Dual Behavior of 2-Azetidinone-Tethered Arylimines as Azadienophiles or Azadienes. Application to the Asymmetric Synthesis of Indolizidine-Type Systems

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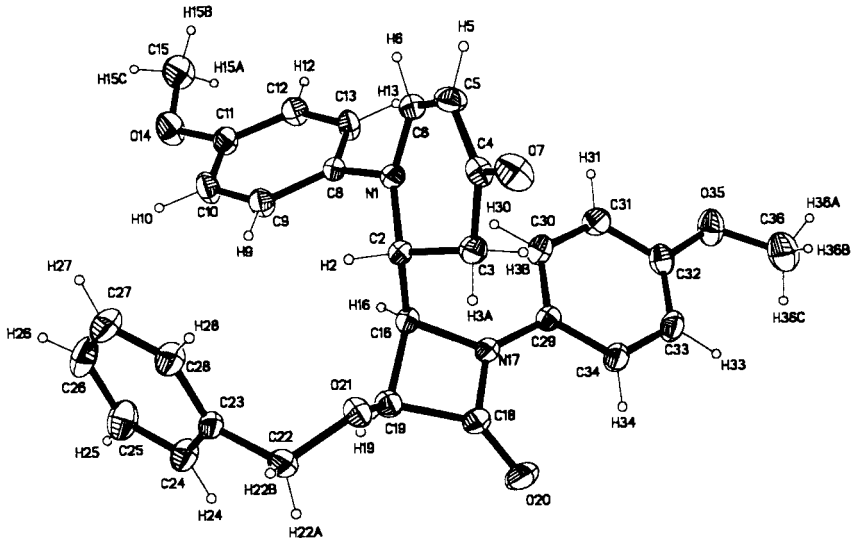
Abstract: The first methodology to prepare indolizidine systems directly from β-lactams has been developed. This process involves the amide bond cleavage of the β-lactam ring in the aza Diels–Alder cycloadducts with concomitant cyclization. Indolizidinone precursors arise from normal, as well as inverse electron-demand condensation involving the C=N moiety of 2-azetidinone-tethered imines as the dienophile or the heterodiene contributor.

Key words: lactams, aza Diels–Alder cycloaddition, rearrangement, indolizidines, asymmetric synthesis

The hetero Diels–Alder reaction involving imino-dienes or imino-dienophiles is widely used for the construction of nitrogen containing compounds, particularly for the preparation of piperidine and tetrahydroquinolidine derivatives.[1] Indolizidine alkaloids have recently attracted a lot of synthetic attention[2] due to their widespread occurrence and their diverse and potent biological activities.[3] In addition, functionalized bicyclic lactams structurally related to indolizidine have been discovered as conformationally restricted peptide mimetics.[4] On the other hand, the importance of 2-azetidinones as synthetic intermediates has been widely recognized in organic synthesis.[5] Despite the versatility of the 2-azetidinone ring,[6] there is no information available on the use of β-lactams as chiral synthons for the synthesis of indolizidine alkaloids. Our interest in the use of 4-oxoazetidine-2-carbaldehydes as substrates for addition reactions and cyclization processes,[7] prompted us to evaluate the combination of the aza-Diels–Alder reaction of 2-azetidinone-tethered imines with rearrangement reactions on the 2-azetidinone ring as a route to complex indolizidine alkaloids. We report herein our preliminary results for the synthesis of different kinds of highly functionalized bi- and tetracyclic indolizidine systems using β-lactams as chiral building blocks.



Figure

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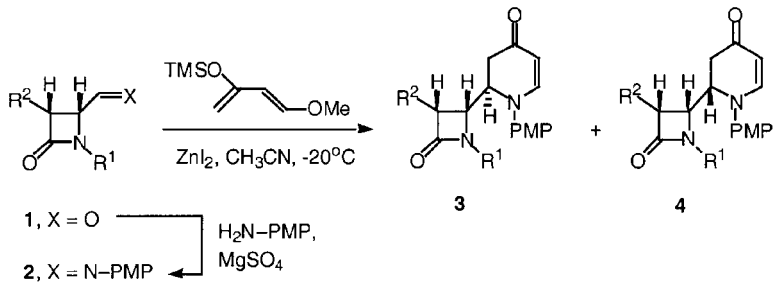
Table Zinc Iodide-Mediated Diels–Alder Cycloaddition between 2-Azetidinone-Tethered Imines and Danishefsky's Diene



Aldehyde	R^1	R^2	Imine	Yield (%)[a]	Cycloadducts	Ratio **3**:**4**[b]	Yield **3**:**4** (%)[a]
1a	PMP	Ph	**2a**	95	**3a**/**4a**	66:34	49/25
1b	PMP	BnO	**2b**	90	**3b**/**4b**	60:40	45/30
(+)-**1c**	PMP	PhO	(+)-**2c**	95	(+)-**3c**/(+)-**4c**	69:31	36/16
(+)-**1d**	Tol	MeO	(+)-**2d**	75	(+)-**3d**/(+)-**4d**	75:25	43/14

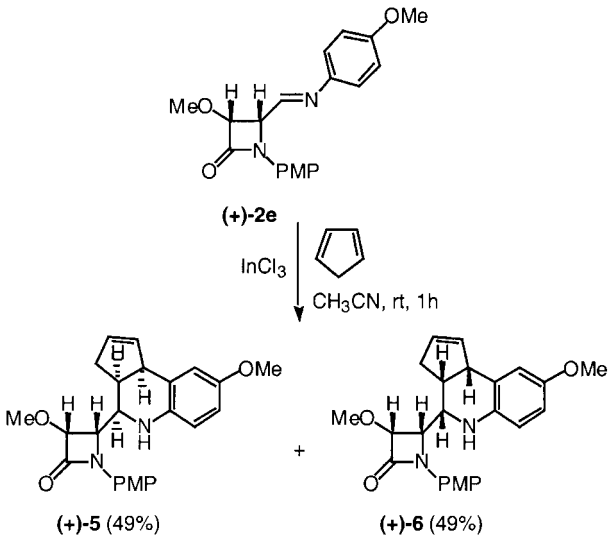
[a] Yield of pure, isolated product with correct analytical and spectral data. PMP = 4-$MeOC_6H_4$. Tol = 4-MeC_6H_4.
[b] The ratio was determined by integration of well-resolved signals in the ^1H NMR spectra of the crude reaction mixtures before purification.

The starting 4-oxoazetidine-2-carbaldehydes **1** were prepared using our methodology reported previously.[7] The requisite cycloadduct precursors, 2-azetidinone-tethered imines **2**, were smoothly prepared by condensation of aldehydes **1** with *p*-anisidine in dichloromethane at r.t. in the presence of magnesium sulfate. Imines **2** were purified by chromatography and obtained in good yields. Importantly, the β-lactam ring stereochemistry was unaffected by this process.

We then used 2-azetidinone-tethered imines **2** as dienophiles by reacting them with 1-methoxy-3-trimethylsilyloxy-1,3-butadiene (Danishefsky's diene). Cycloaddition took place at low temperature under Lewis acid catalysis (zinc iodide, 20 mol%) and gave rise to mixtures of cycloadducts **3** and **4** with modest diastereoselectivity (Table). Fortunately, in all cases the diastereomeric cycloadducts **3** and **4** were easily separated by gravity flow chromatography. Other tested Lewis acids, such as boron trifluoride diethyl etherate and hafnium chloride were less effective to activate the imine.

The structure of the minor product from the reaction with imine **2b** was confirmed by X-ray diffraction. The Figure shows a projection of the minor product **4b** as determined by X-ray crystallography.[8]

Our next aim was to study the reactivity of **2** with less electron rich dienes. Zinc iodide promoted the reaction between imine (+)-**2e** and cyclopentadiene to give poor yield, of an isomeric mixture of cycloadducts (+)-**5** and (+)-**6**. Indium-mediated reactions have emerged as an useful tool in organic synthesis.[9] In particular, it was found that trivalent organoindium reagents can be useful in imino Diels–Alder reactions.[10] Thus, indium trichloride-catalysed (20 mol%) reaction between the 2-azetidinone-tethered imine (+)-**2e** and cyclopentadiene proceeded smoothly at room temperature, to afford the derivatives

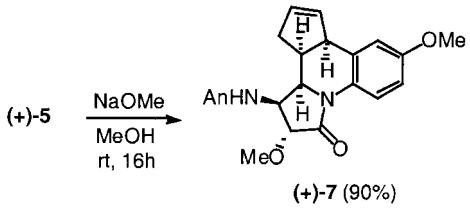


Scheme 1

(+)-**5** and (+)-**6** (1:1 mixture) in an excellent 98% yield (Scheme 1). Again, cycloadducts (+)-**5** and (+)-**6** were easily separable by chromatography. Interestingly, the dienophilic behavior of the imine in the Diels–Alder reaction was reversed to exhibit heterodienic properties.[10] The cycloaddition did not take place with electron poor dienophiles such as 2-cyclohexen-1-one or methyl acrylate, but it proceeded with 2,3-dimethyl-1,3-butadiene and 3,4-dihydro-2*H*-pyran. This confirmed that an inverse electron-demand Diels–Alder reaction was involved. This iminodiene behavior is known for arylimines derived from aromatic or α,β-unsaturated aldehydes,[10,11] but the use of chiral imines as the 4π component in which the chiral matrix is an aliphatic aldehyde is unrecorded.[12] Furthermore,

to the best of our knowledge, the dual behavior of aliphatic aldehyde-derived imines both as imino-diene as well as dienophile is unprecedented.

A common and relevant feature of some indolizidines, which act as glycosidase inhibitors, is the presence of a vicinal amino-alcohol or -alkoxy functionality.[13] In this context, transformation of adduct (+)-**5** into fused tetracycle (+)-**7** was directly effected via a sodium methoxide rearrangement reaction. After aqeous work-up (+)-**7** was obtained in high yield (90%) in high purity without further purification (Scheme 2).[14]



Scheme 2

Cycloadducts (+)-**3** and (+)-**4** require further manipulation to obtain the desired alkaloid system. Thus, the dihydropyridone (+)-**4d** underwent sequential reduction of the alkene and carbonyl moieties to give the corresponding alcohol as a single isomer, whose configuration of at C-4 was established by comparison of the ^{1}H NMR chemical shifts of its acetyl mandelates. Protection of the hydroxyl group followed by oxidative cleavage of the *N*-4-methoxyphenyl substituent provided the key intermediate piperidinyl-β-lactam (–)-**8**. When substrate (–)-**8** was submitted to sodium methoxide treatment, bicyclic indolizidine lactam (+)-**9** was cleanly obtained without byproducts in quantitative yield (Scheme 3).[14]

The transformation of piperidinyl-2-azetidinones into indolizidine derivatives involves the amide bond cleavage of the β-lactam ring, followed by cyclization of the resulting amino ester with concomitant ring expansion. The polycyclic structures (by DEPT, HETCOR, and COSY) and the stereochemistry (by vicinal proton couplings and NOE experiments) of indolizidinones (+)-**7**, and (–)-**9** were established by NMR one- and two-dimensional techniques.

In conclusion, we have developed the first synthesis of indolizidines directly from β-lactams. 2-Azetidinone-tethered arylimines function both as heterodienes and dienophiles in the [4+2] imino Diels–Alder reaction to afford different types of cycloadducts, which after rearrangement serve as valuable chiral intermediates for different indolizidinones. The scope and limitations of the present work are underway and will be reported in due course.

Acknowledgement

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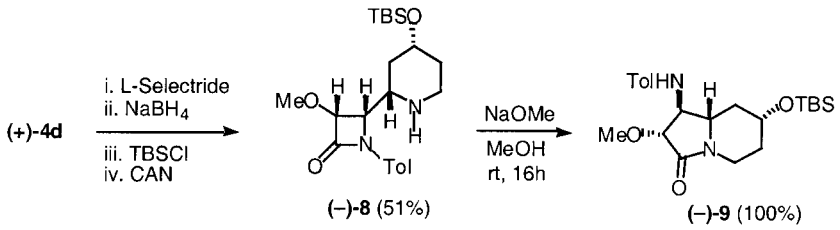

Scheme 3

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(8) X-ray data of **4b**: crystallized from ethyl acetate/*n*-hexane at 20 °C; $C_{29}H_{28}N_2O_5$ (M_r = 484.53); monoclinic; space group = P2(1)/c; a = 9.6518(9)Å, b = 10.2323(9)Å; c = 25.376(2)Å; β = 97.816(2)°; V = 2482.9(4)Å^3; Z = 4; ρ_{calcd} = 1.296 mg m^{-3}; μ = 0.089 mm^{-1}; F(000) = 1024. A transparent crystal of 0.11 · 0.25 · 0.25 mm^3 was used. 6050 independent reflections were collected on a Bruker Smart CCD difractomer. The structure was solved by direct methods and Fourier synthesis. The refinement was done by full matrix least-squares procedures on F^2 (SHELXTL version 5.1). The non-hydrogen atoms were refined anisotropically. The hydrogen atoms were refined the coordinates only. Further crystallographic details for the structure reported in this paper may be obtained from the Cambridge Crystallographic Data Centre, on quoting the depository number CCDC-163979.

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(14) Compounds (+)-**7** and (–)-**9** showed a single set of signals in their ^{1}H NMR spectra, thus proving that these transformations proceeded without detectable racemization. All new compounds were fully characterized by spectroscopic methods and microanalysis and/or HRMS.

General Procedure for the Rearrangement Reaction. Sodium methoxide (108.3 mg, 2.0 mmol) was added in portions at r.t. to a solution of the appropriate piperidinyl-β-lactam (0.50 mmol) in methanol (10 mL). The reaction was stirred for 16 h and then water was added (1 mL). The solution was concentrated under reduced pressure, the aqueous residue was extracted with ethyl acetate (10 × 3 mL), and the organic layer was dried over $MgSO_4$. Then, the solvent was removed under reduced pressure to give analytically pure indolizidine derivatives. Selected data:

Fused Indolizidinone (+)-7. From 93 mg (0.229 mmol)of the cycloadduct (+)-**5**, 83 mg (90%) of compound (+)-**7** was obtained as a pale brown oil. $[\alpha]_D$ = +44.6 (*c* 0.9, $CHCl_3$). ^{1}H NMR (300 MHz, C_6D_6): δ 2.07 (ddq, 1 H, *J* = 18.8, 16.2, 1.4 Hz), 2.66 (m, 1 H), 2.72 (qd, 1 H, *J* = 8.9, 3.4 Hz), 3.20 (m, 1 H), 3.39 and 3.49 (s, each 3 H), 3.68 (m, 2 H), 3.79 (s, 3 H), 3.84 (t, 1 H, *J* = 6.5 Hz), 5.42 (m, 1 H), 5.67 (m, 1 H), 6.73 (m, 2 H), 6.80 and 6.93 (m, each 2 H), 9.09 (d, 1 H, *J* = 9.0 Hz). ^{13}C NMR (75 MHz, C_6D_6): δ 169.5, 156.8, 143.6, 141.3, 133.6, 131.4, 130.2, 129.1, 121.6, 115.8, 115.2, 114.3, 111.7, 85.0, 60.7, 59.1, 58.4, 55.2, 54.9, 46.2, 40.9, 31.8. IR ($CHCl_3$, cm^{-1}): 3330, 1730. MS (EI), *m/z*: 406 (M^+, 100). (Anal. calcd. for $C_{24}H_{26}N_2O_4$: C, 70.92; H, 6.45; N, 6.89. Found: C, 70.99; H, 6.47; N, 6.86).

Indolizidinone (–)-9. From 45 mg (0.107 mmol)of the piperidinyl-β-lactam (–)-**8**, 45 mg (100%) of compound (–)-**9** was obtained as a pale brown oil. $[\alpha]_D$ = –12.5 (*c* 0.9, $CHCl_3$). ^{1}H NMR (300 MHz, CD_3OD): δ 0.04 and 0.06 (s, each 3 H), 0.86 (s, 9 H), 1.30 (m, 4 H), 1.88 and 2.14 (m, each 1 H), 2.19 (s, 3 H), 2.74 (td, 1 H, *J* = 13.2, 2.2 Hz), 3.24 (m, 2 H), 3.52 (s, 3 H), 3.69 (dd, 1 H, *J* = 6.6, 6.1 Hz), 3.83 (dd, 1 H, *J* = 6.1, 1.2 Hz), 4.06 (ddd, 1 H, *J* = 13.4, 5.1, 1.7 Hz), 6.66 and 6.95 (m, each 2 H). ^{13}C NMR (75 MHz, CD_3OD): δ 172.0, 146.7, 130.9, 128.6, 115.6, 85.7, 70.0, 62.8, 60.1, 59.6, 42.8, 38.7, 35.2, 26.4, 20.8, 19.0. IR ($CHCl_3$, cm^{-1}): 3335, 1734. MS (CI), *m/z*: 377 (M^+ +1, 100), 376 (M^+, 44). (Anal. calcd. for $C_{22}H_{36}N_2O_3$: C, 70.18; H, 9.64; N, 7.44. Found: C, 70.24; H, 9.63; N, 7.40).