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Synthetic Studies Directed Toward the Proposed Structure for Heteroscyphic Acid A

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Synthetic studies directed toward the proposed structure for heteroscyphic acid A†

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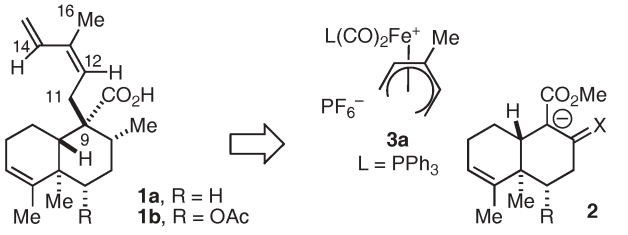
A route to the carbon skeleton of the proposed structure for heteroscyphic acid A was developed utilizing a Mn(III)/Cu(II) mediated oxidative free-radical cyclization and nucleophilic addition to (3-methylpentadienyl)iron(1+) cation.

Heteroscyphic acids A and B are novel clerodane-type diterpenes isolated from cultured cells of the liverwort *Heteroscyphus planus*.[1] The structural assignments for the heteroscyphic acids (**1a** and **1b**, Scheme 1) were made on the basis of their MS and NMR spectral data. In particular, the 12*Z*-stereochemistry for **1b** was assigned on the basis of NOEs between Me-16 and H-12 and between H-14 and H-11. There are no reports of synthetic studies on the heteroscyphic acids. As part of our interest in the application of acyclic (pentadienyl)iron cations to organic synthesis,[2] we recognized that the 12*Z*-dienyl functionality proposed for **1a** might be available by addition of a bicyclo[4.4.0]decene anion (**2**) to a (3-methylpentadienyl)Fe(CO)$_2$L$^+$ cation (**3**)[3] (Scheme 1). The (dicarbonyl)triphenylphosphine ligated cation (**3a**, L = PPh_3) was chosen, since we have recently discovered that addition of carbon nucleophiles to the tricarbonyl ligated cation (**3b**, L = CO) affords cyclohexenone products *via* attack at a C2 internal carbon.[3]

To explore the viability of this strategy, the anions derived from 2-carboethoxycyclohexenone and from methyl cyclohexanecarboxylate were reacted with cation **3a** to afford the neutral diene complexes **4** and **5** respectively (Scheme 2). Oxidative decomplexation of **4** or **5** with cerium ammonium nitrate [CAN] gave the dienes **6** or **7**.



Scheme 1 Retrosynthetic strategy to the proposed structures for heteroscyphic acids A and B.

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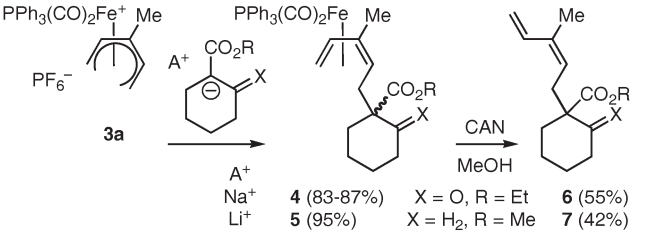
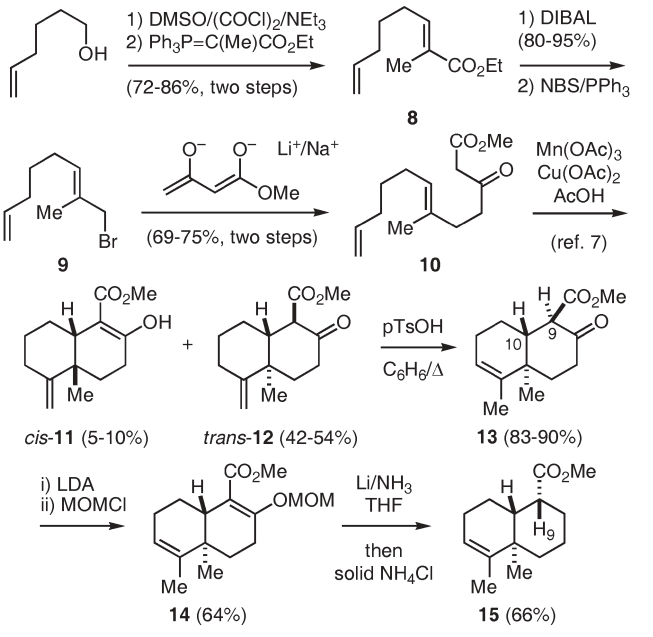
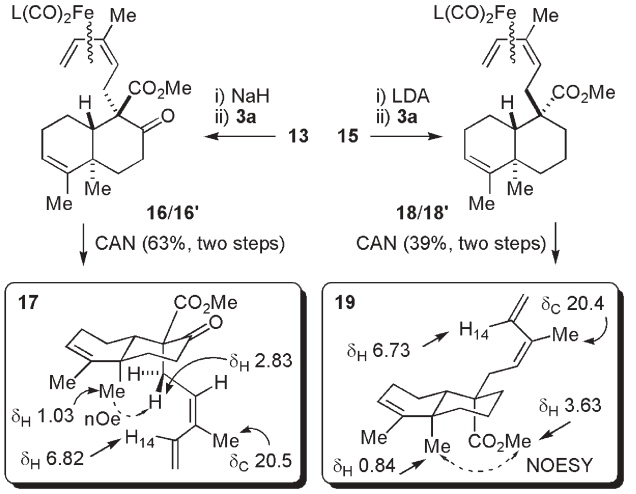


Scheme 2 Model alkylations *via* (3-methylpentadienyl)Fe(CO)$_2$PPh$_3^+$.

It was envisioned that preparation of the requisite bicyclo[4.4.0]-decane skeleton would rely on an oxidative free radical cyclization[4] of a β-ketoester. To this end, Swern oxidation of 5-hexen-1-ol, followed by Wittig olefination of the crude aldehyde gave the 2,7-octadienoate **8** (Scheme 3). Reduction of **8**, followed by treatment of the resultant allylic alcohol with NBS/PPh_3 gave the corresponding bromide **9**.[5] Alkylation of the dianion generated from methyl acetoacetate[6] with **9** gave the requisite acyclic β-ketoester **10**. Treatment of **10** with Mn(III)/Cu(II), according to the literature procedure,[7] gave a separable mixture of *trans*-decalone **12** along with a minor amount of the *cis*-isomer **11**. Acid catalyzed isomerization of the exocyclic olefin **12** smoothly gave the endocyclic isomer **13**. The large axial–axial coupling between H9 and H10 (13.5 Hz) indicated that the C-9 ester group of **13**



Scheme 3 Preparation of the bicyclo[4.4.0]decane skeleton.



Scheme 4 Installation of the 3-methyl-1,3*Z*-pentadienyl side chain.

occupies an equatorial position. Conversion of the β-ketoester into the MOM enol ether **14**, followed by "double reduction"[8] afforded the bicyclic ester **15**. As anticipated,[8] kinetic protonation of the ester enolate intermediate proceeded from the equatorial position, resulting in an axial disposition for the ester group in **15**. The H9 resonance of **15** did not evidence any large couplings (HW = 9.6 Hz), consistent with an equatorial disposition.

Reaction of the anion generated from β-ketoester **13** with cation **3a** gave a mixture of diene-iron complexes **16/16′** (Scheme 4). Due to signal overlap, it was not possible to assign the structure(s) of the components of this mixture, however we anticipated that these complexes were diastereomeric with respect to the diene-iron coordination due to attack at one or the other terminal positions of the achiral pentadienyl cation **3a**. This mixture of diastereomers was of no consequence, since decomplexation of the mixture **16/16′** with CAN gave the "free" ligand **17** as a single product. The relative stereochemistry of **17** at C9 was assigned on the basis of difference NOE experiments; irradiation of the methyl singlet at δ 1.03 ppm caused enhancement of the signal corresponding to one of the C11 protons at δ 2.83 ppm. This relative stereochemistry for alkylation of **13** corresponds to that known for the alkylation of other bicyclo[4.4.0]decane ketoesters (*i.e.* alkylation on the α-face).[9] It should be noted that this stereochemistry is opposite to that required for heteroscyphic acid.

Reaction of the anion generated from **15** with cation **3a** likewise gave a mixture of diene complexes **18/18′**. Decomplexation with CAN and purification by chromatography on $AgNO_3$ impregnated silica gel gave **19**. The relative stereochemistry at C9 was assigned on the basis of the upfield chemical shift of the C19 methyl group (δ 0.84 ppm) and the observed NOESY correlation between this signal and the methyl ester. This relative stereochemistry for alkylation of **15** corresponds to that known for the alkylation of other bicyclo[4.4.0]decane 2-carboxylates (*i.e.* alkylation on the β-face).[10]

The dienyl sidechains of **6**, **7**, **17**, and **19** were all assigned the *Z* stereochemistry on the basis of their NMR spectral data. In particular, the signal for H14 (heteroscyphic acid numbering) appears *ca.* δ 6.8–6.7 (dd) while the signals for the diene carbons C14, C15, and the dienyl methyl C16 appear at *ca.* δ 135, 114 and 20 ppm. These chemical shifts are characteristic of a 3-methyl-1,3*Z*-dienyl group.[11] It was surprising to note that the NMR spectral data for the dienyl sidechains of **17** and **19** *did not match well with that reported for the heteroscyphic acids A and B*. For **1a,b** the signal for H14 appears *ca.* δ 6.35–6.4 (dd) while the signals for the diene carbons C14, C15, and the dienyl methyl C16 appear at *ca.* δ 141, 111 and 12 ppm. These chemical shifts are more consistent with those observed for a number of diterpenes possessing a 3-methyl-1,3*E*-dienyl group.[11b,c,12]

In summary, a stereoselective route to the 3-methyl-1,3*Z*-pentadienyl sidechain *via* nucleophilic addition to the (3-methylpentadienyl)iron cation **3** was devised. This methodology was explored for the synthesis of the proposed structure of heteroscyphic acid A. Re-evaluation of the NMR spectral data for the heteroscyphic acids revealed that the side chains of these compounds more likely possess the *E*-stereochemistry. Assignment of the structure of the heteroscyphic acids awaits their total synthesis.[13]

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