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Enantioselective synthesis of condensed and transannular ring skeletons containing pyrrolidine moiety

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ABSTRACT

A new approach toward condensed and transannular ring structures containing pyrrolidine unit has been developed, based on diastereoselective nucleophilic addition of lithium enolate of α-diazoacetoacetate to chiral *N*-sulfinyl imine and ring-closing metathesis.

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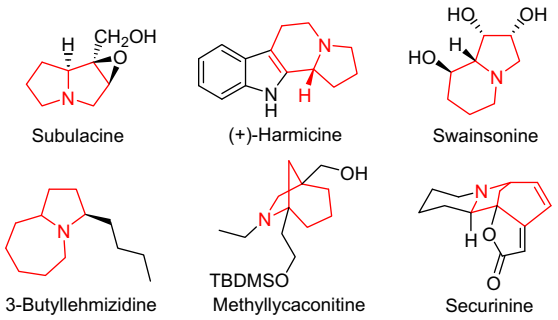
1. Introduction

The enantioselective construction of pyrrolidine skeletons, a frequently observed structural unit in various alkaloid type natural products, pharmaceutical molecules, etc., is of current interest.[1,2] Among the various pyrrolidine-containing structures, condensed and transannluar ring skeletons are important structural subunits present in many alkaloids and are common scaffolds in biologically active and pharmaceutically significant compounds.[3] For example, (+)-harmicine was extracted from the Malaysian plant *Kopsia g iffithii* by Kam and Sim and showed strong anti-Leishmania activity.[4] Polyhydroxylated pyrrolizidines and indolizidines (related to iminosugars) such as Swainsonine have increasingly gained attention because of their ability to inhibit glycosidases (Scheme 1).[5]

Besides the classical total synthesis approach to complex structures, particularly attractive is the development of synthetic methodologies that allow for the preparation of a large number of structurally similar analogs from limited few common intermediates.[6] As a part of our program for the development of novel synthetic methodology based on diazo compounds, we have recently developed a concise and efficient method to construct



Scheme 1.

5-substituted 2-oxo and 3-oxo pyrrolidines with high enantiomeric purity.[7] Here we report the further application of this methodology to the enantioselective synthesis of condensed and transannular ring skeletons containing pyrrolidine units.

This new approach to condensed and transannular ring skeletons is outlined in Scheme 2. With the reactions that have been reported previously, we can easily prepare 2-oxo-5-vinyl-pyrrolidine **1**. Introducing the side chains that contain olefin moiety to either N or C3 position affords key intermediates **2** and **3**, respectively. Ring-closing metathesis (RCM),[8] which has emerged as powerful tool to construct ring system through intramolecular C=C bond formation, is applied to **2** and **3** to afford condensed and transannular ring systems **4** and **5**.[9]

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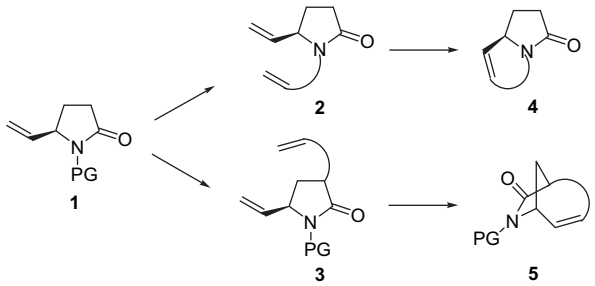
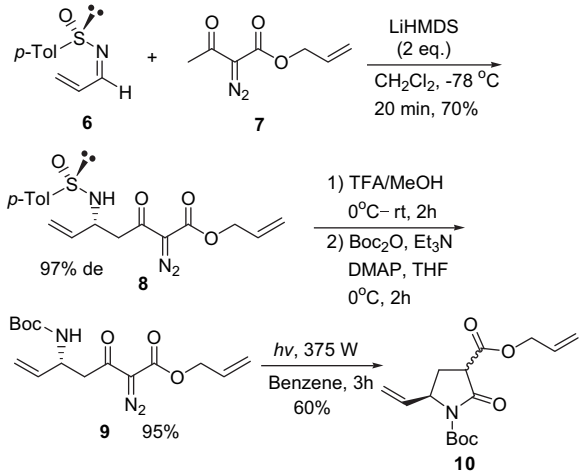
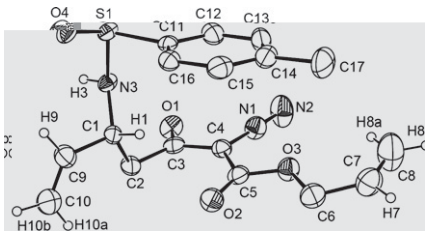


Scheme 2.

1.1. Results and discussions

The investigation began with the preparation of chiral pyrrolidine **10** (Scheme 3). First, diastereoselective addition of lithium enolate of α-diazoacetoacetate **7** to chiral *N*-sulfinyl imine **6** afforded δ-*N*-sulfinylamino α-diazo β-ketoester **8** in 70% yield. HPLC analysis showed compound **8** with 97% de. The absolute configuration of the newly generated chiral center in β-ketoester **8** was established by X-ray analysis of its single crystal.[10] The absolute configuration is also confirmed by converting **8** into known compounds (vide infra). When the chiral center of sulfur has *S* configuration, the newly formed chiral center has *R* configuration. This stereochemical outcome is consistent with the previous reports of the addition of enolates derived from esters or ketones to chiral *N*-sulfinyl imines.[11,12]



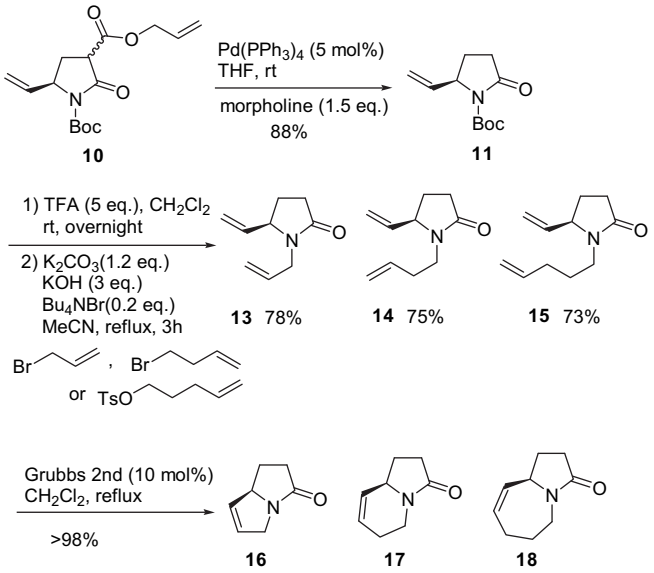


X-ray structure of **8**

Scheme 3.

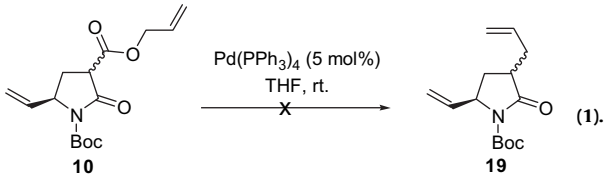
Our previous study has shown that *N*-sulfinyl group is liable to decompose in the Wolff rearrangement reaction, which is under irradiation conditions. Thus, the *N*-sulfinyl group is replaced by *N*-Boc group in two steps. First, β-ketoester **8** was treated with 5 equiv of TFA in MeOH to remove the *N*-sulfinyl auxiliary, giving the free amine as the trifluoroacetate salt. Being neutralized with 6 equiv of Et_3N, the amine was treated with Boc_2O and catalytic amount of DMAP, affording *N*-Boc protected diazo compound **9** in 95% yield. Irradiation of diazo compound **9** with high-pressure Hg lamp (λ>300 nm) in a Pyrex tube gave (5*R*)-2-oxo-3-allyloxycarbonyl-5-vinylpyrrolidine **10** in 60% isolated yield.[7,13]

With **10** in hand, we next proceeded to build the condensed rings based on the strategy summarized in Scheme 2. The condensed alkaloid structure can be built from **10** through N-alkylation and ring-closing metathesis. Thus, $Pd(PPh_3)_4$-catalyzed deallyloxycarbonylation[14] in the presence of morpholine afforded (5*R*)-*N*-Boc-2-oxo-5-vinylpyrrolidine **11** in 88% yield. Removal of the nitrogen protecting group with 5 equiv of TFA in CH_2Cl_2 gave (*R*)-2-oxo-5-vinylpyrrolidine in nearly quantitative yield. (*R*)-2-Oxo-5-vinylpyrrolidine was then reacted with allyl bromide, homoallyl bromide, and pent-4-enyl 4-methylbenzenesulfonate, respectively, in the presence of base to give the products **13**, **14**, and **15** as the precursors for the next RCM reaction. Finally, the pyrrolidines **13**, **14**, and **15** were subjected to the RCM reaction by using second generation Grubbs catalyst. The expected ring-closing products **16**, **17**, and **18** were obtained in nearly quantitative yields (Scheme 4). Products **16**, **17**, and **18** are potentially valuable chiral building blocks for enantioselective synthesis of polysubstituted pyrrolizidines and indolizidines.[15]



Scheme 4.

Next, we conceived the further application of pyrrolidine **10** in the construction of transannular ring structures. As shown in Scheme 2, by introducing an alkene moiety on C3 of pyrolidine ring, the transannular ring structures could be built by the same RCM strategy. First, the pyrrolidine **10** was subjected to Pd-catalyzed decarboxylative allylic alkylation, with the expectation that C3 allylation might occur simultaneously. However, the desired intramolecular allylic alkylation process did not occur when **10** was catalyzed by $Pd(PPh_3)_4$ using THF as solvent (Eq. 1). Changing solvent and Pd catalyst were attempted, but all efforts proved to be fruitless.



(1).

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We then attempted a different approach, which was direct allylic alkylation of **10** followed by deallyloxycarbonylation. As outlined in Scheme 5, treatment of **10** in acetone with allyl bromide and K_2CO_3 at 60 °C for 3 h furnished a pair of diastereoisomers **20** in 87% yield, which was subjected to the Pd-catalyzed deallyloxycarbonylation to afford two products **19a** and **19b** in 1:1 ratio. Compounds **19a** and **19b** could be separated with chromatography column and their structure could be assigned by NOE experiments. The cis isomer **19a** was then subjected to RCM reaction with Grubbs second catalyst, affording the ring-closing product (+)-**23** in nearly quantitative yield.

Compound (−)-**23** is a key intermediate in the total synthesis of an anti-influenza neuramidase inhibitor Oseltamivir (Tamiflu) reported by Corey and co-workers (Scheme 6).[16]

With the same approach, [4.2.1] bicyclic system (+)-**24** could be synthesized by easily changing allyl bromide to homoallyl bromide in the alkylation of **10** and then following the same subsequent steps as for the synthesis of (+)-**23**.

Finally, total synthesis of (*R*)-Pyrrolam A[17] has been achieved with this methodology (Scheme 7). RCM precursor (*R*)-**25** was obtained from **12** via simple reduction and acylation with a yield of 60% and then (*R*)-**25** was subjected to RCM reaction catalyzed by 10 mol % of Grubbs second catalyst to give (*R*)-Pyrolam A **26** in 68% isolated yield.

2. Conclusions

In summary, we have developed versatile routes to condensed and transannular ring structures containing pyrrolidine unit. These products may be potential scaffolds for the synthesis of alkaloids of biological and pharmaceutical interests. In addition, (*R*)-Pyrolam A was synthesized enantioselectively, further exhibiting application flexibility of this methodology. Efforts to apply this chemistry to the synthesis of alkaloids of more structural complexity are underway in our laboratory.

3. Experimental section

3.1. General

Cautio : diazo compounds are generally toxic and potentially explosive. They should be handled with care in a well-ventilated fume hood.

*3.1.1. (R)-Allyl 2-diazo-5-((S)-4- ethylphe ylsulfi a ido)-3-oxo-hept-6-e oate (**8**).* To a solution of **6**[18] (193 mg, 1 mmol) in CH_2Cl_2 (25 mL) was added LiHMDS (2 mmol, 1.0 M in hexane) at −78 °C and then **7** (252 mg, _21T309Td[(x0.855-195((2dm[164-m[16-0.855423.2632.48/T

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in a Pyrex tube was irradiated with a 500 W high-pressure Hg lamp with a water-cooled tube inserted into the solvent. The reaction temperature was kept at about 35 °C. The reaction was complete in about 3 h (monitored by IR and TLC). The solution was concentrated under reduced pressure to give the crude product, which was purified by flash chromatography (petroleum ether/ethyl acetate 8:1) to give the diastereomeric mixture of the corresponding 3-allyloxycarbonyl-2-oxo pyrrolidines **10** (504 mg, yield 60%) as a yellowy oil. The diastereomeric mixture could not be separated by column chromatography. IR (film) 2977, 1786, 1731, 1368, 1298, 1251, 1150, 970, 925 cm^{-1}; ^{1}

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279 (18), 235 (12), 194 (55), 176 (25), 150 (100), 136 (45), 108 (20), 79 (25), 57 (35), 41 (44); HRMS (EI) calcd for $C_{18}H_{25}NO_5$ 335.1733, found 335.1735.

*3.2.5. (5R)-te t-Butyl 3-allyl-2-oxo-5-vi ylpy olidi e-1-ca boxylates (**19a** a d **19b**).* Compound **20** (117 mg, 0.35 mmol) was dissolved in THF (8 mL), and then morpholine (46 mg, 0.524 mmol, 1.5 equiv) and $Pd(PPh_3)_4$ (20 mg, 0.0175 mmol, 5 mol %) were added at room temperature. After the reaction was complete, the solution was concentrated under reduced pressure and purified by flash column chromatography (petroleum ether/ethyl acetate 7:1) to give **19a** (42 mg) and **19b** (41 mg), both as a yellow oil. *Co pou d **19a***: R_f=0.6 (petroleum ether/EtOAc 3:1). IR (film) 2954, 2924, 2853, 1783, 1725, 1458, 1368, 1299, 1255, 1154, 916 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.84–5.70 (m, 2H), 5.23–5.06 (m, 4H), 4.45 (dd, J=9.0, 6.0 Hz, 1H), 2.69–2.53 (m, 2H), 2.39–2.29 (m, 1H), 2.24–2.14 (m, 1H), 1.57–1.52 (m, 1H), 1.50 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.6, 149.9, 138.9, 134.9, 117.2, 115.5, 82.9, 58.6, 42.2, 35.2, 30.2, 27.8; EIMS (/z, relative intensity): 251 (28), 236 (4), 195 (100), 151 (92), 109 (95), 79 (83), 67 (92), 56 (85), 41 (84); HRMS (EI) calcd for $C_{14}H_{21}NO_3$ 251.1521, found 251.1523. $[\alpha]_D^{20}$ −17.1 (*c* 0.96, $CHCl_3$). *Co pou d **19b***: R_f=0.7 (petroleum ether/EtOAc 3:1). IR (film) 2954, 2924, 2845, 1783, 1717, 1461, 1299, 1255, 1154, 912 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.91–5.69 (m, 2H), 5.19–5.05 (m, 4H), 4.62–4.57 (m, 1H), 2.72–2.60 (m, 2H), 2.23–2.12 (m, 1H), 2.01–1.86 (m, 2H), 1.50 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.0, 149.7, 136.3, 134.8, 117.2, 115.1, 82.7, 57.3, 40.7, 34.2, 30.4, 27.8; EIMS (/z, relative intensity): 251 (30), 236 (6), 195 (100), 151 (90), 109 (93), 79 (82), 67 (90), 56 (84), 41 (82); HRMS (EI) calcd for $C_{14}H_{21}NO_3$ 251.1521, found 251.1523; $[\alpha]_D^{20}$ +33.5 (*c* 1.1, $CHCl_3$).

*3.2.6. (1R,5R)-te t-Butyl 7-oxo-6-azabicyclo[3.2.1]oct-3-e e-6-ca boxylate ((+)-**23**)*[16]. Compound **19a** (20 mg, 0.08 mmol) was dissolved in dry CH_2Cl_2 (40 mL) under nitrogen atmosphere. Second generation Grubbs catalyst (1 mg, 1 mol %) was added. The resulting mixture was heated at reflux temperature for 0.5 h (monitored by TLC). The solvent was then evaporated, and the residual oil was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate 5:1) to give the ring-closing product (+)-**23** (18 mg, quant.) as a pale yellow oil. IR (film) 2978, 2929, 1782, 1751, 1707, 1345, 1309, 1252, 1160, 1138, 911, 784, 676 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.34–6.29 (m, 1H), 5.72–5.66 (m, 1H), 4.36–4.33 (m, 1H), 2.85–2.84 (m, 1H), 2.52–2.36 (m, 2H), 2.31–2.24 (m, 1H), 2.00 (dd, J=9, 12 Hz, 1H,), 1.52 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.3, 149.4, 130.7, nit665

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in dry toluene 100 mL under nitrogen atmosphere. The resulting mixture was heated at 80 °C for 12 h (monitored by TLC). The solvent was then evaporated, and the residual oil was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate 1:1) to give the ring-closing product **26** (23 mg, 68% yield) as a white solid. ^{1}H NMR (200 MHz, $CDCl_3$) 7.20 (dd, J=1.7, 5.8 Hz, 1H), 6.04 (dd, J=1.5, 5.7 Hz, 1H), 4.30–4.22 (m, 1H), 3.55–3.41 (m, 1H), 3.33–3.20 (m, 1H), 2.37–2.24 (m, 2H), 2.20–2.04 (m, 1H), 1.23–0.96 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ175.6, 148.7, 128.4, 67.7, 41.8, 29.8, 28.9; $[\alpha]_D^{20}$ −25.9 (*c* 0.7 in $CHCl_3$).

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2009.12.013.

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