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SYNTHESIS AND ABSOLUTE CONFIGURATION OF (–)-STYPOLDIONE

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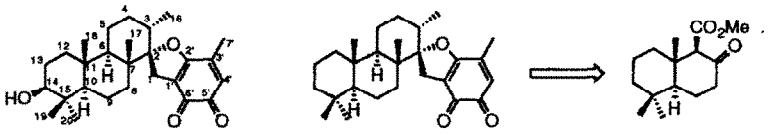
Abstract: (*S*)-3-Hydroxy-2,2-dimethylcyclohexanone (**4**) was converted into (–)-stypoldione (**1**), the ichthyotoxic and cytotoxic metabolite of the brown alga, *Stypopodium zonale* (Lamouroux) Papenfus. The present synthesis established the absolute configuration of (–)-stypoldione as depicted in (**1**).

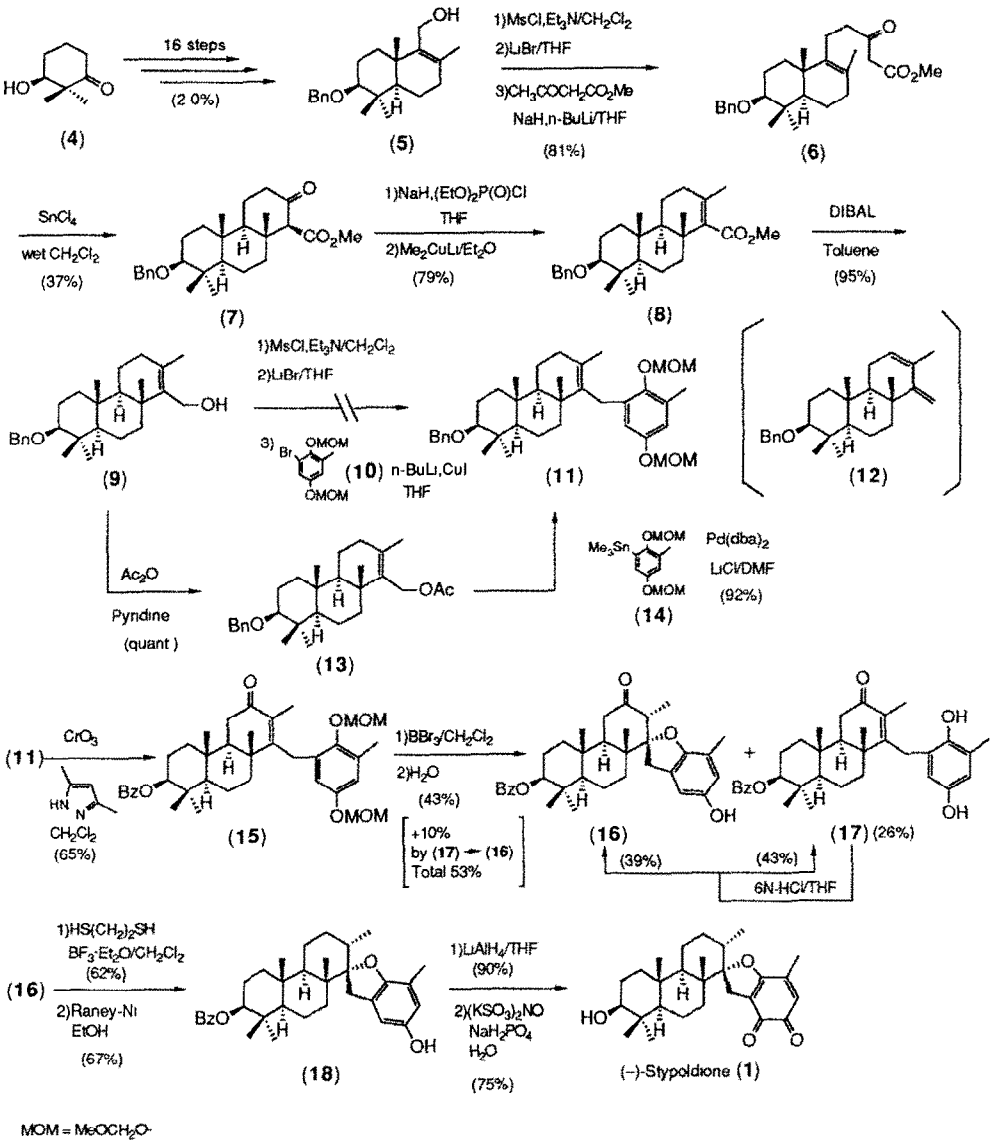
In 1979, Fenical and his co-workers isolated (–)-stypoldione (**1**) as an ichthyotoxic and cytotoxic metabolite of the tropical brown alga *Stypopodium zonale* (Lamouroux) Papenfuss in the Western Caribbean Sea.[2,3] Its structure was established as (**1**) by an X-ray analysis without assignment of the absolute configuration.[2] This unique diterpene (**1**) with a spiro-*o*-benzoquinonefuran-C_7 unit is extremely toxic to the reef-dwelling hervivorous fish *Eupomacentrus leucostictus*, and probably functions as a chemical defense weapon of the alga.[2,3]



(–)-Stypoldione (**1**) (±)-(**2**) (±)-(**3**)

Although there were some attempts[4-6] to synthesize (**1**), the first successful construction of the whole ring-system of (**1**) was achieved as recently as in 1991.[7] Thus, (±)-14-deoxystypoldione (**2**) was synthesized by us from (±)-(**3**).[7] In order to establish the absolute configuration of (–)-stypoldione, however, it was necessary to carry out a synthesis of the optically active form of stypoldione by starting from a compound with known absolute configuration. We now report the synthesis of (–)-stypoldione itself, and have determined its absolute configuration as depicted in (**1**).

Our synthesis started from (*S*)-3-hydroxy-2,2-dimethylcyclohexanone (**4**),[8] which was converted to the known bicyclic intermediate (**5**) as reported previously.[9] The corresponding bromide derived from (**5**) was used for the alkylation of the dianion of methyl acetoacetate to give (**6**).[10] Treatment of (**6**) with tin(IV) chloride in wet dichloromethane[11] gave tricyclic keto ester (**7**) (m.p. 160.5-162℃) in 37% yield. The enol phosphate of (**7**) was then treated with lithium dimethylcuprate according to Weiler.[12] The resulting



methylation product (**8**) (m.p. 94-95℃) was reduced with DIBAL to afford an allylic alcohol (**9**) [m.p. 125-126℃, $[\alpha]_D^{23}$ –25.0° (c = 1.18, $CHCl_3$)], the diterpene part of stypoldione.

We then attempted the coupling of the diterpene portion (**9**) with the C_7-aromatic part (**10**) following the method which had been successful in the case of the synthesis of (±)-(**2**).[7] Accordingly, (**9**) was converted

to the corresponding bromide via the mesylate, and allowed to react with an organocopper reagent prepared from (**10**). However, the coupling did not take place at all. Instead of the desired product (**11**), diene (**12**) was generated by elimination of hydrogen bromide from the allylic bromide. Since the coupling reaction was successful in the case of the previous synthesis of (±)-(**2**), this failure was due to the presence of the benzyloxy group at such a remote position as C-14 of (**9**). At this stage, we fortunately became aware of Hegedus' palladium-catalyzed coupling of allylic acetates with arylstannanes.[13] This coupling method was highly successful in the present case. Coupling of the acetate (**13**) (derived from (**9**)) with stannane (**14**) (prepared from (**10**) and trimethyltin chloride) in the presence of a catalytic amount of bis(dibenzylideneacetone)palladium (0) [$Pd(dba)_2$] and lithium chloride in DMF[13] smoothly yielded (**11**) in 92% yield.

For the construction of the spirobenzofuran moiety of (**1**), we followed the protocol detailed in the synthesis of (±)-(**2**).[7] Oxidation of (**11**) with chromic anhydride-3,5-dimethylpyrazole[14,15] furnished 3-benzoyloxy α,β-unsaturated ketone (**15**) in 65% yield with concomitant oxidation of the benzyloxy group at C-14 to a benzoyloxy group. When (**15**) was treated with boron tribromide in dichloromethane to remove the MOM protective groups, a mixture of (**16**) (43%) and (**17**) (26%) was obtained after aqueous work-up. Another possible stereoisomer of (**16**) could not be isolated. This was due to the stereoselective axial Michael addition of the phenolic hydroxyl group to the α,β-unsaturated carbonyl system of (**17**) to give only (**16**). The phenolic enone (**17**) yielded an additional amount of (**16**) by treatment with dilute hydrochloric acid. The combined yield of (**16**)[16] was 53% from (**15**). Reduction of the C-4 carbonyl group of (**16**) to methylene was executed by thioacetalization followed by hydrogenolysis with Raney nickel to give (**18**). The benzoyl protective group at C-14 of (**18**) was then removed by treatment with lithium aluminum hydride, and the resulting phenolic alcohol was oxidized with Fremy's salt to give stypoldione (**1**) as a dark red solid, darkening at ca. 160-173℃, $[\alpha]_D^{25}$ –62° (c = 0.042, $CHCl_3$) [lit. $[\alpha]_D$ –65.1°(c = 0.461, $CHCl_3$)]. The IR, ^1H NMR (300 MHz) and ^{13}C NMR (22.4 MHz) spectra of our synthetic (**1**) were identical to those of the authentic sample of (**1**) kindly provided by Professor W. Fenical. The levo-rotation of our synthetic (**1**) coincided with that of the natural (**1**), and therefore the absolute configuration of (–)-stypoldione (**1**) was firmly established as depicted in (**1**).

In summary, the naturally occurring form of stypoldione (**1**) was first synthesized from (*S*)-(**4**). The overall yield of (**1**) was 2.0% from the known bicyclic alcohol (**5**) (17 steps).

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16. Physical data of (**16**) : a white solid, m.p.157.5-159.0℃, $[\alpha]_D^{20}$+2.6° (c = 0.20, $CHCl_3$). ^1H NMR (250 MHz, $CDCl_3$) : δ 0.90 (3H, s), 0.92 (3H, d, *J*=6.5 Hz), 0.99(3H, s), 1.03(3H, s), 1.19(3H, s), 1.20 - 2.58(12H, m), 2.12(3H, s), 2.61(1H, q, *J*=6.5 Hz), 2.94(1H, d, *J*=16.5 Hz), 3.38(1H, d, *J*=16.5 Hz), 4.76(1H, dd, *J*=5.0, 11.0 Hz), 6.42(1H, br. s), 6.44(1H, br. s), 7.44(2H, t, *J*=7.2 Hz), 7.56(1H, t, *J*=7.2 Hz), 8.04(2H, d, *J*=7.2 Hz).
17. ^1H NMR data (300 MHz, $CDCl_3$) of synthetic (–)-(**1**) : δ 0.78 (3H, s), 0.79 (3H, d, *J*=6.0 Hz), 0.87(3H, s), 0.97(3H, s), 0.98(3H, s), 0.65 - 1.85(16H, m), 2.18(3H, d, *J*=1.5 Hz), 2.61(1H, d, *J*=16.0 Hz), 3.01(1H, d, *J*=16.0 Hz), 3.21(1H, m), 6.13(1H, br. s). ^{13}C NMR data (22.4 MHz, $CDCl_3$) of synthetic (–)-(**1**) : δ 15.3, 15.3, 16.3, 16.9, 17.0, 17.6, 20.2, 27.3, 28.0, 30.5, 30.9, 32.9, 37.0, 37.1, 38.4, 38.9, 42.5, 51.6, 55.3, 78.7, 103.8, 114.5, 128.7, 143.1, 170.2, 174.5, 182.7.