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Stereoselective total synthesis of (±)-hyperforin via intramolecular cyclopropanation

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ABSTRACT

Total synthesis of (±)-hyperforin is described. This total synthesis features an approach via a bicyclo[3.3.1]nonane derivative prepared by a three-step sequence: intramolecular cyclopropanation, construction of the C8 all-carbon quaternary stereogenic center, and subsequent regioselective ring opening of cyclopropane. Further steps to obtain (±)-hyperforin include chemo- and stereoselective hydrogenation to generate the C7 stereogenic center, formation of the C9 isopropyl ketone using an organocerium reagent, and cross-metathesis at high temperatures to construct trisubstituted alkenes in side-chains.

Hyperforin (Fig. 1) was isolated from *Hypericum perforatum* L. (St. John's wort), a herbal remedy widely used for the treatment of depression.[1] St. John's wort is a complex mixture of constituents, but recent evidence indicates that hyperforin is responsible for the antidepressant activity of the herb. Hyperforin inhibits the reuptake of neurotransmitters in synapses,[2] and the clinical effects of St. John's wort on depression correlate well with the hyperforin content.[3] It has also been reported that hyperforin exhibits antibacterial activity against multi-resistant *Staphylococcus aureus* and other Gram-positive bacteria,[4] accelerates hepatic drug metabolism through activation of the pregnane X receptor,[5] and inhibits tumor cell growth,[6] among other activities.[7]

Hyperforin belongs to a family of polycyclic polyprenylated acylphloroglucinols (PPAPs), which feature complex and diverse structures.[8] Most of PPAPs contain a highly oxygenated and densely substituted bicyclo[3.3.1]nonane (Fig. 1) or bicyclo[3.2.1]octane core with prenyl or geranyl side chains, among others. The family currently includes more than 110 compounds and is still acquiring new members.

Some PPAPs possess the same scaffold, bearing different substituents, but exhibit diverse bioactivities. For example, although the three PPAPs shown in Figure 1 contain bicyclo[3.3.1]nonane cores, nemorosone exhibits anti-HIV and anti-tumor activities,[9] garsubellin A is a promising compound for Alzheimer's therapeutics,[10] and hyperforin shows anti-depressant activity, as described above.

We were interested in structure–activity relationship studies on PPAPs and designing molecules for new drugs. Hence, we started to develop an approach to the bicyclo[3.3.1]nonane scaffold[11] which would allow a collective total synthesis of some PPAPs and their derivatives. We recently reported the total synthesis of nemorosone.[12] As a component of the collective total synthesis of PPAPs, we herein report the total synthesis of (±)-hyperforin.

Hyperforin is structurally related to nemorosone, garsubellin A, and others. These compounds contain the bicyclo[3.3.1]nonane core bearing oxygen functionalities at the C2, C4, and C9 positions; prenyl groups at C3, C5, and C7 positions; and an acyl group at the C9 position.

Hyperforin additionally possesses an all-carbon quaternary stereogenic center at C8; this is a unique structural feature among PPAPs, because most PPAPs have an achiral quaternary carbon center at C8 bearing germinal methyl groups. The different C8 structure makes the total synthesis of hyperforin difficult when compared with others.[13–15] Indeed, Danishefsky's group achieved the total synthesis of nemorosone in 14 steps.[16] However, the first total synthesis of *ent*-hyperforin achieved by Kanai and Shibasaki et al., required 50 steps,[13] suggesting that enantioselective total synthesis of hyperforin is difficult and still challenging.

We established a synthetic approach to bicyclo[3.3.1]nonane derivatives **3** and **4** as shown in Scheme 1.[12] This approach features a three-step sequence: intramolecular cyclopropanation (IMCP) of **1**, which was prepared from methyl 2,6-dimethoxybenzoate by seven steps, followed by stereoselective alkylation of the cyclopropane **2**, and finally, regioselective ring opening of the cyclopropane moiety to afford **3** and **4**. Since the desymmetrization occurs in the

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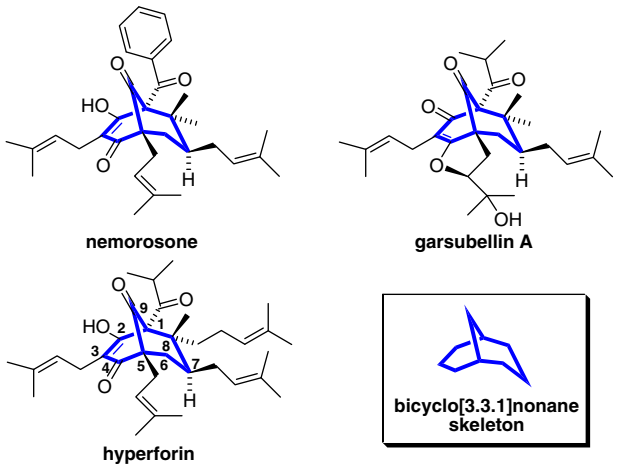
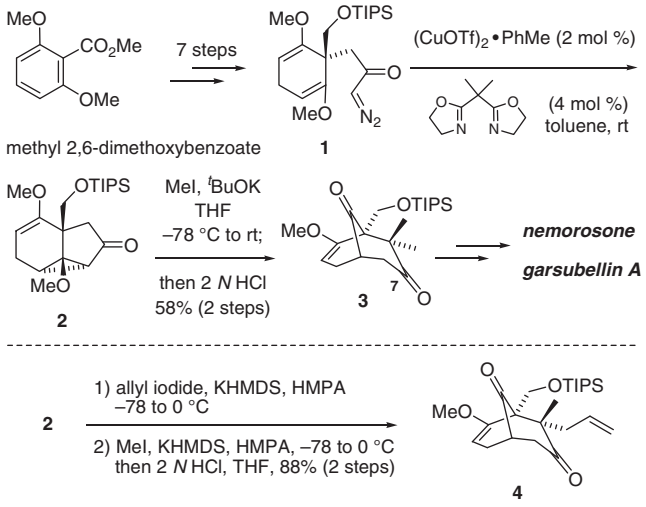


Figure 1. Structures of nemorosone, garsubellin A, and hyperforin.



Scheme 1.

first step, the reaction could be made enantioselective when using a chiral catalyst. The second step enables sequential stereoselective alkylations from the less-hindered convex face to install two different substituents at the C8 position, generating the all-carbon quaternary stereogenic center of hyperforin. The third step leads to compounds **3** and **4** because the electron-donating methoxy group on cyclopropane and the electron-withdrawing ketone would cooperatively facilitate regioselective ring opening of the cyclopropane moiety under acidic conditions.

Compound **3** was successfully used for the total syntheses of nemorosone.[12] Therefore, we examined preparation of **4** and its congeners, which would acquire an all-carbon quaternary stereogenic center at C8 by sequential stereoselective alkylation. However, compound **2** resisted installation of a homoprenyl group at C8 and only permitted sequential allylation-methylation to provide compound **4** after acid treatment.[12]

Consequently, the total synthesis of hyperforin was begun from **4**. Considering the step economy, we initially attempted the construction of C7 and C8 substituents via a coupling reaction of a triflate with a vinyl cuprate which was successfully used in the total synthesis of nemorosone.[12] However, despite extensive efforts, all the coupling reactions failed because the substrates containing a leaving group at C7 or C8 suffered from intramolecular reactions with the alkene or the oxygen atom in the C8 or C7 substituents, respectively. Thus, the close proximity of the C7 and C8 substituents promoted the competing intramolecular reactions. For example, we were unable to prepare compounds **4a–d** (Fig. 2). Consequently, we discarded the coupling reaction method and employed Wittig reactions to construct the C7 and C8 substituents.

Compound **4** was converted to compound **8** as shown in Scheme 2. Chemo- and stereo-selective hydroboration of **4** with disiamylborane and protection of the resultant hydroxyl as a TIPS ether afforded **5**. Formation of the enol triflate of **5** with Comins' reagent[17] and palladium-catalyzed carbonylation gave **6**.[18] Chemo- and stereoselective reduction of the C6–C7 alkene in **6** was achieved by hydrogenation using Crabtree's catalyst,[19] which proceeded in refluxing dichloroethane to afford **7** as the sole product. This stereoselectivity could be attributed to the directing effect of the C2–C3 electron-rich methoxyalkene, which we observed previously.[12] Reduction of **7** with DIBAL-H afforded the corresponding diol; selective acetylation of the primary hydroxyl and Dess–Martin oxidation of the C9 secondary hydroxyl afforded compound **8**.

Allylic oxidation of **8** was achieved using the palladium-catalyzed oxidation reported by Corey and Yu to afford **9** (Scheme 3),[20] followed by the removal of the TBS group, Dess–Martin oxidation, and Wittig reaction to give **10**.

As noted in the beginning, the construction of the allyl group at the C7 position was also carried out via Wittig reactions (Scheme 4). That is, the acetyl group of **10** was removed by potassium carbonate in methanol, which was followed by Dess–Martin oxidation

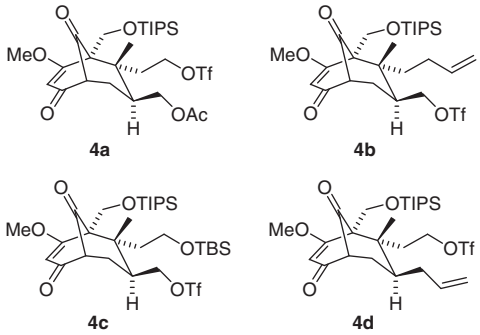
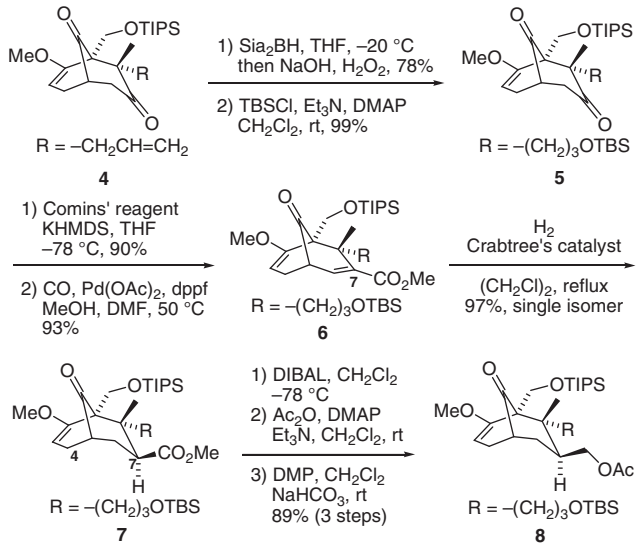


Figure 2. Structures of **4a–d**.



Scheme 2.