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.

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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 antitubercular2 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 (IC50 = 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 Mehta4b, Katoh4c,d and Clive4e 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).

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

Initially, the enantioselective Diels–Alder reactions of cyclopentadiene and 2-iodo-1,4-quinone monoketal \( \text{4} \), which is easily prepared from 2-iodophenol, were attempted. The reaction was carried out at \(-78^\circ C\) by stirring 2-iodo-1,4-quinone monoketal \( \text{4} \) and cyclopentadiene in the presence of \( \text{ent-5} \) (20 mol %) in CH\(_2\)Cl\(_2\) under nitrogen. The reaction was complete after 2 h. Only the endo-cycloadduct \( \text{3} \) was generated in 95% yield with excellent 95% ee. Enantioselectivities were determined by HPLC analysis using chiralcel OJ-H column with hexane-iPrOH (9:1) for elution.

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

\[ \text{Scheme 2. Reagents and conditions: (a) CeCl}_3\cdot7\text{H}_2\text{O, MeOH, NaBH}_4, -78^\circ C; (b) (i) O}_3\text{, CH}_2\text{Cl}_2, -78^\circ C, (ii) Me}_2\text{S, rt; (c) DBU, benzene, 65^\circ C, 78\% (three step); (d) Ph}_3\text{PCl}_3\cdot\text{Br, NaHMDS, THF, 0^\circ C, 97\%; (e) n-Bu}_3\text{SnH, benzene, 80^\circ C, 95\%.} \]

\[ \text{Scheme 3. Reagents and conditions: (a) 1N H}_2\text{SO}_4, \text{acetone, THF, 0^\circ C \to rt, 93\%; (b) PCC, Celite, CH}_2\text{Cl}_2, \text{rt, 95\%; (c) (IPrCu(OAc))}_2, \text{PMHS, toluene, r-BuOH, rt, 87\%; (d) Ph}_3\text{PCl}_3\cdot^+, \text{NaHMDS, benzene, 80^\circ C, 65\%.} \]
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 anti-cancer activities will be reported elsewhere.

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References and notes


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