

Synthesis of the bicyclic dienone core of the antitumor agent ottelione B

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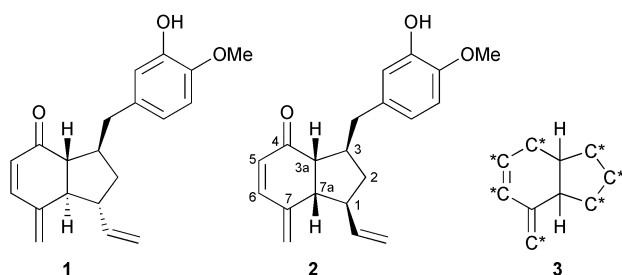
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Received (in Corvallis, OR, USA) 5th June 2002, Accepted 28th June 2002

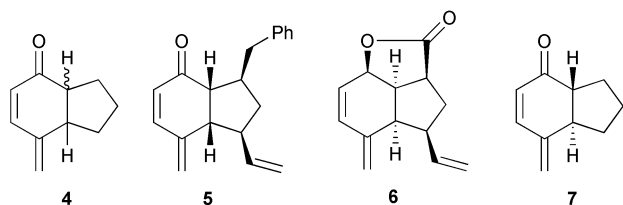
First published as an Advance Article on the web 31st July 2002

The intramolecular Diels–Alder adduct **12** was converted *via* dimesylate **20** into dienone **7**, which represents the unusual, and apparently quite stable, core of the antitumor agent ottelione B (**1**).

Ottelione B (**1**), was isolated from a sample of the freshwater plant *Ottelia alsimoides*.¹ The substance has conspicuously high antitumor activity,¹ as judged by *in vitro* tests using a panel of human tumor cell lines—many of the IC₅₀ values being at the nanomolar level. A stereoisomer, tentatively assigned structure **2**,^{1,2} was isolated from the same extract, and was named ottelione A. The 1 α ,3 α ,3 α ,7 α relative stereochemistry shown in **2** was judged¹ more likely than the 1 α ,3 α ,3 β ,7 α stereochemistry, but in a more recent publication³ the assignment made is 1 α ,3 β ,3 α ,7 α . Ottelione A also has antitumor properties;^{1–3} it appears to be even more potent than **1**,¹ and has been shown to inhibit tubulin polymerization.² The impressive biological activity of **1** and **2**, and their unusual structures—as well as the need to confirm those structures—make them worthy synthetic targets.



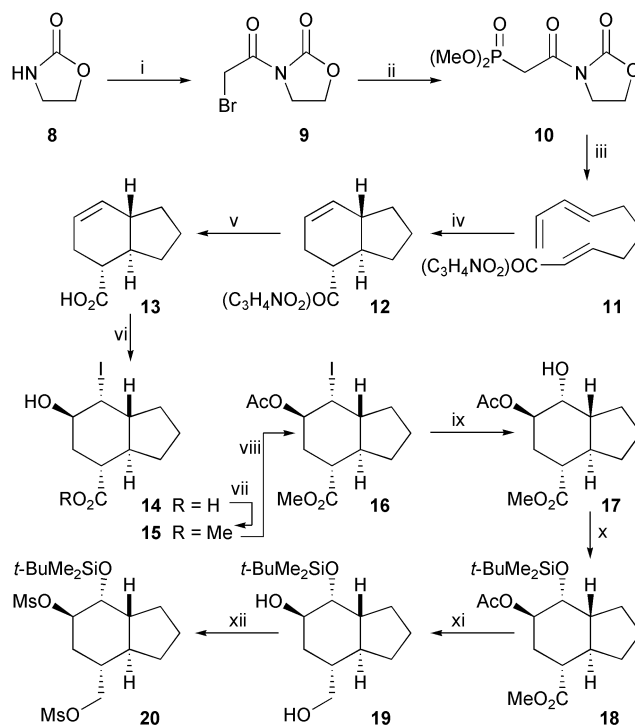
The otteliones represent a rare compound class, and a search of the Beilstein database, using substructure **3**,⁴ retrieved few relevant examples,⁵ apart from the two otteliones and the models mentioned below; none of the examples had *trans* ring fusion. The dienone substructures **4**, characteristic of the otteliones, have not been studied extensively,⁵ and little synthetic work has yet been published on the otteliones themselves. The synthesis of (\pm)-**5**⁶ and of optically pure **6**⁷ have been reported, as has a route⁸ to functionalized hydrindanones structurally related to ottelione A.



Before embarking on a synthesis of ottelione B, we thought it advisable to make the fundamental carbon skeleton **7** so as to establish its properties—in particular the stability of the stereogenic center α to the carbonyl and the tendency, if any, of the dienone to aromatize. Although the relative stability of *cis* and *trans* isomers of hydrindanones is influenced by the

substitution pattern⁹ and can be changed by introduction of a double bond,¹⁰ the situation with respect to **7** was not predictable by appeal to experimental evidence.¹¹ We report here the preparation of **7** by two related approaches, as well as some observations on its properties.

The known¹² phosphonate **10** was made as indicated in Scheme 1. Olefination of (*5E*)-5,7-octadienal¹³ with phosphonate **10** gave the expected triene **11**¹² (53–75%), and Diels–Alder cycloaddition, using the chiral catalyst [Cu(*S,S*)-*t*-Bu-box](SbF₆)₂,¹⁴ led to **12** (44–58%). Material prepared in this way is reported to have an ee of 86%,¹² but in this study we did not monitor the optical purity of our compounds. Detachment of the auxiliary (LiOH, H₂O₂, 90–98%) liberated acid **13**, whose structure was confirmed by X-ray analysis.[†] Treatment with I₂–KI–NaHCO₃ produced iodohydrin **14**, and the structure of this compound was also determined by X-ray analysis.[†] While there is precedent for formation of iodohydrins from olefins,¹⁵ the normal outcome where a suitably-placed carboxy is present is

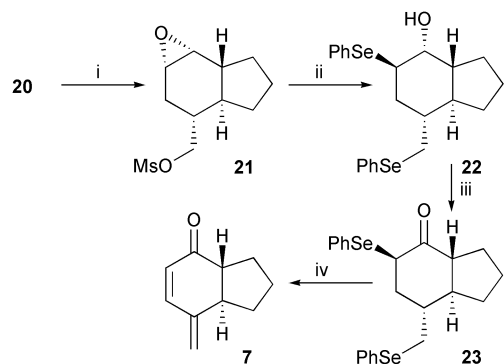


Scheme 1 Reagents and conditions: (i) NaH, THF, reflux; add bromoacetyl bromide at 0 °C, 18 h at 0 °C, 49%; (ii) (MeO)₃P, 0 °C, 6 h, then 15 h at room temperature, then reflux 2 h, 81%; (iii) (*5E*)-5,7-octadienal, Et₃N, LiCl, MeCN, 4 h, 53–75%; (iv) [Cu(*S,S*)-*t*-Bu-box](SbF₆)₂, CH₂Cl₂, 1 week, 44–58%; (v) LiOH·H₂O, 30% H₂O₂, 3:1 THF–water, 4 h, 90–98%; (vi) I₂, KI, NaHCO₃, water–CH₂Cl₂, 13 h; (vii) CH₂N₂, Et₂O, 20 min, 73% over two steps; (viii) Ac₂O, pyridine, DMAP, CH₂Cl₂, 12 h, 94%; (ix) (a) TEMPO, Bu₃SnH (added in portions), PhMe, 70 °C, *ca.* 1.5 h; (b) Zn, AcOH, THF, water, 70 °C, 4 h, 67% over two steps; (x) *t*-BuMe₂SiO₂SO₂CF₃, 2,6-lutidine, CH₂Cl₂, 0 °C, 4 h, room temperature, 15 h, 92–98%; (xi) LiBH₄, THF, 5 days, 97%; (xii) MeSO₂Cl, Et₃N, CH₂Cl₂, 0 °C, 40 min, room temperature, 4 h, 94%.

iodolactonization. In the present case, however, inspection of Dreiding models shows that generation of an iodonium ion on the β -face of **13** and intramolecular trapping by the carboxylate must proceed by way of a boat-like six-membered ring, and either of the resulting lactones would be highly strained. In contrast, these unfavorable geometrical changes are avoided by formation of an α -iodonium ion, followed by intermolecular *trans* diaxial ring opening by H_2O or HO^- , leading to **14**. The positive charge on such an α -iodonium ion may well be stabilized by the negatively charged carboxylate.¹⁶

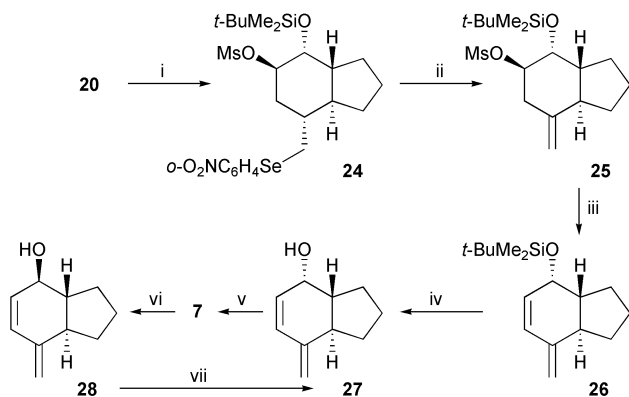
Esterification (**14**→**15**) and acetylation gave iodide **16**, and the halogen was then replaced by an hydroxy (**16**→**17**), using a standard free radical method¹⁷ (see Scheme 1, 67%). Silylation (**17**→**18**, 92–98%) and reduction (LiBH_4) gave the crystalline diol **19** (97%), which was subjected to X-ray analysis.[†] The diol was then converted (94%) into the bis-mesylate **20**, which is a key intermediate in our synthesis.

Desilylation of **20** (Scheme 2) led directly to epoxide **21** (79%) and, on treatment with PhSeNa , the bis-selenide **22** was obtained (81%). In order to facilitate the subsequent selenoxide elimination, the hydroxy group was oxidized (**22**→**23**, Dess-Martin reagent, 69%), and then treatment with H_2O_2 afforded the target ketone **7** (58%).



Scheme 2 Reagents and conditions: (i) Bu_4NF , THF, 2 h, 79%; (ii) PhSeSePh , NaBH_4 , MeOH, 40 h, 81%; (iii) Dess-Martin periodinane, CH_2Cl_2 , 70 min, 69%; (iv) 30% H_2O_2 , CH_2Cl_2 , 25 h, 58%.

Bis-mesylate **20** was also converted into **7** by the reactions summarized in Scheme 3. The primary methanesulfonyloxy group was displaced (**20**→**24**) with $o\text{-O}_2\text{NC}_6\text{H}_4\text{Se}^-$ (5 equiv.), and selenoxide elimination then produced the exocyclic olefin **25** [58% from **20**, after correction for recovered **20** (11%)]. Treatment with DBU in refluxing *o*-xylene now served to generate the diene system (**25**→**26**), and desilylation released alcohol **27** (79% from **25**). Oxidation, again with the Dess-Martin reagent, afforded **7** (90%).



Scheme 3 Reagents and conditions: (i) $o\text{-O}_2\text{NC}_6\text{H}_4\text{SeCN}$ (5 equiv.), NaBH_4 , MeOH, 70 °C, 7 h; (ii) 30% H_2O_2 , THF, 14 h, 58% over two steps, corrected for recovered dimesylate (11%); (iii) DBU, *o*-xylene, reflux, 10 h; (iv) Bu_4NF , THF, 24 h, 79% over two steps; (v) Dess-Martin periodinane, CH_2Cl_2 , 2 h, 90%; (vi) $\text{CeCl}_3\cdot 7\text{H}_2\text{O}$, NaBH_4 , MeOH, -78 °C, 10 min, ca. 86%; (vii) $p\text{-O}_2\text{NC}_6\text{H}_4\text{CO}_2\text{H}$, DEAD, Ph_3P , PhH, 5 °C, 1.5 h, 79%; K_2CO_3 , MeOH, 30 min, 69%.

Although dienone **7** is crystalline, we were unable to obtain material suitable for X-ray analysis. Therefore, in order to prove that no epimerization had occurred α to the carbonyl in **23** or **7**, the latter was reduced with $\text{NaBH}_4/\text{CeCl}_3\cdot 7\text{H}_2\text{O}$, giving a new alcohol to which we assign structure **28**. Although crystalline, adequately diffracting crystals could not be obtained for this substance either. Fortunately, Mitsunobu inversion¹⁸ converted **28** back into **27**, the structure and stereochemistry of which can be assigned on the basis of the X-ray data obtained for its precursor **19** (Scheme 1). These observations show that no change in ring fusion stereochemistry occurs in any of the steps involving generation or manipulation of ketones **23** or **7**.

The *trans* ring-fused dienone **7** appears to be a quite robust compound. It can be distilled unchanged (Kugelrohr, oven at 170 °C), is stable to silica gel chromatography, and is largely recovered after being heated for 1 h in THF containing $\text{TsOH}\cdot\text{H}_2\text{O}$ (3 equiv.). Evidently, the substituents of otellione B are not essential to stabilize the dienone substructure.

Acknowledgment is made to NSERC and to Wyeth-Ayerst (Pearl River) for financial support. We thank Dr R. McDonald for crystal structure determinations, Professor M. Klobukowski for the calculations, and Professor K. Narasaka for advice on the preparation of **9**. S. F. holds an NSERC Postgraduate Scholarship.

Notes and references

[†] CCDC 189592, 189593 and 190875. See <http://www.rsc.org/suppdata/cc/b2/b205753k/> for crystallographic data in CIF or other electronic format.

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