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Formal total synthesis of (±)-magellanine

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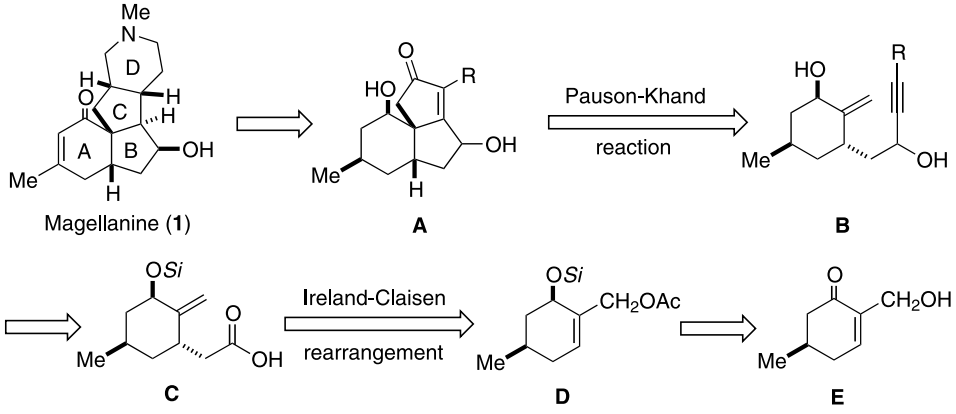
Abstract—Formal total synthesis of magellanine is described. Key features in the synthesis were stereoselective Ireland–Claisen rearrangement and intramolecular Pauson–Khand reaction of *exo*-cyclic enynes.

Magellanine (**1**) is one of alkaloids isolated from Lycopodium species.[1] Because of its unique tetracyclic structure bearing six contiguous stereocenters, many synthetic efforts on its total synthesis have been reported.[2] Our recent studies[3] concerning intramolecular Pauson–Khand reaction of *exo*-cyclic enynes have revealed facile construction of bi- and tri-cyclic skeletons, promising stereoselective construction of ABC rings in magellanine (**1**).[4] Here, we describe formal total synthesis of magellanine (**1**) by using stereoselective Ireland–Claisen rearrangement and intramolecular Pauson–Khand reaction of *exo*-cyclic enynes as key steps.

Retrosynthetic plan of **1** is shown in Scheme 1. The D ring of **1** would be constructed from angular tricyclic compound (**A**), which could be synthesized by intramolecular Pauson–Khand reaction of *exo*-cyclic enyne (**B**). The enyne (**B**) could be obtained from carboxylic acid (**C**) by stereoselective Ireland–Claisen rearrangement of **D**. Furthermore, the allyl acetate (**D**) should be synthesized from known keto alcohol (**E**).[5]

At first, Pauson–Khand precursors (**9a**,**b**)[6] were synthesized as follows. Acetylation of **2**[5] followed by Luche reduction gave stereoselectively **4**, stereochemistry of which was determined by NOE experiment. Silylation of **4** afforded TIPS ether (**5**) in 74% yield. Ireland–Claisen rearrangement of **5** and subsequent reduction with $LiAlH_4$ furnished an alcohol (**6**) in 70% yield as a single isomer as expected. Dess–Martin oxidation of **6** gave an aldehyde (**7**) in quantitative yield. Then, the reaction of **7** with *N*-Boc-protected lithium butynylamide gave an inseparable 1:1 diastereomeric mixture of alkynyl alcohols (**8**), which could be separated by desilylation with TBAF into alcohols **9a** and **9b** in 40% and 44% yields.



Scheme 1.

Keywords: Pauson–Khand reaction; *exo*-cyclic enyne; magellanine; total synthesis.
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With enynes (**9a**,**b**) in hands, Pauson–Khand reaction was examined under thermal or oxidative conditions. Alkyne–cobalt complex of **9a** was treated in boiling toluene to result in the formation of intractable mixture. However, reaction using trimethylamine *N*-oxide (TMANO)[7a] gave expected tricycle (**10a**) in 35% yield along with starting enyne (**9a**) (37%), which was produced by decomplexation of alkyne–cobalt complex. The similar reaction of **9b** using TMANO afforded **10b** and **9b** in 70 and 18% yields, respectively.[8] The difference of yield in the reaction of **9a**,**b** could be explained as follows. Inspection with Dreiding model suggested more severe interaction of hydroxyl group and side-chain in transition state (**9aT**) than that in **9bT** as depicted in Figure 1. Therefore, yield of **10a** would decrease. This findings suggested that stereochemistry on B ring of **10a** is the same as that of **1**. Moreover, starting enynes (**9a**,**b**), generated by decomplexation during the reaction, could be reused for Pauson–Khand reaction to give **10a**,**b**. Also, **10b** could be converted into **10a** (98%) (Scheme 2).

Construction of piperidine ring was performed as follows. Catalytic hydrogenation[9] of enone (**10a**) gave **11** in 80% yield, which might be formed by isomerization of C3 position in the reaction due to steric repulsion between side-chain and hydroxyl group. Then, two hydroxyl groups in **11** were protected as MOM ethers[10] leading to **12**. Olefination of keto group in **12** was performed with Tebbe reagent to give *exo*-alkene (**13**) in 44% yield together with unchanged **12** (38%). Hydroboration–oxidation of **13** produced alcohols (**14a**,**b**) as a 1:3.4 diastereomeric mixture, in which major product was undesired **14b**. Mesylation of alcohol (**14a**) followed by treatment with *t*-BuOK readily constructed a piperidine ring to afford tetracyclic compound (**15**) in 64% yield (Scheme 3).

Reduction of **15** with $LiAlH_4$ and deprotection of MOM ethers furnished diol (**17**) in quantitative yield. Selective silylation of **17** produced mono-TBS ether (**18**), Dess–Martin oxidation of which gave a silyl ketone (**19**). Finally, ketone (**19**) was converted by Mukaiyama method[11] into enone (**20**), ^1H NMR[12] of which was identical with that reported in a literature.[2h]

In summary, we have accomplished formal total synthesis of (±)-magellanine (**1**) by stereoselective Ireland–Claisen rearrangement and intramolecular Pauson–Khand reaction of *exo*-cyclic enynes as key steps.

Acknowledgements

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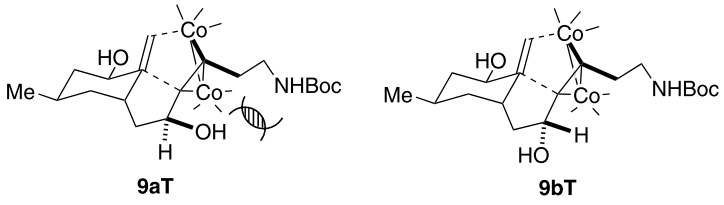
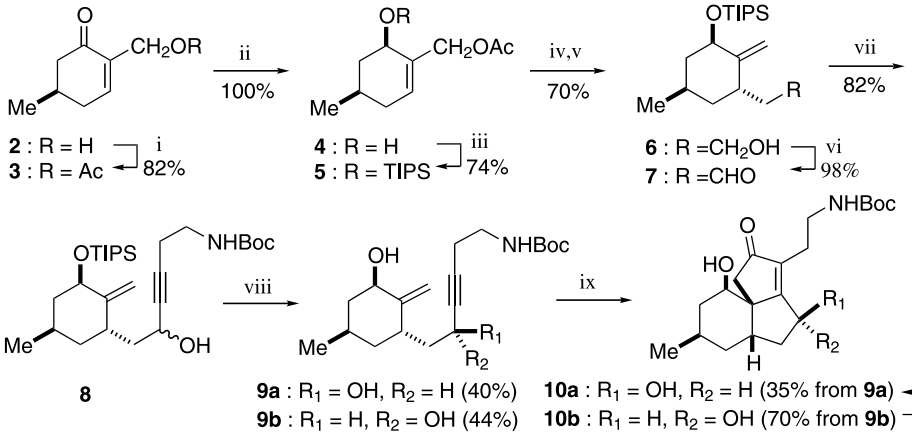
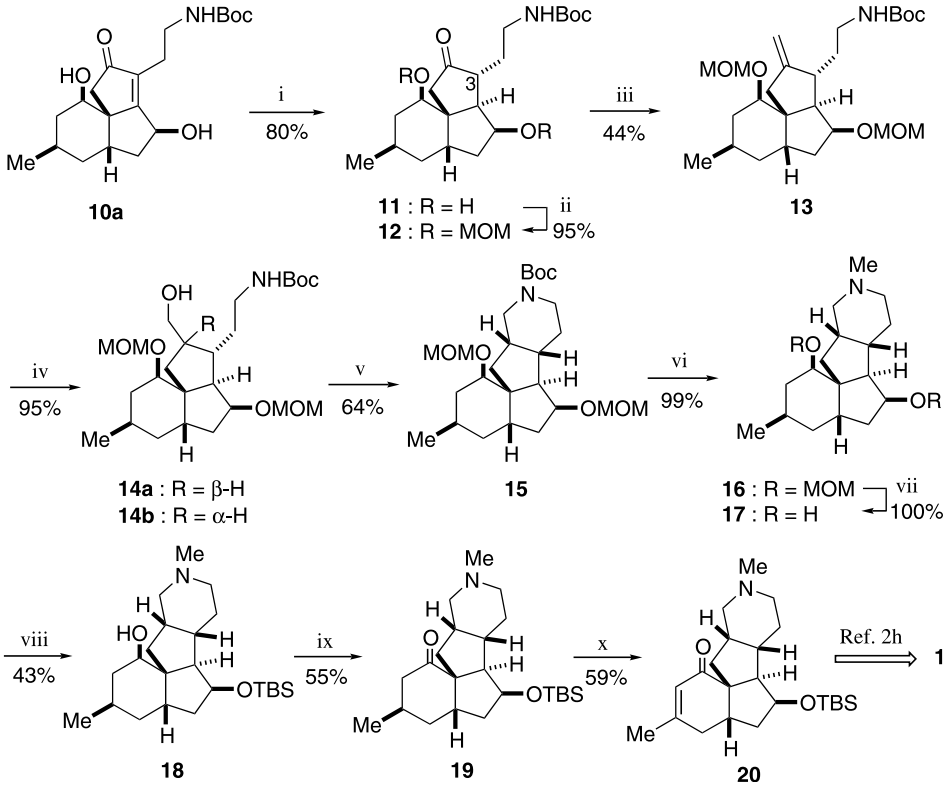


Figure 1.



Scheme 2. *Reagents and conditions*: (i) Ac_2O, Et_3N, CH_2Cl_2, rt, 24 h; (ii) $CeCl_3{\cdot}7H_2O$, $NaBH_4$, MeOH, rt, 1.5 h; (iii) TIPSOTf, 2,6-lutidine, CH_2Cl_2, 0°C, 1 h; (iv) LDA, HMPA, THF, −78°C→rt, 1 day then rt, 2 days; (v) $LiAlH_4$, THF, Δ, 1 h; (vi) Dess–Martin periodinane, CH_2Cl_2, rt, 2 h; (vii) BuLi, HC≡CCH_2CH_2NHBoc, THF, HMPA, 0°C, 1.5 h; (viii) TBAF, THF, Δ, 2.5 h; (ix) $Co_2(CO)_8$, THF, rt, 1 h then TMANO, rt, 1 h; (x) $PhCO_2H$, PPh_3, DEAD, THF, rt, 4 h; 1 M NaOH, THF–MeOH, rt, 1 h.



Scheme 3. *Reagents and conditions*: (i) 10% Pd/C, H_2, MeOH–H_2O, rt, 38.5 h; (ii) *i*-Pr_2NEt, MOMCl, CH_2Cl_2, rt, 18.5 h; (iii) Tebbe reagent, THF, 0°C, 1 h; (iv) BH_3·THF, THF, 0°C, 3 h then 3 M NaOH, 30% H_2O_2, rt, 0.5 h; (v) MsCl, Et_3N, CH_2Cl_2, 0°C, 0.5 h; *t*-BuOK, THF, 0°C, 1 h; (vi) $LiAlH_4$, THF, Δ, 2 h; (vii) 6 M HCl, THF, rt, 24 h; (viii) TBSOTf, 2,6-lutidine, CH_2Cl_2, −78°C, 10 min; (ix) Dess–Martin periodinane, CH_2Cl_2, 0°C, 1 h; (x) LDA, THF, −78°C then Ph(Cl)S=NO*t*-Bu, 0°C, 1 h.

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8. The reaction of **9a** and **9b** with *N*-methylmorpholine *N*-oxide (NMO)[7b] afforded corresponding tricyclic compounds **10a** and **10b** in 18 and 50% yield, respectively.
9. Reduction in MeOH containing 5% water proceeded cleanly, while that without water afforded **11** (70%) along with unknown by-products.
10. Hydrogenation of MOM ether of **10a** did not proceed. It should be attributable to steric hindrance of the MOM group.
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12. Spectral data for **20**; ^1H NMR (270 MHz, $CDCl_3$) δ 5.82 (1H, s), 4.03–4.10 (1H, m), 2.75–2.83 (2H, m), 2.40–2.65 (4H, m), 2.22 (3H, s), 1.95–2.38 (5H, m), 1.90 (3H, s), 1.80–1.90 (1H, m), 1.48–1.68 (4H, m), 0.86 (9H, s), 0.02, 0.01 (each 3H, s); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 203.3, 158.6, 125.6, 72.3, 60.6, 59.0, 56.2, 55.1, 46.4, 42.4, 40.6, 40.1, 37.5, 37.0, 30.5, 26.3, 25.5, 24.5, 18.0, –4.6; MS *m*/*z* 389 (M^+); high-resolution mass *m*/*z* calcd for $C_{23}H_{39}NO_2Si$ (M^+) 389.2750, found: 389.2761.