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

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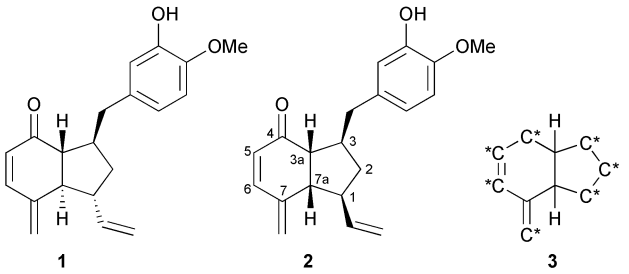
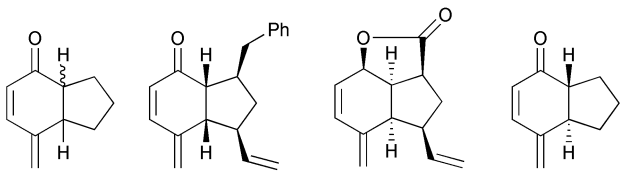
The intramolecular Diels–Alder adduct 12 was converted *via* dimesylate 20 into dienone 7, which represents the unusual, and apparently quite stable, core of the antitumor agent ottelione B (1).

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 IC_{50} 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 1α,3α,3aα,7aα relative stereochemistry shown in **2** was judged[1] more likely than the 1α,3α,3aβ,7aβ stereochemistry, but in a more recent publication[3] the assignment made is 1α,3β,3aα,7aα. 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.

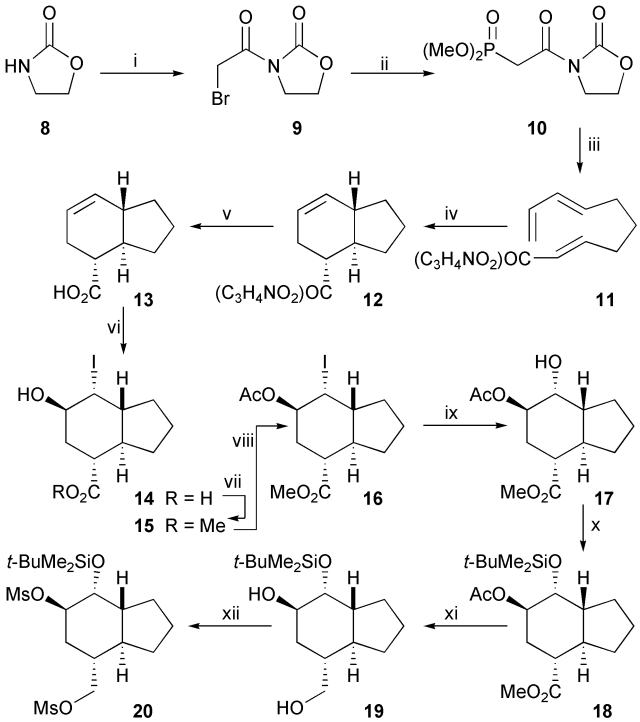


The otteliones represent a rare compound class, and a search of the Beilstein database, using substructure **3**,[4] retrieved few relevant examples,[5] apart from the two otteliones and the models mentioned below; none of the examples had *trans* ring fusion. The dienone substructures **4**, characteristic of the otteliones, have not been studied extensively,[5] and little synthetic work has yet been published on the otteliones themselves. The synthesis of (±)-**5**[6] and of optically pure **6**[7] have been reported, as has a route[8] to functionalized hydrindenones 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 pattern[9] 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 known[12] phosphonate **10** was made as indicated in Scheme 1. Olefination of (5*E*)-5,7-octadienal[13] 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](SbF$_6$)$_2$,[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, H_2O_2, 90–98%) liberated acid **13**, whose structure was confirmed by X-ray analysis.† Treatment with I_2–KI–$NaHCO_3$ 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) (5*E*)-5,7-octadienal, Et_3N, LiCl, MeCN, 4 h, 53–75%; (iv) [Cu((*S*,*S*)-*t*-Bu-box)](SbF$_6$)$_2$, CH_2Cl_2, 1 week, 44–58%; (v) LiOH·H_2O, 30% H_2O_2, 3 : 1 THF–water, 4 h, 90–98%; (vi) I_2, KI, $NaHCO_3$, water–CH_2Cl_2, 13 h; (vii) CH_2N_2, Et_2O, 20 min, 73% over two steps; (viii) Ac_2O, pyridine, DMAP, CH_2Cl_2, 12 h, 94%; (ix) (a) TEMPO, Bu_3SnH (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*-$BuMe_2SiO$-SO_2CF_3, 2,6-lutidine, CH_2Cl_2, 0 °C, 4 h, room temperature, 15 h, 92–98%; (xi) $LiBH_4$, THF, 5 days, 97%; (xii) $MeSO_2Cl$, Et_3N, CH_2Cl_2, 0 °C, 40 min, room temperature, 4 h, 94%.

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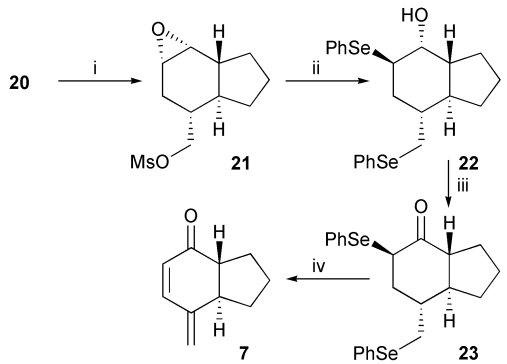
iodolactonization. In the present case, however, inspection of Dreiding models shows that generation of an iodonium ion on the β-face of **13** and intramolecular trapping by the carboxylate must proceed by way of a boat-like six-membered ring, and either of the resulting lactones would be highly strained. 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]

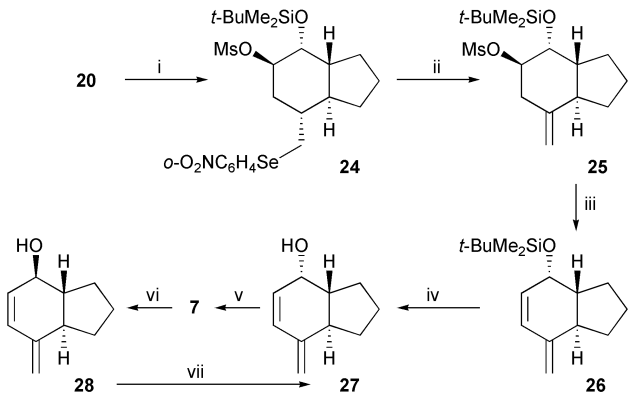
Esterification (**14**→**15**) and acetylation gave iodide **16**, and the halogen was then replaced by an hydroxy (**16**→**17**), using a standard free radical method[17] (see Scheme 1, 67%). Silylation (**17**→**18**, 92–98%) and reduction ($LiBH_4$) gave the crystalline diol **19** (97%), which was 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*-$O_2NC_6H_4Se^-$ (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*-$O_2NC_6H_4SeCN$ (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) $CeCl_3·7H_2O$, $NaBH_4$, MeOH, −78 °C, 10 min, *ca.* 86%; (vii) *p*-$O_2NC_6H_4CO_2H$, 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 $NaBH_4/CeCl_3·7H_2O$, 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 inversion[18] 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 $TsOH·H_2O$ (3 equiv.). Evidently, the substituents of ottelione B are not essential to stabilize the dienone substructure.

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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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