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Enantioselective formal synthesis of antitumor agent (+)-ottelione A

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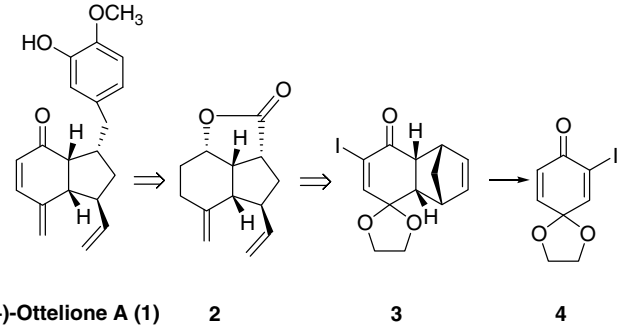
Abstract

The enantioselective formal synthesis of a natural antitumor product, (+)-ottelione A, was achieved through a catalytic enantioselective Diels–Alder strategy. These endeavors have led to the synthesis of a variety of synthetic analogues of this biologically potent natural product.

Ottelione A, **1** was isolated from the widely occurring fresh water plant, *Ottelia alismoides*, by the Hoye group.[1] Ottelione A showed quite remarkable biological activity, such as antitubercular[2] and antitumor activities.[1] Screening against a panel of 60 human cancer cell lines at the National Cancer Institute in the United States revealed the cytotoxicity of compound **1** at the nM–pM levels.[1] Biological studies by a research group at Aventis reported that compound **1** is an efficient inhibitor of tubulin polymerization ($IC_{50} = 1.2$ μM) and can disassemble preformed microtubules to represent a new class of inhibitor of microtubule assembly with potential therapeutic value.[3] However, the rarity of this natural product has prevented further extensive biological studies. Since the first synthesis of racemic compound **1** was reported,[4a] the enantioselective total syntheses of compound **1** was reported by Mehta[4b], Katoh[4c,d] and Clive[4e] groups, and the absolute configuration of compound **1** was assigned by their syntheses. This Letter reports the efficient asymmetric synthesis of compound **2**, which Mehta and co-workers had previously converted to the natural product **1** (Scheme 1).



Scheme 1. Retrosynthetic analysis of (+)-ottelione A **1**.

As part of an ongoing investigation into catalytic enantioselective Diels–Alder reactions,[5] we considered that the selective oxidative cleavage of the Diels–Alder adduct **3** could provide the intermediate lactone **2**. In addition, it was envisaged that the enantioselective Diels–Alder reaction between 2-iodo-1,4-quinone monoketal **4** and cyclopentadiene would provide chiral *endo*-Diels–Alder adduct **3**, which has the correct *cis*-bicyclic core structure.

The cationic chiral oxazaborolidium catalysts **5** generated from the corresponding oxazaborolidines via protonation by trifluoromethanesulfonic acid are excellent catalysts for an enantioselective Diels–Alder reaction with a variety of dienes and dienophiles, for example

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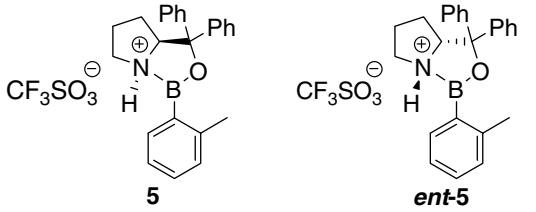
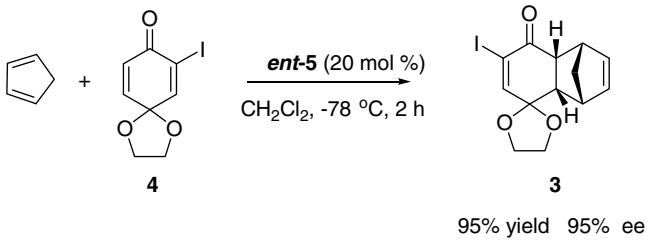
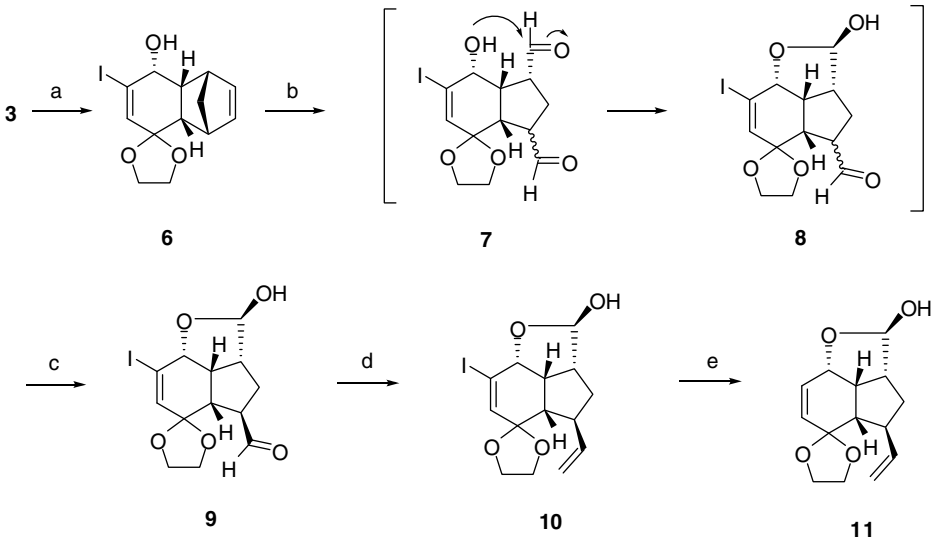
α,β-enones, esters and quinone monoketals.[5] Recently, it was found that the Diels–Alder reaction of furans with catalyst **5** provides 7-oxabicyclo [2.2.1] hept-5-enes with high *endo*-selectivity and excellent enantioselectivity.[6]



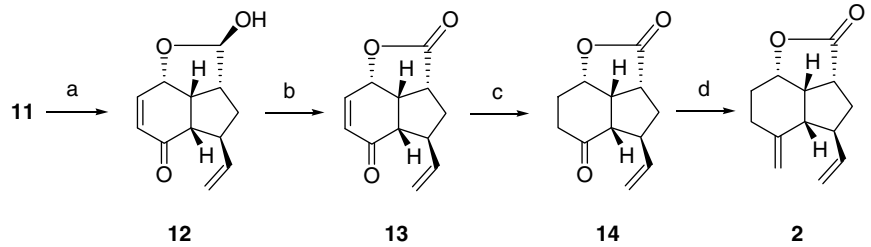
Initially, the enantioselective Diels–Alder reactions of cyclopentadiene and 2-iodo-1,4-quinone monoketal **4**, which is easily prepared from 2-iodophenol,[7] were attempted. The reaction was carried out at −78 °C by stirring 2-iodo-1,4-quinone monoketal **4** and cyclopentadiene in the presence of ***ent*-5** (20 mol %) in CH_2Cl_2 under nitrogen. The reaction was complete after 2 h. Only the *endo*-cycloadduct **3** was generated in 95% yield with excellent 95% ee. Enantioselectivities were determined by HPLC analysis using chiralcel OJ-H column with hexane–*i*PrOH (9:1) for elution.



The next stage is the preparation of the key intermediate **11** from the chiral Diels–Alder *endo*-adduct **3**. After the Luche reduction of adduct **3** using sodium borohydride in the presence of cerium chloride,[8] alcohol **6** was subjected to ozonolysis to give the 5-*exo* cyclized product **8** through the intermediate **7**. However, the lactol **8** was a mixture of diastereomers. Epimerization with DBU[4c] provided aldehyde **9** with all requisite stereocenters in 78% yield in three steps. A Wittig reaction with a methylphosphonium salt using NaHMDS[9] introduced the vinyl group in 97% yield. The structure of compound **10** was determined unambiguously from the NOESY and COSY spectra. The removal of iodine was performed using tributyltin hydride to afford compound **11** in 95% yield (Scheme 2).



Scheme 2. Reagents and conditions: (a) $CeCl_3{\cdot}7H_2O$, MeOH, $NaBH_4$, −78 °C; (b) (i) O_3, CH_2Cl_2, −78 °C, (ii) Me_2S, rt; (c) DBU, benzene, 65 °C, 78% (three step); (d) $Ph_3PCH_3{}^+Br$, NaHMDS, THF, 0 °C, 97%; (e) *n*-Bu_3SnH, benzene, 80 °C, 95%.



Scheme 3. Reagents and conditions: (a) 1N H_2SO_4, acetone, THF, 0 °C → rt, 93%; (b) PCC, Celite, CH_2Cl_2, rt, 95%; (c) $(IPr)Cu(OAc)_2$, PMHS, toluene, *t*-BuOH, rt, 87%; (d) $Ph_3PCH_3{}^+$, NaHMDS, benzene, 80 °C, 65%.

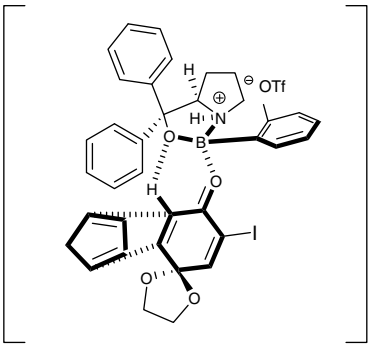


Fig. 1. The transition-state assembly of the Diels–Alder reaction of cyclopentadiene and **4** in the presence of ***ent*-5**.

Deprotection of ketal, followed by pyridinium chlorochromate oxidation of lactol **12**, gave lactone **13** in two steps in 88% yield. Finally, the reduction of the conjugated ketone[10] and a Wittig reaction of ketone **14** were carried out efficiently to release the known intermediate **2**. The spectral data and optical rotation of the synthetic compound **2** were in well accord with that of the reported one[4a,b] (Scheme 3).

As we predicted, the mechanistic model of cationic oxazabororidium catalyst ***ent*-5** was supported (Fig. 1).[5] For α,β-unsaturated carbonyl compounds having an α-C–H substituent (e.g., esters, quinones, ketones) α-C–H···O hydrogen bonding leads to a preferred pathway.

In summary, the bicyclic core intermediate **2** for the synthesis of (+)-ottelione A was synthesized using a catalytic enantioselective Diels–Alder strategy. A variety of chiral derivatives were obtained using this method and their anticancer activities will be reported elsewhere.

Acknowledgements

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