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An efficient construction of bridged chiral tetracyclic indolidines, a core structure of asperparaline, via stereocontrolled catalytic Pauson–Khand reaction

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Abstract—A reaction of chiral enyne **22** derived from L-proline with a catalytic amount of cobalt (0) octacarbonyl in the presence of *N*-methylmorphorine *N*-oxide gave tricyclic enone **24** in 54% yield (73% based on consumed starting material). Treatment of enone **11** with aqueous methylamine followed by silica gel afforded bridged tetracyclic indolidine **1**, a common structural motif of natural metabolites, an asperparaline series of compounds and also a potential intermediate for the synthesis of a paralytic alkaloid, asperparaline C (**4**), in 70% yield.

1. Introduction

In our previous report,[1] we briefly communicated the racemic synthesis of tetracyclic indolidine **1**, which constitutes the C3 and C10–C25 portions of a paralytic alkaloid, asperparaline C (**4**) (Fig. 1),[2] via Pauson–Khand cycloaddition reaction[3] mediated by a stoichiometric amount of cobalt (0) octacarbonyl. In this paper, we wish to describe full details of the work which includes additional new work such as a catalytic version of the key Pauson–Khand reaction,[4] chiral synthesis of **1** starting from L-proline using Seebach's protocol[5] and also improvement of the yield of each step to result in a concise, enantio- and stereo-controlled synthesis of **1**.

The indolidine alkaloids, asperparalines A to C (**2** to **4**), were discovered by Hayashi and co-workers from 'okara' (the insoluble residue of whole soybeans) that has been fermented with *Aspergillus japonicus* JV-23.[2] Asperparalines showed interesting paralytic activity within 1 h against silkworms at a dose of 10 μg of diet which lasted for 7 to 10 h upon oral administration. On the other hand, Everett and co-workers also isolated the same compound as asperparaline A (**2**) named aspergillimide (VM55598) along with SB202327 (**5**) possessing anthelmintic activity.[6] There are numerous other structurally related natural methabolites including brevinamides **6**,[7] paraherquamides **7**,[8] macrofortine **8**,[9] and sclerotamide **9**,[10] which have a variety of biological activities such as anthelmintic,[6] antinematodal,[8] and antiinsectant[10] activities.

Asperparalines and related compounds have a common unique diazabicyclo[2.2.2]octane skeleton formed from biosynthetic intramolecular [4+2] cycloaddition.[11] Asperparalines and asperdillimides have also 3-*spiro*-succinimide which is rare in naturally occurring products.[12] Previously, we reported the model studies for constructing spirosuccinimide from 2,2-dimethylcyclopentanone as shown in Scheme 1.[13]

Our retro-synthetic plan for asperparaline C (**4**) is shown in Figure 2. Following the results of our previous model studies for the construction of spirosuccinimide from cyclopentanone (Scheme 1),[13] tetracyclic ketone **1** could be a precursor for introducing the spirosuccinimide. The energy minimized 3D-structure of α,β-unsaturated dinitrile **10**,[14] which would be derived from ketone **1** by Knoevenagel condensation based on the model study,[13] indicated that a Michael-type nucleophilic attack such as the cyanide anion to the β-position of an unsaturated system would occur from the convex face to produce the corresponding trinitrile possessing the correct stereochemistry at C-3 (asperparaline numbering) in accord with asperparaline. The ketone **1** could be transformed from enone **11** by stereoselective 1,4-addition of methylamine

Keywords: Asperparaline; Pauson–Khand reaction; Indolidine alkaloid; Paralytic activity; Spiro-succinimide.
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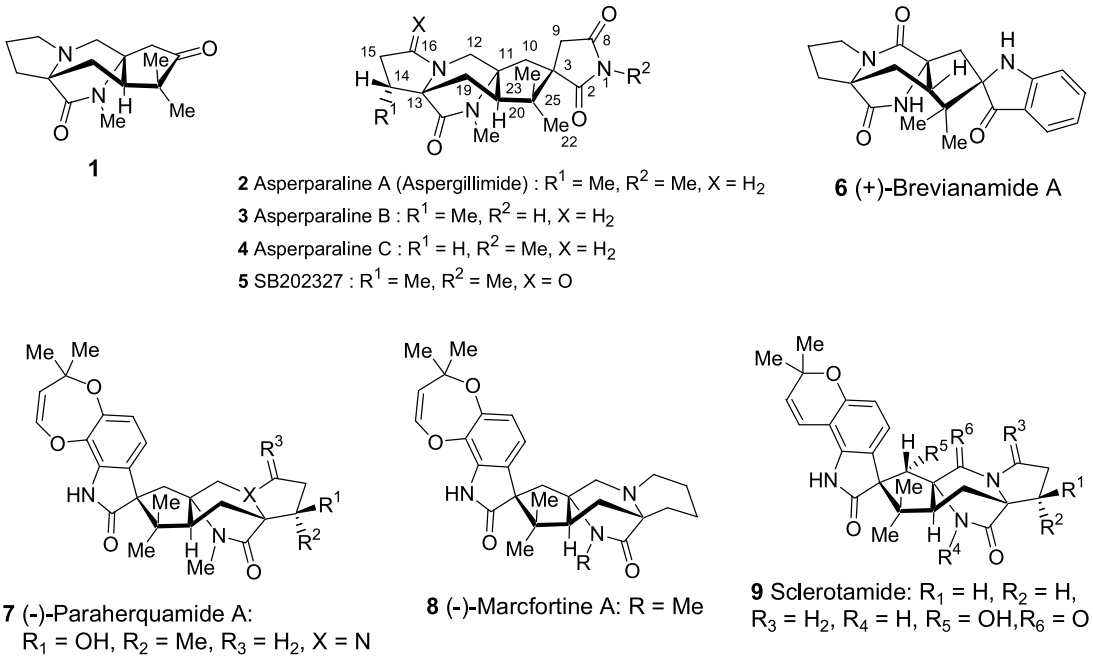
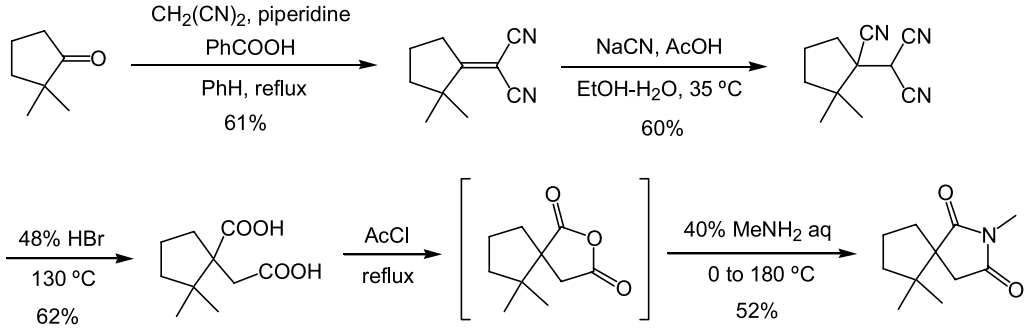


Figure 1. Asperparaline and related methabolites.



Scheme 1. Model studies for the synthesis of 3-spiro-succinimide.[13]

followed by intramolecular amide formation with an ester. The 3D structure of enone **11** suggested that the amine would attack from the same face with the ester group at C-13 (asperparaline numbering) to produce the desired stereochemistry at C-11. The precursor of **11** would be enyne **12** by the transformation using Pauson–Khand [2+2+1] cycloaddition reaction. The reaction would proceed via the stable conformer **13** other than **14** to produce **11**, as a major product. Enyne **12** could be prepared starting from L-proline as a chiral form by the use of Seebach's protocol[5] for synthesizing chiral α-substituted proline.

2. Results and discussion

We initially intended to establish the synthetic route by the use of readily available racemic material. The racemic enyne **12** was prepared from *N*-Cbz-proline by the standard method involving the sequential alkylation of ester enolate, deprotection, followed by *N*-alkylation via **15** and **18** (Scheme 2). Disappointingly, the Pauson–Khand reaction of **12** under various conditions (Table 1) gave no desired product **11**. Probably, the approach of the cobalt complex formed on alkyne to alkene would be prevented due to the steric bulk of the terminal geminal dimethy group. To confirm this speculation, two enynes, allyl proline **21** and crotyl proline **22**, were synthesized along the same reaction sequences. Indeed, as shown in Table 2, allyl proline **21** yielded tricyclic enone **23** in high yield by the use of a stoichiometric amount of cobalt (0) octacarbonyl in THF in the presence of DMSO as promoter[15] as a single stereoisomer. At this point, the stereochemistry of the newly produced C-20 position (asperparaline numbering) of enone **23** was tentatively estimated by molecular calculation as follows. A plausible mechanism of the Pauson–Khand reaction is shown in Scheme 3.[3] The stereo-discrimination step should be the stage from complex **25** to metallacycle **26**. Although the best way to predict the stereochemical outcome would be to calculate the transition state energy of every possible conformer of **25**, it is necessary to use an accurate molecular calculation program. We conducted the calculation with **26** instead of transition state **25** based upon the hypothesis that the steric energy of **26** would reflect that

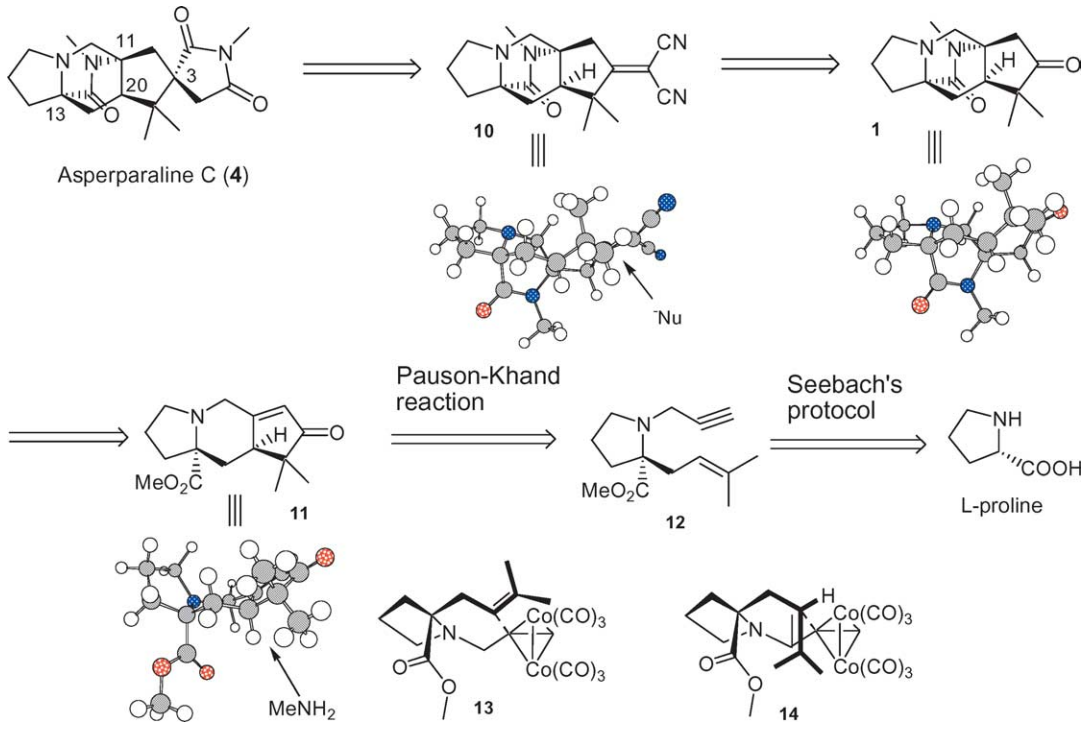
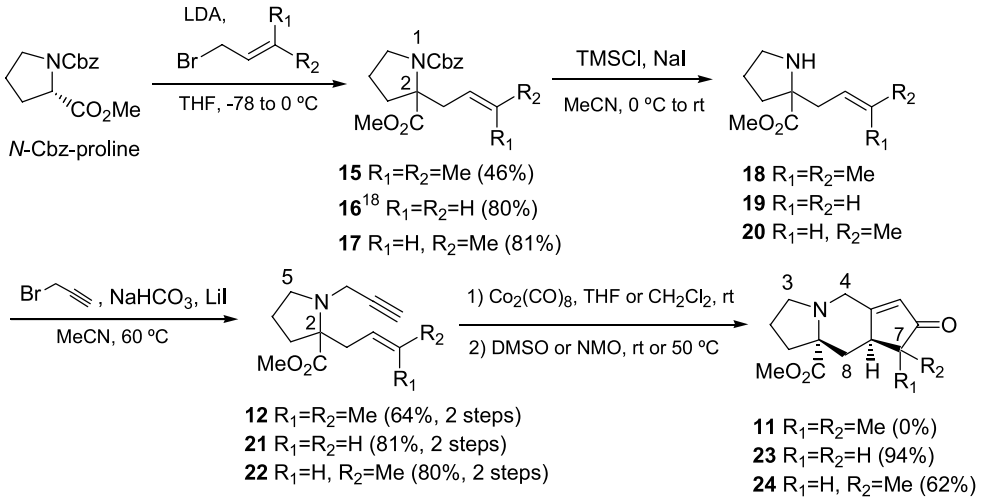
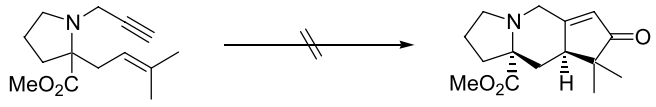


Figure 2. Retro-synthetic approach to asperparaline C.



Scheme 2. Synthesis of racemic enone **11**, **23** and **24**.

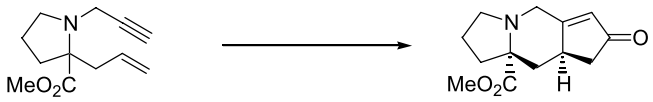
Table 1. Reaction condition from enyne **12** to enone **11**



12 **11**

Entry	$Co_2(CO)_8$ (equiv)	Solvent	Conditions for the formation of cobalt–alkyne complex	Promoter	Conditions for the reaction of cobalt–alkyne complex with alkene	Yield (%)
1	1.05	THF	Ar, rt, 2 h	DMSO (6 equiv)	Ar, 50 °C, 72 h	0
2	1.05	CH_2Cl_2	Ar, rt, 2 h	NMO (9 equiv)	Ar, rt, 96 h	0
3	1.0	THF	Ar, rt, 2 h	NMO (6 equiv)	Ar, rt, 15 h	0
4	1.05	THF	Ar, rt, 2 h	TMANO·$2H_2O$ (6 equiv)	Ar, rt, 12 h	0
5	1.0	THF	Ar, rt, 2 h	TMANO (6 equiv)	Ar, rt, 24 h	0

Table 2. Reaction conditions for the synthesis of enone **23**



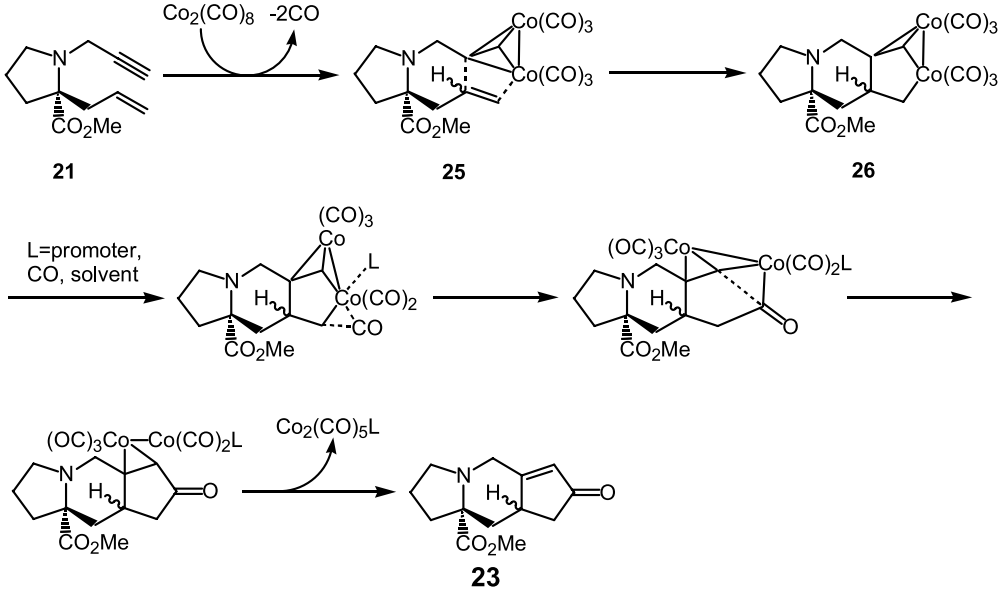
21 **23**

Entry	$Co_2(CO)_8$ (equiv)	Solvent	Conditions for the formation of cobalt–alkyne complex	Promoter	Conditions for the reaction of cobalt–alkyne complex with alkene	Isolated yield (%)
1	1.2	CH_2Cl_2	CO, rt, 2 h	NMO (6 equiv)	CO, rt, 22 h	72
2	1.1	PhH	Ar, rt, 2 h	DMSO (0.1 equiv)	O_2, 50 °C, 72 h	46
3	1.05	THF	Ar, rt, 2 h	DMSO (6 equiv)	Ar, 50 °C, 26 h	94
4	0.1	DME	CO, rt, 10 min	CO	CO, 60 °C, 42 h	6

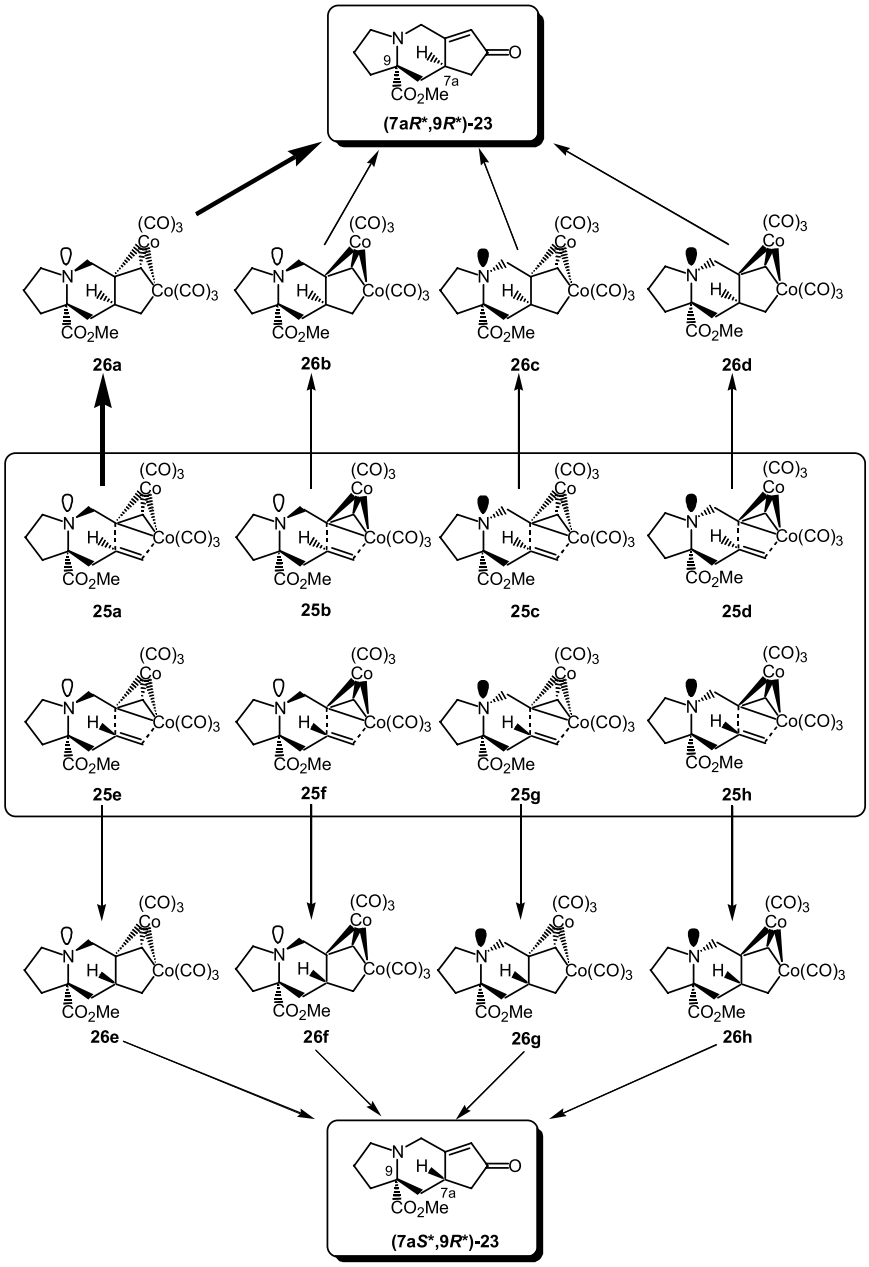
of **25**. The possible conformer of transition state **25** would be **25a** to **25h** (Scheme 4) and the corresponding metallacycle **26a** to **26d** should afford enone (7a*R**,9*R**)-**23**; on the other hand, **26e** to **26h** from **25e** to **25h** should provide diastereomer (7a*S**,9*R**)-**23**. Table 3 shows the calculated steric energy of **26a** to **26h**, the difference in energy between **26b** to **26h** and the most stable conformer **26a**, the equilibrium constants based on Boltzmann equation, the calculated distribution of **26a** to **26h**, and the ratio of formation on (7a*R**,9*R**)-**23** and (7a*S**,9*R**)-**23** based on the MM2 calculation composed in Chem3D program.[14] The carbonyl group on cobalt was replaced to hydrogen to simplify the calculation. These results well reflected the experimental results.

The formation of bridged lactam was studied using enone **23** (Table 4). Thus, enone **23** was treated with methyl amine in the presence of additives followed by acidic treatment to produce lactam **27** in excellent yield as a single diastereomer. The reaction pathway was assumed as follows shown in Scheme 5. The first Michael-type addition of methylamine to enone **23** would give intermediate **28** stereoselectively (not isolated), then spontaneous intramolecular lactam formation afforded imine **29**. Acidic treatment to hydrolyze imine **29** would produce the desired lactam **27**. Especially, silica gel in aqueous methanol was extremely effective (Table 4, entry 5). The relative stereochemistry of **27** and also the precursor enone **23** became undoubtedly apparent by this transformation, because another Michael adduct **30** from stereoisomer 7a-*epi*-**23** could not cyclyze to lactam as shown in Scheme 5. It was assumed that the attack of methylamine to enone **23** would occur from the convex face of the molecule, predominantly. Consequently, the chirality of the quaternary carbon of enyne **21** was effectively transformed into C-1 and C-5 of the product **27** via the Pauson–Khand reaction followed by Michael-type addition.

Unfortunately, introduction of a geminal dimethyl group on enone **23** at C7 position was ineffective to yield the desired **11** in only 3% yield along with mono methylated **24** (14%) and recovered **23** (28%) by treatment of **23** with LDA and MeI in the presence of HMPA at −78 °C (Scheme 6). We next examined the cycloaddition of enyne **22** possessing a crotyl side chain. Although the efficiency rather declined in comparison to **21**, the enone **24** was obtained in 62% yield in a ratio of 4:1 based on the stereochemistry of the secondary methyl group at C7 (Table 5). Introduction of a lacked



Scheme 3. Plausible mechanism of Pauson–Khand reaction.

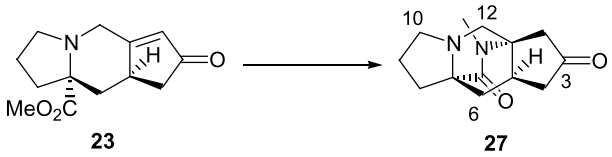


Scheme 4. Reaction pathway from transition state **25** to enone **23** via metallacycle **26**.

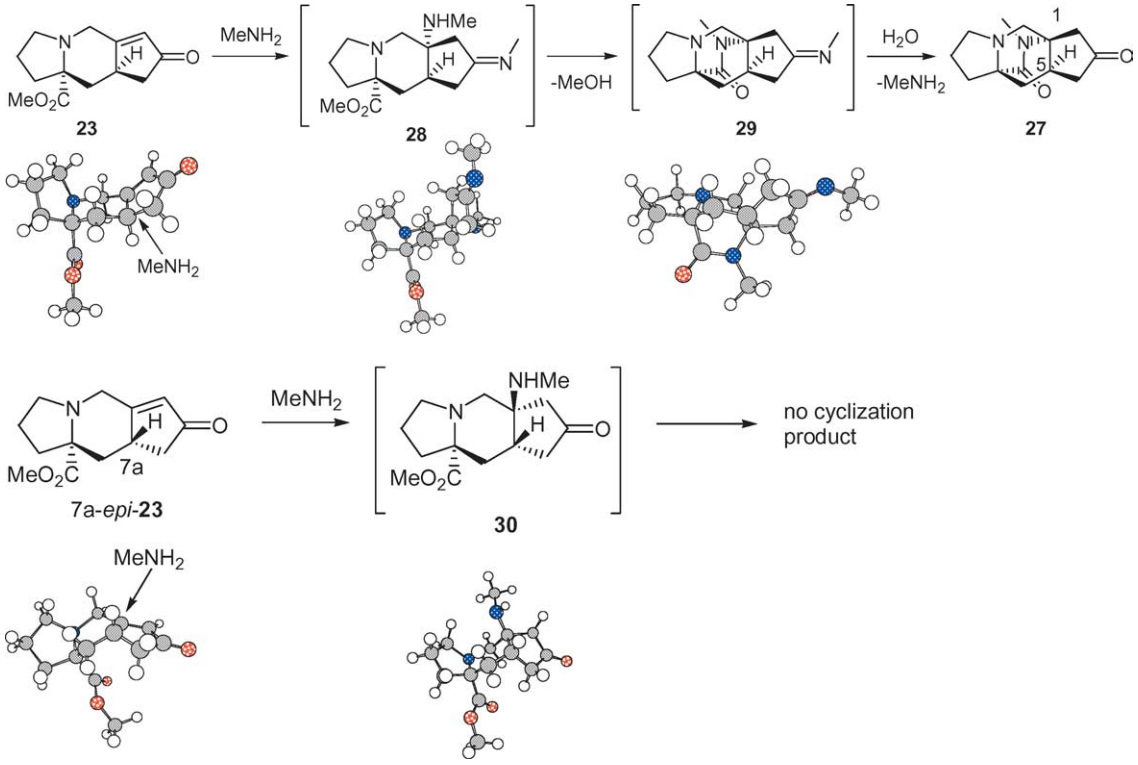
Table 3. Calculated product distribution based on steric energy of metallacycle **26**

	26a	**26b**	**26c**	**26d**
Steric energy (kcal/mol)	299.55	301.62	300.97	302.66
Difference of steric energy to **26a** (kcal/mol)	0	2.07	1.42	3.11
Equilibrium constant	1	3.97×10^{-2}	1.09×10^{-1}	7.90×10^{-3}
Calculated distribution	85.8	3.41	9.35	6.78×10^{-1}
Total distribution of (7a*R**,9*R**)-**23** (%)			99	
	26e	**26f**	**26g**	**26h**
Steric energy (kcal/mol)	302.58	304.63	307.35	305.54
Difference of steric energy to **26a** (kcal/mol)	3.03	5.08	7.80	5.99
Equilibrium constant	8.87×10^{-3}	3.67×10^{-4}	5.28×10^{-6}	8.92×10^{-5}
Calculated distribution	7.61×10^{-1}	3.15×10^{-2}	4.53×10^{-4}	7.65×10^{-3}
Total distribution of (7a*S**,9*R**)-**23** (%)			1	

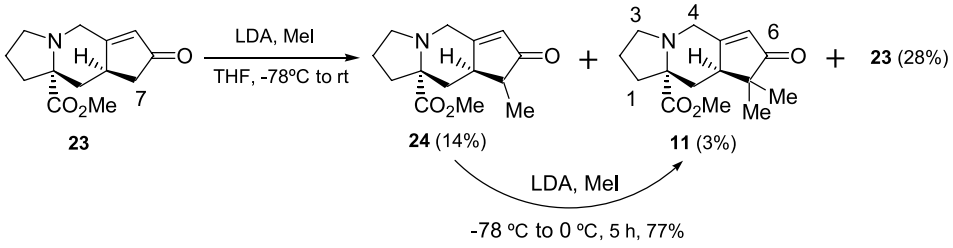
Table 4. Reaction conditions for the synthesis of lactam **27** from enone **23**



Entry	Conditions	Isolated yield (%)
1	(1) 40% $MeNH_2$ aq (20 equiv), Na_2CO_3 (0.2 equiv), rt, 24 h (2) Concd HCl, rt, 24 h→40 °C, 3 h	52
2	(1) 40% $MeNH_2$ aq (20 equiv), Na_2CO_3 (0.05 equiv), rt, 15 h (2) Concd HCl, 45 °C, 24 h	57
3	(1) 40% $MeNH_2$ aq (20 equiv), $NaHCO_3$ (0.1 equiv), rt, 13 h (2) Concd HCl, rt, 7 h	60
4	(1) 40% $MeNH_2$ aq (20 equiv), $MeNH_3Cl$ (0.2 equiv), rt, 21 h (2) Concd HCl, 45 °C, 13 h	69
5	(1) 40% $MeNH_2$ aq (20 equiv), $MeNH_3Cl$ (0.2 equiv), rt, 16 h (2) SiO_2, MeOH–H_2O, rt–45 °C, 7 h	95

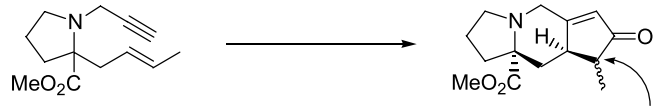


Scheme 5. Reaction pathway from enone **23** to lactam **27**.



Scheme 6. Introduction of methyl group at C7 of enone **23**.

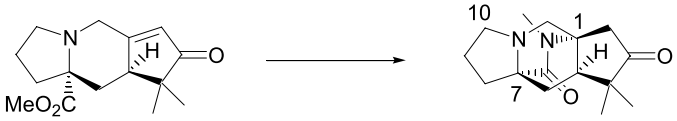
Table 5. Reaction conditions for the synthesis of enone **24** from enyne **22**



22 **24**

Entry	$Co_2(CO)_8$ (equiv)	Solvent	Conditions for the formation of cobalt–alkyne complex	Promoter	Conditions for the reaction of cobalt–alkyne complex with alkene	Isolated yield (%)
1	1.0	THF	Ar, rt, 2 h	DMSO (6 equiv)	Ar, 50 °C, 35 h	34
2	1.0	THF	Ar, rt, 2 h	DMSO (12 equiv)	Ar, 50 °C, 72 h	48
3	1.0	CH_2Cl_2	Ar, rt, 2 h	TMANO (9 equiv)	Ar, rt, 21 h	53
4	1.0	CH_2Cl_2	Ar, rt, 2 h	NMO (9 equiv)	Ar, rt, 15 h	53
5	1.0	CH_2Cl_2	Ar, rt, 2 h	NMO (9 equiv)	Ar, rt, 24 h→O_2, 1 h	62

Table 6. Reaction conditions for the synthesis of lactam **1** from enone **11**



11 **1**

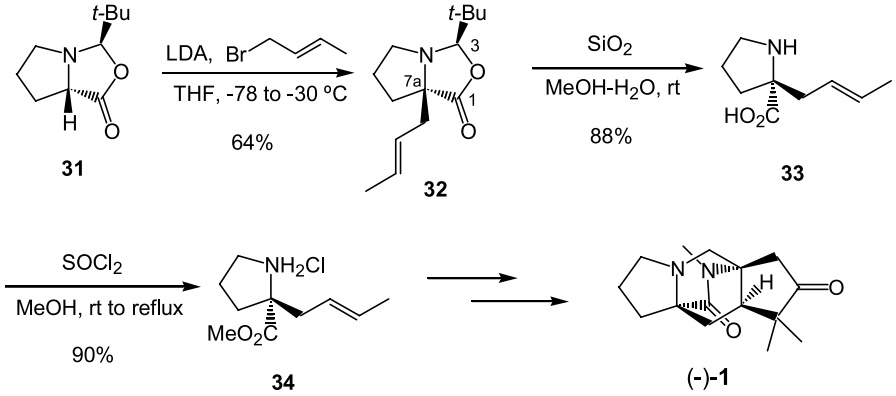
Entry	Conditions	Isolated yield (%)
1	(1) 40% $MeNH_2$ aq (20 equiv), $MeNH_3Cl$ (0.2 equiv), rt, 16 h (2) Concd HCl, 45 °C, 18 h→rt, 41 h	28
2	(1) 40% $MeNH_2$ aq (20 equiv), $MeNH_3Cl$ (0.5 equiv), rt, 96 h (2) SiO_2, MeOH, H_2O, reflux, 4 h	39
3	(1) 40% $MeNH_2$ aq (20 equiv), $MeNH_3Cl$ (0.5 equiv), rt, 48 h (2) SiO_2, MeOH, H_2O, rt, 18 h→reflux, 1 h	39
4	(1) 40% $MeNH_2$ aq (40 equiv), rt, 48 h→reflux, 4 h (2) SiO_2, MeOH, H_2O, rt, 18 h	70

methyl group on **24** was successfully accomplished to give enone **11** in 77% yield by treatment with LDA and MeI (Scheme 6). The lactam formation of **11** needed stronger conditions (Table 6) to produce racemic lactam **1** in 70% yield again as a single diastereomer.

As the synthetic route to **1** was established as racemic form, we next examined the chiral synthesis of **1** and also a catalytic approach for the key Pauson–Khand reaction.

The optically active indolidine **1** was synthesized starting from chiral crotyl proline **34**, prepared from bicyclic compound **31**[5] via **32** and **33** by the stereoselective crotylation, hydrolysis, followed by esterification (Scheme 7), by the same reaction sequence as the racemic series.

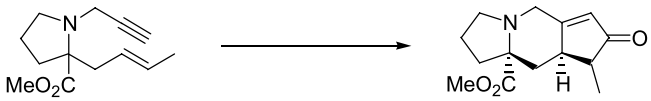
The catalytic Pauson–Khand reaction[4] was successively introduced as shown in Table 7. The reaction was undertaken under a carbon monoxide atmosphere using a catalytic amount of $Co_2(CO)_8$ and NMO as promoter to yield **24** in moderate yield. The efficiency was almost the same as that of the stoichiometric series (see Table 5).



31 **32** **33** **34** **(-)-1**

Scheme 7. Synthesis of chiral indolidine (−)-**1**.

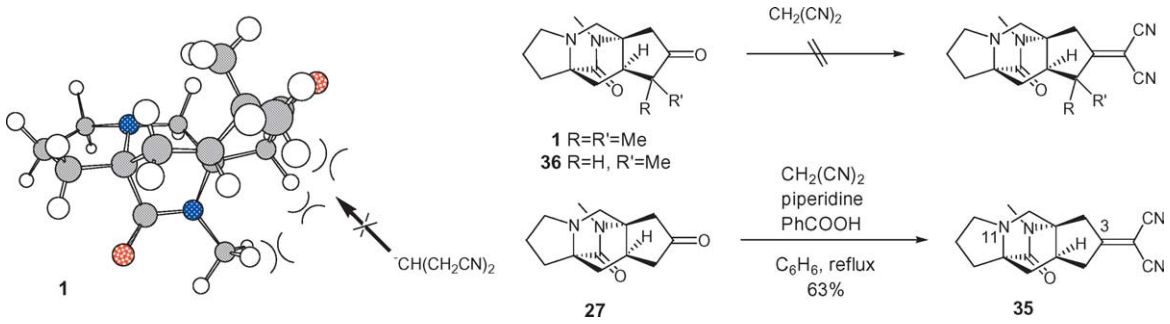
Table 7. Catalytic Pauson–Khand reaction of enyne **22** to enone **24**



22 **24**

Entry	$Co_2(CO)_8$ (equiv)	Solvent	Conditions	Promoter (equiv)	Isolated yield (%)
1	0.05	CH_2Cl_2	CO, 22 h, rt	NMO (0.05)	23 (76)[a]
2	0.05	Benzene	CO, 22 h, 70 °C	NMO (0.05)	54 (26)[a]
3	0.05	Toluene	CO, 22 h, 120 °C	NMO (0.05)	49 (33)[a]

[a] Values in parentheses represent recovery yields of compound **22**.



Scheme 8. Knoevenagel reaction of lactams.

The next stage was set for the construction of 3-*spiro*-succinimide relying on our earlier study (Scheme 1).[13] Unfortunately, the Knoevenagel reaction of ketone **1** with malononitrile under the same reaction condition as the model studies and also stronger conditions such as heating and using a Lewis acid catalyst[16] gave no desired product.[17] The results would be attributed to the additional steric bulk by the bridged lactam on the convex face from which the nucleophile would approach and also the neighboring geminal dimethyl group and hydrogens, one of which would occupy pseudo axial position, respectively, to carbonyl group. Energy minimized conformation of **1** suggested that the *N*-methyl group would shield the convex face of the molecule and the pseudo axial methyl group and hydrogen would also prevent the nucleophilic attack (Scheme 8). To confirm this point, the Knoevenagel reaction of **27** and **36**, derived from enone **24** in 73% yield by the same procedure as the synthesis of **1** and **27**, was examined. Although unsaturated dinitrile **35** was obtained in 63% yield, **36** gave no condensed product.

3. Conclusion

In summary, a concise and stereocontrolled approach for the construction of tetracyclic indolidine **1**, a common structural motif for the biologically active alkaloid asperparaline series of natural products and a potential intermediate for asperparaline C (**4**), has been demonstrated in 8 steps in 12% overall yield starting from L-proline as a chiral process. This protocol constitutes the following three key features: (i) an efficient synthesis of chiral enyne **22** using Seebach's protocol from L-proline; (ii) a stereocontrolled catalytic Pauson–Khand cycloaddition reaction (from **22** to **24**); (iii) a novel facile formation of bridged lactam (from **11** to **1**). The molecular modeling calculation using a popular program (Chem3D) satisfactorily predicted the stereochemical outcome in the key metal-mediated cycloaddition step (from **21** to **23**) and this assumption was confirmed later by the chemical transformation (from **23** to **27**). Further study directed toward the total synthesis of asperparaline C (**4**) from tetracycle **1** by another approach is currently under investigation.

In addition, biological tests for most of the synthetic compounds described in this paper were conducted. As a result, all compounds have not revealed remarkable paralysis against silkworms at a dose of 0.1 mg of diet and also agrochemical profiles on the usual random screening program such as antifungal, insecticidal, and herbicidal activity at 100 ppm. The results suggested that the whole molecular architecture of asperparaline should be essential for exhibiting biological activities.

4. Experimental

4.1. General

Infrared (IR) spectra were recorded on a Perkin–Elmer FT-IR 1760X spectrometer. NMR spectra were recorded on a JEOL JNM-GX 270 spectrometer, operating at 270 MHz for ^{1}H NMR and 67.5 MHz for ^{13}C NMR. Chemical shifts in $CDCl_3$ are reported on the δ scale relative to $CHCl_3$ (7.26 ppm for ^{1}H NMR and 77.00 ppm for ^{13}C NMR) as an internal reference. The following abbreviations are used to multiplicities: 's' (singlet), 'd' (doublet), 't' (triplet), 'm' (multiplet), 'br' (broad). Optical rotations were measured on a JASCO DIP-360 polarimeter. Mass spectra were measured on a JEOL JNM-AX 500 mass spectrometer. Column chromatography was carried out with silica gel Merck 60 (230–400 mesh ASTM). Reactions were carried out in dry solvents under an argon atmosphere. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl.

Dichloromethane (CH_2Cl_2) was distilled from calcium hydride. Other reagents were purified by usual methods.

4.1.1. 2-(3-Methyl-but-2-enyl)-pyrrolidine-1,2-dicarboxylic acid 1-benzyl ester 2-methyl ester (15), 2-allyl-pyrrolidine-1,2-dicarboxylic acid 1-benzyl ester 2-methyl ester (16), and 2-but-2-enyl-pyrrolidine-1,2-dicarboxylic acid 1-benzyl ester 2-methyl ester (17). 15% *n*-BuLi in hexane (18.8 mL, 30.4 mmol) was added slowly to a solution of diisopropylamine (3.08 g, 4.27 mL, 30.4 mmol) in anhydrous THF (100 mL) at −78 °C under nitrogen atmosphere and stirred for 30 min at 0 °C. After cooling to −78 °C, *N*-Cbz-proline methyl ester (5.0 g, 19.0 mmol) in anhydrous THF (25 mL) was added over 20 min. After stirring for 1 h, HMPA (6.81 g, 6.61 mL, 38.0 mmol) was added dropwise over 5 min and stirred for 10 min. Crotyl bromide (3.13 mL, 30.4 mmol) in anhydrous THF (25 mL) was added over 1 h and warmed to 0 °C over 30 min and stirred for 1 h at 0 °C. 1 N HCl solution (50 mL) was added to the reaction mixture and the organic layer was separated. The water layer was extracted with ethyl acetate (50 mL) and the combined organic layer was washed with satd aq $NaHCO_3$ (30 mL) and brine (30 mL) and dried over $MgSO_4$. Concentration in vacuo gave a crude product, which was purified by silica gel column chromatography (eluting with EtOAc–hexane=1:9) to give crotyl proline methyl ester **17** (4.88 g, 81%) as a pale yellow oil. R_f=0.67 (EtOAc–hexane=1:2, I_2). IR (NaCl, film) ν_{max} cm^{-1}: 2954, 2881, 1742 (ester C=O), 1704 (carbamate C=O), 1408, 1357, 1169, 1120, 1025, 699. ^1H NMR δ ($CDCl_3$): 1.64 (3H, d, J=6.4 Hz, CH=CH–CH_3), 1.77–2.15 (4H, m), 2.48–3.07 (2H, m, CH_2–CH=CH), 3.47 (2H, s, O–CH_2–Ph), 3.70 (3H, s, O–CH_3), 5.11 (1H, dd, J=12.2, 47.3 Hz), 5.14 (1H, br s), 5.23–5.38 (1H, m), 5.38–5.58 (1H, m), 7.32–7.37 (5H, m, Ph). ^{13}C NMR δ ($CDCl_3$): 18.2, 18.7, 23.3, 36.6, 48.3, 52.1, 67.0, 68.2, 125.0, 127.5, 127.5, 127.7, 127.8, 128.0, 130.3, 136.9, 154.0, 174.6. FAB MS *m/z* (%):318 (MH^+, 19), 274 ($[M-CO_2]^+$, 9), 182 ($[M-Cbz]^+$, 16). HRMS (FAB) *m/z* (MH^+): calcd for $C_{18}H_{24}NO_4$, 318.1705; found, 318.1694.

Compound **15**. Pale yellow oil. R_f=0.61 (EtOAc–hexane=1:2, I_2). IR (NaCl, film) ν_{max} cm^{-1}:2955, 2880, 1742 (ester C=O), 1705 (carbamate C=O), 1409, 1355, 1127, 1028, 699. ^1H NMR δ ($CDCl_3$): 1.58 (3H, s), 1.70 (3H, s), 1.74–2.08 (4H, m), 2.58–3.05 (2H, m, CH_2–CH=C(CH_3)$_2$), 3.46 (2H, s, O–CH_2–Ph), 3.71 (3H, s, O–CH_3), 4.97–5.24 (3H, m), 7.26–7.36 (5H, m, Ph). ^{13}C NMR δ ($CDCl_3$) *cis*+*trans* rotamers: 18.1, 18.1, 22.8, 23.3, 26.1, 26.2, 31.9, 33.2, 35.7, 37.1, 48.4, 49.2, 52.1, 52.4, 66.6, 67.0, 68.0, 68.8, 118.3, 118.5, 127.5, 127.7, 127.8, 128.0, 128.3, 128.3, 135.1, 135.3, 136.3, 136.9, 154.0, 154.2, 174.7, 174.8. FAB MS *m/z* (%): 332 (MH^+, 15), 288 ($[M-CO_2]^+$, 10), 196 ($[M-Cbz]^+$, 8). HRMS (FAB) *m/z* (MH^+): calcd for $C_{19}H_{26}NO_4$, 332.1862; found, 332.1850.

Compound **16**.[18] Pale yellow oil. R_f=0.59 (EtOAc–hexane=1:2, I_2).IR (NaCl, film) ν_{max} cm^{-1}: 2954, 2880, 1742 (ester C=O), 1704 (carbamate C=O), 1408, 1357, 1170, 1119, 1026, 699. ^1H NMR δ ($CDCl_3$): 1.82–2.16 (4H, m), 2.56–2.72 (1H, m, *H*–CH–CH=CH_2), 2.88–3.17 (1H, m, *H*–CH–CH=CH_2), 3.47 (2H, s, O–CH_2–Ph), 3.71 (3H, s, O–CH_3), 5.00–5.23 (4H, m), 5.62–5.80 (1H, m, C*H*=CH_2), 7.27–7.37 (5H, m, Ph). ^{13}C NMR δ ($CDCl_3$): 18.0, 28.5, 35.3, 43.0, 50.7, 66.1, 69.0, 117.3, 127.3, 127.6, 128.1, 128.5, 128.6, 140.6, 140.9, 159.3, 174.1.

4.1.2. 2-(3-Methyl-but-2-enyl)-1-prop-2-ynyl-pyrrolidine-2-carboxylic acid methyl ester (12), 2-allyl-1-prop-2-ynyl-pyrrolidine-2-carboxylic acid methyl ester (21), and 2-but-2-enyl-1-prop-2-ynyl-pyrrolidine-2-carboxylic acid methyl ester (22). Under nitrogen atmosphere, sodium iodide (7.36 g, 49.1 mmol) was added to a solution of *N*-Cbz-crotyl proline 17 (2.0 g, 6.3 mmol) in anhydrous MeCN (20 mL) and cooled to 0 °C. TMSCl (3.20 mL, 25.2 mmol) was added to the mixture and the mixture was stirred for 6 h at room temperature. After cooling to 0 °C, 1 N HCl (20 mL) was added to the mixture. After stirring for 30 min, the phases were separaterd and the water layer was washed with hexane (20 mL×2). The water layer was converted to pH 9–10 by adding 50% K_2CO_3 and extracted with methylene chloride (20 mL×3). The organic phase was washed with brine, dried over $MgSO_4$, and concentrated in vacuo to give free amine **20**.

A mixture of the above amine **20**, propargyl bromide (0.71 mL, 9.4 mmol), sodium bicarbonate (1.59 g, 18.9 mmol), LiI (84.3 mg, 0.63 mmol) in MeCN (20 mL) was heated at 60 °C with stirring for 14 h. After cooling, water (20 mL) was added to the mixture and the two layers were separated. The water layer was extracted with ether (20 mL×2) and the combined organic phase was washed with brine, dried ($MgSO_4$) and evaporated. The residue was purified by silica gel column chromatography (EtOAc–hexane=1:19) to give enyne **22** (1.12 g, 80%) as a colorless oil. R_f=0.72 (EtOAc–hexane=1:2, I_2). IR (NaCl, film) ν_{max} cm^{-1}: 3300 (C≡*C*–*H*), 2950, 2856, 1728 (C=O), 1435, 1195, 970, 651. ^1H NMR δ ($CDCl_3$): 1.65 (3H, d, J=7.1 Hz, CH=CH–CH_3), 1.72–1.90 (3H, m), 2.16–2.26 (3H, m), 2.60 (1H, dd, J=7.0, 13.7 Hz, *H*–CH–CH=CH–CH_3), 2.72–2.84 (1H, m), 3.16–3.22 (1H, m), 3.34 (1H, dd, J=2.4, 16.8 Hz, *H*–CH–C≡CH), 3.61 (1H, dd, J=2.4, 16.8 Hz, *H*–CH–C≡CH), 3.68 (3H, s, O–CH_3), 5.30–5.41 (1H, m, CH=C*H*–CH_3), 5.46–5.59 (1H, m, C*H*=CH–CH_3). ^{13}C NMR δ ($CDCl_3$): 18.2, 21.4, 33.9, 37.7, 38.2, 51.2, 51.3, 69.7, 71.3 (C≡*C*H), 80.9 (*C*≡CH), 125.8 (CH=*C*H–CH_3), 128.7 (*C*H=CH–CH_3), 173.7. FAB MS *m/z* (%): 222 (MH^+, 13), 190 ($[M-OMe]^+$, 56), 162 ($[M-CO_2Me]^+$, 100). HRMS (FAB) *m/z* (MH^+): calcd for $C_{13}H_{20}NO_2$, 222.1494; found, 222.1499.

Compound **12**. R_f=0.79 (EtOAc–hexane=1:2, I_2). IR (NaCl, film) ν_{max} cm^{-1}: 3298 (C≡*C*–*H*), 2951, 1727 (C=O), 1435, 1195, 1175, 647. ^1H NMR δ ($CDCl_3$): 1.63 (3H, s), 1.70 (3H, s), 1.58–1.86 (3H, m), 2.19–2.24 (3H, m), 2.65 (1H, dd, J=7.6, 14.3 Hz, *H*–CH–CH=C(CH_3)$_2$), 2.74–2.83 (1H, m, H–C5), 3.17–3.24 (1H, m, H–C5), 3.34 (1H, dd, J=2.4, 16.8 Hz, *H*–CH–C≡CH), 3.67 (3H, s, O–CH_3), 3.60–3.68 (1H, m), 5.02–5.08 (1H, m, C*H*=C(CH_3)$_2$). ^{13}C NMR δ ($CDCl_3$):18.1, 21.4, 26.1, 33.6, 34.0, 37.8, 51.2, 51.3, 70.0 (C2), 71.3 (C≡*C*H), 81.0 (*C*≡CH), 119.0 (*C*H=C(CH_3)$_2$), 134.2 (CH=*C*(CH_3)$_2$), 173.7 (C=O). FAB MS *m/z* (%): 236 (MH^+, 31), 176 ($[M-CO_2Me]^+$, 38), 166 ($[M-CH_2CH=C(CH_3)_2]^+$, 100). HRMS (FAB) *m/z* (MH^+): calcd for $C_{14}H_{22}NO_2$, 236.1651; found, 236.1628.

Compound **21**. R_f=0.72 (EtOAc–hexane=1:2, I_2). IR (NaCl, film) ν_{max} cm^{-1}: 3299, 2952, 2837, 1727 (C=O), 1641 (C=C), 1433, 1197, 1171, 989, 918, 649. ^1H NMR δ ($CDCl_3$): 1.81–1.88 (3H, m), 2.18–2.23 (2H, m), 2.32 (1H, dd, J=7.1, 14.3 Hz, *H*–CH–CH=CH_2), 2.65 (1H, dd, J=7.3, 14.6 Hz, *H*–CH–CH=CH_2), 2.77–2.85 (1H, m), 3.17–3.23 (1H, m), 3.35 (1H, dd, J=7.6, 15.6 Hz, *H*–CH–C≡CH), 3.61 (1H, dd, J=7.4, 15.4 Hz, *H*–CH–C≡CH), 3.68 (3H, s, O–CH_3), 5.06–5.13 (2H, m, CH=CH_2), 5.69–5.85 (1H, m, C*H*=CH_2). ^{13}C NMR δ ($CDCl_3$): 21.4, 33.9, 37.6, 39.3, 51.2, 51.3, 69.2, 71.3 (C≡*C*H), 80.8 (*C*≡CH), 118.0 (CH=*C*H_2), 133.5 (*C*H=CH_2), 173.6.

4.1.3. 6-Oxo-2,3,6,7,7a,8-hexahydro-1*H*,4*H*-3a-aza-s-indacene-8a-carboxylic acid methyl ester (23) and 7-methyl-6-oxo-2,3,6,7,7a,8-hexahydro-1*H*,4*H*-3a-aza-s-indacene-8a-carboxylic acid methyl ester (24).

4.1.3.1. Synthesis of 23 by a stoichiometric Pauson–Khand reaction (Table 2, entry 3). 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 **21** (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 **23** (201 mg, 94%) as a pale yellow crystal. R_f=0.25 (EtOAc). Mp 80.2–81.1 °C. $[\alpha]_D^{18}$ +34.1° (*c* 1.9, $CHCl_3$). 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–C7), 2.70–2.77 (1H, m, H–C7a), 2.91 (1H, dd, J=7.3, 16.5 Hz, H–C3), 3.09–3.17 (1H, m, H–C3), 3.79 (3H, s, O–CH_3), 3.79–3.94 (2H, m, H_2–C4), 5.98 (1H, br s, H–C5). ^{13}C NMR δ ($CDCl_3$): 21.0, 36.5, 38.1, 38.7, 42.0, 47.8, 49.9, 52.1, 67.3 (C8a), 128.4 (C5), 174.5 (C4a), 176.4 (*C*O_2Me), 207.7 (C6). FAB MS *m*/*z* (%): 236 (MH^+, 69), 176 ($[M-CO_2Me]^+$, 100). HRMS (EI) *m*/*z* (M^+): calcd for $C_{13}H_{17}O_3N$, 235.1209; found, 235.1220.

4.1.3.2. Synthesis of 24 by a catalytic Pauson–Khand reaction (Table 7, entry 2). To a stirred solution of $Co_2(CO)_8$ (37 mg, 0.11 mmol) in dry benzene (50 mL) under CO atmosphere at room temperature was added dropwise a solution of enyne **22** (500 mg, 2.26 mmol) in benzene (5 mL). After 2 h of stirring at room temperature, NMO (50% in water, 0.028 mL, 0.11 mmol) was added in one portion. The reaction mixture was stirred for 22 h at 70 °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 **24** (304 mg, 54%) as a brown oil and recovered enyne **22** (130 mg, 26%). R_f=0.30 (EtOAc, I_2). $[\alpha]_D^{22}$ +44.9°(*c* 1.0, $CHCl_3$). IR (NaCl, film) ν_{max} cm^{-1}: 2957, 2878, 1728 (ester C=O), 1708 (ketone C=O), 1632 (C=C), 1449, 1176. ^1H NMR δ ($CDCl_3$): 1.07 (3H, d, J=7.3 Hz, CH_3–C7), 1.36 (1H, t, J=12.9 Hz, H-8), 1.73–1.85 (1H, m, H–C1), 1.85–1.95 (2H, m, H_2–C2), 1.99 (1H, dq, J=2.9, 7.3 Hz, H–C7), 2.16 (1H, dt, J=12.2, 7.1 Hz, H–C1), 2.27–2.36 (1H, m, H–C7a), 2.67 (1H, dd, J=5.6, 12.9 Hz, H–C8), 2.93 (1H, dd, J=8.5, 15.3 Hz, H–C3), 3.12 (1H, dd, J=8.5, 15.3 Hz, H–C3), 3.68–3.92 (2H, m, H_2–C4), 3.79 (3H, s, O–CH_3), 5.95 (1H, br s, H–C5); ^{13}C NMR δ ($CDCl_3$): 14.2, 21.0, 36.5, 37.8, 46.4, 47.8, 47.9, 50.0, 52.1, 67.3 (C8a), 127.2 (C5), 174.0 (C4a), 174.5 (*C*O_2Me), 209.9 (C6). EI-MS *m*/*z* (%): 249 (M^+, 39), 190 ($[M-CO_2Me]^+$, 32), 154 (100), 136 (83). HRMS (EI) *m*/*z* (M^+): calcd for $C_{14}H_{19}NO_3$, 249.1365; found, 249.1382.

4.1.4. 7,7-Dimethyl-6-oxo-2,3,6,7,7a,8-hexahydro-1*H*,4*H*-3a-aza-s-indacene-8a-carboxylic acid methyl ester (11).

15% *n*-BuLi in hexane (2.61 mL, 4.21 mmol) was added slowly to a solution of diisopropylamine (0.43 g, 0.59 mL, 4.21 mmol) in anhydrous THF (15 mL) at −78 °C under nitrogen atmosphere and stirred for 30 min at 0 °C. After cooling to −78 °C, enone **24** (350 mg, 1.40 mmol) in anhydrous THF (1.5 mL) was added to the above solution over 5 min. After stirring for 5 min, HMPA (0.50 g, 0.49 mL, 2.81 mmol) was added dropwise and stirred for 10 min. MeI (0.80 g, 0.35 mL, 5.61 mmol) was added and stirred for 1 h at −78 °C. Saturated aqueous NaCl (15 mL) was added and the organic layer was separated. The water layer was extracted with ethyl acetate (30 mL) and the combined organic layer was washed with brine (30 mL) and dried over $MgSO_4$. Concentration in vacuo gave a residue, which was purified by silica gel column chromatography (hexane–EtOAc=3:2) to give enone **11** (285 mg, 77%) as a pale yellow oil. R_f=0.30 (EtOAc, I_2). $[\alpha]_D^{22}$ +18.1° (*c* 0.65, $CHCl_3$); IR (NaCl, film) ν_{max} cm^{-1}: 2965, 2869, 1729 (ester C=O), 1708 (ketone C=O), 1633 (C=C), 1449, 1191, 1152. ^1H NMR δ ($CDCl_3$): 0.92 (3H, s, CH_3–C6), 1.03 (3H, s, CH_3–C6), 1.26–1.38 (1H, m, H–C8), 1.71–1.88 (3H, m), 2.04–2.13 (1H, m), 2.27–2.39 (2H, m), 2.92 (1H, dd, J=7.6, 15.6 Hz, H–C12), 3.12 (1H, dd, J=7.5, 15.4 Hz, H–C12), 3.72 (3H, s, O–CH_3), 3.79–3.87 (2H, m, H_2–C2), 5.83 (1H, br s, H–C4). ^{13}C NMR δ ($CDCl_3$): 20.4, 21.0, 25.2, 33.8, 36.7, 46.3, 48.0, 49.7, 50.0, 52.1, 67.2, (C8a), 125.3 (C5), 174.0 (C4a), 174.5 (*C*O_2Me), 209.9 (C6). EI-MS *m*/*z* (%): 263 (M^+, 100), 204 ($[M-CO_2Me]^+$, 82), 154 (62), 136 (43). HRMS (EI) *m*/*z* (M^+): calcd for $C_{15}H_{21}NO_3$, 263.1521; found, 263.1544.

4.1.5. 11,13-Diaza-4,4,13-trimethyltetracyclo-[5.5.2.0^{1,5}.0^{7,11}]tetradecane-3,14-dione (1), 11,13-diaza-13-methyltetracyclo[5.5.2.0^{1,5}.0^{7,11}]tetradecane-3,14-dione (27), and 11,13-diaza-4,13-dimethyltetracyclo-[5.5.2.0^{1,5}.0^{7,11}]tetradecane-3,4-dione (36).

A solution of enone **11** (0.2 g, 0.76 mmol) in 40% aqueous methylamine (2.62 mL, 30.4 mmol) was stirred for 48 h at room temperature. Water (10 mL) was added to the mixture and the solution was heated at reflux for 4 h. After cooling, the mixture was concentrated in vacuo, the residue was dissolved in MeOH (6 mL) and water (1.2 mL), and SiO_2 (0.8 g) was added. The mixture was stirred for 18 h at room temperature. After cooling, the mixture was filterd 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 **1** (140 mg, 70%) as a brown oil. R_f=0.7 (acetone, I_2). $[\alpha]_D^{22}$ −43.6°(*c* 0.96, $CHCl_3$). IR (NaCl, film) ν_{max} cm^{-1}: 2991, 2887, 1766

(ketone C=O), 1660, (lactam C=O), 1650, 1388, 1095. ^{1}H NMR δ ($CDCl_3$): 0.97 (3H, s, CH_3–C4), 1.07 (3H, s, CH_3–C4), 1.38–1.49 (1H, m, H–C6), 1.65–1.74 (1H, m, H–C6), 1.83–1.99 (2H, m), 2.15–2.44 (4H, m), 2.47 (1H, dd, J=1.5, 2.0 Hz), 2.53–2.67 (2H, m), 2.99 (3H, s, CH_3–N13), 3.05–3.13 (1H, m, H–C10), 3.24 (1H, d, J=11.3 Hz, H–C12). ^{13}C NMR δ ($CDCl_3$): 17.7, 20.9, 22.2, 23.1, 27.9, 29.8, 36.5, 43.9, 46.2, 52.2, 54.0, 56.0, 61.2, 173.0 (C14), 217.6 (C3). EI-MS m/z (%): 262 (M^+, 1), 247 (1), 234 (1), 219 (8), 203 (80), 190 (6), 176 (7), 165 (8), 138 (17), 133 (33), 120 (13), 96 (27), 83 (12), 68 (15), 55 (25), 41 (100). HRMS (EI) m/z (M^+): calcd for $C_{15}H_{22}N_2O_2$, 262.1681; found, 262.1679.

Compound **27**. 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. ^{1}H NMR δ ($CDCl_3$): 1.35–1.46 (1H, m, H–C6), 1.69 (1H, dd, J=5.5, 12.5 Hz, 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). HRMS (EI) m/z (M^+): calcd for $C_{13}H_{18}N_2O_2$, 234.1368; found, 234.1349.

Compound **36**. R_f=0.49 (acetone, I_2). Mp 116–118.2 °C. IR (KBr, disk) ν_{max} cm^{-1}: 2980, 2875, 2798, 1746 (ketone C=O), 1662 (lactam C=O), 1651, 1390, 1324, 1098. ^{1}H NMR δ ($CDCl_3$): 1.15 (3H, d, J=7.0 Hz, CH_3–C4), 1.36–1.48 (1H, m, H–C6), 1.64–1.73 (1H, m, H–C6), 1.84–1.96 (3H, m), 2.18–2.39 (4H, m), 2.51–2.64 (3H, m), 2.98 (3H, s, CH_3–N13), 3.05–3.13 (1H, m, H–C10), 3.24 (1H, d, J=11.3 Hz, H–C12). ^{13}C NMR δ ($CDCl_3$): 12.8, 22.1, 26.6, 27.6, 33.4, 44.1, 47.9, 48.3, 53.7, 54.7, 60.9, 65.8, 172.6 (C14), 213.4 (C3). EI-MS m/z (%): 249 (MH^+, 56), 189 (37), 154 (100), 136 (89). HRMS (EI) m/z (M^+): calcd for $C_{14}H_{20}N_2O_2$, 248.1525; found, 248.1521.

4.1.6. 7a-But-2-enyl-3-*tert*-butyl-tetrahydro-pyrrolo-[1,2-*c*]oxazol-1-one (32). 15% n-BuLi in hexane (28.71 mL, 46.4 mmol) was added slowly to a solution of diisopropylamine (6.52 mL, 46.4 mmol) in anhydrous THF (100 mL) at −78 °C under nitrogen atmosphere and stirred for 30 min at 0 °C. After cooling to −78 °C, oxazolidone **31** (5.00 g, 27.3 mmol) in anhydrous THF (25 mL) was added over 20 min. After stirring for 1 h, HMPA (9.49 mL, 54.6 mmol) was added dropwise over 5 min and stirred for 10 min. Crotyl bromide (4.77 mL, 46.4 mmol) in anhydrous THF (25 mL) was added over 1 h and stirred for 1 h at −78 °C. The mixture was warmed to −30 °C over 1 h and saturated aqueous $NaHCO_3$ (50 mL) was added. The organic layer was separated. The water layer was extracted with ethyl acetate (50 mL) and the combined organic layer was washed with satd aq $NaHCO_3$ (50 mL) and brine (50 mL) and dried over $MgSO_4$. Concentration in vacuo gave a residue, which was purified by distillation under reduced pressure to give crotyl Oxazolidinone **32** (3.78 g, 64%) as a pale yellow oil. R_f=0.60 (EtOAc–C_6H_6=1:200). Bp$_3$: 85–90 °C. $[\alpha]_D^{22}$ +13.5°(c 1.0, $CHCl_3$). IR (NaCl, film) ν_{max} cm^{-1}: 2963, 2871, 1780 (C=O), 1633, 1191. ^{1}H NMR δ ($CDCl_3$): 0.92 (9H, s), 1.64 (3H, d, J=7.1 Hz, CH=CH–CH_3), 1.73–1.90 (4H, m), 2.35 (2H, d, J=7.4 Hz, CH_2–CH=CH), 2.74–2.99 (2H, m), 4.24 (1H, s), 5.46–5.58 (2H, m). ^{13}C NMR δ ($CDCl_3$): 17.3, 21.1, 21.2, 21.3, 28.8, 34.3, 36.8, 49.5, 107.1, 124.8, 133.1, 174.5 (C=O). FAB MS m/z (%): 238 (MH^+, 4), 180 ([M−t-Bu]$^+$,100), 135 (89). HRMS (FAB) m/z (MH^+): calcd for $C_{14}H_{24}NO_2$, 238.1807; found, 238.1834.

4.1.7. 2-But-2-enyl-pyrrolidine-2-carboxylic acid (33). A mixture of crotyl oxazolidone **32** (3.0 g, 13.4 mmol) and silica gel (SiO_2, 3.0 g) in MeOH/H_2O (6:1, 30 mL) was stirred for 48 h at room temperature. After filtration, the residue was washed with MeOH and the filtrate was concentrated in vacuo. The residue was dissolved in $CHCl_3$/MeOH (20:1, 30 mL) and again filtered. The residue was washed with $CHCl_3$/MeOH (20:1) and the filtrate was concentrated in vacuo. The residue was washed with ether and dried over P_2O_5 under reduced pressure to give carboxylic acid **33** (2.0 g, 88%) as a colorless crystal. R_f=0.23 (MeOH–$CHCl_3$=1:4, ninhydrin).Mp 280–285 °C. $[\alpha]_D^{20}$ −70.4°(c 1.0, CH_3OH). IR (KBr, disk) ν_{max} cm^{-1}: 3085, 1628 (C=O), 1390, 933. ^{1}H NMR δ (D_2O): 1.64 (3H, d, J=6.4 Hz, CH=CH–CH_3), 1.73–1.90 (4H, m), 2.24 (1H, dd, J=7.1, 14.6 Hz, H–CH–CH=CH), 2.69 (1H, dd, J=7.3, 14.6 Hz, H–CH–CH=CH), 2.88–3.03 (2H, m), 5.46–5.58 (2H, m). ^{13}C NMR δ (D_2O): 17.3, 22.6, 31.3, 37.8, 42.5, 77.1, 123.8, 133.2, 179.5 (CO_2H). FAB MS m/z (%):170 (MH^+, 100), 124 ([M−CO_2H]$^+$, 100). HRMS (FAB) m/z (MH^+): calcd for $C_9H_{16}NO_2$, 170.1181; found, 170.1100.

4.1.8. (*R*)-2-(−)-Crotylproline methyl ester hydrochloride (34). Thionyl chloride (4.31 mL, 59.1 mmol) was added dropwise to a solution of α-crotyl proline **33** (2.00 g, 11.82 mmol) in anhydrous MeOH (50 mL) at 0 °C and the mixture was stirred for 48 h at room temperature. After refluxing for 1 h, the mixture was concentrated in vacuo. The residue was crystallized in MeOH/EtOAc followed by drying over P_2O_5 under reduced pressure to give methyl ester **34** (2.34 g, 90%) as a colorless crystal. R_f=0.74 (MeOH–$CHCl_3$=1:4, ninhydrin). Mp 166.5–170.0 °C. $[\alpha]_D^{22}$ −48.7°(c 1.0, CH_3OH). IR (KBr, disk) ν_{max} cm^{-1}: 2880, 2711, 2490, 1759 (C=O), 1644 (C=C), 1588, 1341, 1220, 1154, 946. ^{1}H NMR δ (CD_3OD): 1.73 (3H, d, J=6.4 Hz, CH=CH–CH_3), 1.88–2.50 (4H, m), 2.71 (1H, dd, J=7.1, 14.6 Hz, H–CH–CH=CH), 2.93 (1H, dd, J=7.1, 14.6 Hz, H–CH–CH=CH), 3.40–3.48 (2H, m), 3.89, (3H, s, O–CH_3), 5.55–5.78 (2H, m). ^{13}C NMR δ (CD_3OD): 17.6, 20.8, 31.3, 37.8, 42.2, 50.7, 67.7, 123.1, 133.0, 174.5.

4.1.9. 11,13-Diaza-3-(dicyanomethylene)-13-methyl-tetracyclo-[5.5.2.0^{1,5}.0^{7,11}]tetradecan-14-one (35). The lactam **27** (90.3 mg, 0.385 mmol) and malononitrile (51 mg, 0.77 mmol) were added to benzene (10 mL) containing piperidine (7.99 mg, 0.039 mmol) and benzoic acid (18.8 mg, 0.154 mmol), and the mixture was heated to reflux with azeotropic removal of water by Dean–Stark trap for 28 h. After cooling, the mixture was diluted with diethyl ether (20 mL), and successively washed with water (10 mL), a 10% $NaHCO_3$ solution (10 mL) and brine (10 mL). The organic phase was dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by flash chromatography over silica gel (eluting with EtOAc) to give unsaturated dinitrile **35** (68.5 mg, 63%) as an pale yellow

crystal. $R_f = 0.70$ (acetone, I_2). Mp 151.6–153.0 °C. IR (KBr, disk) ν_{max} cm^{-1}:3437 (br), 2946, 2806, 2234 (C≡N), 1661 (amide C=O), 1620 (C=C), 1386, 1320, 1103. ^1H NMR δ ($CDCl_3$): 1.34–1.46 (1H, m, H–C6), 1.68 (1H, dd, $J = 6.3$, 13.2 Hz, H–C6), 1.80-1.92 (2H, m), 2.13–2.39 (5H, m), 2.48–2.72 (4H, m), 2.96 (3H, s, CH_3–N13), 3.01–3.15 (1H, m, H–C10), 3.21 (1H, dd, $J = 7.8$, 20.0 Hz, H–C12). ^{13}C NMR δ ($CDCl_3$): 22.3, 27.0, 27.7, 33.2, 37.9, 40.3, 43.0, 53.6, 53.7, 64.7, 66.0, 84.9 ($C(CN)_2$), 110.5 (CN), 110.9 (CN), 172.5 (C14), 184.4 (C3). FAB MS *m/z* (%): 283 (MH^+, 100), 223 (53). HRMS (FAB) *m/z* (MH^+): calcd for $C_{16}H_{19}N_4O$, 283.1559; found, 283.1548.

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