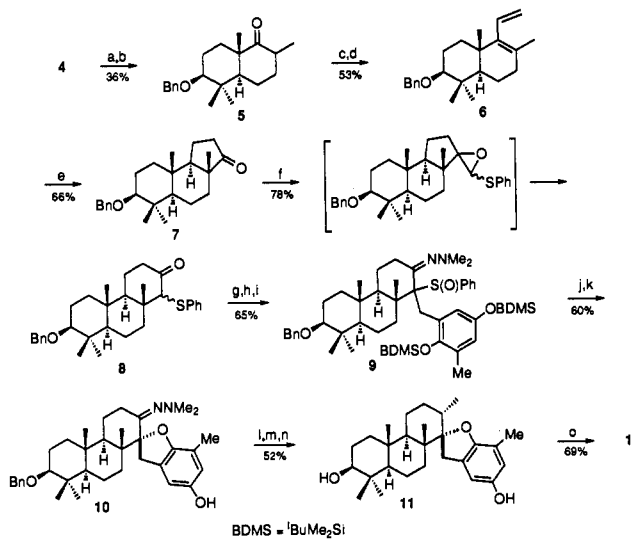
Stypoldione

ichthyotoxic properties, **1** inhibits synchronous cell division in the fertilized sea urchin egg assay[4] and blocks *in vitro* microtubule polymerization by a novel mechanism which differs from other mitotic spindle poisons.[5] Accordingly, it has engendered considerable synthetic attention[6] and provided a forum for the demonstration of novel synthetic procedures.[7] Herein, we describe a conceptually distinct approach to **1** featuring methodologies designed to address outstanding issues confronted during the total synthesis of **1**, *viz.*, (a) utilization of a chiral AB-ring precursor excised from a commercial steroid,[8] (b) regiospecific ring expansion affording a functionalized cyclohexanone, and (c) stereoselective intramolecular heteroatom spiroannulation. It is anticipated that these procedures will be applicable to other systems of interest in natural products total synthesis.

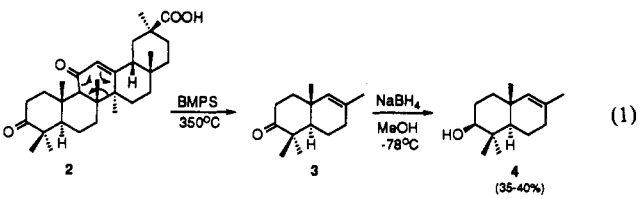
Octalone **4**,[9] comprising rings A and B, was conveniently obtained albeit in modest yield by thermolysis of the Jones oxidation product **2** derived from commercial 18β-glycyrrhetinic acid. Best results were achieved when **2** was admixed with the antioxidant 3-*tert*-butyl-4-hydroxy-5-methylphenyl sulfide (BMPS)

Scheme I[a]



[a]Reaction conditions: (a) BnBr, NaH, DMF, 25 °C, 2 h. (b) BH_3, THF, 24 °C, 4 h; PCC, CH_2Cl_2, 1.5 h. (c) C_2H_3MgBr, THF, 0 → 24 °C, 2 h. (d) HMPA, 210 °C, 1 h. (e) BH_3, THF, 15 °C, 12 h; CO (12 atm), $PhCH_3$, 6 h; H_2O_2. (f) $Ph_3AsCHSPh$ (1.5 equiv), THF, -10 °C, 3 h; SiO_2. (g) Oxone, THF/H_2O (2:1), 0 °C, 6 h. (h) Me_2NNH_2, EtOH, 68 °C, 12 h. (i) **12**, LDA, THF, 0 → 24 °C, 2 h. (j) Bu_4NF, THF, 0 °C, 7 h. (k) MeI (1 equiv), CH_3CN, 80 °C, 1.5 h. (l) $CuCl_2$, THF/H_2O (3:1), 23 °C, 4 h. (m) Ph_3PCHLi, THF, –78 → 0 °C, 12 h; HOAc. (n) Pd/C, H_2 (40 psi), EtOAc, 23 °C, 6 h. (o) $NO(KSO_3)_2$, KH_2PO_4, acetone/H_2O (2:1), 23 °C, 2 h.

(10% w/w) and distilled (350 °C, 40 mmHg, 3 h) from a kugelrohr or simple bulb-to-bulb distillation apparatus (eq 1).[10] This



(1)

degradation can be envisioned as a retro-Diels–Alder reaction but is more likely a heterolytic process.[11] Sodium borohydride reduction of the crude pyrolysate **3** led stereospecifically to **4** in 35-40% overall yield.

Sequential benzylation of the C(3)-alcohol in **4**, olefin hydroboration, and pyridinium chlorochromate (PCC) oxidation of the adduct readily afforded ketone **5** (Scheme I). Ring C was subsequently grafted onto **5** by a two-stage process that regioselectively established the α-(phenylsulfenyl)cyclohexanone which played a crucial role in introducing later functionality. To this end, **5** was converted to **6** by addition of vinylmagnesium bromide and dehydration in hot HMPA.[12] Ring closure via transannular hydroboration from the less hindered α-face and *in situ* carbonylation of the resultant borane according to Brown[13] yielded cyclopentanone **7**. Exposure of **7** to (phenylthiomethylidene)-triphenylarsorane as described previously[14] generated a labile exocyclic epoxy sulfide that, in practice, was allowed to rearrange to **8** during SiO_2 chromatographic isolation.

(1) Presented in part at the 205th ACS National Meeting, Denver, CO, March 28–April 2, 1993; ORGN 112.

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(8) For the preceding paper in this series on chiral precursors via steroid degradation, see: Manna, S.; Yadagiri, P.; Falck, J. R. *J. Chem. Soc., Chem. Commun.* **1987**, 1324–1325.

(9) All isolated intermediates were fully characterized by ^1H and ^{13}C NMR and MS analysis. The elemental composition of an analytical sample was confirmed by combustion analysis or high-resolution mass spectroscopy.

(10) While somewhat sensitive to scale, the sequence of thermolysis and hydride reduction on a 50 mmol scale consistently furnished over 2 g of **4**. Dedicated pyrolysis equipment and high-temperature ovens were not required, but caution should be exercised during the destructive distillation of organic material.

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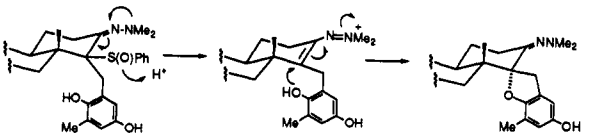
Oxone oxidation of **8** and condensation with *unsym*-dimethylhydrazine yielded a mixture of diastereomeric α-sulfinylhydrazones (1.5:1 by ^{1}H NMR), which were influenced by the α-sulfinyl group to enolize toward the ring junction. Ring E was stereoselectively attached by alkylation of the hydrazone anion with benzyl bromide **12**,[15] resulting in **9**. Fluoride-mediated desilylation and spiroannulation induced by catalytic HI produced **10** as anticipated,[16] with exclusive intramolecular axial attack by the oxygen nucleophile (eq 2). Removal of the hydrazone with cupric ion,[17] methylenation[18] of the liberated carbonyl, and catalytic reduction of the resultant exocyclic olefin with simultaneous hydrogenolysis of the benzyl ether gave rise to **11**. Hydrogenation in this instance from the normally more hindered β-face reflects the residency of ring E beneath ring C, thus shielding it from α-side attack. Oxidation of **11** with Fremy's salt, as described by Pattenden,[7a,b] completed the synthesis of **1**, identical in all respects with an authentic sample.



(2)

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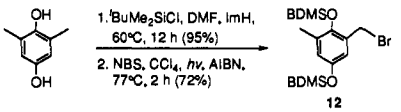
Supplementary Material Available: Spectroscopic and physical data for intermediates **4**, **5**, **7**, **10**, and **12** (2 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any currnet masthead page for ordering information.

(15) Prepared from 2,6-dimethylhydroquinone by silylation and NBS bromination under free-radical conditions. The product **12** was generally contaminated by <10% of dibromide arising from reaction at both methyls. This could be removed, if desired, by hydrolysis to the corresponding benzyl alcohol ($AgNO_3$, 50% aqueous acetone, 20 °C, 12 h; 55%), chromatographic purification (hexane/Et_2O, 85:15), and alcohol/bromide interchange under standard conditions (CBr_4, Ph_3P, CH_2Cl_2, 0 → 24 °C, 2 h; 75%).



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