Synthetic Studies on Lycopodium Alkaloid, Magellanine: Stereoselective Construction of Functionallized Angular Tricyclic Skeletons by Intramolecular Pauson–Khand Reaction

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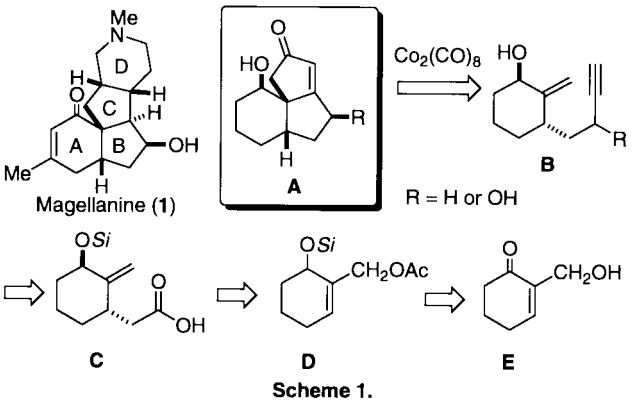
(Received March 27, 2001; CL-010277)

Angular tricyclic compounds as intermediates for total synthesis of magellanine were synthesized by stereoselective Ireland–Claisen rearrangement and intramolecular Pauson–Khand reaction of *exo*-methylenecyclohexylalkynes. Interestingly, remarkably different reactivity was observed in the Pauson–Khand reaction of *cis*- and *trans*-disubstituted *exo*-methylenecyclohexylalkynes.

Magellanine (**1**), which belongs to *Lycopodium* alkaloids, was isolated and characterized by MacLean and co-workers.[1] Magellanine possesses a unique tetracyclic skeleton, which is constituted by angular tricyclic framework with piperidine ring. Due to its interesting structural characteristics, magellanine lends itself as a challenging synthetic target and several synthetic approaches have been reported.[2] We recently reported[3] intramolecular Pauson–Khand reaction[4] of various *exo*-cyclic enynes to give angular tricyclic compounds. Thus, functionallized angular type 6-5-5 tricyclic framework of magellanine could be constructed by the present reaction. Here, we wish to describe stereoselective synthesis of various functionallized angular type 6-5-5 tricyclic compounds (**12**, **16**) directed toward for total synthesis of magellanine (**1**).

Synthetic plan of angular 6-5-5 tricyclic compounds (**A**) is depicted in Scheme 1. Thus, compounds (**A**) should be obtained by intramolecular Pauson–Khand reaction of *exo*-cyclic enynes (**B**), which would be synthesized by stereoselective Ireland–Claisen rearrangement[5] of siloxyallyl acetate (**D**) and subsequent conversion via **C**. Synthesis of **D** could be performed from **E**.

Pauson–Khand precursors (**11a,b, 15**) were prepared as follows (Scheme 2). Acetylation of 2-hydroxymethyl-2-cyclohexenone (**2**)[6] followed by Luche reduction[7] gave an alcohol (**4**). In order to examine effect of steric factor on diastereoselectivity of Ireland–Claisen rearrangement, various silyl ethers (**5a-c**) were synthesized. Among them, Ireland–Claisen rearrangement of



Scheme 1.

Table 1. Ireland–Claisen rearrangement of allylic alcohols (**5a–c**)[a]

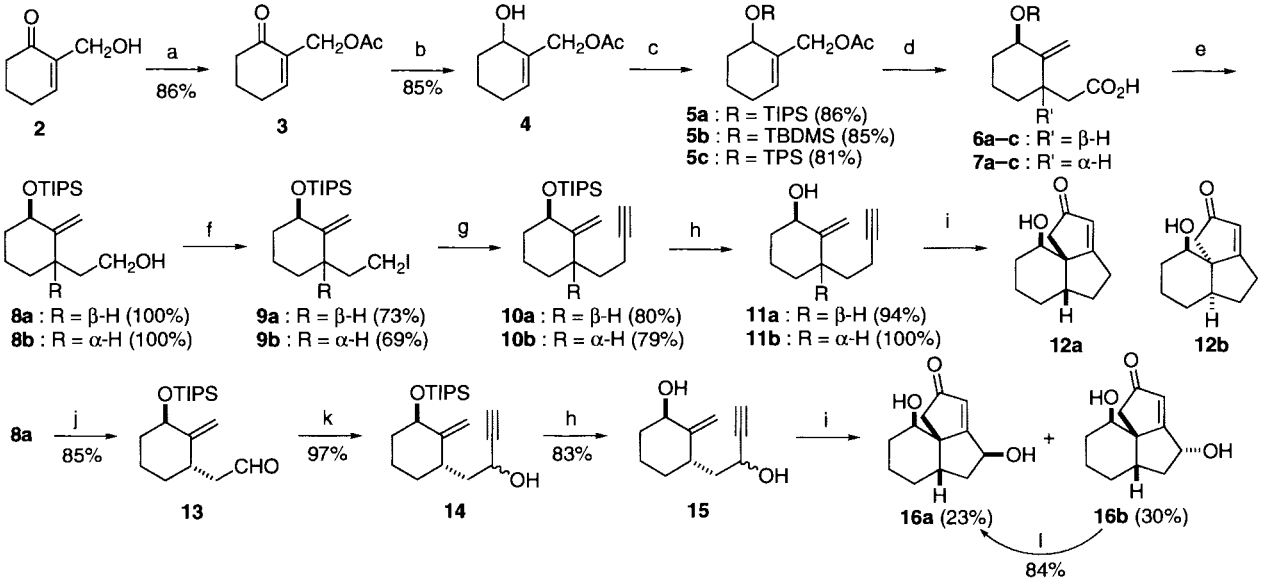
Run	Substrate	R	Product	Yield/%[b]	**6** : **7**[c]
1	**5a**	TIPS	**6a+7a**	61 (26)	10.5 : 1
2[d]	**5a**	TIPS	**6a+7a**	15 (-)	5.4 : 1
3[e]	**5a**	TIPS	**6a+7a**	9 (29)	8.0 : 1
4	**5b**	TBDMS	**6b+7b**	64 (-)	3.7 : 1
5	**5c**	TPS	**6c+7c**	51 (44)	2.0 : 1

[a]All reactions were performed in THF with LDA(1.4 equiv),TBDMSCl(1.4 equiv) and HMPA (1.2 equiv), unless otherwise noted. [b]Combined isolated yield of **6** and **7**. Yield in parenthesis was recovery of starting material. [c]Determined by ^{1}H NMR. [d]TIPSCl was used instead of TBDMSCl. [e]The reaction was performed without HMPA.

TIPS ether (**5a**) gave *trans*-carboxylic acid (**6a**) with the highest diastereoselectivity (Table 1, entry 1). With TIPSCl as additive instead of TBDMSCl, both the yield and diastereoselectivity were decreased remarkably (entry 2). When HMPA was not added, the reaction was sluggish to give the product in low yield, although diastereoselectivity was still good (entry 3).

After separation of carboxylic acids (**6a**, **7a**), at first, we synthesized Pauson–Khand precursors (**11a,b**) bearing a hydroxy group only on cyclohexane ring. Although *cis*-isomer (**7a**) was minor product, its conversion to Pauson–Khand precursor (**11b**) was also performed, because its reactivity in Pauson–Khand reaction could be compared with that of **11a**. Reduction of **6a** and **7a** with $LiAlH_4$ afforded alcohols (**8a,b**) in quantitative yield, respectively. Iodination of **8a,b** followed by ethynylation of resulting iodides (**9a,b**) gave enynes (**10a,b**) in 58% and 55% yield, respectively. Unfortunately, Pauson–Khand reaction of both **10a** and **10b** did not give corresponding cyclized products probably due to bulkiness of TIPS group. Therefore, desilylation of **10a,b** with TBAF was carried out to afford *trans*- (**11a**) (94% yield) and *cis*-alcohols (**11b**) (100% yield). Gratifyingly, Pauson–Khand reaction (NMO, CH_2Cl_2, r.t.)[8] of *trans*-isomer (**11a**) furnished angular tricyclic compound (**12a**)[9] in 52% yield, although similar reaction of *cis*-isomer (**11b**) gave **12b**[9] in only 5% yield. The reaction of **11a** in refluxing benzene afforded **12a** in 26% yield, whereas that of **11b** did not give **12b** at all. These results would be rationalized by consideration of transition state of two isomers (Figure 1). The reaction of *cis*-isomer (**11b**) would suffer severe 1,3-diaxial interaction between alkyne-cobalt complex moiety and hydroxy group in transition state (**TS2**) and the complex might exist as **TS3** rather than **TS2**. On the other hand, *trans*-isomer (**11a**) does not undergo such interaction in **TS1** to furnish **12a**. Inspection of Dreiding model suggested that the reaction of alkyne-cobalt complex moiety to olefin in **TS1** would more easily occur than that in **TS3**.

Since Pauson–Khand reaction of hydroxy-*exo*-cyclic enynes (**11**) was found to proceed, we synthesized enyne (**15**), which has hydroxy groups on both cyclohexane ring and side chain. Oxidation of alcohol (**8a**) with Dess–Martin periodinane



Scheme 2. Reagents and conditions : a) Ac_2O, Et_3N, CH_2Cl_2, r.t., 3 h. b) $CeCl_3 \cdot 7H_2O$, $NaBH_4$, MeOH, r.t., 20 min. c) RCl, imidazole, DMF, r.t., 1-2 d. d) LDA, TBDMSCl or TIPSCl, HMPA, THF, −78 °C → r.t., 3 d. e) $LiAlH_4$, THF, Δ, 0.5 h. f) PPh_3, I_2, Py, CH_2Cl_2, 0 °C, 0.5 h. g) HC≡CLi(en), Et_2O, DMSO, 5 °C, 1 h. h) TBAF, THF, Δ, 10 min. i) $Co_2(CO)_8$, CH_2Cl_2, r.t., 1 h; NMO, r.t., 2 h. j) Dess−Martin periodinane, CH_2Cl_2 , r.t., 1 h. k) HC≡CMgBr, THF, 0 °C, 1.5 h. l) $PhCO_2H$, PPh_3, DEAD, THF, r.t., 2 h; 1 M NaOH, MeOH, r.t., 10 min.

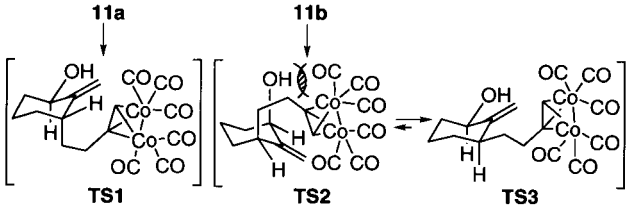


Figure 1. Plausible transition state of Pauson–Khand reaction of **11a** and **11b**.

afforded an aldehyde (**13**), which was treated with ethynylmagnesium bromide to furnish inseparable ca. 1:1 mixture of propargyl alcohols (**14**) in 82% yield. Desilylation of **14** with TBAF gave a diol (**15**) in 83% yield. Pauson–Khand reaction of **15** followed by chromatographic separation afforded desired angular tricyclic compounds (**16a,b**)[10] in 23% and 30% yields, respectively. Stereochemistry of **16a** and **16b** was determined by NOE experiment. Furthermore, **16b** could be converted to **16a** (84% yield), which has stereochemistry of the hydroxy group on B ring corresponding to that in **1**, by Mitsunobu reaction and subsequent hydrolysis.

In summary, we have investigated to synthesize various angular type 6-5-5 tricyclic compounds (**12**, **16**) by intramolecular Pauson–Khand reaction of *exo*-methylenecyclohexylalkynes. Among them, **16a**, which has two hydroxy groups on both A and B rings, could serve a potential key intermediate for total synthesis of magellanine (**1**). Approach to **1** by the present methodology is in progress.

References and Notes

1 M. Castillo, L. A. Loyala, G. Morales, I. Singh, C. Calvo, H. L. Holland, and D. B. MacLean, *Can. J. Chem.*, **54**, 2893 (1976).

2 Total synthesis; a) G. C. Hirst, T. O. Johnson, Jr., and L. E. Overman, *J. Am. Chem. Soc.*, **115**, 2992 (1993). b) L. A. Paquette, D. Friedrich, E. Pinard, J. P. Williams, D. St. Laurent, and B. A. Roden, *J. Am. Chem. Soc.*, **115**, 4377 (1993). c) J. P. Williams, D. St. Laurent, D. Friedrich, E. Pinard, B. A. Roden, and L. A. Paquette, *J. Am. Chem. Soc.*, **116**, 4689 (1994). Synthetic approach; d) G. Mehta and M. S. Reddy, *Tetrahedron Lett.*, **31**, 2039 (1990). e) M. T. Crimmins and P. S. Watson, *Tetrahedron Lett.*, **34**, 199 (1993). f) D. A. Sandham and A. I. Meyers, *J. Chem. Soc., Chem. Commun.*, **1995,** 2511. g) G. Mehta, M. S. Reddy, and A. Thomas, *Tetrahedron*, **54**, 7865 (1998).

3 a) M. Ishizaki, K. Iwahara, K. Kyoumura, and O. Hoshino, *Synlett*, **1999,** 587. b) M. Ishizaki, K. Iwahara, Y. Niimi, H. Satoh, and O. Hoshino, *Tetrahedron*, **57**, 2729 (2001).

4 For a review, K. M. Brummond and J. L. Kent, *Tetrahedron*, **56**, 3263 (2000).

5 S. Pereira and M. Srebnik, *Aldrichimica Acta*, **26**, 17 (1993).

6 F. Rezqui and M. M. E. Gaied, *Tetrahedron Lett.*, **39**, 5965 (1998).

7 J. L. Luche and A. L. Gemal, *J. Am. Chem. Soc.*, **101**, 5848 (1979).

8 S. Shambayati, W. E. Crowe, and S. L. Schreiber, *Tetrahedron Lett.*, **31**, 5289 (1990).

9 All new compounds gave satisfactory ^1H and ^{13}C NMR, IR, and mass spectral data.

10 Spectral data for **16a**; mp 173–175 °C; ^1H NMR (270 MHz, $CDCl_3$–CD_3OD) δ 6.06 (1H, s), 5.10 (1H, d, J = 9.9 Hz), 3.57 (1H, dd, J = 3.6, 11.9 Hz), 3.80 (2H, brs), 2.69, 1.98 (each 1H, d, J = 17.5 Hz), 2.52 (1H, dt, J = 10.9, 14.2 Hz), 2.26 (1H, dt, J = 4, 11 Hz), 1.44–1.88 (6H, m), 1.18–1.27 (1H, m); ^{13}C NMR (67.5 MHz, $CDCl_3$–CD_3OD) δ 212.3, 194.4, 125.0, 69.0, 68.6, 58.9, 43.6, 43.0, 37.5, 32.0, 24.3, 20.5; IR 3360, 3327, 2934, 1689, 1630 cm^{-1}; FAB MS *m/z* 209 (M^++1); high-resolution FAB mass *m/z* calcd for $C_{12}H_{17}O_3$ (M^++1) 209.1178, found: 209.1168. For **16b**; mp 168–170 °C; ^1H NMR (270 MHz, $CDCl_3$–CD_3OD) δ 6.03 (1H, s), 4.85 (1H, dd, J = 5.3, 7.6 Hz), 4.02 (1H, dd, J = 3.8, 12 Hz), 3.30 (2H, brs), 2.71, 1.87 (each 1H, d, J = 17.5 Hz), 2.35 (1H, dt, J = 7.8, 13.2 Hz), 2.02 (1H, dt, J = 5.3, 12.9 Hz), 1.85–1.88 (2H, m), 1.46–1.75 (4H, m), 1.19–1.36 (1H, m); ^{13}C NMR (67.5 MHz, $CDCl_3$–CD_3OD) δ 212.8, 187.7, 127.6, 67.9, 67.4, 58.6, 44.0, 42.4, 38.3, 32.1, 24.1, 20.6; IR 3357, 3279, 2937, 1691, 1625 cm^{-1}; FAB MS *m/z* 209 (M^++1); high-resolution FAB mass *m/z* calcd for $C_{12}H_{17}O_3$ (M^++1) 209.1178, found: 209.1172.