Useful Dual Diels–Alder Behavior of 2-Azetidinone-Tethered Aryl Imines as Azadienophiles or Azadienes: A β-Lactam-Based Stereocontrolled Access to Optically Pure Highly Functionalized Indolizidine Systems

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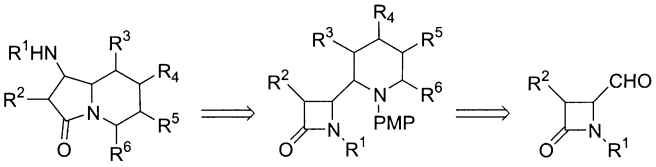
Abstract: Imines derived from 4-oxoazetidine-2-carbaldehydes have been found to be versatile Diels–Alder reagents in that they exhibit two reactivity patterns. 2-Azetidinone-tethered imines undergo diastereoselective reaction with Danishefsky's diene in the presence of different Lewis acids. The effect of the amount of catalyst on the conversion rate as well as on the product ratio has been studied. Under standard reaction conditions, indium(III) chloride and zinc(II) iodide provided the best yields, and indium(III) triflate the highest diastereoselectivity in the Lewis acid promoted aza-Diels–Alder cycloaddition. Treatment of the aforementioned imines with cyclopentadiene, 2,3-dimethyl-1,3-butadiene or 3,4-dihydro-2*H*-pyran led to cycloadducts arising from inverse electron-demand condensation involving the β-lactam-tethered aryl imine as the heterodiene component. In addition, the first methodology for preparing indolizidines from β-lactams has been developed. This process involves amide bond cleavage of the β-lactam ring in the aza-Diels–Alder cycloadducts with concomitant cyclization. Full chirality transfer occurs when the reaction is performed with an enantiomerically pure substrate.

Keywords: asymmetric synthesis · cyclization · cycloaddition · lactams · small ring systems

Introduction

Hetero Diels–Alder reactions involving imino-dienes or imino-dienophiles are widely used for the construction of nitrogen-containing compounds.[1] Indolizidine alkaloids have recently attracted a lot of attention due to their widespread occurrence and their utility as research tools in pharmacology. Their structural and stereochemical complexity, coupled with their diverse and potent biological activities,[2] makes indolizidine alkaloids as well as related non-natural compounds very attractive synthetic targets in the search for efficient and selective synthetic methods.[3] In addition, functionalized bicyclic lactams structurally related to indolizidine have been found to act as conformationally restricted peptide mimetics,[4] and they have been utilized in asymmetric synthesis leading to natural products.[5] On the other hand, the importance of 2-azetidinones as synthetic intermediates has been widely recognized in organic synthesis.[6]–[8] Despite the versatility of the 2-azetidinone ring,[9] there is no information available on the use of β-lactams as chiral synthons for the synthesis of indolizidine alkaloids.[10] Our interest in the use of carbonyl β-lactams as starting substrates for the preparation of potentially bioactive products[11] 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 (Scheme 1). We report herein full details of the asymmetric synthesis of different kinds of highly functionalized bi-, tri-, and tetracyclic indolizidine systems using β-lactams as chiral building blocks.



Scheme 1. Retrosynthetic analysis of indolizidine-type systems from 4-oxoazetidine-2-carbaldehydes.

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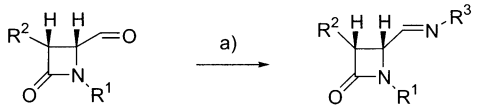
Supporting information for this article is available on the www under http://www.chemeurj.org/ or from the author.

 DOI: 10.1002/chem.200304712

Results and Discussion

Starting substrates, 4-oxoazetidine-2-carbaldehydes **1a–g**, were prepared both in the racemic form and in optically pure form by using standard methodology. Racemic compounds **1a–c** were obtained as single *cis* diastereoisomers, following our one-pot method from *N*,*N*-di-(*p*-methoxyphenyl)glyoxal diimine.[12] Enantiopure 2-azetidinones **1c–g** were obtained as single *cis* enantiomers from imines of (*R*)-2,3-*O*-isopropylideneglyceraldehyde, through Staudinger reaction with the appropriate alkoxyacetyl chloride in the presence of Et_3N, followed by sequential acidic acetonide hydrolysis and oxidative cleavage.[11b] Treatment of aldehydes **1** with *p*-anisidine or benzylamine at room temperature in the presence of magnesium sulfate provided the corresponding imines **2** (Scheme 2). Aldimines **2** were amenable to purification by flash chromatography and were obtained in good yields. Importantly, the β-lactam ring stereochemistry was unaffected by this process.



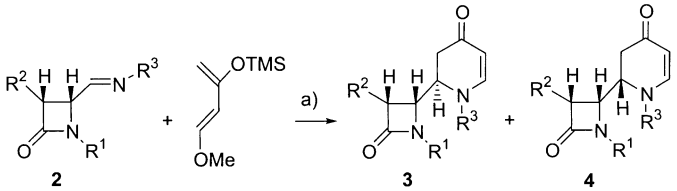
(±)-1a R^1 = PMP, R^2 = Ph — **(±)-2a** R^3 = PMP (95%)
(±)-1a R^1 = PMP, R^2 = Ph — **(±)-2b** R^3 = Bn (85%)
(±)-1b R^1 = PMP, R^2 = Pht — **(±)-2c** R^3 = PMP (80%)
(±)-1c R^1 = PMP, R^2 = BnO — **(±)-2d** R^3 = PMP (75%)
(+)-1c R^1 = PMP, R^2 = BnO — **(+)-2e** R^3 = Bn (64%)
(+)-1d R^1 = PMP, R^2 = PhO — **(–)-2f** R^3 = PMP (95%)
(+)-1e R^1 = PMP, R^2 = MeO — **(+)-2g** R^3 = PMP (95%)
(+)-1f R^1 = Tol, R^2 = MeO — **(+)-2h** R^3 = PMP (75%)
(+)-1g R^1 = allyl, R^2 = MeO — **(+)-2i** R^3 = PMP (100%)

PMP = 4-$MeOC_6H_4$; Pht = phthalimido; Tol = 4-MeC_6H_4

Scheme 2. Preparation of 2-azetidinone-tethered imines **2a–i**. Reagents and conditions: a) R^3NH_2, $MgSO_4$, dichloromethane, room temperature.

Abstract in Spanish: *Se ha descubierto que las iminas derivadas de 4-oxoazetidin-2-carbaldehidos son unos reactivos muy versátiles en la reacción de Diels–Alder al presentar dos modos diferentes de reactividad. Estas iminas, por tratamiento con el dieno de Danishefsky dan una reacción aza-Diels–Alder catalizada por ácidos de Lewis. Se llevó a cabo un estudio exhaustivo sobre el efecto del catalizador ácido de Lewis. Los mejores rendimientos en la reacción de aza-Diels–Alder se obtuvieron utilizando cloruro de indio(III) o yoduro de cinc(II), mientras que la mejor diastereoselectividad se logró con triflato de indio(III). Cabe destacar, que las iminas β-lactámicas por reacción con ciclopentadieno, 2,3-dimetil-1,3-butadieno o 3,4-dihidro-2 H-pirano experimentan una cicloadición de demanda electrónica inversa, comportándose ahora el componente imínico como heterodieno. Además, se describe la primera metodología para la preparación de indolizidinas a partir de β-lactamas. Este proceso implica la ruptura del enlace amida en el anillo de β-lactama y su ciclación posterior. Cuando se utilizaron sustratos enantioméricamente puros la transferencia de quiralidad fue total, permitiendo una síntesis asimétrica.*

Because 1-methoxy-3-trimethylsilyloxy-1,3-butadiene (Danishefsky's diene) is among the best dienes traditionally used in Diels–Alder reactions, we decided to attempt the use of 2-azetidinone-tethered imines **2** as dienophiles. First, we studied the aza-Diels–Alder reaction of aldimine (−)-**2f** with Danishefsky's diene in the presence of various catalysts. The cycloaddition took place at low temperature under Lewis acid catalysis. Diastereoselectivities were generally reasonable, in all cases giving rise to mixtures of cycloadducts (+)-**3f** and (+)-**4f**, but the chemical yield of the process proved to be a function of the nature of the Lewis acid (Scheme 3, Table 1).



2 **3** **4**

Scheme 3. Lewis acid mediated Diels–Alder cycloaddition between 2-azetidinone-tethered imines and Danishefsky's diene. Reagents and conditions: a) Lewis acid, acetonitrile, −20 °C.

These results show that under standard reaction conditions, zinc(II) iodide (Table 1, entries 1 and 2) and indium(III) chloride (Table 1, entries 3 and 4) provided the best yields, and indium(III) triflate (Table 1, entry 6) the highest diastereoselectivity in the Lewis acid promoted aza-Diels–Alder cycloaddition. The use of boron trifluoride diethyl etherate or tin(IV) chloride resulted in a sluggish reaction, leading mainly to decomposition products (Table 1, entries 9 and 10). The effect of the amount of catalyst on the conversion rate as well as on the product ratio was studied, and it was found that the efficiency of the process did not increase on increasing the amount of catalyst. On the basis of these results, we chose to use zinc(II) iodide (20 mol%) in our study with different substituted 2-azetidinone-tethered imines **2**. The effect of altering the reaction solvent (acetonitrile, tetrahydrofuran, diethyl ether or dichloromethane) was then explored. No significant solvent effect on the diastereoselectivity was observed, but the reaction proceeded more quickly in polar solvents. In terms of achieving good yields with a reasonable rate of reaction, acetonitrile seemed to be the solvent of choice for this reaction. Reaction of aldimines **2** with Danishefsky's diene in acetonitrile at −20 °C in the presence of zinc(II) iodide gave cycloadducts **3** and **4** with moderate to good *anti* stereoselectivities (*de* 20–100%, by integration of well-resolved signals in the ^1H NMR spectra of the crude reaction mixtures before purification) (Table 1). Fortunately, in all cases, the diastereomeric tetrahydropyridin-4-ones **3** and **4** could be easily separated by gravity flow chromatography.

The vicinal coupling constants of the two protons (H4 in the β-lactamic ring, hydrogen α to the nitrogen in the six-membered ring) located at the single bond connecting the two rings were diagnostic of the relative stereochemistry of these stereocenters. The vicinal coupling constants for cycloadducts **3** are approximately 10.0 Hz, which suggests a relative *anti* stereochemistry for this connection, whereas these vicinal coupling constants for the minor isomers **4** are approximately

Table 1. Lewis acid mediated Diels–Alder cycloaddition between 2-azetidinone-tethered imines and Danishefsky's diene.[a]

Entry	Imine	R^1	R^2	R^3	LA (mol%)	t [h]	**3/4** Ratio[b]	Yield **3/4**[c]
1	(−)-**2f**	PMP	PhO	PMP	ZnI_2 (100)	6	(+)-**3f**/(+)-**4f** 75:25	65/22
2	(−)-**2f**	PMP	PhO	PMP	ZnI_2 (20)	6	(+)-**3f**/(+)-**4f** 72:28	61/24
3	(−)-**2f**	PMP	PhO	PMP	$InCl_3$ (100)	2	(+)-**3f**/(+)-**4f** 76:24	62/20
4	(−)-**2f**	PMP	PhO	PMP	$InCl_3$ (20)	2	(+)-**3f**/(+)-**4f** 78:22	63/18
5	(−)-**2f**	PMP	PhO	PMP	$In(TfO)_3$ (100)	2	(+)-**3f**/(+)-**4f** 80:20	33/8
6	(−)-**2f**	PMP	PhO	PMP	$In(TfO)_3$ (20)	2	(+)-**3f**/(+)-**4f** 82:18	33/7
7	(−)-**2f**	PMP	PhO	PMP	$HfCl_4$ (100)	3.5	(+)-**3f**/(+)-**4f** 74:26	49/17
8	(−)-**2f**	PMP	PhO	PMP	$HfCl_4$ (20)	3.5	(+)-**3f**/(+)-**4f** 75:25	49/16
9	(−)-**2f**	PMP	PhO	PMP	$BF_3 \cdot Et_2O$	16		
10	(−)-**2f**	PMP	PhO	PMP	$SnCl_4$	14		
11	(±)-**2a**	PMP	Ph	PMP	ZnI_2 (20)	6	(±)-**3a**/(±)-**4a** 71:29	60/25
12	(±)-**2b**	PMP	Ph	Bn	ZnI_2 (20)	6	(±)-**3b**/(±)-**4b** 100:0	64/0
13	(±)-**2c**	PMP	Pht	PMP	ZnI_2 (20)	6	(±)-**3c**/(±)-**4c** 70:30	34/14
14	(±)-**2d**	PMP	BnO	PMP	ZnI_2 (20)	6	(±)-**3d**/(±)-**4d** 60:40	45/30
15	(+)-**2e**	PMP	BnO	Bn	ZnI_2 (20)	6	(+)-**3e**/(+)-**4e** 70:30	56/24
16	(+)-**2g**	PMP	MeO	PMP	ZnI_2 (20)	6	(+)-**3g**/(+)-**4g** 70:30	57/25
17	(+)-**2h**	Tol	MeO	PMP	ZnI_2 (20)	6	(+)-**3h**/(+)-**4h** 75:25	43/14

[a] PMP = 4-$MeOC_6H_4$. Pht = phthalimido. 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. [c] Yield (%) of pure, isolated product with correct analytical and spectral data.

3.0 Hz, and indicate a relative *syn* stereochemistry. This configurational assignment was confirmed by means of an X-ray diffraction analysis of the cycloadduct (±)-**4d**,[13] which is the minor product from the reaction of imine (±)-**2d** with Danishefsky's diene. The stereochemical course of the reaction can be explained by assuming that the Lewis acid catalyst coordinates to the imine nitrogen and that the β-lactam moiety preferentially adopts an anti-Felkin–Anh conformation, in which the large substituent of the four-membered ring (the amino group) is oriented perpendicular to the imine group. The silyloxydiene should then preferentially attack from the *Re*-side and give the observed major product (Figure 1).[14] The stereoselectivity of the aza-Diels–Alder reaction was found to be dependent on the bulkiness of the N substituents on the imines. Thus, on fixing both substituents at the β-lactam ring (Table 1, entries 11 and 12), when less hindered *N*-benzyl imine (±)-**2b** rather than the *N*-4-methoxyphenyl imine (±)-**2a** was used for cycloadduct formation, fully distereoselective conversion was obtained.

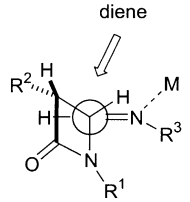
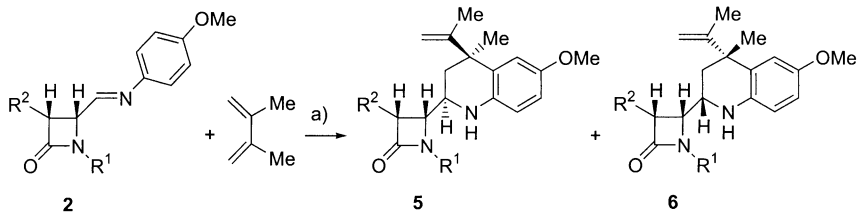


Figure 1. Model showing the origin of the observed *syn* stereochemistry.

We next turned our attention to studying the reactivity of aldimines **2** with less electron-rich dienes. Reaction of 2-azetidinone-tethered imine (−)-**2f** with 2,3-dimethyl-1,3-butadiene in acetonitrile at room temperature in the presence of zinc(II) iodide led to cycloadducts (+)-**5f** and (+)-**6f** as a chromatographically separable mixture (60:40) of two diastereomers (Scheme 4, Table 2) in good yield. Interestingly, the dienophilic behavior of the imine in the Diels–Alder reaction was reversed such that it exhibited heterodienic properties.[15] The cycloaddition did not take place with electron-poor dienophiles such as 2-cyclohexen-1-one or methyl acrylate, confirming that an inverse electron-demand Diels–Alder reaction was involved. This azadiene behavior is well known for aryl imines derived from aromatic or α,β-unsaturated aldehydes,[16] but little is known about the use of aliphatic aldehyde derived-imines as the 4π component,[17] and even less on their optically active derivatives.[18] Furthermore, to the best of our knowledge, the dual behavior of aliphatic aldehyde-derived imines as both azadienes and as dienophiles is unprecedented.



Scheme 4. Lewis acid-mediated Diels–Alder cycloaddition between 2-azetidinone-tethered imines and 2,3-dimethyl-1,3-butadiene. Reagents and conditions: a) Lewis acid, acetonitrile, room temperature.

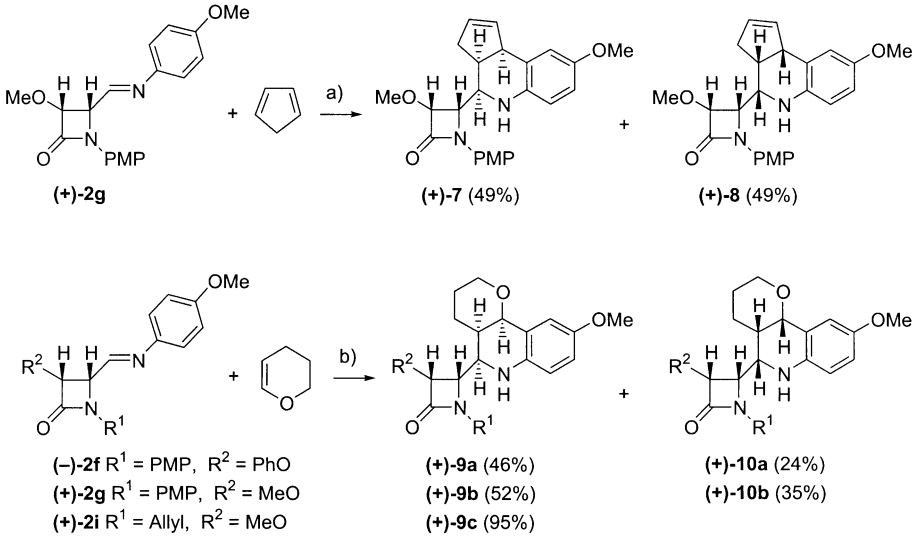
Next, the effect of Lewis acid on the conversion rate and diastereoselectivity was explored. No improvements in stereoselectivity were obtained with indium(III) chloride or indium(III) triflate (Table 2, entries 4 and 6), but the reactions were faster. Of the Lewis acids surveyed at this point, indium(III) triflate gave good yields and good conversion rates. Therefore, we focused on further exploration of the indium(III) triflate mediated reaction of 2,3-dimethyl-1,3-butadiene with a variety of imines **2** (Table 2, entries 9–12). The nature of the N substituent on the β-lactam nucleus appeared to influence the stereoselectivity of the cycloaddition. While *N*-aryl-substituted β-lactams afforded moderate selectivities (60:40 to 75:25), by far the best selectivity (100:0) was observed when the N functionality at the four-membered ring was an aliphatic moiety (Table 2, entry 12). Again, cycloadducts **5** and **6** were easily separable by column chromatography.

Table 2. Lewis acid mediated Diels–Alder cycloaddition between 2-azetidinone-tethered imines and 2,3-dimethyl-1,3-butadiene.[a]

Entry	Imine	R^1	R^2	LA (mol%)	t [h]	**5/6** Ratio[b]	Yield **5/6**[c]
1	(−)-**2f**	PMP	PhO	ZnI_2 (100)	216	(+)-**5f**/(+)-**6f** 60:40	47/31
2	(−)-**2f**	PMP	PhO	ZnI_2 (20)	216	(+)-**5f**/(+)-**6f** 60:40	51/34
3	(−)-**2f**	PMP	PhO	$InCl_3$ (100)	16	(+)-**5f**/(+)-**6f** 60:40	49/32
4	(−)-**2f**	PMP	PhO	$InCl_3$ (20)	16	(+)-**5f**/(+)-**6f** 60:40	49/32
5	(−)-**2f**	PMP	PhO	$In(TfO)_3$ (100)	3	(+)-**5f**/(+)-**6f** 60:40	51/34
6	(−)-**2f**	PMP	PhO	$In(TfO)_3$ (20)	3	(+)-**5f**/(+)-**6f** 60:40	52/35
7	(−)-**2f**	PMP	PhO	$HfCl_4$ (100)	16	(+)-**5f**/(+)-**6f** 60:40	35/24
8	(−)-**2f**	PMP	PhO	$HfCl_4$ (20)	16	(+)-**5f**/(+)-**6f** 60:40	36/24
9	(±)-**2a**	PMP	Ph	$In(TfO)_3$ (20)	1	(±)-**5a**/(±)-**6a** 75:25	62/21
10	(+)-**2g**	PMP	MeO	$In(TfO)_3$ (20)	1.5	(+)-**5g**/(+)-**6g** 65:35	56/30
11	(+)-**2h**	Tol	MeO	$In(TfO)_3$ (20)	1	(+)-**5h**/(+)-**6h** 65:35	58/31
12	(+)-**2i**	Allyl	MeO	$In(TfO)_3$ (20)	1	(+)-**5i**/(+)-**6i** 100:0	67/0

[a] 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. [c] Yield (%) of pure, isolated product with correct analytical and spectral data.

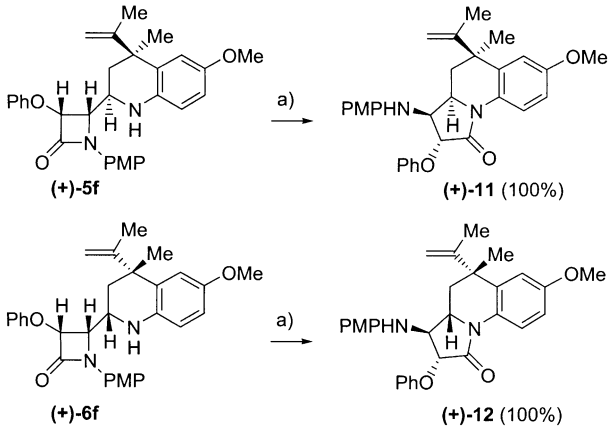
Cyclic alkenes such as cyclopentadiene and 3,4-dihydro-2*H*-pyran (DHP) were tested as well. The reactions proceeded smoothly at ambient temperature under trivalent indium salt catalysis. Thus, indium trichloride catalyzed (20 mol%) reaction between the 2-azetidinone-tethered imine (+)-**2g** and cyclopentadiene afforded the chromatographically separable derivatives (+)-**7** and (+)-**8** (1:1 mixture) in an excellent 98% yield (Scheme 5). Further reactions of *N*-benzylidene-2-azetidinones **2** with DHP in the presence of catalytic amounts of indium(III) triflate resulted in the formation of isomeric pyrano[3,2-*c*]quinoline-β-lactams **9** and **10**. These adducts, which could be separated by column chromatography on silica gel, were obtained in good yields (70–95%) with acceptable levels of stereoselectivity (60:40 to 100:0). Thus, for example, adduct (+)-**9c** was obtained as a single diastereomer (Scheme 5). Detailed NMR studies have established the structure and stereochemistry of compounds **7**–**10**.



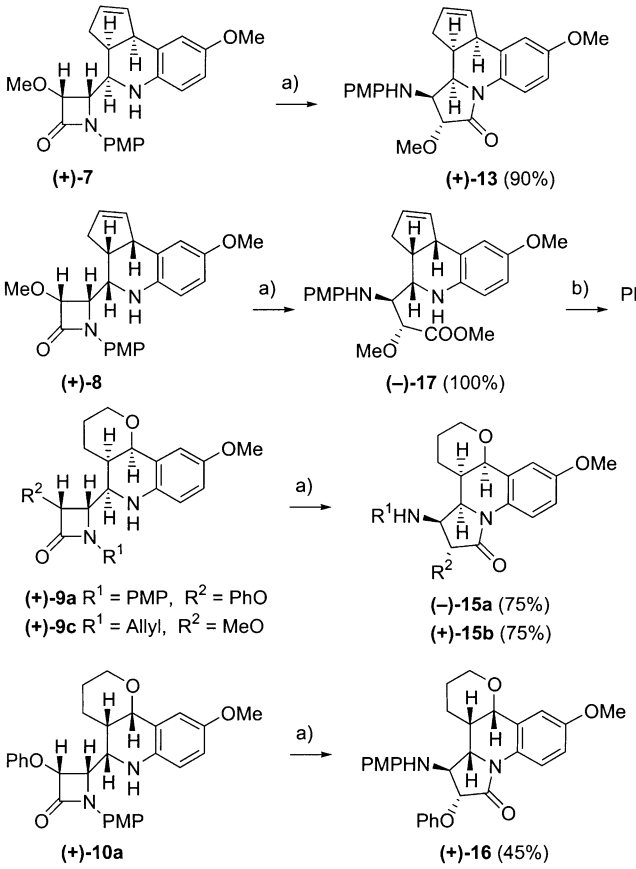
Scheme 5. Lewis acid mediated Diels–Alder cycloaddition between 2-azetidinone-tethered imines and cyclic alkenes. Reagents and conditions: a) indium(III) chloride, acetonitrile, room temperature, 1 h. b) indium(III) triflate, acetonitrile, room temperature.

Both of the observed products from the [4+2] cycloaddition step, when using less electron-rich dienes, are derived from *endo* cycloaddition of the dienophile to the azadiene. Stereoselectivity must be achieved by controlling the approach of the dienophile to the azadiene from either the top or the bottom face. Therefore, the approach of the dienophile from the appropriate face when the N of the 2-azetidinone bears an allyl group results in only a slight steric interaction.

A common and relevant feature of some indolizidines that act as glycosidase inhibitors is the presence of a vicinal amino-alcohol or -alkoxy functionality.[19] In this context, our aim was to find an expedient transformation of our cycloadducts into indolizidine systems bearing this substitution pattern. To our delight, quantitative transformation of adducts (+)-**5f** and (+)-**6f** into fused azatricycles **11** and **12** was directly effected by means of a sodium methoxide rearrangement reaction (Scheme 6). Similarly, indolizidinones **13**–**16** were obtained in good yields and in high purity after aqueous workup, without the need for further purification (Scheme 7). The



Scheme 6. Sodium methoxide promoted transformation of quinoline-β-lactams into enantiopure fused tricyclic indolizidinones. Reagents and conditions: a) MeONa, MeOH, room temperature, 16 h.

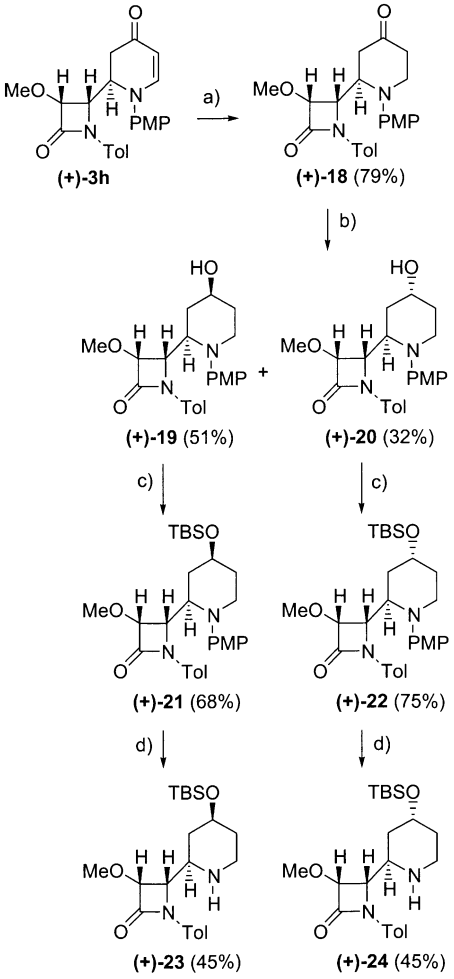


Scheme 7. Sodium methoxide promoted transformation of quinoline-β-lactams into enantiopure fused tetracyclic indolizidinones. Reagents and conditions: a) MeONa, MeOH, room temperature, 16 h. b) PTSA, toluene, reflux, 30 min.

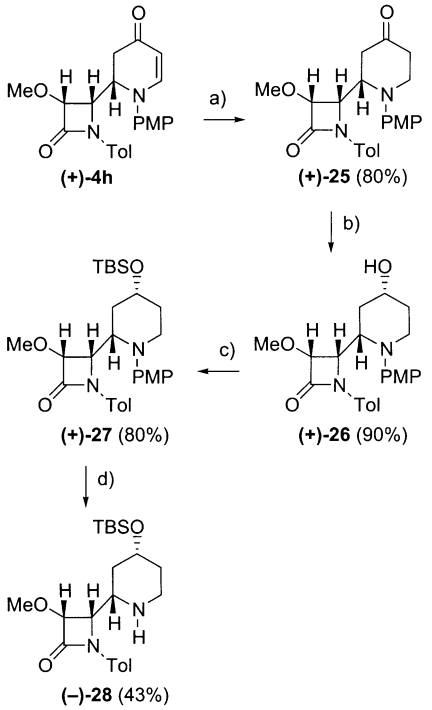
reaction of compound (+)-**8** with sodium methoxide in methanol overnight gave in quantitative yield as crude product the compound (−)-**17**. Product (−)-**17** has a fused tricyclic tetrahydroquinoline structure, and it was found to require heating for 30 min in toluene under PTSA catalysis using a Dean–Stark apparatus to give the expected indolizidinone system (−)-**14**. Aza-polycyclic compounds **11**–**16** showed a single set of signals in their ^{1}H NMR spectra, thus proving that these transformations proceeded without detectable isomerization.

Alternatively, this transformation can be carried out by dissolving the aza-Diels–Alder adducts **5**–**10** in a saturated solution of HCl(g) in 2-propanol. However, the ^{1}H NMR spectra of the crude reaction mixtures showed mainly **11**–**16** together with unquantifiable traces of other isomer, which could arise from partial epimerization. Fused aza-polycycles **11**–**16** are pyrrolidinoisoquinolines, and the isomeric pyrrolidino[2,1-*a*]quinolines represent a structural fragment of erytrinan alkaloids that exhibit significant pharmacological activity.[20]

Cycloadducts **3** and **4** require further manipulation to obtain the desired alkaloid system. Thus, the dihydropyridone (+)-**3h** underwent sequential reduction of the alkene and carbonyl moieties. L-Selectride reduction of the alkene moiety at the six-membered ring is a convenient way to obtain the tetrahydropyridone (+)-**18**. Sodium borohydride reduction of the ketone moiety on compound (+)-**18** gave a 60:40 mixture of epimeric alcohols (+)-**19** and (+)-**20**, which were separated by flash chromatography. Protection of the hydroxyl group to give the corresponding *tert*-butyldimethylsilyl ethers (+)-**21** and (+)-**22**, followed by CAN-promoted oxidative cleavage of the *N*-4-methoxyphenyl substituent, provided the key intermediate oxoazetidinyl-piperidines (+)-**23** and (+)-**24** (Scheme 8). Compounds **25**–**28** were obtained in a similar way starting from the minor cycloadduct (+)-**4h** (Scheme 9). Fortunately, the



Scheme 8. Preparation of oxoazetidinyl-piperidines (+)-**23** and (+)-**24**. Reagents and conditions: a) L-Selectride, THF, −78 °C, 5 h. b) $NaBH_4$, MeOH, 0 °C. c) TBSCl, imidazole, DMF, room temperature. d) CAN, CH_3CN/H_2O, −35 °C.

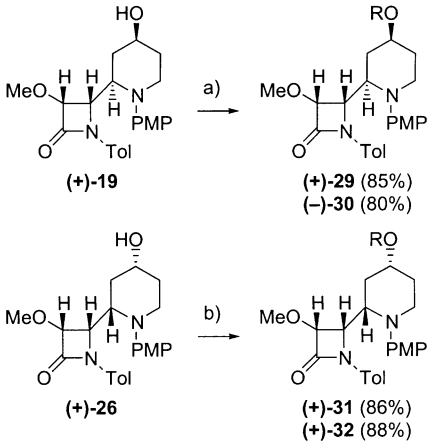


Scheme 9. Preparation of oxoazetidinyl-piperidine (−)-**28**. Reagents and conditions: a) L-Selectride, THF, −78 °C, 1 h. b) $NaBH_4$, MeOH, 0 °C. c) TBSCl, imidazole, DMF, room temperature. d) CAN, CH_3CN/H_2O, −35 °C.

reduction of ketone (+)-**25** was totally stereoselective, and alcohol (+)-**26** was obtained as the sole product without any sign of the diastereomeric isomer.

The configuration at the carbinolic chiral centers of the above major alcohols (+)-**19** and (+)-**26** was established by comparison of the ^{1}H NMR chemical shifts of their acetylmandelates **29**–**32** (Scheme 10).[21]

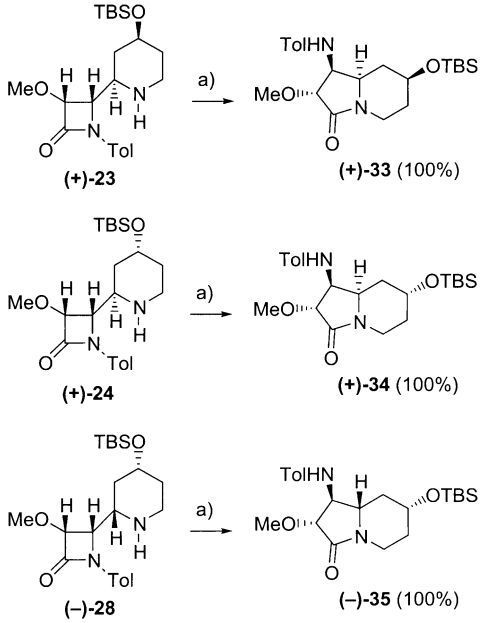
Substrates (+)-**23**, (+)-**24**, and (−)-**28** were submitted to sodium methoxide treatment to afford bicyclic indolizidine



29, **31** R = (*R*)-PhCHOAcCO
30, **32** R = (*S*)-PhCHOAcCO

Scheme 10. Synthesis of acetylmandelates **29**–**32**. Reagents and conditions: a) (*R*)-acetylmandelic acid, DCC, DMAP, dichloromethane, room temperature. b) (*S*)-acetylmandelic acid, DCC, DMAP, dichloromethane, room temperature.

lactams **33**–**35**. Enantiopure indolizidinones (+)-**33**, (+)-**34**, and (−)-**35** were cleanly produced without byproducts in quantitative yields (Scheme 11). This result demonstrates that efficient asymmetric access to a plethora of stereochemically different indolizidine moieties can be achieved through β-lactam chemistry.



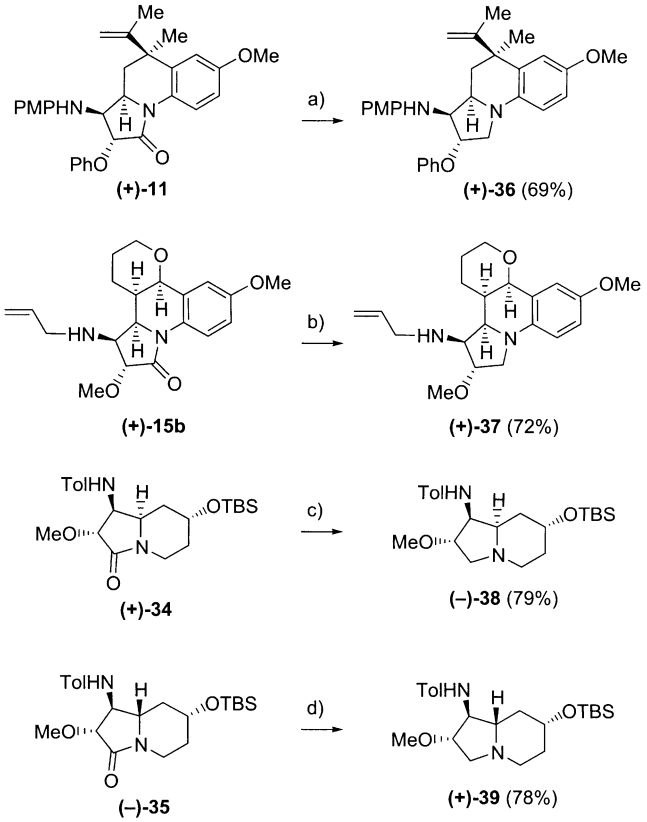
Scheme 11. Sodium methoxide promoted transformation of piperidine-β-lactams into enantiopure functionalized bicyclic indolizidinones. Reagents and conditions: a) MeONa, MeOH, room temperature, 16 h.

The transformation of piperidine-2-azetidinones **5**–**10**, (+)-**23**, (+)-**24**, and (−)-**28** into indolizidine derivatives **11**–**16** and **33**–**35** involves 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 **11**–**16** and **33**–**35** were established by one- and two-dimensional NMR techniques.

To further illustrate the use of this chemistry in alkaloid synthesis, the conversion of indolizidinones to indolizidines was easily accomplished by reduction of the amide group. Thus, the fused-lactams (+)-**11**, (+)-**15b**, (+)-**34**, and (−)-**35**, on treatment with a suspension of powdered lithium aluminum hydride in tetrahydrofuran or diethyl ether, smoothly afforded the cyclic amines **36**–**39** (Scheme 12).

Conclusion

In conclusion, imines derived from 4-oxoazetidine-2-carbaldehydes have been found to be versatile aza-Diels–Alder reagents in that two reactivity patterns have been observed. These imines lead to cycloadducts arising from normal as well as inverse electron-demand [4+2] cycloaddition. Furthermore, we have presented the first methodology for the preparation of indolizidines from β-lactams. This β-lactam-



Scheme 12. LAH-promoted transformation of indolizidinones into enantiopure functionalized indolizidines. Reagents and conditions: a) $LiAlH_4$, THF, room temperature, 16 h. b) $LiAlH_4$, Et_2O, room temperature, 30 min. c) $LiAlH_4$, Et_2O, room temperature, 45 min. d) $LiAlH_4$, Et_2O, room temperature, 40 min.

based stereocontrolled route to bi- or polycyclic alkaloid scaffolds is carried out asymmetrically, allowing efficient access to a variety of optically pure highly functionalized indolizidines.

Experimental Section

General methods: ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance-300, Varian VRX-300S or Bruker AC-200 spectrometer. NMR spectra were recorded in $CDCl_3$ solutions, except where otherwise stated. Chemical shifts are given in ppm relative to TMS (^1H, 0.0 ppm) or $CDCl_3$ (^{13}C, 76.9 ppm). Low- and high-resolution mass spectra were measured on a HP5989A spectrometer, operating in chemical ionization (CI) mode unless otherwise stated. Specific rotations $[\alpha]_D$ are given in deg per dm at 20 °C, and the concentration (c) is expressed in g/100 mL. All commercially available compounds were used without further purification.

General procedure for the preparation of imines 2: A solution of the corresponding amine (1.50 mmol) in dichloromethane (4 mL) was added dropwise to a stirred suspension of the appropriate 4-oxoazetidine-2-carbaldehyde **1** (1.0 mmol) and magnesium sulfate (1.50 mmol) in dichloromethane (100 mL) at room temperature. After stirring for 16 h at room temperature, the mixture was filtered and the solvent was removed under reduced pressure. Chromatography of the residue eluting with ethyl acetate/hexanes mixtures (containing 1% triethylamine) gave analytically pure compounds **2**. Spectroscopic and analytical data for some representative pure forms of **2** follow.[22]

Imine (+)-2g: Compound (+)-**2g** (4.12 g; 95%) was obtained from the aldehyde (+)-**1e** (3.0 g, 12.7 mmol) after column chromatography (elution with ethyl acetate/hexanes (1:1; containing 1% triethylamine)); yellow solid; m.p. 121–122 °C (hexanes/ethyl acetate); $[\alpha]_D = +107.3$ ($c = 1.0$ in $CHCl_3$); ^1H NMR (300 MHz, C_6D_6, 25 °C): $\delta = 7.62$ (d, $J = 7.1$ Hz, 1H), 6.89 and 7.40 (d, $J = 8.9$ Hz, each 2H), 6.47 (m, 4H), 4.27 (dd, $J = 7.0$, 5.1 Hz, 1H), 3.99 (d, $J = 5.1$ Hz, 1H), 3.04 and 3.07 (s, each 3H), 2.96 ppm (s, 3H); ^{13}C NMR (75 MHz, C_6D_6, 25 °C): $\delta = 163.3$, 159.5, 158.8, 144.0, 132.2, 122.9, 118.4, 114.9, 114.7, 85.5, 61.3, 58.6, 55.0 ppm; IR (KBr): $\tilde{\nu} = 1742$, 1644 cm^{-1}; MS (EI): m/z (%): 340 (100) $[M]^+$; elemental analysis calcd (%) for $C_{19}H_{20}N_2O_4$ (340.4): C 67.05, H 5.92, N 8.23; found: C 67.12, H 5.90, N 8.25.

Imine (+)-2h: Compound (+)-**2h** (3.12 g; 75%) was obtained from the aldehyde (+)-**1f** (3.0 g, 12.9 mmol), after column chromatography (elution with ethyl acetate/hexanes (1:1; containing 1% triethylamine)); yellow solid; m.p. 117–118 °C (hexanes/ethyl acetate); $[\alpha]_D = +92.5$ ($c = 0.8$ in $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$, 25 °C): $\delta = 7.88$ (m, 1H), 7.04 (m, 4H), 6.76 and 7.25 (m, each 2H), 4.78 (m, 2H), 3.48 and 3.74 (s, each 3H), 2.23 ppm (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): $\delta = 163.7$, 159.1, 158.9, 143.5, 135.2, 134.6, 129.9, 122.4, 117.1, 114.5, 85.2, 61.3, 59.3, 55.6, 21.1 ppm; IR (KBr): $\tilde{\nu} = 1744$, 1645 cm^{-1}; MS (EI): m/z (%): 326 (7) $[M+H]^+$, 325 (100) $[M]^+$; elemental analysis calcd (%) for $C_{19}H_{20}N_2O_3$ (324.4): C 70.35, H 6.21, N 8.64; found: C 70.43, H 6.23, N 8.60.

General procedure for the synthesis of cycloadducts 3 and 4: A solution of the corresponding imine (1.0 mmol) in acetonitrile (5 mL) was added dropwise to a stirred suspension of the appropriate Lewis acid (0.2 mmol) in acetonitrile (13 mL) at −20 °C. The reaction mixture was stirred at −20 °C for 15 min and then Danishefsky's diene (1.20 mmol) was added. After the imine had been consumed (TLC), saturated aqueous $NaHCO_3$ (1 mL) was added, and the mixture was extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue eluting with ethyl acetate/hexanes mixtures (containing 1% triethylamine) gave analytically pure compounds **3** and **4**. Spectroscopic and analytical data for some representative pure forms of **3** and **4** are given below.

Preparation of cycloadducts (+)-3f and (+)-4f: The less polar compound (+)-**3f** (150 mg; 63%) and the more polar compound (+)-**4f** (42 mg; 18%) were obtained from the imine (+)-**2f** (201 mg; 0.5 mmol), after column chromatography (elution with ethyl acetate/hexanes (1:1 containing 1% triethylamine)).

Cycloadduct (+)-3f: Colorless oil; $[\alpha]_D = +425.3$ ($c = 0.9$ in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 7.08$ (m, 7H), 6.65 (m, 7H), 5.39 (d, $J = 5.9$ Hz, 1H), 5.28 (d, $J = 7.3$ Hz, 1H), 5.07 (dd, $J = 10.3$, 5.9 Hz, 1H), 3.65 (s, 6H), 4.75 (m, 1H), 3.01 (dd, $J = 17.1$, 5.9 Hz, 1H), 2.44 ppm (d, $J = 17.1$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = 191.0$, 164.2, 157.5, 157.1, 156.8, 148.3, 137.5, 129.9, 129.8, 123.2, 120.7, 119.8, 116.3, 114.7, 114.2, 102.2, 80.1, 58.1, 55.6, 55.5, 52.7, 38.1 ppm; IR ($CHCl_3$): $\tilde{\nu} = 1757$, 1638 cm^{-1}; MS (CI): m/z (%): 471 (100) $[M+H]^+$, 470 (39) $[M]^+$; elemental analysis calcd (%) for $C_{28}H_{26}N_2O_5$ (470.5): C 71.47, H 5.57, N 5.95; found: C 71.58, H 5.54, N 5.92.

Cycloadduct (+)-4f: Yellow solid; m.p. 186–187 °C (hexanes/ethyl acetate); $[\alpha]_D = +128.7$ ($c = 0.7$ in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 7.01$ (m, 14H), 5.24 (d, $J = 5.2$ Hz, 1H), 4.86 (d, $J = 7.9$ Hz, 1H), 4.71 (m, 2H), 3.72 and 3.74 (s, each 3H), 2.94 (dd, $J = 17.0$, 7.3 Hz, 1H), 2.71 ppm (dd, $J = 17.0$, 5.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = 190.0$, 163.2, 157.9, 157.3, 151.2, 137.5, 129.8, 129.7, 124.1, 122.8, 120.5, 115.6, 115.3, 114.4, 101.2, 79.3, 58.5, 56.9, 55.7, 55.5, 37.3 ppm; IR (KBr): $\tilde{\nu} = 1751$, 1711 cm^{-1}; MS (CI): m/z (%): 471 (100) $[M+H]^+$, 470 (27) $[M]^+$; elemental analysis calcd (%) for $C_{28}H_{26}N_2O_5$ (470.5): C 71.47, H 5.57, N 5.95; found: C 71.39, H 5.53, N 5.98.

Cycloadduct (±)-3b: Compound (±)-**3b** (305 mg; 64%) was obtained as a colorless oil from the imine (±)-**2b** (400 mg, 1.08 mmol), after column chromatography (elution with ethyl acetate/hexanes (2:1 containing 1% triethylamine)); ^1H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 7.01$ (m, 14H), 6.75 (d, $J = 7.4$ Hz, 1H), 4.97 (d, $J = 7.4$ Hz, 1H), 4.92 (dd, $J = 10.6$, 5.9 Hz, 1H), 4.66 (d, $J = 5.9$ Hz, 1H), 3.87 (d, $J = 15.0$ Hz, 1H), 3.73 (s, 3H), 3.68 (d, $J = 14.8$ Hz, 1H), 3.26 (m, 1H), 2.09 (dd, $J = 17.0$, 6.9 Hz, 1H), 1.61 ppm (d, $J = 17.0$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = 189.6$, 165.9, 156.9, 153.2, 135.9, 130.9, 130.6, 129.8, 129.0, 128.9, 128.4, 128.3, 127.6, 119.9, 114.4, 97.7, 59.7, 57.4, 55.5, 55.4, 51.3, 36.6 ppm; IR ($CHCl_3$): $\nu = 1753$, 1703 cm^{-1}; MS (CI): m/z (%): 439 (100) $[M+H]^+$, 438 (23) $[M]^+$; elemental analysis calcd (%) for $C_{28}H_{26}N_2O_3$ (438.5): C 76.99, H 5.98, N 6.39; found: C 76.90, H 5.95, N 6.43.

Preparation of cycloadducts (+)-3e and (+)-4e: The less polar compound (+)-**3e** (327 mg; 56%) and the more polar compound (+)-**4e** (141 mg; 24%) were obtained from the imine (+)-**2e** (599 mg, 1.25 mmol), after column chromatography (elution with ethyl acetate/hexanes (2:1 containing 1% triethylamine)).

Cycloadduct (+)-3e: Colorless oil; $[\alpha]_D = +201.1$ ($c = 0.5$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 7.28$ (m, 12H), 6.80 (d, $J = 7.8$ Hz, 1H), 6.79 (m, 2H), 5.02 (d, $J = 7.8$ Hz, 1H), 4.86 (m, 2H), 4.75 (d, $J = 4.8$ Hz, 1H), 4.66 (d, $J = 11.7$ Hz, 1H), 3.92 (d, $J = 15.6$ Hz, 1H), 3.89 (m, 1H), 3.73 (s, 3H), 3.68 (d, $J = 15.6$ Hz, 1H), 2.72 (dd, $J = 17.1$, 6.8 Hz, 1H), 2.24 ppm (d, $J = 17.1$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta =$ 190.2, 165.5, 156.9, 152.9, 136.4, 130.3, 129.0, 128.6, 128.5, 128.3, 128.2, 128.0, 127.2, 119.3, 114.4, 98.0, 80.2, 73.5, 59.6, 55.9, 55.5, 52.5, 37.8 ppm; IR ($CHCl_3$): $\tilde{\nu} = 1749$, 1705 cm^{-1}; MS (CI): m/z (%): 469 (100) $[M+H]^+$, 468 (17) $[M]^+$; elemental analysis calcd (%) for $C_{29}H_{28}N_2O_4$ (468.6): C 74.34, H 6.02, N 5.98; found: C 74.44, H 6.05, N 5.94.

Cycloadduct (+)-4e: Colorless oil; $[\alpha]_D = +150.0$ ($c = 0.7$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 7.27$ (m, 10H), 7.01 (d, $J = 7.6$ Hz, 1H), 6.90 (m, 2H), 6.78 (m, 2H), 4.94 (d, $J = 7.6$ Hz, 1H), 4.78 (m, 5H), 4.21 (d, $J = 14.9$ Hz, 1H), 3.94 (m, 1H), 3.68 (s, 3H), 2.47 (dd, $J = 17.4$, 7.3 Hz, 1H), 2.15 ppm (d, $J = 17.6$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta =$ 189.9, 165.6, 157.4, 153.1, 137.1, 136.5, 129.7, 129.1, 128.9, 128.8, 128.7, 128.3, 127.5, 120.8, 114.5, 99.7, 80.3, 73.5, 58.3, 56.6, 55.5, 54.5, 37.2 ppm; IR ($CHCl_3$): $\nu = 1756$, 1711 cm^{-1}; MS (CI): m/z (%): 469 (100) $[M+H]^+$, 468 (31) $[M]^+$; elemental analysis calcd (%) for $C_{29}H_{28}N_2O_4$ (468.6): C 74.34, H 6.02, N 5.98; found: C 74.23, H 6.00, N 6.01.

Preparation of cycloadducts (+)-3h and (+)-4h: The less polar compound (+)-**3h** (518 mg; 43%) and the more polar compound (+)-**4h** (169 mg; 14%) were obtained from the imine (+)-**2h** (1.0 g, 3.09 mmol), after column chromatography (elution with ethyl acetate/hexanes (1:1 containing 1% triethylamine)).

Cycloadduct (+)-3h: Yellow solid; m.p. 144–145 °C (hexanes/ethyl acetate); $[\alpha]_D = +58.0$ ($c = 1.0$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 7.08$ (d, $J = 7.6$ Hz, 1H), 6.82 (m, 8H), 5.29 (d, $J = 7.6$ Hz, 1H), 4.95 (dd, $J = 10.1$, 5.5 Hz, 1H), 4.63 (d, $J = 5.5$ Hz, 1H), 4.54 (m, 1H), 3.59 and 3.66 (s, each 3H), 2.99 (d, $J = 17.1$ Hz, 1H), 2.35 (dd, $J = 17.1$, 6.2 Hz, 1H), 2.16 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = 191.3$, 165.8, 156.7, 148.5, 137.5, 134.7, 134.2, 129.3, 120.7, 118.0, 114.5, 101.8, 82.6, 59.9, 57.9, 55.5, 52.2, 38.0, 20.9 ppm; IR (KBr): $\nu = 1740$, 1705 cm^{-1}; MS (CI): m/z (%): 393 (100) $[M+H]^+$, 392 (22) $[M]^+$; elemental analysis calcd (%) for $C_{23}H_{24}N_2O_4$ (392.5): C 70.39, H 6.16, N 7.14; found: C 70.30, H 6.14, N 7.17.

Cycloadduct (+)-4h: Yellow solid; m.p. 150–151 °C (hexanes/ethyl acetate); $[\alpha]_D = +114.2$ ($c = 0.7$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 7.15$ (m, 9H), 4.98 (d, $J = 7.8$ Hz, 1H), 4.68 (m, 1H), 4.60 (dd, $J = 5.4$, 2.9 Hz, 1H), 4.48 (d, $J = 5.4$ Hz, 1H), 3.46 and 3.83 (s, each 3H), 2.93 (dd, $J = 17.1$, 7.5 Hz, 1H), 2.64 (dd, $J = 17.1$, 6.3 Hz, 1H), 2.31 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = 190.3$, 165.1, 157.8, 151.5, 137.6, 134.9, 134.2, 129.5, 124.2, 118.6, 114.9, 101.1, 82.3, 59.4, 57.7, 56.7, 55.6, 37.4, 20.9 ppm; IR (KBr): $\tilde{\nu} = 1743$, 1706 cm^{-1}; MS (CI): m/z (%): 393 (100) $[M+H]^+$, 392 (17) $[M]^+$; elemental analysis calcd (%) for $C_{23}H_{24}N_2O_4$ (392.5): C 70.39, H 6.16, N 7.14; found: C 70.47, H 6.15, N 7.11.

General procedure for the synthesis of cycloadducts 5 and 6: Indium(III) triflate (0.2 mmol) was added in portions to a solution of the appropriate imine **2** (1.0 mmol) and 2,3-dimethyl-1,3-butadiene (2.0 mmol) in acetonitrile (7 mL) at 0 °C. After the imine had been consumed (TLC), saturated aqueous $NaHCO_3$ (1 mL) was added, and the mixture was extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue eluting with ethyl acetate/hexanes mixtures gave analytically pure compounds **5** and **6**. Spectroscopic and analytical data for some representative pure forms of **5** and **6** are given below.

Preparation of cycloadducts (+)-5f and (+)-6f: The less polar compound (+)-**5f** (121 mg; 52%) and the more polar compound (+)-**6f** (82 mg; 35%) were obtained from the imine (−)-**2f** (200 mg, 0.498 mmol), after column chromatography (elution with ethyl acetate/hexanes (1:6)).

Cycloadduct (+)-5f: Colorless solid; m.p. 158–159 °C (hexanes/ethyl acetate); $[\alpha]_D = +75.5$ ($c = 0.6$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 7.44$ (m, 2H), 7.05 (m, 5H), 6.74 (m, 2H), 6.46 (m, 2H), 6.28 (d, $J = 9.4$ Hz, 1H), 5.37 (d, $J = 5.2$ Hz, 1H), 4.92 and 5.02 (s, each 1H), 4.38 (dd, $J = 6.8$, 5.4 Hz, 1H), 3.94 (m, 1H), 3.61 and 3.74 (s, each 3H), 1.97 (m, 1H), 1.49 (m, 1H), 1.41 and 1.48 ppm (s, each 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = 163.9$, 157.4, 157.0, 152.5, 150.8, 137.6, 130.4, 129.6, 128.7, 122.5, 120.7, 116.3, 115.7, 114.2, 113.2, 112.9, 111.9, 79.5, 61.4, 55.6, 55.4, 50.3, 42.4, 37.4, 29.4, 19.7 ppm; IR (KBr): $\tilde{\nu} = 3420$, 1757 cm^{-1}; MS (CI): m/z (%): 485 (100) $[M+H]^+$, 484 (37) $[M]^+$; elemental analysis calcd (%) for $C_{30}H_{32}N_2O_4$ (484.6): C 74.36, H 6.66, N 5.78; found: C 74.46, H 6.63, N 5.81.

Cycloadduct (+)-6f: Colorless oil; $[\alpha]_D = +22.1$ ($c = 0.8$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 7.49$ (m, 2H), 7.09 (m, 5H), 6.83 (m, 2H), 6.55 (dd, $J = 5.7$, 3.9 Hz, 1H), 6.43 (d, $J = 2.9$ Hz, 1H), 5.43 (d, $J = 5.3$ Hz, 1H), 4.88 and 4.97 (s, each 1H), 4.33 (t, $J = 5.4$ Hz, 1H), 4.01 (m, 1H), 3.62 and 3.73 (s, each 3H), 1.98 (m, 1H), 1.57 (m, 1H), 1.31 and 1.39 ppm (s, each 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = 163.8$, 157.5, 156.9, 152.9, 150.8, 137.8, 130.9, 129.9, 129.8, 129.6, 122.8, 120.3, 116.4, 115.9, 114.4, 113.4, 113.3, 112.2, 79.8, 62.4, 55.8, 55.6, 49.6, 42.5, 37.3, 29.7, 20.0 ppm; IR ($CHCl_3$): $\tilde{\nu} = 3421$, 1755 cm^{-1}; MS (CI): m/z (%): 485 (100) $[M+H]^+$, 484 (29) $[M]^+$; elemental analysis calcd (%) for $C_{30}H_{32}N_2O_4$ (484.6): C 74.36, H 6.66, N 5.78; found: C 74.27, H 6.69, N 5.80.

Cycloadduct (+)-5i: Compound (+)-**5i** (518 mg; 67%) was obtained from the imine (+)-**2i** (200 mg, 0.73 mmol), after column chromatography (elution with ethyl acetate/hexanes (1:1)); colorless oil; $[\alpha]_D = +41.8$ ($c = 0.6$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 6.52$ (m, 3H), 5.70 (m, 1H), 5.18 (m, 2H), 4.94 and 5.04 (s, each 1H), 4.47 (d, $J = 4.9$ Hz, 1H), 3.95 (m, 2H), 3.61 (m, 2H), 3.55 and 3.60 (s, each 3H), 1.97 (m, 1H), 1.56 (m, 1H), 1.35 and 1.49 ppm (s, each 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = 167.8$, 152.5, 151.1, 138.3, 132.6, 128.6, 118.8, 116.4, 113.5, 113.2, 112.2, 83.9, 62.1, 59.8, 55.9, 48.1, 44.5, 42.8, 38.1, 29.5, 20.1 ppm; IR ($CHCl_3$): $\tilde{\nu} = 3429$, 1751 cm^{-1}; MS (CI): m/z (%): 357 (100) $[M+H]^+$, 356 (25) $[M]^+$; elemental analysis calcd (%) for $C_{21}H_{28}N_2O_3$ (356.5): C 70.76, H 7.92, N 7.86; found: C 70.86, H 7.96, N 7.83.

Procedure for the synthesis of cycloadducts (+)-7 and (+)-8: Indium(III) chloride (44 mg, 0.2 mmol) was added in portions to a solution of the imine (+)-**2g** (340 mg, 1.0 mmol) and cyclopentadiene (120 mg, 2.0 mmol) in acetonitrile (7 mL) at −20 °C. The reaction mixture was stirred at room temperature for 1 h, and then saturated aqueous $NaHCO_3$ (1 mL) was added and the mixture was extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue eluting with dichloromethane/ethyl acetate/hexanes (1:1:1 containing 1% triethylamine) gave the less polar compound (+)-**8** (398 mg; 49%) and the more polar compound (+)-**7** (398 mg; 49%).

Cycloadduct (+)-7: Pale green oil; $[\alpha]_D = +243.2$ ($c = 0.6$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 6.80$ and 7.20 (m, each 2H), 6.43 (m, 3H), 5.70 (m, 1H), 5.56 (m, 1H), 4.68 (d, $J = 5.3$ Hz, 1H), 4.17 (dd, $J = 9.0$, 5.3 Hz, 1H), 3.71 (m, 4H), 3.63 (m, 7H), 2.54 (m, 2H), 2.11 ppm (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = 165.6$, 157.7, 153.2, 138.4, 133.9, 130.1, 129.4, 127.1, 122.4, 117.3, 114.4, 113.9, 112.5, 83.2, 59.8, 59.3, 56.0, 55.7, 55.5, 46.1, 40.6, 31.4 ppm; IR ($CHCl_3$): $\tilde{\nu} = 3345$, 1743 cm^{-1}; MS (CI): m/z (%): 407 (100) $[M+H]^+$, 406 (47) $[M]^+$; elemental analysis calcd (%) for $C_{24}H_{26}N_2O_4$ (406.5): C 70.92, H 6.45, N 6.89; found: C 70.99, H 6.44, N 6.91.

Cycloadduct (+)-8: Pale green solid; m.p. 166–167 °C (hexanes/ethyl acetate); $[\alpha]_D = +243.2$ ($c = 0.8$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 6.94$ and 7.51 (m, each 2H), 6.57 (d, $J = 2.8$ Hz, 1H), 6.46 (ddd, $J = 8.6$, 2.9, 0.5 Hz, 1H), 6.21 (d, $J = 8.6$ Hz, 1H), 5.86 (m, 1H), 5.75 (m, 1H), 4.68 (d, $J = 5.5$ Hz, 1H), 4.34 (dd, $J = 9.8$, 5.5 Hz, 1H), 3.98 (m, 1H), 3.83 (m, 4H), 3.67 and 3.71 (s, each 3H), 3.06 (qd, $J = 10.8$, 2.9 Hz, 1H), 2.81 (m, 1H), 2.38 ppm (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = 166.0$, 157.1, 153.3, 138.1, 134.3, 130.9, 130.1, 127.1, 120.2, 117.3, 114.6, 113.9, 112.3, 82.8, 60.5, 59.8, 59.7, 56.1, 55.7, 55.6, 46.2, 39.1, 31.6 ppm; IR (KBr): $\tilde{\nu} =$ 3342, 1744 cm^{-1}; MS (CI): m/z (%): 407 (100) $[M+H]^+$, 406 (36) $[M]^+$; elemental analysis calcd (%) for $C_{24}H_{26}N_2O_4$ (406.5): C 70.92, H 6.45, N 6.89; found: C 70.84, H 6.43, N 6.87.

General procedure for the synthesis of cycloadducts 9 and 10: Indium(III) triflate (0.2 mmol) was added in portions to a solution of the appropriate imine **2** (1.0 mmol) and 3,4-dihydro-2*H*-pyran (1.2 mmol) in acetonitrile (7 mL) at 0 °C. After the imine had been consumed (TLC), saturated aqueous $NaHCO_3$ (1 mL) was added, and the mixture was extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue eluting with ethyl acetate/hexanes mixtures gave

analytically pure compounds **9** and **10**. Spectroscopic and analytical data for some representative pure forms of **9** and **10** are given below.

Preparation of cycloadducts (+)-9a and (+)-10a: The less polar compound (+)-**9a** (53 mg; 46%) and the more polar compound (+)-**10a** (21 mg; 24%) were obtained from the imine (−)-**2f** (95 mg, 0.236 mmol), after column chromatography (elution with ethyl acetate/hexanes (1:6)).

Cycloadduct (+)-9a: Yellow oil; $[\alpha]_D = +66.0$ ($c = 1.0$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 7.48$ (m, 2H), 7.25 (m, 2H), 6.97 (m, 3H), 6.74 (m, 3H), 6.56 (ddd, $J = 8.7$, 2.9, 0.5 Hz, 1H), 6.18 (d, $J = 8.7$ Hz, 1H), 5.00 and 5.37 (d, $J = 5.4$ Hz, each 1H), 4.63 (dd, $J = 9.8$, 5.4 Hz, 1H), 3.92 (m, 1H), 1.46 (m, 4H), 3.67 and 3.77 (s, each 3H), 3.51 (m, 2H), 2.40 ppm (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = 164.2$, 157.5, 157.0, 153.2, 137.9, 130.4, 129.6, 122.6, 121.5, 120.1, 116.4, 115.8, 114.9, 114.3, 111.6, 79.5, 71.5, 60.9, 57.8, 56.6, 55.6, 55.4, 33.0, 24.9, 18.8 ppm; IR ($CHCl_3$): $\tilde{\nu} = 3418$, 1751 cm^{-1}; MS (CI): m/z (%): 487 (100) $[M+H]^+$, 486 (46) $[M]^+$; elemental analysis calcd (%) for $C_{29}H_{30}N_2O_5$ (486.6): C 71.59, H 6.21, N 5.76; found: C 71.69, H 6.25, N 5.73.

Cycloadduct (+)-10a: Yellow oil; $[\alpha]_D = +35.7$ ($c = 0.7$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 7.18$ (m, 6H), 6.84 (m, 3H), 6.65 (dd, $J = 8.7$, 2.9 Hz, 1H), 6.37 (d, $J = 8.7$ Hz, 1H), 4.93 and 5.46 (d, $J = 5.2$ Hz, each 1H), 4.51 (dd, $J = 9.4$, 5.2 Hz, 1H), 4.07 (m, 1H), 3.68 and 3.77 (s, each 3H), 3.41 (m, 3H), 1.57 ppm (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = 163.6$, 157.6, 157.0, 153.3, 137.9, 129.7, 129.6, 129.1, 122.8, 121.7, 116.3, 115.7, 115.1, 114.4, 111.4, 80.4, 71.7, 60.6, 57.2, 56.7, 55.6, 55.4, 33.7, 24.9, 18.6 ppm; IR ($CHCl_3$): $\tilde{\nu} = 3422$, 1750 cm^{-1}; MS (CI): m/z (%): 487 (100) $[M+H]^+$, 486 (33) $[M]^+$; elemental analysis calcd (%) for $C_{29}H_{30}N_2O_5$ (486.6): C 71.59, H 6.21, N 5.76; found: C 71.48, H 6.18, N 5.73.

Cycloadduct (+)-9c: Compound (+)-**9c** (620 mg; 95%) was obtained as a colorless oil from the imine (+)-**2i** (500 mg (1.825 mmol), after column chromatography (elution with ethyl acetate/hexanes (1:1)); $[\alpha]_D = +43.5$ ($c = 0.5$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 6.90$ (d, $J = 2.9$ Hz, 1H), 6.61 (dd, $J = 8.6$, 2.9 Hz, 1H), 6.39 (d, $J = 8.6$ Hz, 1H), 5.77 (m, 1H), 5.30 (m, 2H), 4.95 (d, $J = 5.6$ Hz, 1H), 4.49 (d, $J = 5.1$ Hz, 1H), 3.99 (m, 1H), 3.81 (m, 2H), 3.69 (s, 3H), 3.55 (m, 2H), 3.50 (s, 3H), 3.42 (m, 1H), 2.24 (m, 1H), 1.67 ppm (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = 168.4$, 153.3, 138.4, 133.4, 121.9, 118.5, 116.4, 115.1, 111.8, 83.4, 71.8, 60.9, 60.3, 59.4, 55.8, 54.6, 44.7, 33.5, 25.2, 19.1 ppm; IR ($CHCl_3$): $\tilde{\nu} = 3419$, 1755 cm^{-1}; MS (CI): m/z (%): 359 (100) $[M+H]^+$, 358 (43) $[M]^+$; elemental analysis calcd (%) for $C_{20}H_{26}N_2O_4$ (358.4): C 67.02, H 7.31, N 7.82; found: C 67.11, H 7.28, N 7.86.

Sodium methoxide promoted reaction of tetrahydroquinolinyl-β-lactams: general procedure for the preparation of polycyclic indolizidinones 11–16: Sodium methoxide (108.3 mg, 2.0 mmol) was added in portions at 0 °C to a solution of the appropriate tetrahydroquinolinyl-β-lactam (0.50 mmol) in methanol (10 mL). The reaction mixture was stirred at room temperature until the starting material had been completely consumed (TLC), and then water (1 mL) was added. The methanol was evaporated under reduced pressure, the aqueous residue was extracted with ethyl acetate (10 × 3 mL), and the combined organic extracts were dried over $MgSO_4$ and then concentrated under reduced pressure. Chromatography of the residue eluting with ethyl acetate/hexanes mixtures gave analytically pure compounds **11–16**.

Fused indolizidinone (+)-11: Compound (+)-**11** (70 mg; 100%) was obtained from the cycloadduct (+)-**5f** (70 mg, 0.145 mmol); pale orange oil; $[\alpha]_D = +140.3$ ($c = 0.7$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 8.38$ (d, $J = 9.0$ Hz, 1H), 7.21 (m, 2H), 7.02 (m, 3H), 6.63 (m, 6H), 4.95 and 5.05 (s, each 1H), 4.68 (d, $J = 3.5$ Hz, 1H), 4.49 (m, 1H), 4.24 (m, 1H), 3.66 and 3.68 (s, each 3H), 1.49 and 2.09 (m, each 1H), 1.41 and 1.45 ppm (s, each 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = 167.4$, 157.9, 156.5, 152.9, 150.2, 140.1, 134.8, 129.5, 128.9, 122.1, 121.4, 116.3, 115.1, 115.0, 113.4, 112.6, 112.0, 81.4, 55.6, 55.5, 55.3, 55.2, 43.4, 34.7, 29.2, 19.9 ppm; IR ($CHCl_3$): $\tilde{\nu} = 3304$, 1684 cm^{-1}; MS (EI): m/z (%): 485 (100) $[M]^+$; elemental analysis calcd (%) for $C_{30}H_{32}N_2O_4$ (484.6): C 74.36, H 6.66, N 5.78; found: C 74.46, H 6.69, N 5.76.

Fused indolizidinone (+)-12: Compound (+)-**12** (40 mg; 100%) was obtained from the cycloadduct (+)-**6f** (40 mg, 0.083 mmol); pale orange oil; $[\alpha]_D = +34.4$ ($c = 1.0$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 8.50$ (d, $J = 9.0$ Hz, 1H), 7.14 (m, 4H), 6.82 (m, 7H), 4.97 and 5.05 (s, each 1H), 4.80 (d, $J = 7.9$ Hz, 1H), 3.97 (m, 2H), 3.66 and 3.67 (s, each 3H), 1.97 (m, 2H), 1.37 and 1.44 (s, each 3H), 1.18 ppm (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = 167.4$, 158.6, 156.2, 153.0, 149.8, 140.3, 134.0, 129.3, 128.4, 122.1, 120.8, 116.8, 115.9, 114.8, 113.3, 112.7, 112.1, 82.9, 61.8, 55.8, 55.6, 55.2, 43.0, 38.9, 29.1, 19.8 ppm; IR ($CHCl_3$): $\tilde{\nu} = 3305$, 1690 cm^{-1}; MS (EI): m/z (%): 485 (100) $[M]^+$; elemental analysis calcd (%) for $C_{30}H_{32}N_2O_4$ (484.6): C 74.36, H 6.66, N 5.78; found: C 74.25, H 6.68, N 5.77.

Fused indolizidinone (+)-13: Compound (+)-**13** (83 mg; 90%) was obtained from the cycloadduct (+)-**7** (93 mg, 0.229 mmol); pale brown oil; $[\alpha]_D = +44.6$ ($c = 0.9$ in $CHCl_3$); ^{1}H NMR (300 MHz, C_6D_6, 25 °C): $\delta = 9.09$ (d, $J = 9.0$ Hz, 1H), 6.80 and 6.93 (m, each 2H), 6.73 (m, 2H), 5.67 (m, 1H), 5.42 (m, 1H), 3.84 (t, $J = 6.5$ Hz, 1H), 3.79 (s, 3H), 3.68 (m, 2H), 3.39 and 3.49 (s, each 3H), 3.20 (m, 1H), 2.72 (qd, $J = 8.9$, 3.4 Hz, 1H), 2.66 (m, 1H), 2.07 ppm (ddq, $J = 18.8$, 16.2, 1.4 Hz, 1H); ^{13}C NMR (75 MHz, C_6D_6, 25 °C): $\delta = 169.5$, 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 ppm; IR ($CHCl_3$): $\tilde{\nu} = 3330$, 1730 cm^{-1}; MS (EI): m/z (%): 406 (100) $[M]^+$; elemental analysis calcd (%) for $C_{24}H_{26}N_2O_4$ (406.5): C 70.92, H 6.45, N 6.89; found: C 70.99, H 6.47, N 6.86.

Fused indolizidinone (+)-15b: Compound (+)-**15b** (38 mg; 75%) was obtained from the cycloadduct (+)-**9c** (50 mg, 0.139 mmol); colorless oil; $[\alpha]_D = +38.0$ ($c = 0.7$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 7.91$ (d, $J = 8.9$ Hz, 1H), 7.03 (d, $J = 2.9$ Hz, 1H), 6.78 (dd, $J = 8.9$, 2.9 Hz, 1H), 5.90 (m, 1H), 5.15 (m, 2H), 4.92 (d, $J = 5.6$ Hz, 1H), 3.86 (m, 2H), 3.74 and 3.76 (s, each 3H), 3.51 (m, 2H), 3.29 (m, 2H), 3.19 (m, 1H), 2.29 (m, 1H), 1.69 ppm (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = 169.8$, 157.4, 136.1, 129.4, 128.3, 122.5, 116.7, 113.9, 111.9, 83.4, 72.4, 61.1, 59.1, 58.8, 58.2, 55.5, 51.5, 33.3, 24.5, 20.3 ppm; IR ($CHCl_3$): $\tilde{\nu} = 3318$, 1710 cm^{-1}; MS (ES): m/z (%): 381 (3) $[M+Na]^+$, 359 (100) $[M+1]^+$, 358 (3) $[M]^+$; elemental analysis calcd (%) for $C_{20}H_{26}N_2O_4$ (358.4): C 67.02, H 7.31, N 7.82; found: C 67.10, H 7.34, N 7.79.

General procedure for the synthesis of piperidones (+)-18 and (+)-25: A cooled solution of L-Selectride (49 mg, 0.259 mmol) in tetrahydrofuran (0.259 mL) was added dropwise to a stirred solution of the appropriate cycloadduct (+)-**3h** or (+)-**4h** (0.236 mmol) in tetrahydrofuran (3.5 mL) at −78 °C, and the mixture was stirred at −78 °C [5 h for (+)-**3h** and 1 h for (+)-**4h**]. Saturated aqueous sodium hydrogen carbonate (0.5 mL) was then added, and the mixture was allowed to warm to room temperature, before being extracted with ethyl acetate. The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue eluting with ethyl acetate/hexanes (1:1 containing 1% triethylamine) gave analytically pure compounds (+)-**18** and (+)-**25**.

Piperidone (+)-25: Compound (+)-**25** (152 mg; 80%) was obtained from the cycloadduct (+)-**4h** (188 mg, 0.479 mmol); yellow solid; m.p. 158–159 °C (hexanes/ethyl acetate); $[\alpha]_D = +21.2$ ($c = 1.0$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 7.48$ (m, 4H), 7.04 (m, 4H), 6.82 (m, 2H), 4.34 and 4.41 (d, $J = 5.6$ Hz, each 1H), 4.00 (m, 1H), 3.54 and 3.74 (s, each 3H), 3.28 (m, 2H), 2.48 (m, 4H), 2.25 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = 207.2$, 165.4, 154.3, 144.1, 135.4, 134.6, 129.7, 122.9, 118.4, 115.2, 82.5, 59.8, 59.1, 57.4, 55.7, 52.7, 41.9, 40.9, 21.1 ppm; IR (KBr): $\tilde{\nu} = 1751$, 1720 cm^{-1}; MS (CI): m/z (%): 395 (100) $[M+1]^+$, 394 (15) $[M]^+$; elemental analysis calcd (%) for $C_{23}H_{26}N_2O_4$ (394.5): C 70.03, H 6.64, N 7.10; found: C 69.92, H 6.61, N 7.13.

General procedure for the synthesis of hydroxypiperidines (+)-19, (+)-20, and (+)-26: Sodium borohydride (51 mg, 1.29 mmol) was added in portions to a stirred solution of the appropriate piperidone (+)-**18** or (+)-**25** (0.645 mmol) in methanol (6.5 mL) at 0 °C, and the mixture was stirred at 0 °C until the starting material had been consumed (TLC). Saturated aqueous ammonium chloride (1.0 mL) was added, and the mixture was allowed to warm to room temperature, before being extracted with ethyl acetate. The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue eluting with ethyl acetate/hexanes mixtures gave analytically pure compounds (+)-**19**, (+)-**20**, and (+)-**26**.

Hydroxypiperidine (+)-26: Compound (+)-**26** (230 mg; 90%) was obtained from the piperidone (+)-**25** (254 mg, 0.645 mmol); yellow solid; m.p. 71–72 °C (hexanes/ethyl acetate); $[\alpha]_D = +22.2$ ($c = 0.6$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 7.60$ (m, 2H), 7.05 (m, 4H), 6.78 (m, 2H), 4.20 and 4.38 (d, $J = 4.0$ Hz, each 1H), 3.81 (m, 4H), 3.64 (s, 3H), 3.46 (dd, $J = 7.6$, 2.0 Hz, 1H), 3.22 (dt, $J = 7.8$, 2.2 Hz, 1H), 2.66 (td, $J = 8.0$, 1.6 Hz, 1H), 2.32 (s, 3H), 2.27 (dt, $J = 7.8$, 2.0 Hz, 1H), 1.87 (m, 1H), 1.69

(m, 1H), 1.60 (m, 1H), 1.41 ppm (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 165.1, 156.8, 144.5, 135.8, 133.7, 129.2, 125.9, 117.9, 114.7, 81.8, 68.7, 59.4, 58.9, 57.1, 55.4, 55.3, 36.6, 35.1, 20.8 ppm; IR ($CHCl_3$): $\tilde{\nu}$ = 3511, 1745 cm^{-1}; MS (CI): *m*/*z* (%): 397 (100) $[M+1]^+$, 396 (15) $[M]^+$; elemental analysis calcd (%) for $C_{23}H_{28}N_2O_4$ (396.5): C 69.67, H 7.12, N 7.07; found: C 69.57, H 7.15, N 7.03.

General procedure for the synthesis of *tert*-butyldimethylsilyl ethers (+)-21, (+)-22, and (+)-27: A solution of the appropriate hydroxypiperidine (+)-**19**, (+)-**20**, or (+)-**26** (0.505 mmol) in dimethylformamide (1.0 mL) was added dropwise to a stirred suspension of *tert*-butyldimethylsilyl chloride (126 mg, 0.833 mmol) and imidazole at 0 °C, and the mixture was stirred at room temperature until the starting material had been consumed (TLC). Saturated aqueous ammonium chloride (1.0 mL) was added, and the mixture was extracted with dichloromethane. The combined organic extracts were washed with brine and water, dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue eluting with ethyl acetate/hexanes mixtures gave analytically pure compounds (+)-**21**, (+)-**22**, and (+)-**27**.

***tert*-Butyldimethylsilyl ether (+)-27**: Compound (+)-**27** (207 mg; 80%) was obtained from the hydroxypiperidine (+)-**26** (200 mg, 0.505 mmol); yellow oil; $[\alpha]_D$ = +68.1 (*c* = 1.0 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.62 (m, 2H), 7.05 (m, 4H), 6.77 (m, 2H), 4.17 and 4.38 (d, *J* = 5.6 Hz, 1H), 3.64 and 3.79 (s, each 3H), 3.41 (m, 1H), 3.19 (dt, *J* = 12.4, 3.4 Hz, 1H), 2.64 (td, *J* = 11.9, 2.7 Hz, 1H), 2.32 (s, 3H), 2.15 (m, 1H), 1.53 (m, 3H), 0.87 (s, 9H), 0.05 ppm (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 165.5, 156.9, 145.0, 136.0, 133.9, 129.4, 126.2, 118.4, 114.9, 81.9, 70.1, 59.5, 59.2, 57.8, 56.1, 55.6, 36.9, 36.0, 26.0, 25.8, 21.0, 18.4 ppm; IR ($CHCl_3$): $\tilde{\nu}$ = 1747 cm^{-1}; MS (CI): *m*/*z* (%): 511 (100) $[M+1]^+$, 510 (31) $[M]^+$; elemental analysis calcd (%) for $C_{29}H_{42}N_2O_4Si$ (510.8): C 68.20, H 8.29, N 5.48; found: C 68.11, H 8.25, N 5.51.

General procedure for the CAN-mediated N-deprotection: synthesis of piperidines (+)-23, (+)-24, and (−)-28: A solution of CAN (171 mg, 0.313 mmol) in water (2 mL) was slowly added to a stirred solution of the corresponding *N*-protected piperidine (+)-**21**, (+)-**22**, or (+)-**27** (0.136 mmol) in acetonitrile (2 mL) at −35 °C. The reaction mixture was stirred at −35 °C for 30 min. Aqueous 10% sodium sulfite (1.0 mL) was then added, and the mixture was extracted with ethyl acetate. The combined organic extracts were washed with brine and water, dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue eluting with ethyl acetate/hexanes mixtures gave analytically pure compounds (+)-**23**, (+)-**24**, and (−)-**28**.

Piperidine (−)-28: Compound (−)-**28** (56 mg; (43%) was obtained from the N-protected piperidine (+)-**27** (160 mg, 0.311 mmol); red oil; $[\alpha]_D$ = −32.5 (*c* = 0.6 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.31 (m, 2H), 7.10 (m, 2H), 6.99 (s, 1H), 4.60 (d, *J* = 5.4 Hz, 1H), 4.16 (dd, *J* = 5.9, 5.4 Hz, 1H), 3.65 (s, 3H), 3.56 (m, 1H), 3.16 (m, 2H), 2.55 (td, *J* = 12.4, 2.2 Hz, 1H), 2.29 (s, 3H), 1.80 (m, 2H), 1.27 (m, 2H), 0.79 (s, 9H), 0.00 ppm (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 165.2, 134.6, 134.3, 129.4, 118.4, 82.7, 69.7, 60.5, 59.3, 55.5, 44.5, 39.7, 36.1, 25.6, 20.7, 17.9 ppm; IR ($CHCl_3$): $\tilde{\nu}$ = 3438, 1743 cm^{-1}; MS (CI): *m*/*z* (%): 405 (100) $[M+1]^+$, 404 (17) $[M]^+$; elemental analysis calcd (%) for $C_{22}H_{36}N_2O_3Si$ (404.6): C 65.30, H 8.97, N 6.92; found: C 65.42, H 9.00, N 6.89.

General procedure for the preparation of *O*-acetylmandelates 29–32: (*R*)- or (*S*)-*O*-Acetylmandelic acid (20 mg, 0.10 mmol) and 4-dimethylaminopyridine (DMAP) (cat.) were added to a solution of the corresponding alcohol (0.09 mmol) in dichloromethane (1.0 mL), followed by a solution of dicyclohexylcarbodiimide (DCC) (37 mg, 0.18 mmol) in dichloromethane (500 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 16 h. The solvent was removed under reduced pressure and diethyl ether was added. The resulting mixture was then filtered and the filtrate was concentrated under reduced pressure. Chromatography of the residue eluting with dichloromethane/ethyl acetate mixtures gave analytically pure *O*-acetylmandelates **29–32**.

(*R*)-*O*-Acetylmandelate (+)-31: Compound (+)-**31** (38 mg; 86%) was obtained from the hydroxypiperidine (+)-**26** (31 mg, 0.078 mmol); yellow oil; $[\alpha]_D$ = +47.1 (*c* = 0.6 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.42 (m, 13H), 5.77 (s, 1H), 4.88 (m, 1H), 4.16 and 4.34 (d, *J* = 5.8 Hz, each 1H), 3.79 (s, 3H), 3.59 (s, 3H), 3.22 and 3.45 (m, each 1H), 2.69 (t, *J* = 12.5 Hz, 1H), 2.34 (s, 3H), 2.16 (s, 3H), 1.42 ppm (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 170.3, 168.4, 165.2, 156.9, 144.2, 135.8, 133.8, 133.3, 129.2, 129.1, 128.7, 127.4, 125.9, 117.9, 114.8, 81.8, 74.7, 72.8, 59.5, 58.9, 56.6, 55.5, 55.3, 32.1, 25.3, 20.8, 20.5 ppm; IR ($CHCl_3$): $\tilde{\nu}$ = 1744 cm^{-1}; MS (CI): *m*/*z* (%): 573 (100) $[M+1]^+$, 572 (18) $[M]^+$; elemental analysis calcd (%) for $C_{33}H_{36}N_2O_7$ (572.7): C 69.21, H 6.34, N 4.89; found: C 69.28, H 6.37, N 4.86.

(*S*)-*O*-Acetylmandelate (+)-32: Compound (+)-**32** (39 mg; 88%) was obtained from the hydroxypiperidine (+)-**26** (31 mg, 0.078 mmol); yellow oil; $[\alpha]_D$ = +25.1 (*c* = 0.8 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.10 (m, 13H), 5.86 (s, 1H), 4.96 (m, 1H), 4.18 and 4.38 (d, *J* = 5.8 Hz, each 1H), 3.79 (s, 3H), 3.64 (s, 3H), 3.16 and 3.49 (m, each 1H), 2.67 (t, *J* = 12.5 Hz, 1H), 2.33 (s, 3H), 2.16 (s, 3H), 1.57 ppm (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 170.2, 168.3, 165.4, 157.1, 144.3, 135.9, 133.9, 133.3, 129.4, 129.2, 128.8, 127.7, 126.1, 118.1, 114.9, 81.9, 74.6, 72.7, 59.7, 58.9, 56.7, 55.8, 55.5, 32.5, 31.4, 20.9, 20.7 ppm; IR ($CHCl_3$): $\tilde{\nu}$ = 1746 cm^{-1}; MS (CI): *m*/*z* (%): 573 (100) $[M+1]^+$, 572 (33) $[M]^+$; elemental analysis calcd (%) for $C_{33}H_{36}N_2O_7$ (572.7): C 69.21, H 6.34, N 4.89; found: C 69.43, H 6.38, N 4.87.

Sodium methoxide promoted reaction of piperidinyl-β-lactams: general procedure for the preparation of indolizidinones 33–35: Sodium methoxide (0.6 mmol) was added in portions at 0 °C to a solution of the appropriate piperidinyl-β-lactam (0.15 mmol) in methanol (3 mL). The reaction mixture was stirred at room temperature until the starting material had been completely consumed (TLC), and then water (0.5 mL) was added. The methanol was evaporated under reduced pressure, the aqueous residue was extracted with ethyl acetate (5 × 3 mL), and the combined organic layers were dried over $MgSO_4$ and then concentrated under reduced pressure. Chromatography of the residue eluting with ethyl acetate/hexanes mixtures gave analytically pure compounds **33–35**.

Indolizidinone (+)-33: Compound (+)-**33** (18 mg; 100%) was obtained from the piperidinyl-β-lactam (+)-**23** (18 mg, 0.043 mmol); colorless oil; $[\alpha]_D$ = +23.6 (*c* = 1.0 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.01 (m, 2H), 6.58 (m, 2H), 4.20 (ddd, *J* = 13.7, 5.1, 1.5 Hz, 1H), 4.09 (t, *J* = 6.8 Hz, 1H), 3.76 (m, 3H), 3.61 (s, 3H), 2.69 (td, *J* = 13.7, 3.2 Hz, 1H), 2.25 (s, 3H), 1.84 (m, 2H), 1.27 (m, 2H), 0.83 (s, 9H), 0.02 (s, 3H), 0.00 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 169.2, 144.3, 129.9, 127.9, 113.4, 82.6, 69.4, 58.5, 55.6, 55.3, 38.3, 36.2, 34.4, 25.7, 20.3, 17.9 ppm; IR ($CHCl_3$): $\tilde{\nu}$ = 3432, 1710 cm^{-1}; MS (CI): *m*/*z* (%): 405 (100) $[M+1]^+$, 404 (25) $[M]^+$; elemental analysis calcd (%) for $C_{22}H_{36}N_2O_3Si$ (404.6): C 65.30, H 8.97, N 6.92; found: C 65.20, H 9.00, N 6.96.

Indolizidinone (+)-34: Compound (+)-**34** (50 mg; 100%) was obtained from the piperidinyl-β-lactam (+)-**24** (50 mg, 0.119 mmol); colorless oil; $[\alpha]_D$ = +42.9 (*c* = 0.6 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 6.99 (m, 2H), 6.55 (m, 2H), 4.26 (m, 1H), 4.20 (m, 1H), 4.05 (dd, *J* = 6.9, 6.8 Hz, 1H), 3.97 (m, 1H), 3.82 (d, *J* = 6.6 Hz, 1H), 3.61 (s, 3H), 3.13 (td, *J* = 12.5, 3.9 Hz, 1H), 2.23 (s, 3H), 1.49 (m, 4H), 0.86 (s, 9H), 0.05 (s, 3H), 0.00 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 168.9, 144.6, 129.9, 127.8, 113.4, 83.0, 64.9, 58.3, 55.4, 52.3, 35.5, 33.7, 32.3, 25.8, 20.4, 18.1 ppm; IR ($CHCl_3$): $\tilde{\nu}$ = 3426, 1712 cm^{-1}; MS (CI): *m*/*z* (%): 405 (100) $[M+1]^+$, 404 (25) $[M]^+$; elemental analysis calcd (%) for $C_{22}H_{36}N_2O_3Si$ (404.6): C 65.30, H 8.97, N 6.92; found: C 65.42, H 9.01, N 6.88.

Indolizidinone (−)-35: Compound (−)-**35** (45 mg; 100%) was obtained as a colorless oil from the piperidinyl-β-lactam (−)-**28** (45 mg, 0.107 mmol); $[\alpha]_D$ = −12.5 (*c* = 0.9 in $CHCl_3$); ^{1}H NMR (300 MHz, CD_3OD, 25 °C): δ = 6.95 (m, 2H), 6.66 (m, 2H), 4.06 (ddd, *J* = 13.4, 5.1, 1.7 Hz, 1H), 3.83 (dd, *J* = 6.1, 1.2 Hz, 1H), 3.69 (dd, *J* = 6.6, 6.1 Hz, 1H), 3.52 (s, 3H), 3.24 (m, 2H), 2.74 (td, *J* = 13.2, 2.2 Hz, 1H), 2.19 (s, 3H), 1.88 and 2.14 (m, each 1H), 1.30 (m, 4H), 0.86 (s, 9H), 0.06 (s, 3H), 0.04 ppm (s, 3H); ^{13}C NMR (75 MHz, CD_3OD, 25 °C): 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 ppm; IR ($CHCl_3$): $\tilde{\nu}$ = 3335, 1722 cm^{-1}; MS (CI): *m*/*z* (%): 405 (100) $[M+1]^+$, 404 (18) $[M]^+$; elemental analysis calcd (%) for $C_{22}H_{36}N_2O_3Si$ (404.6): C 65.30, H 8.97, N 6.92; found: C 65.19, H 8.93, N 6.89.

General procedure for the reduction of indolizidinones: Synthesis of indolizidines 36–39: A solution of the appropriate indolizidinone (0.10 mmol) in tetrahydrofuran or diethyl ether (1 mL) was added dropwise to a well-stirred suspension of lithium aluminum hydride (0.80 mmol) in the same solvent (1 mL) at 0 °C, and the mixture was stirred at room temperature until the starting material had been consumed (TLC). Saturated aqueous ammonium chloride (1.0 mL) was added at 0 °C, and the mixture was allowed to warm to room temperature, before being

extracted with ethyl acetate. The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue eluting with ethyl acetate/hexanes mixtures gave analytically pure compounds **36**–**39**.

Fused indolizidine (+)-37: Compound (+)-**37** (18 mg; 72%) was obtained from the indolizidinone (+)-**15b** (26 mg, 0.073 mmol); colorless oil; $[\alpha]_D = +71.0$ ($c = 0.6$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 6.93$ (d, $J = 2.9$ Hz, 1H), 6.67 (dd, $J = 8.7$, 2.9 Hz, 1H), 6.35 (d, $J = 8.7$ Hz, 1H), 5.87 (m, 1H), 5.01 (m, 2H), 4.97 (d, $J = 5.6$ Hz, 1H), 3.69 (m, 7H), 3.32 (m, 7H), 3.12 (dd, $J = 9.4$, 5.8 Hz, 1H), 1.64 ppm (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = 153.7$, 140.8, 134.2, 127.9, 122.2, 114.4, 113.4, 112.7, 83.8, 72.8, 60.6, 60.4, 57.7, 55.9, 53.3, 51.5, 32.7, 29.2, 26.7, 22.1 ppm; IR ($CHCl_3$): $\tilde{\nu} = 3320\ cm^{-1}$; MS (CI): m/z (%): 345 (100) $[M+1]^+$, 344 (25) $[M]^+$; elemental analysis calcd (%) for $C_{20}H_{28}N_2O_3$ (344.5): C 69.74, H 8.19, N 8.13; found: C 69.85, H 8.22, N 8.10.

Indolizidine (−)-38: Compound (−)-**38** (30 mg; 79%) was obtained from the indolizidinone (+)-**34** (40 mg, 0.098 mmol); colorless oil; $[\alpha]_D = -36.0$ ($c = 0.6$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 6.99$ (m, 2H), 6.58 (m, 2H), 4.11 (m, 1H), 3.89 (m, 1H), 3.65 (m, 2H), 3.39 (m, 1H), 3.31 (s, 3H), 2.82 (m, 2H), 2.47 (td, $J = 10.9$, 4.5 Hz, 1H), 2.21 (s, 3H), 2.12 (dd, $J = 9.9$, 4.9 Hz, 1H), 1.61 (m, 3H), 0.86 (s, 9H), 0.01 ppm (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = 144.9$, 129.8, 126.4, 113.4, 85.0, 64.9, 60.3, 59.2, 57.1, 47.7, 33.7, 32.9, 29.8, 25.9, 20.4, 18.1 ppm; IR ($CHCl_3$): $\tilde{\nu} = 3431\ cm^{-1}$; MS (CI): m/z (%): 391 (100) $[M+1]^+$, 390 (19) $[M]^+$; elemental analysis calcd (%) for $C_{22}H_{38}N_2O_2Si$ (390.6): C 67.64, H 9.80, N 7.17; found: C 67.75, H 9.76, N 7.11.

Acknowledgements

Support of this work by the DGI-MCYT (Project BQU2000–0645) is gratefully acknowledged. J. M. Alonso thanks the Universidad Complutense de Madrid for a fellowship.

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[22] Full spectroscopic and analytical data for compounds not included in this Experimental Section are described in the Supporting Information.

Received: January 3, 2003 [F4712]