Total syntheses of ent-hypocoprin A and ent-hypocoprin B†

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This study reports the stereoselective total syntheses of the antipodes of the unique 3/10 bicyclic skeletal sesquiterpenoids, namely, hypocoprin A and hypocoprin B. The synthesis involved conjugate addition accelerated by trimethylsilyl chloride, construction of the ten-membered ring via the intramolecular SN2 reaction promoted by 1,8-diazabicyclo[5.4.0]undec-7-ene, and osmium-mediated π-facial selective dihydroxylation to functionalize the 1,1-disubstituted alkene.

Introduction

Hypocoprin A and hypocoprin B, isolated from the coprophilous fungus Hypocopa rostrata on horse dung, are sesquiterpenoids with an unprecedented 3/10 bicyclic ring system (Fig. 1). The 3/10 bicyclic scaffold of these sesquiterpenoids is thought to arise biosynthetically by 8,11-cyclization of the trans-humulyl cation derived from farnesyl diphosphate. The only other examples with the same scaffold are the marine diterpenoid palmatol and pacificins (from the Mediterranean octocoral Alcyonium palmatum) and pacificins (from the Formosan soft coral Nephthea sp.). Consequently, the biosynthetic origins of the bicyclic system in hypocoprins are largely unknown. Hypocoprin A moderately inhibits the growth of the Gram-positive bacteria Staphylococcus aureus and Bacillus subtilis but is ineffective against Candida albicans or the Gram-negative bacterium Escherichia coli. To explore the unreported biological properties of hypocoprins A and B with novel bicyclic scaffolds, we describe novel total syntheses of ent-hypocoprin A (1) and ent-hypocuprin B (2) starting from the optically active acetonide 3.

Results and discussion

Our retrosynthetic analysis of hypocoprin A is depicted in Scheme 1. In the initial planning stage, we recognized that the C-7 tertiary alcohol moiety can be constructed in hypocoprin A via diastereoselective addition of the C1-unit to bicyclic ketone A. We thus planned the synthesis of bicyclic ketone A with a core ten-membered ring from β-ketosulfone B via an intramolecular SN2 reaction followed by reductive desulfonylation. We assumed that β-ketosulfone B would arise from the chemo-selective addition of a vinyllithium species to ketoaldehyde C and the introduction of a halogen (X) atom. The β,β-

Fig. 1 Structures of natural hypocoprin A and hypocoprin B.

Scheme 1 Retrosynthetic analysis of ent-hypocoprin A (1) and ent-hypocuprin B (2).
disubstituted aldehyde moiety in β-ketosulfone C can be constructed by the Horner–Wadsworth–Emmons homologation of cyclopropyl ketone D followed by conjugate addition with an organocopper reagent. Cyclopropyl ketone D can be obtained from acetone E, which possesses C-8 and C-10 stereochemistry established by substrate-controlled stereoselective cyclopropanation. We established a synthetic route for the antipodes of hypocoprin A and B from acetone 3, which corresponds to the enantiomer of acetone E synthesized from β-mannitol, an inexpensive and ideal chiral pool for total synthesis. The total syntheses of ent-hypocoprin A (1) and ent-hypocoprin B (2) were initiated from acetone 3 via a retrosynthetic analysis.

Our synthesis commenced from acetone 3 (>97% ee), a known enantiopure compound prepared from β-mannitol (Scheme 2). After sequential acidic deprotection of the isopropylidene group of 3 and oxidative cleavage with periodic acid, the aldehyde was methylated with MeMgBr and the resulting secondary alcohol was oxidized with 2-iodoxybenzoic acid (IBX) to afford cyclopropyl ketone 4. C2-Homologation of cyclopropyl ketone 4 by the Horner–Wadsworth–Emmons reaction afforded α,β-unsaturated esters 5 and 6 in 95% yield (E : Z = 9 : 1). We next examined various conditions for the conjugate addition of 5 and 6, but unexpectedly, the starting material was recovered with only trace amounts of the desired adducts, presumably because the conjugate addition of organocopper reagents was inhibited by steric hindrance of the adducts, presumably because the conjugate addition of organocopper reagents was inhibited by steric hindrance of the evanescence of the trisubstituted alkene moiety was introduced to the ten-membered ring (Scheme 3). The trisubstituted alkene moiety was introduced to β-ketosulfone 9 by aldehyde-selective addition of the vinylithium species derived from [E]-tert-butyl(3-iodobut-2-en-1-yl)oxy)diphenylsilane and BuLi, forming the secondary alcohol 10 as a pair of inseparable diastereomers (79% yield, dr = 1 : 1). After acetylation the secondary alcohol 10, primary alcohol was selectively unmasked to allylic alcohol 11 (89% overall yield over two steps), which was converted to allylic bromide with CBr4 and Ph3P. The resulting allylic bromide was an important precursor for cyclizing the ten-membered ring, but was unstable. Therefore, after confirming the disappearance of the starting material by thin-layer chromatography, we immediately added 1,8-diazacyclo[5.4.0]undec-7-ene (DBU). To our delight, the intramolecular S2 reaction proceeded smoothly, followed by SmI2-mediated reductive desulfonylation to give a pair of ten-membered cyclic ketones (12 and 13) as an inseparable diastereomeric mixture (76% overall yield over two steps).

The ten-membered cyclic ketones 12 and 13 were deacylated and separated as secondary alcohols 14 and 15, respectively, and then re-acetylated to give ketones 12 and 13 as single stereoisomers (Scheme 4). The ten-membered cyclic ketones 12 and 13 were exposed to Wittig methylenation, providing the exo-olefins 2 and 16 in 92% and 90% yield, respectively. Comparing the 1H and 13C NMR spectral data of the exo-olefins 2 and 16 with the reported data, the NMR spectrum of 2 was found to be consistent with that of natural hypocoprin B. However, whereas the specific rotation should be opposite to that of natural hypocoprin B ([c]D20 +13 (c 0.58 in MeOH), it was instead consistent with that of synthesized 2 ([c]D20 +55.3 (c 1.29 in MeOH)). In the previous isolation paper, the absolute configuration of natural hypocoprin B was determined by conversion.
from hypocoprin A, whose absolute configuration was determined by the Mosher method. Therefore, withholding our doubts on stereochemistry at this stage, we continued with the synthesis of ent-hypocoprin A (1). Toward the completion of the total synthesis of ent-hypocoprin A (1), we first attempted a direct nucleophilic addition of MeLi to the intermediate ten-membered cyclic ketone 12, obtaining the tertiary alcohol 17 as a single diastereomer in 98% yield. Unfortunately, the 1H and 13C NMR spectra of 17 were inconsistent with those of natural hypocoprin A. Although the relative configuration of 17 could not be determined by nuclear Overhauser effect (NOE) spectroscopy, most of the substrate was converted to ent-hypocoprin B (2) by dehydration during three-weeks’ storage of 17 in CDCl3. Consequently, compound 17 was inferred as the C-7 epimer of ent-hypocoprin A (1).

The exclusive diastereoselectivity of alkylation was attributable to steric congestion inside the ten-membered ring. We then estimated the conformation of ent-hypocoprin B (2) based on the observed NOE correlations (Fig. 2a). The results suggested that the C-3/C-13 single bond and the C-7/C-12 double bond are approximately perpendicular to the average plane of the ten-membered ring in the same direction, whereas the C-3/C-4 double bond and the C-8/C-10 single bond preferentially face each other in parallel across the ten-membered ring. That is, the C-3/C-4 and C-7/C-12 double bonds are clearly distinguished inside and outside the ten-membered ring, suggesting the feasibility of a π-facial selective approach to alkene moieties.

Diene 18 obtained by acetylation of ent-hypocoprin B (2) was subjected to osmium-mediated dihydroxylation using AD-mix-α or AD-mix-β (Scheme 5). In dihydroxylation using AD-mix-β, diene 18 was converted to completely unrecoverable high-polarity compounds within six hours. However, when AD-mix-α was attempted, the starting material 18 disappeared around 24 hours, yielding the desired stereoisomer 19 with complete selectivity for C-7 as a mixture with MeSO2NH2. The stereochemistry of C-7 after derivatization to ent-hypocoprin A (1) was determined by X-ray crystallography. Interestingly, the C-3/C-4 trisubstituted alkene moiety was unaffected during this reaction. To understand this ideal π-facial selectivity, we employed a mnemonic device for predicting the stereo-selectivity of dihydroxylation using AD-mix. The two alkene moieties of 18 were considered individually because they belong to different alkene-substitution classes. Considering the trisubstituted alkene (C-3/C-4) moiety, AD-mix-β and AD-mix-
NMR spectra of absolute configuration is reversed. To conclude that the synthesized ent-hypocoprin B, one or both of the reported spectra were derived from impurities (mainly hypocoprin A but the values of the two compounds were quite different. Many signals in the reported NMR spectrum of natural hypocoprin A were derived from impurities (mainly hypocoprin B), so the accuracy of the reported specific rotation was doubtful. In addition, the specific rotation of acetonide 3 was $[\alpha]^27_D = -7.7$ (c 1.07 in CHCl$_3$) (ref. 6 $[\alpha]^27_D = -7.9$ (c 1.15 in CHCl$_3$)).

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