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A new pathway to chiral tetracyclic indolidines via Pauson–Khand reaction

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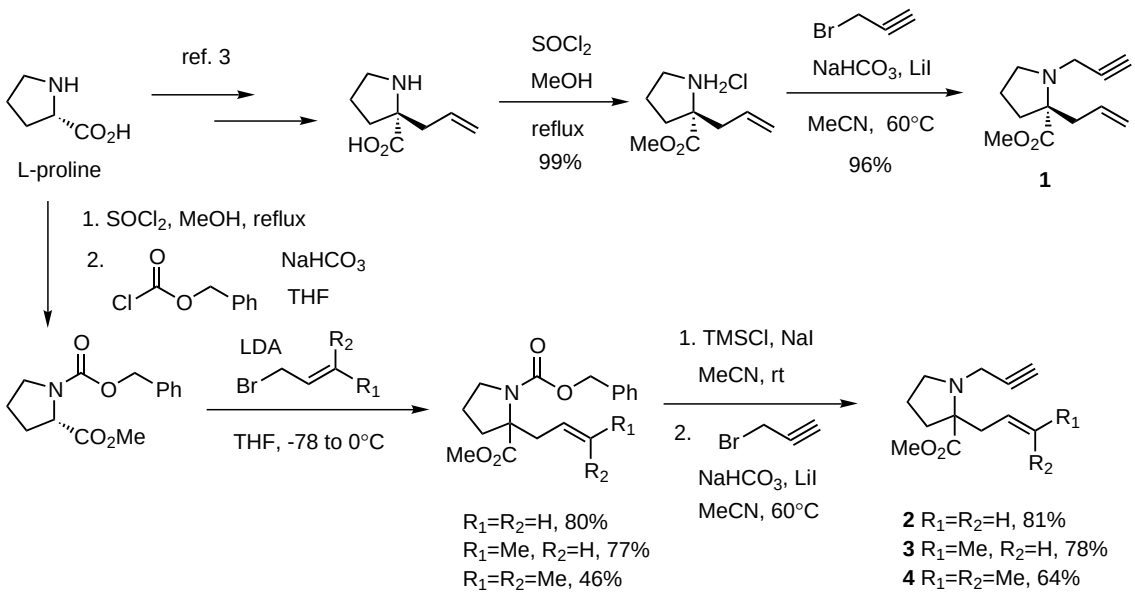
Abstract—Reaction of enynes **1** and **3** with $Co_2(CO)_8$ in the presence of DMSO, NMO or TMANO as promoters produced tricyclic indolidine derivatives **5** and **7** stereoselectively in moderate to excellent yield. The stereochemistry at the C-7 position of the indolidines **5** and **7** was confirmed by their conversion into the bridged azacycles **10** and **13**. © 2001 Elsevier Science Ltd. All rights reserved.

The Pauson–Khand reaction has come to be considered as a valuable and convergent method for synthesizing cyclopentenone derivatives.[1] Especially, an intramolecular series of the Pauson–Khand reaction such as that of enyne in which three or four atoms separate the double and triple bonds give bicyclic enones, and the methodology has been widely applied to the synthesis of cyclopentane-based polycyclic natural products.[2] Despite the rich literature on the chemistry of constructing fused terpenoids and derivatives such as triquinanes based on the Pauson–Khand methodology,[2] to the best of our knowledge, there are few reports dealing with the synthesis of other types of natural products. We now report a new pathway to chiral tri-



Scheme 1.

Keywords: Pauson–Khand reaction; diazabicyclo[2.2.2]octane; asperparaline.

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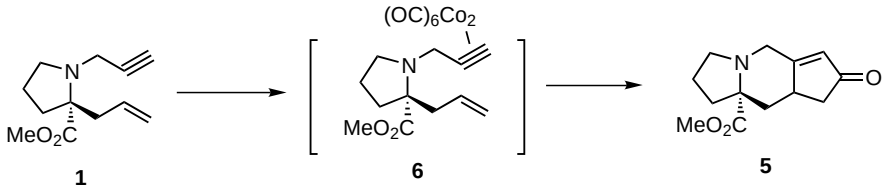
Table 1. The Pauson–Khand reaction of **1**

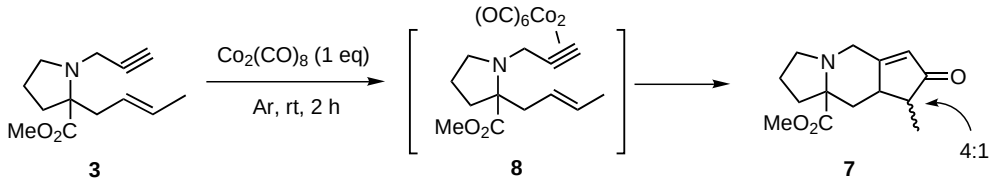


1 6 5

Entry	$Co_2(CO)_8$ (equiv.)	Solvent	Conditions for formation of **6**	Promoter (equiv.)	Conditions for formation of **5**	Yield (%)[a]
1	0.1	DME	CO, rt, 10 min	CO	CO, 60°C, 42 h	6
2	1.1	PhH	Ar, rt, 2 h	DMSO (0.1)	O_2, 50°C, 3 days	46
3	1.2	CH_2Cl_2	CO, rt, 2 h	NMO (6)	CO, rt, 22 h	72
4	1.05	THF	Ar, rt, 2 h	DMSO (6)	Ar, 50°C, 26 h	94

[a] Isolated yield.

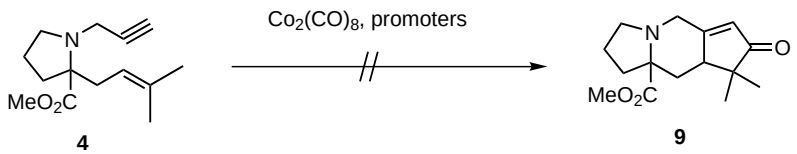
Table 2. The Pauson–Khand reaction of **3**



3 8 7

Entry	Solvent	Promoter (equiv.)	Conditions for formation of **7**	Yield (%)[a]
1	THF	DMSO (6)	Ar, 50°C, 35 h	34
2	THF	DMSO (12)	Ar, 50°C, 3 days	48
3	CH_2Cl_2	TMANO (9)	Ar, rt, 15 h	53
4	CH_2Cl_2	NMO (9)	Ar, rt, 22 h	61

[a] Isolated yield.



4 9

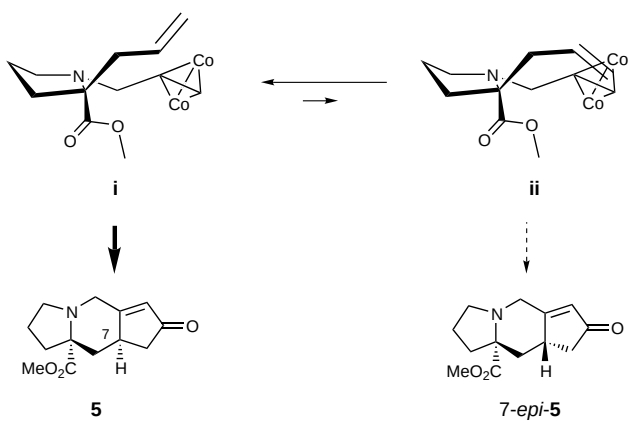
Scheme 2.

and tetracyclic indolidine derivatives starting from L-proline via Pauson–Khand cycloaddition reaction of enynes **1** and **3**.

The starting enynes **1**–**4** were synthesized from L-proline by the standard procedure[3] as chiral and racemic forms as shown in Scheme 1.

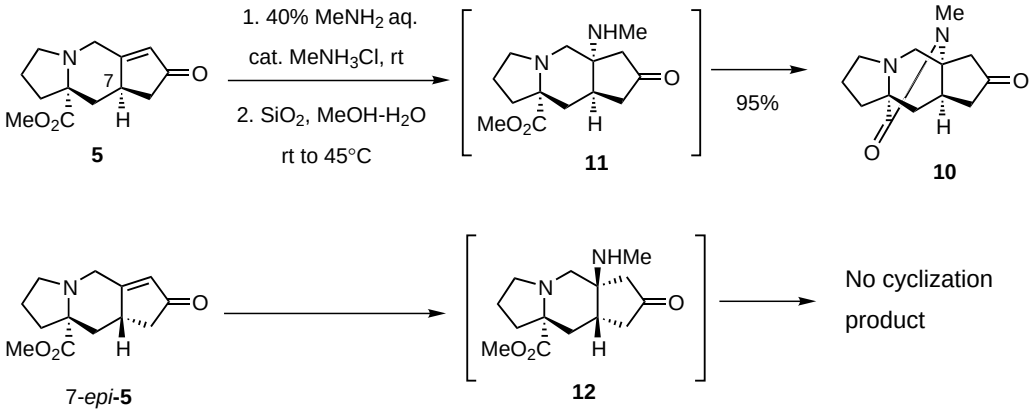
The [2+2+1] cycloaddition of enyne **1** using a stoichiometric amount of $Co_2(CO)_8$ gave tricyclic indolidinone **5** as a single diastereomer in a moderate to excellent yield depending on the reaction conditions (Table 1).[4] It was found that the use of an excess amount (6 equiv.) of DMSO[5] as promoter[6] in an argon atmosphere is essential for the efficiency of the cycloaddition step (entry 4).

The same reaction of enyne **3** possessing *E*-olefin was less effective than **1** (Table 2). Indeed, almost the same conditions as in **1** gave enone **7** in only 34% yield as a 4:1 mixtures of diastereomers resulting from the addi-



i ii 5 7-*epi*-**5**

Figure 1.



Scheme 3.

tional methyl group (entry 1).[7] Accordingly, the yield was increased to 61% by using NMO[8] as a promoter in CH_2Cl_2 at room temperature for 22 h (entry 4).

Reaction of enyne **4** possessing trisubstituted olefin gave no [2+2+1] cycloaddition product in spite of using a large excess of promoters, heating and prolonging the reaction times and the starting material was recovered or a complex mixture was obtained (Scheme 2). It is assumed that due to the steric hindrance of the geminal dimethyl group, the approach of the cobalt complexed alkyne part to alkene is difficult or due to the instability of the transition state or intermediate, the reaction resulted in decomposition of the intermediate.

The stereochemical outcome of the newly produced asymmetric center (C-7) of enone **5** was estimated as follows. At first, it was postulated by considering a transition state model (**i** and **ii**, Fig. 1). Clearly, *transoid* conformer **i** is more stable than *cisoid* one **ii** to produce (7*R*)-isomer **5**. Furthermore, the speculation was confirmed chemically as follows (Scheme 3). Thus, enone **5** was treated with 40% methylamine and a catalytic amount of methylamine hydrochloride followed by silica-gel in aqueous methanol at 45°C to afford bridged tetracyclic lactam **10** in 95% yield.[9] This result suggests that the arrangement of the carbomethoxy group of **5** and the C-7 hydrogen should be *cis* because the attack of methylamine to the β-position of the enone would occur smoothly only from the convex face of molecular **iii** to produce intermediate **11** (Fig. 2). Then, intramolecular amide bond formation would afford lactam **10**. On the other hand, the same pathway could not occur in the case of stereoisomer 7-*epi*-**5**, because the potential intermediate **12** has an *anti* relationship of the methoxycarbonyl and *N*-methyl amino group (**vi**).

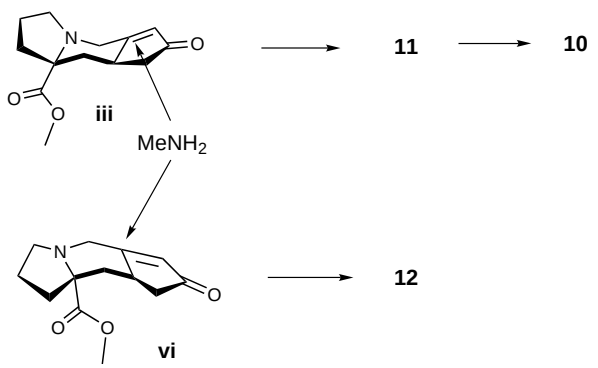
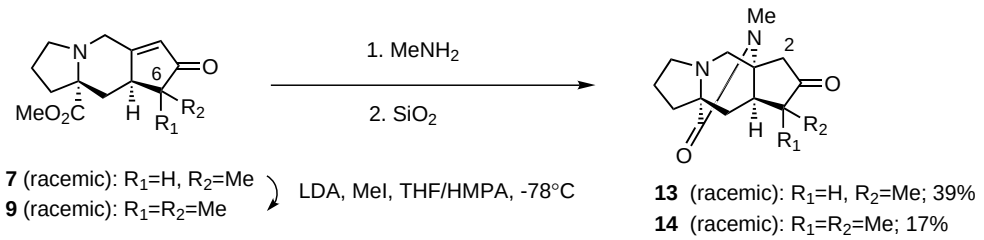


Figure 2.

In the same way, the conversion of enone **7** and **9** to lactam **13** and **14**[10] was achieved in 39 and 17% yield, respectively (Scheme 4). The enone **9** was prepared from **7** by treating with LDA and MeI at −78°C in 58% yield. The inefficiency of these cyclizations was probably due to the steric hindrance of the additional methyl substituents at the C-6 position.

In summary, we have demonstrated a new pathway to chiral indolidine derivatives starting from L-proline using the Pauson–Khand reaction followed by facile formation of a bridged lactam. These results described above would serve for the synthesis of an indolidine alkaloid such as asperparaline[11] and derivatives[12] (Fig.



Scheme 4.

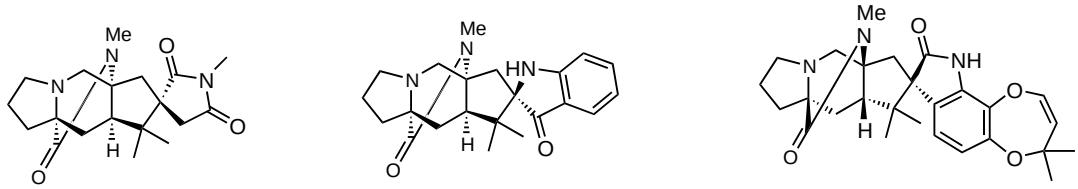


Figure 3.

3) possessing a common diazabicyclo[2.2.2]octane core and exhibiting potent paralytic, insecticidal, antifeedant and anthelmintic activity in the search for effective drugs.

Acknowledgements

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4. Typical experimental procedure for Pauson–Khand reaction (synthesis of enyne **5**): To a stirred solution of $Co_2(CO)_8$ (0.31 g, 0.91 mmol) in dry THF (9 ml) under Ar at room temperature was added dropwise a solution of enyne **1** (0.19 g, 0.91 mmol) in THF (1 ml). After 2 h of stirring at room temperature, DMSO (0.39 ml, 5.46 mmol) was added in one portion. The reaction mixture was stirred for 26 h at 50°C. After cooling, the mixture was filtered through Celite, which was thoroughly washed with acetone. The solvent was eliminated under reduced pressure, and the crude product was purified by silica-gel column chromatography (eluting with hexane: EtOAc = 1:1) to give enone **5** (201 mg, 94%) as a pale yellow crystal. $R_f = 0.25$ (EtOAc); $[\alpha]_D^{18}$ +56.2° (*c* 1.0, $CHCl_3$); IR (NaCl, film) ν_{max} cm^{-1}: 2954, 1713 (C=O), 1630 (C=C), 1445, 1198, 1152; ^1H NMR δ ($CDCl_3$): 1.37 (1H, t, $J = 12.5$ Hz, H-C8), 1.73–2.19 (5H, m), 2.57–2.66 (2H, m, H_2-C6), 2.70–2.77 (1H, m, H-C7), 2.87–2.96 (1H, m, H-C12), 3.09–3.17 (1H, m, H-C12), 3.79–3.94 (5H, m), 5.98 (1H, s, H-C4); ^{13}C NMR δ ($CDCl_3$): 21.0, 36.5, 38.1, 38.7, 42.0, 47.8, 49.9, 52.1, 67.3 (C9), 128.4 (C4), 174.5 ($\underline{C}O_2Me$), 176.4 (C3), 207.7 (C5); FAB MS *m*/*z* (%): 236 ($[M+H]^+$, 69), 176 ($[M-CO_2Me]^+$, 100); HRMS (EI) *m*/*z* (M^+): calcd. For $C_{13}H_{17}O_3N$, 235.1209. Found: 235.1220.
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9. Typical experimental procedure for lactam formation (synthesis of **10**): Enone **5** (0.1 g, 0.43 mmol) was dissolved in 40% aqueous methylamine and methylamine hydrochloride (5.8 mg, 85 μmol) was added. After stirring for 16 h at room temperature, $NaHCO_3$ (14 mg, 0.17 mmol) and water (2 ml) was added and the mixture was stirred for 10 min at room temperature. After concentration, the residue was dissolved in MeOH (5 ml) and water (1 ml) and SiO_2 (1 g) was added. The mixture was stirred for 3 h at room temperature and then 45°C for 4 h. After cooling, the mixture was filtered and the filtrate was washed with methanol, and the solvent was concentrated in vacuo. The residue was purified by silica-gel column chromatography (eluting with EtOAc:acetone = 1:1) to give lactam **10** (201 mg, 94%) as a brown oil. $R_f = 0.43$ (acetone); $[\alpha]_D^{20}$ −149.6° (*c* 1.1, $CHCl_3$); IR (KBr, disk) ν_{max} cm^{-1}: 3440 (br), 2923, 1750 (ketone C=O), 1666 (lactam C=O), 1651, 1390, 1097; ^1H NMR δ ($CDCl_3$): 1.35–1.46 (1H, m, H-C6), 1.65–1.73 (1H, m, H-C6), 1.82–1.95 (2H, m), 2.16–2.36 (5H, m), 2.48–2.68 (4H, m), 2.98 (3H, s, CH_3-N13), 3.06–3.13 (1H, m, H-C10), 3.18–3.22 (1H, d, $J = 11.6$ Hz, H-C12); ^{13}C NMR δ ($CDCl_3$): 22.2, 26.9, 27.8, 34.3, 40.9, 42.6, 45.5, 53.7, 53.8, 62.8, 66.0 (C7), 172.8 (C14), 211.4 (C3); EI MS *m*/*z* (%): 234 (M^+, 5), 206 (3), 175 (100), 149 (51), 137 (21), 108 (12), 96 (20).
10. The direct conversion of enone **10** to **14** was unsuccessful. Methylation of **10** with MeI in the presence of several bases (LDA, NaHMDS, NaH, *t*-BuOK, NaOMe) occurred predominantly at C-2 position to give undesired regioisomer.
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