論文の内容の要旨

論文題目　Catalytic Asymmetric Total Synthesis of *ent*-Hyperforin
(*ent*-Hyperforin の触媒的不斉全合成)

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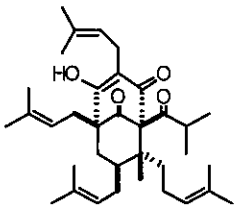
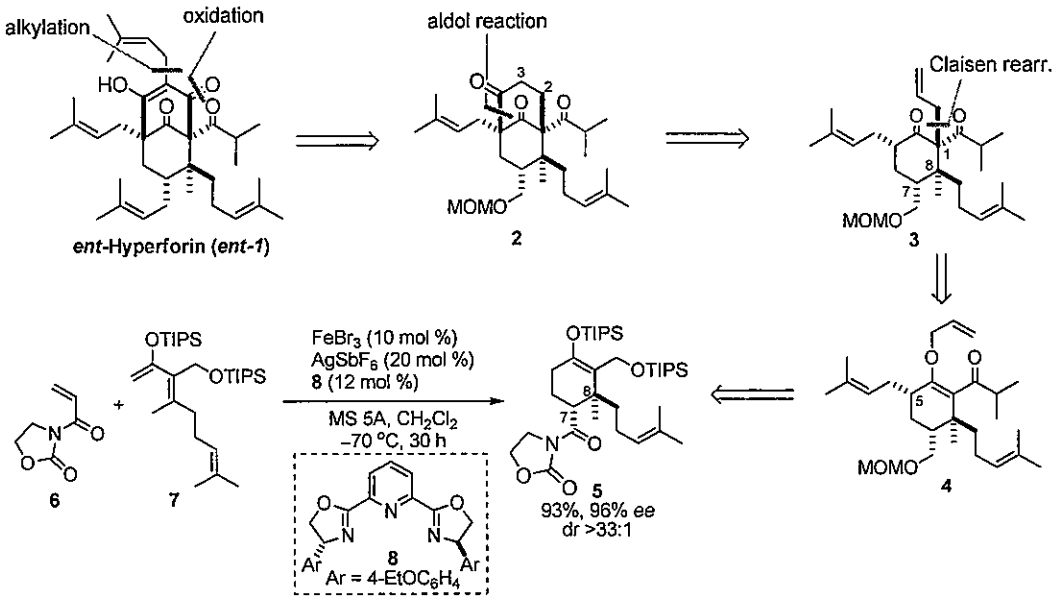


Hyperforin (1)

Polycyclic Polyprenylated Acylphloroglucinols (PPAPs) are a unique group of natural products which have densely substituted bicyclo[3.3.1] nonanone core. Hyperforin (1), isolated from St. John's wort (*Hypericum perforatum*) in 1971, is one of the representatives of this family. Recent studies revealed that hyperforin has several interesting biological activities, such as mild antidepressant activity, antimalarial activity and drug-drug interaction through inducing CYP3A4. Because of its complex structure and potential utility as pharmaceutical lead, extensive synthetic studies have been reported, but none of them accomplished the total synthesis of hyperforin. Herein, I report the first catalytic asymmetric total synthesis of *ent*-hyperforin.

1. Retrosynthetic Analysis

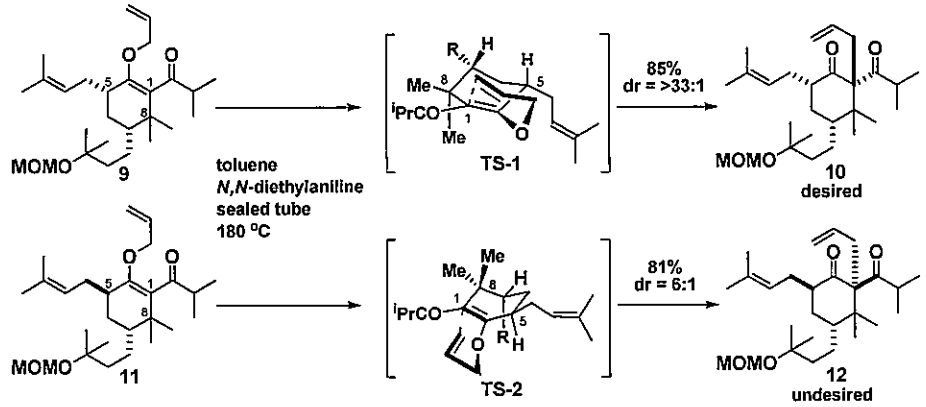
Planned approach toward *ent*-hyperforin is shown below (Scheme 1). C2 oxidation and C3 alkylation could retrosynthetically lead to bicyclo compound 2. The bicyclo[3.3.1] core of the key intermediate 2 could be constructed through Claisen rearrangement-intramolecular aldol cyclization sequence from *O*-allylated intermediate 4. The Claisen rearrangement precursor 4 could be produced from multi substituted cyclohexene 5, and it could be constructed by a catalytic asymmetric Diels-Alder reaction between dienophile 6 and diene 7 in high yield, high dr and high *ee*.[1)]



Scheme 1. Retrosynthetic analysis.

2. Construction of Bicyclo[3.3.1] Core

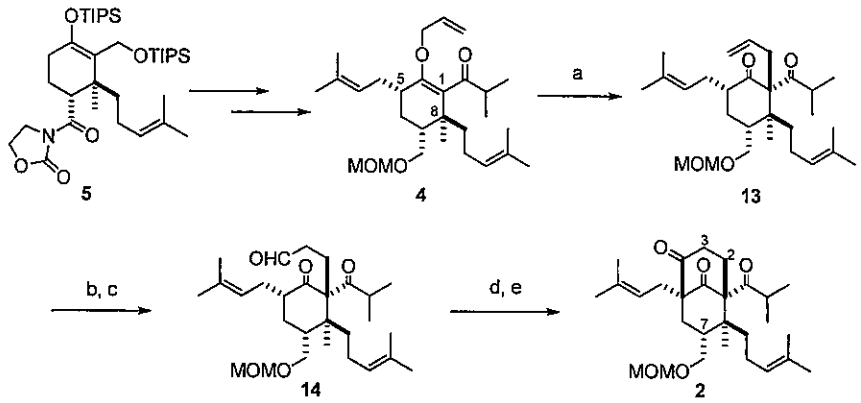
Construction of a bicyclo[3.3.1] core in correct stereochemistry depends on the diastereoselectivity of the planned Claisen rearrangement. Terefore, the stereoselectivity of the Claisen rearrangement was examined first using model substrates (Scheme 2). This study showed the importance of stereochemistry of C5 prenyl groups. The α-prenyl substrate **9** rearranged stereoselectively constructing desired C1 quaternary carbon center. On the other hand, the β-prenyl substrate **11** rearranged to give **12** which has undesired stereochemistry at C1 quaternary carbon. These results demonstrated that the C5 prenyl group was a main factor in determining the conformation during the transition state and the rearrangement proceeded from the indicated face, avoiding steric repulsion between the pseudo axial methyl group at C8 and the allyl group.[2)]



Scheme 2. Diastereoselectivity of Claisen rearrangement.

The Claisen rearrangement of the actual substrate **4** also proceeded in high diastereoselectivity (Scheme 3). Following selective hydroboration and oxidation afforded

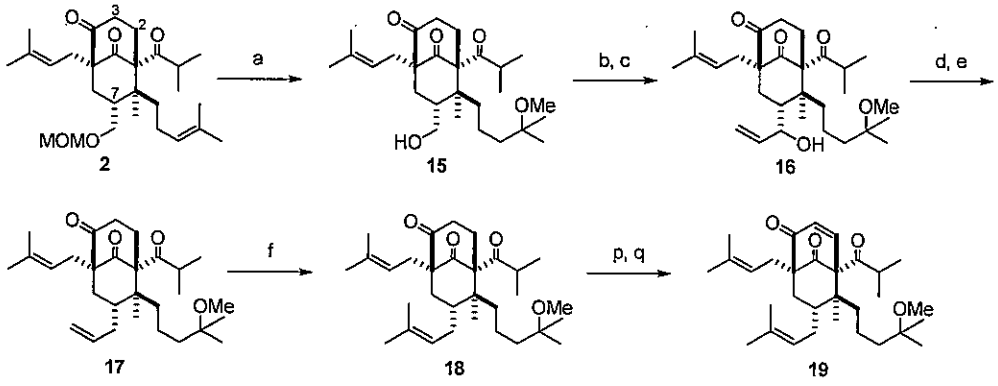
the intramolecular aldol reaction precursor **14**. The critical cyclization proceeded smoothly under basic conditions, and the obtained secondary alcohol was oxidized to give key bicyclo[3.3.1] compound 2.



Scheme 3. Construction of bicyclo[3.3.1] core. Reagents and conditions: (a) toluene, *N,N*-diethylaniline, 170 ℃, >99% (dr = 12:1). (b) $(Sia)_2BH$, THF; H_2O_2 aq., NaOH aq., EtOH, 81%. (c) DMP, CH_2Cl_2, 91%. (d) NaOEt, EtOH. (e) DMP, CH_2Cl_2, 86% (2 steps).

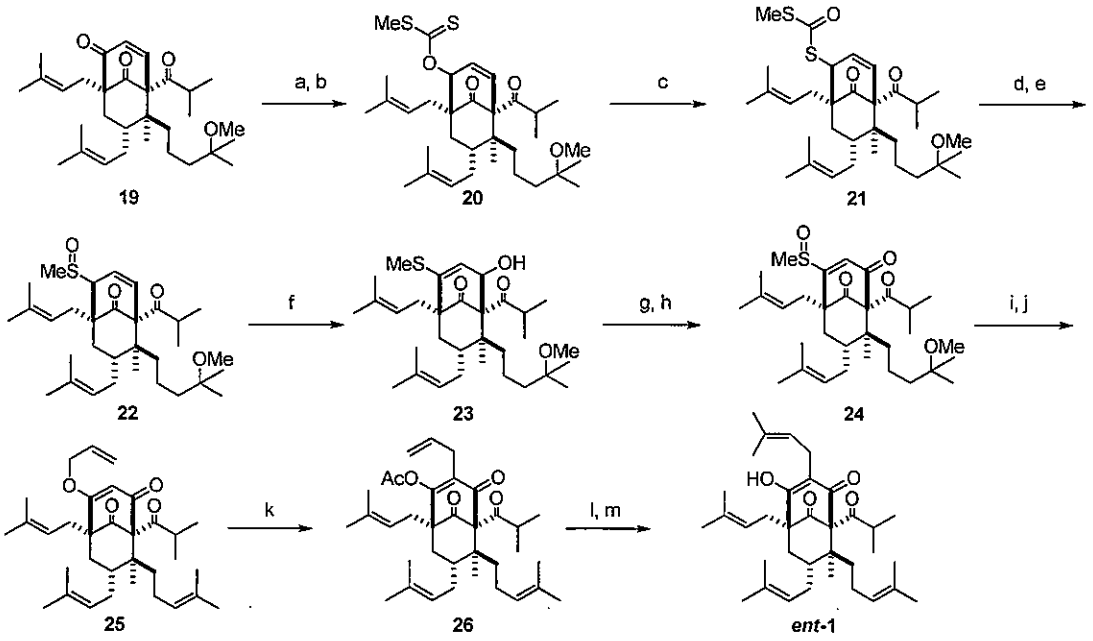
3. Completion of the Total Synthesis

Remaining tasks were C3, C7 prenyl introduction and a C2 oxidation. Among these tasks, installation of the C7 prenyl group was conducted first. Cleavage of the C7 MOM ether under acidic conditions proceeded with concomitant protection of the homoprenyl group at C8 to give **15**. Swern oxidation of **15** followed by the addition of a vinyl Grignard reagent afforded allylic alcohol **16** as a single isomer, which was deoxygenated through acetylation and a palladium-catalyzed allylic reduction. The subsequent cross-metathesis with isobutene using the Hoveyda–Grubbs 2nd generation catalyst produced a third prenyl group at C7. The obtained product **18** was oxidized to enone **19** through a conventional palladium mediated Saegusa-Ito oxidation.



Scheme 4. Introduction of C7 prenyl group. Reagents and conditions: (a) (+)-CSA, MeOH, 66% (3 cycles). (b) $(COCl)_2$, DMSO, CH_2Cl_2; NEt_3, 95%. (c) vinylmagnesium bromide, THF, 92% (dr > 33:1). (d) Ac_2O, DMAP, *i*Pr_2NEt, CH_2Cl_2, 98%. (e) $Pd(PPh_3)_4$ (20 mol %), HCO_2NH_4, toluene, 95%. (f) Hoveyda-Grubbs 2nd cat. (15 mol %), 2-methyl-2-butene, CH_2Cl_2, >99%. (g) TMSCl, NEt_3, DMAP, 84%. (h) $Pd(OAc)_2$, DMSO, O_2, >99%

Next is an introduction of oxygen functionality at C2 position. After extensive investigation, it turned out to be difficult to functionalize C2. 1,4-addition of several kinds of nucleophiles resulted in failure due to the steric hindrance around C2 position. The key of the C2 functionalization was a vinylogous-Pummerer rearrangement. Enone **19** was converted to sulfoxide **22** through a [1.3]-xanthate rearrangement. When the obtained **22** was treated with TFAA in the presence of bulky pyridine derivative, 2,6-di-*tert*-butylpyridine, a rearrangement proceeded preferentially in 1,4-manner. The product **23** was oxidized to sulfoxide **24**, which was treated with allyl alcohol under basic conditions to give *O*-allyl intermediate **25**. Next, Claisen rearrangement was examined to introduce a C3 prenyl group. Although thermal or Lewis acid-mediated conditions gave only a trace amount of the rearranged product, a palladium-catalyzed allyl transfer followed by acetylation afforded the product **26** in moderate yield. Subsequent cross metathesis and deacetylation finally afforded *ent*-hyperforin.[3)]



Scheme 4. Completion of the total synthesis. Reagents and conditions: (a) $NaBH_4$, MeOH, 95% (dr > 33:1). (b) CS_2, NaH, THF; MeI, >99%. (c) toluene, 150 ℃. (d) EtSLi, THF; MeI, NEt_3, 98% (2 steps). (e) $NaBO_3 \cdot 4H_2O$, AcOH (dr = 1.3:1), 95%. (f) TFAA, 2,6-di-t-butylpyridine, CH_2Cl_2, -40 ℃; H_2O, 65% (dr > 33:1). (g) H_2O_2, HFIP, 87% (dr = 9:1). (h) DMP, CH_2Cl_2, 86%. (i) Amberlyst 15DRY, toluene, 55%. (j) LiH, allyl alcohol, 67%. (k) $Pd_2dba_3 \cdot CHCl_3$ (10 mol %), (*S*)-tol-BINAP (20 mol %), THF; Ac_2O, pyridine, 50%. (l) Hoveyda-Grubbs 2nd cat. (15 mol %), 2-methyl-2-butene, CH_2Cl_2, 34%. (m) K_2CO_3, MeOH, 94%.

4. References

1) Ususda, H; Kuramochi, A.; Kanai, M.; Shibasaki, M. *Org. Lett.* **2004**, *6*, 4387.

2) Shimizu, Y.; Kuramochi, A.; Usuda, H.; Kanai, M.; Shibasaki, M. *Tetrahedron Lett.* **2007**, *48*, 4173.

3) (a) Shimizu, Y.; Shi, S.-L.; Usuda, H.; Kanai, M.; Shibasaki, M. *Angew. Chem. Int. Ed.* **2010**, *49*, 1103. (b) Shimizu, Y.; Shi, S.-L.; Usuda, H.; Kanai, M.; Shibasaki, M. *Tetrahedron* **2010**, *66*, 6569.