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Synthesis of Fused Bicyclic Systems with Nitrogen Atom at the Bridgehead, Including Indolizidines and Quinolizidines

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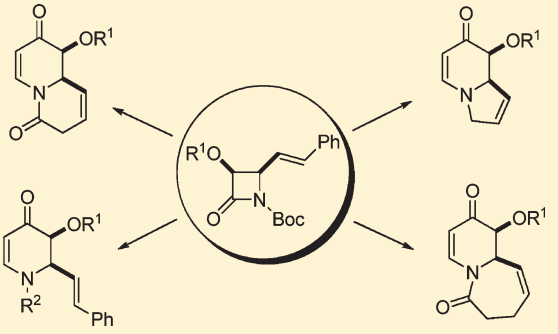
Supporting Information

ABSTRACT: Monocyclic as well as fused bicyclic systems with a nitrogen 10 atom at the bridgehead, including indolizidines and quinolizidines, can be prepared in four steps from *N*-Boc β-lactams. These easily prepared, highly robust, and flexible building blocks allow the incorporation of chirality and structural diversity, rendering the method feasible for diversity- as well as target-oriented synthesis.



Nitrogen-containing heterocycles are a recurrent structural motif in biologically active molecules, including alkaloids such as (−)-swainsonine[1] and quinazolidine (−)-217A, imino sugars such as 1-deoxynojirimycin,[2] and synthetic molecules such as ciprofloxacin (Figure 1).

Synthetic methods that enable the efficient preparation of these ubiquitous scaffolds are the object of continuous research. Our own investigations have focused on the synthesis of nitrogen-containing heterocyclic rings,[3] including β-lactams, and their application to the synthesis of natural products.[4] Furthermore, the paradigm of diversity-oriented synthesis[5] for the preparation of screening libraries has emphasized the need for flexible synthetic strategies that allow for the preparation of a variety of scaffolds from a common intermediate.

We have turned our attention to β-lactams, which for ease of preparation, stability to long-term storage, and selective reactivity are valuable building blocks for the development of more complex molecules.[6]

On the basis of these premises, we have investigated the conversion of β-lactams to 2,3-dihydropyridin-4(1*H*)-ones and their subsequent conversion into fused rings, including indolizidines and quinolizidines. Despite the extensive number of reports on the reactivity of β-lactams, only a few examples include the N_1-C_2 β-lactam opening with carbon nucleophiles,[7] none of which involve alkynyl Grignard reagents.

Herein we report a new method developed for the synthesis of fused ring systems, using β-lactams as building blocks.

In planning the reaction sequence, we hypothesized that, upon treatment with alkynyl magnesium bromide, 3-hydroxy-β-lactams would open to form the corresponding ynones and either cyclize in situ to the desired 3-hydroxydihydropyridone, or be protonated during workup to afford the corresponding amino-ynone. In case the ynone is formed as a stable intermediate, it could then be cyclized to the desired 3-hydroxydihydropyridone via the protocol reported by us before.[3a] This chemistry would enable the preparation of dihydropyridones, which are not readily available through other methods and that carry functional groups that can be used for further conversions.[8] Moreover, the presence of the 3-hydroxyl group is expected to enhance the aqueous solubility of the dihydropyridones and the bicyclic target molecules.

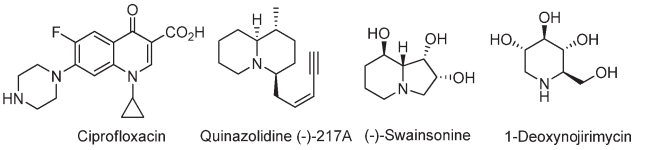


Figure 1. Examples of biologically active molecules with nitrogen-containing heterocycles.

For the design of intermediates **4**, we chose β-lactams that carry a ^{t}Boc group on the nitrogen, to facilitate nucleophilic addition,[7a,9] and that have unsaturated side chains at C-4, to allow for ring-closing metathesis.

The β-lactams **4** were prepared as racemic mixtures through a Staudinger reaction, followed by a series of functional group manipulations, as shown in Scheme 1. β-Lactam esters **1** were hydrolyzed

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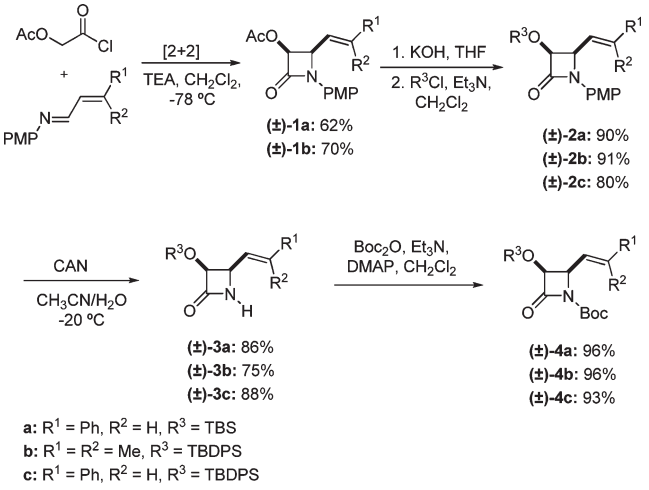
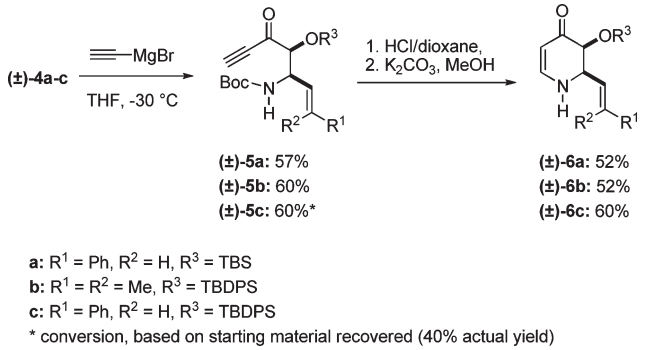
Scheme 1. β-Lactam Preparation



Scheme 2. β-Lactam Ring-Opening and Ynone Cyclization

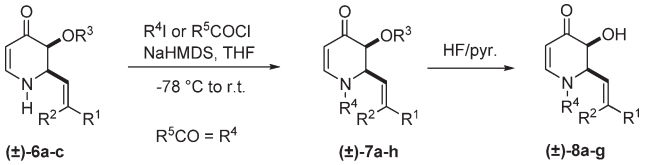


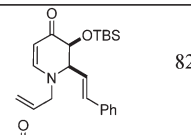
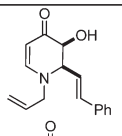
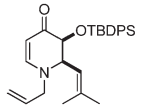
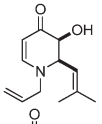
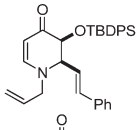
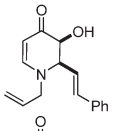
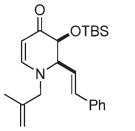
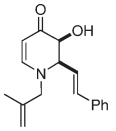
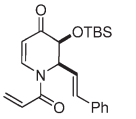
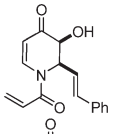
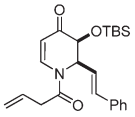
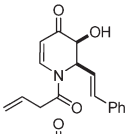
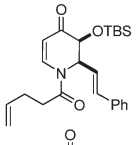
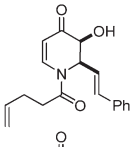
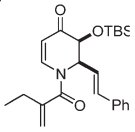
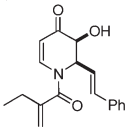
with potassium hydroxide in tetrahydrofuran and reprotected with protecting groups stable to nucleophilic attack by reaction with *tert*-butyldiphenylsilyl chloride or *tert*-butyldimethylsilyl chloride to yield intermediates **2**. The *p*-methoxyphenyl group (PMP) was cleaved with an aqueous solution of cerium ammonium nitrate in acetonitrile at −20 °C. The resulting NH β-lactams **3** were then reprotected with the *tert*-butoxycarbonyl group to yield the desired β-lactams **4**.

Ring-opening of the β-lactam occurred by addition of ethynyl magnesium bromide to a tetrahydrofuran solution of **4**, at −30 °C (Scheme 2). As previously reported by others,[7a] better results were obtained when at least 3 equiv of the Grignard reagent was added quickly. In addition, at temperatures lower than −40 °C, the nucleophilic addition did not proceed, and unaltered starting material was recovered, while at temperatures higher than −20 °C, over-addition was observed.[7a] According to the few published reports of Grignard additions to β-lactams, the yield varies with the size of the organometallic reagent, and is lower when Grignard reagents generated from primary alkyl halides are used.

The ynones resulting from the β-lactam ring-opening of intermediates **5** were cyclized to the corresponding dihydropyridones, following our published protocol.[3a] Slightly improved yields were observed when the hydroxyl group was protected as the more stable *tert*-butyldiphenylsilyl group. Studies toward further optimization of the cyclization reaction are currently ongoing in our laboratories.

Table 1. *N*-Functionalization and Hydroxyl Deprotection



N°	product 7	yield (%)	N°	product 8	yield (%)
7a		82	**8a**		76
7b		70	**8b**		75
7c		86	**8a**		90
7d		98[a]	**8c**		78
7e		51	**8d**		0[b]
7f		50	**8e**		70
7g		94	**8f**		82
7h		64	**8g**		89

[a] On the basis of recovered starting material, 30% actual yield. [b] No product isolated, decomposition occurred.

With dihydropyridones **6** in hand, the nitrogen was functionalized with different unsaturated alkyl chains, from allyl to pentenoyl, with generally good yields (Table 1). The modest yields observed for **7d**, **7e**, **7f**, and **7h** are probably due to the unfavorable $A^{(1,3)}$ strain with the adjacent alkyl chain.

The silyl-protected dihydropyridones were subsequently treated with HF/pyridine in a mixture of acetonitrile and pyridine to afford the corresponding alcohols **8**. These reaction conditions were quite general, apart from **8d**. In this case no product was isolated and decomposition of the starting material was observed.

The subsequently performed ring-closing metathesis reactions proceeded in good yield after some optimization, as shown in Table 2.

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We started our investigations with *N*-allyl dihydropyridones **7c** and **8a**, and the more reactive second-generation Grubbs catalyst, which is reported to successfully catalyze the cyclization of small rings when the first-generation catalyst fails.[10] We also investigated the use of catalytic amounts of $Ti(O^iPr)_4$ as Lewis acid, which was successfully applied to the cyclization of diallyl amines.[11] The Lewis acid is expected to complex to the amino group and avoid poisoning the catalyst.[11a] We verified that the Lewis acid is not required. In our case, the nucleophilicity of the nitrogen is attenuated by being part of a vinylogous amide and therefore the ring-closing metathesis was successfully achieved in toluene, at room temperature using the Grubbs II catalyst to furnish **9b** from **7c** and **9c** from **8a** in 89% and 87% yield, respectively. All reactions were stirred for about 2 h, and when no product was observed the reaction was stirred for as long as 24 h.

The same conditions were then applied to the other substrates (Table 3) and several fused ring systems were synthesized in good yields, including indolizidines, quinolizidines, and pyridoazepines. The presence of a silyl or a benzoyl on the hydroxyl group did not influence the outcome of the cyclization (**9a**, **9c** and **9g**, **9h**). Dihydropyridones with different C-2 olefins could be cyclized in good yields (conversion of **7b** and **7c** to **9b**). The substitution of the nitrogen was critical for the ring-closing metathesis, as demonstrated by lack of reactivity of **7d**, **7e**, and **7h** to form **9d**, **9e**, and **9i**, respectively. With these substrates, the cyclization did not occur, and when the temperature was increased, decomposition of the starting material was observed.

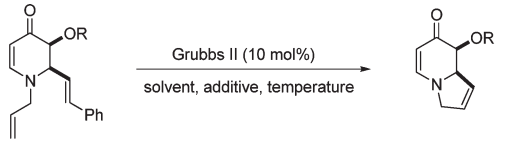
Although dihydropyridones have been used as synthons for the preparation of complex molecules for over a decade, no reports are available on the ring-closing metathesis of these substrates with side chains pendant on the nitrogen and the adjacent carbon.

In conclusion, we have developed an efficient protocol for the preparation of fused bicyclic systems with a nitrogen at the bridgehead. The easily accessible *N*-Boc-β-lactams are converted to the 3-hydroxyl-2,3-dihydropyridones in a two-step sequence and then are further functionalized and cyclized to indolizidine, quinolizidine, or pyridoazepine ring systems.

EXPERIMENTAL SECTION

Synthesis of *tert*-Butyl (3*R,4*S**,*E*)-4-(*tert*-Butyldimethylsilyloxy)-5-oxo-1-phenylhept-1-en-6-yn-3-ylcarbamate (5a).** A solution of **4a** (2.00 g, 4.96 mmol) in dry THF (15 mL) was cooled to −40 °C (external temperature). A 0.5 M solution of ethynylmagnesium bromide in THF (29.7 mL, 14.9 mmol) was added. The reaction was stirred at −40 °C for 7 h and then was quenched by addition of a saturated aqueous solution of NH_4Cl. The aqueous layer was extracted with ethyl acetate, and the

Table 2. Ring-Closing Metathesis Screening

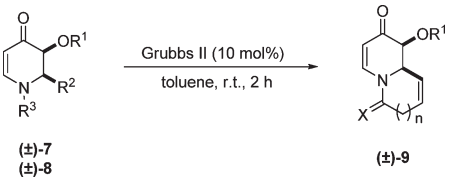


(±)-**7c**: R = TBDPS
(±)-**8a**: R = H

(±)-**9b**: R = TBDPS
(±)-**9c**: R = H

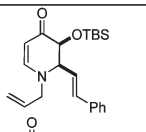
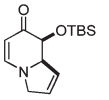
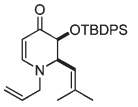
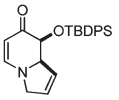
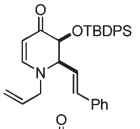
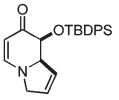
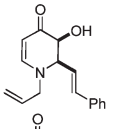
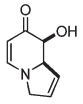
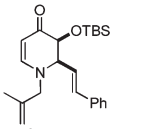
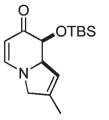
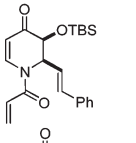
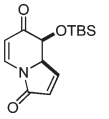
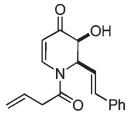
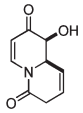
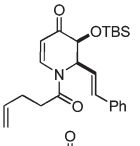
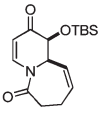
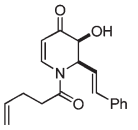
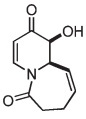
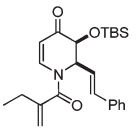
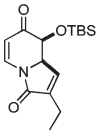
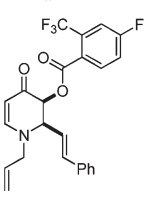
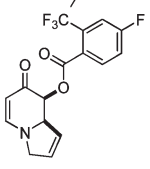
solvent	R	additive	temp (°C)	yield (%)
CH_2Cl_2	TBDPS	$Ti(O^iPr)_4$	40	50
CH_2Cl_2	H	$Ti(O^iPr)_4$	40	0
CH_2Cl_2	H	none	40	0
CH_2Cl_2	H	none	rt	0
toluene	TBDPS	none	rt	89
toluene	H	none	rt	87

Table 3. Ring-Closing Metathesis



(±)-**7**
(±)-**8**

(±)-**9**

	substrate	product		yield (%)
7a			**9a**	98
7b			**9b**	89
7c			**9b**	89
8a			**9c**	87
7d			**9d**	0
7e			**9e**	0 Grubbs I, Grubbs II, and Hoveyda
8e			**9f**	50
7g			**9g**	74
8f			**9h**	98
7h			**9i**	0
8h			**9j**	98

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combined organic layers were treated with brine and anhydrous Na_2SO_4. After evaporation of the solvent, the crude was purified by silica gel flash column chromatography with a mixture of ethyl acetate in hexanes 5% to 20%, to afford 1.22 g (2.84 mmol, 57% yield) of the title compound as a colorless solid. This molecule presents rotamers at room temperature as well as at 40 °C in the NMR spectra. ^{1}H NMR (400 MHz, 40 °C, $CDCl_3$) δ 7.35−7.25 (m, 5H), 6.47 (d, J = 16 Hz, 1H), 6.02 (dd, J = 16, 6 Hz, 1H), 4.86 (m 2H), 4.23 (br s, 1H), 3.28 (s, 1H), 1.32 (s, 9H), 0.81 (s, 9H), −0.08 (s, 3H), 0.12 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.8, 165.7, 154.9, 148.0, 136.4, 136.3, 136.1, 131.8, 128.6, 128.5, 128.1, 127.7, 126.8, 126.6, 126.4, 122.7, 83.2, 82.6, 80.9, 80.1, 79.8, 77.6, 60.9, 55.1, 28.3, 28.0, 25.7, 25.5, 18.3, −4.7, −5.2. IR (thin film) ν 3445, 3219, 2955, 2930, 2887, 2858, 2092, 1810, 1699, 1489, 1366, 1254. HRMS (ESI$^+$) calcd for $C_{24}H_{35}NNaO_4Si$ $[M + Na]^+$ 452.2228, found 452.2236.

(2*R,3*S**)-3-(*tert*-Butyldimethylsilyloxy)-2-styryl-2,3-dihydropyridin-4(1*H*)-one (6a).** Ynone **5a** (140 mg, 0.32 mmol) was dissolved in a 4 M solution of HCl in dioxane (3.0 mL) under inert atmosphere at 0 °C (ice/water bath). The reaction mixture was stirred for 4 h and the conversion was monitored by TLC. Upon disappearance of the starting material, the solvent was evaporated under reduced pressure. Then HPLC-grade methanol (15 mL) and solid K_2CO_3 (45 mg) were added to the HCl salt. The reaction was stirred at room temperature for 15 min. Then, CH_2Cl_2 was added to the reaction mixture, and the K_2CO_3 was filtered off over Celite. The solvent was evaporated under reduced pressure. The residue was purified by flash silica gel column chromatography, using a mixture of hexanes and ethyl acetate from 3:1 to 1:1, to afford 54 mg (52%) of the desired product as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40−7.20 (m, 5H), 7.16 (dd, J = 7.2, 7 Hz, 1H), 6.66 (d, J = 16 Hz, 1H), 6.41 (dd, J = 8, 16 Hz, 1H), 5.34 (dd, J = 1.6, 8 Hz, 1H), 4.98 (m, 1H), 4.20 (m, 1H), 3.95 (d, J = 3.8 Hz, 1H), 0.89 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.5, 149.6, 136.0, 134.4, 134.3, 128.7, 128.2, 126.5, 123.7, 97.1, 73.5, 61.3, 25.7, 18.5, −4.59, −5.15. HRMS (ESI$^+$) calcd for $C_{19}H_{27}NNaO_2Si$ $[M + Na]^+$ 352.1709, found 352.1700.

Synthesis of (8*S,8a*R**)-8-(*tert*-Butyldimethylsilyloxy)-8,8a-dihydroindolizin-7(3*H*)-one (9a).** Under an N_2 atmosphere **7a** (75.0 mg, 0.203 mmol) was dissolved in anhydrous toluene (60.0 mL) that had been degassed with nitrogen gas for 1 h, and then a toluene solution of Grubbs' II catalyst in CH_2Cl_2 (5 mL) was added dropwise. The reaction mixture was stirred at room temperature for 2 h, and then a few drops of DMSO were added to the reaction mixture and the reaction was stirred overnight. The solvent was evaporated under reduced pressure, and the crude product was purified by silica gel flash column chromatography by using a mixture of hexanes and ethyl acetate (3:1 to 1:1) to yield 53 mg (98%) of the title compounds as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, J = 7.6 Hz, 1H), 5.95 (m, 1H), 5.76 (d, J = 6.5 Hz, 1H), 4.96 (dd, J = 7.0, 1.3 Hz, 1H), 4.60 (br, 1H), 4.37 (ddd, J = 14.7, 4.5, 2.3 Hz, 1H), 4.21 (ddt, J = 14.6, 4.3, 2.1 Hz, 1H), 3.70 (m, 1H), 0.81 (s, 9H), 0.08 (s, 3H), 0.04 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.7, 149.1, 127.4, 126.5, 95.8, 70.6, 69.3, 56.27, 25.6, 18.1, −4.77, −5.20. IR (thin film) ν 2954, 2928, 2857, 1635, 1616, 1568, 1462, 1362, 1251. HRMS (FAB$^+$) calcd for $C_{14}H_{23}NNaO_2Si$ $[M + Na]^+$ 288.1396, found 288.1397.

■ ASSOCIATED CONTENT

Supporting Information. General experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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