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Diastereodivergent Pictet–Spengler Cyclization of Bicyclic *N*-Acyliminium Ions: Controlling a Quaternary Stereocenter

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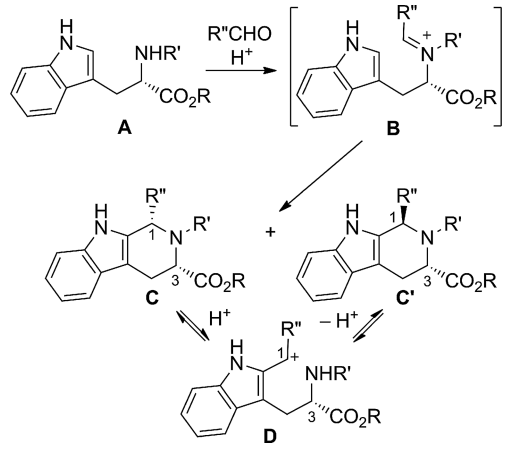
The diastereoselectivity of the Pictet–Spengler cyclization of bicyclic *N*-acyliminium ions that contain a 3-azabicyclo-[*n*.3.0]alkane core and an electron-rich π-nucleophilic moiety, such as an indol-2-yl, indol-3-yl, 1-methylpyrrol-2-yl, or 3,5-dimethoxyphenyl group, was examined. The *N*-acyliminium ions were generated by protonation of the corresponding enamides or hemiaminals, which were derived from imides. Control of the quaternary stereocenter created at the newly formed ring junction was achieved in a diastereodivergent manner by fine-tuning the reaction conditions, which determined whether the reaction proceeded under kinetic or thermodynamic control. Mechanistic studies indicated that a retro-Pictet–Spengler reaction pathway is involved in the equilibration process.

Introduction

The intramolecular reaction between an electron-rich heteroaromatic or aromatic group and an iminium ion species, known as the Pictet–Spengler cyclization, is a powerful method for the biomimetic synthesis of bioactive isoquinoline and indole alkaloids.[1,2] The control of the configuration of the new stereocenter that is formed during the course of a Pictet–Spengler cyclization has been the focus of numerous investigations.[1–8] In the last decade, these research efforts have culminated in the development of catalytic enantioselective reactions by using chiral thioureas[3] or Brønsted acids,[4] but the control of the newly formed asymmetric carbon often relies on diastereoselective reactions.[1,2] One of the classical versions of the Pictet–Spengler reaction arguably involves the condensation of *N*-substituted tryptophan ester **A** with an aldehyde in the presence of an acid catalyst. The subsequent cyclization of the resulting iminium ion **B** provides tetrahydro-β-carbolines **C** and **C′** with stereocenters at C-1 and C-3.[1] The diastereoselectivity of this reaction, which depends on the substituents of the ester group, the nitrogen atom, and the aldehyde as well as on the experimental conditions, has been widely investigated.[5] It is now well established that *cis* diastereomer **C** is preferentially formed under kinetic control and that a thermodynamically controlled epimerization to give the more stable *trans* diastereomer **C′** can occur.[5] Mechanistic studies have shown this equilibration process to proceed by ionization of the C-1–N bond under acidic conditions, which leads to carbocationic intermediate **D** and a ring closure, rather than by a retro-Pictet–Spengler process (Scheme 1).[5q]



Scheme 1. Classical version of the Pictet–Spengler cyclization to lead to tetrahydro-β-carbolines **C** and **C′** by starting from tryptophan ester **A**.

The Pictet–Spengler cyclization, which generally proceeds under mild conditions, involves π-nucleophiles and *N*-acyliminium ions, which are more electrophilic than iminium ions.[2] Substituted *N*-acyliminium ions **E**, with stereocenters contained within the structure, can be generated from a wide variety of precursors,[2] and in recent years, elegant organocatalyzed processes have been devel-

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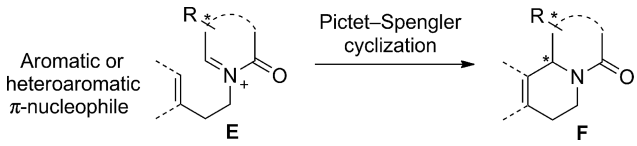
oped.[6,7] The configuration of the newly formed stereocenter at the ring junction of resulting heterocycle **F** is then produced by a diastereoselective Pictet–Spengler cyclization (Scheme 2).

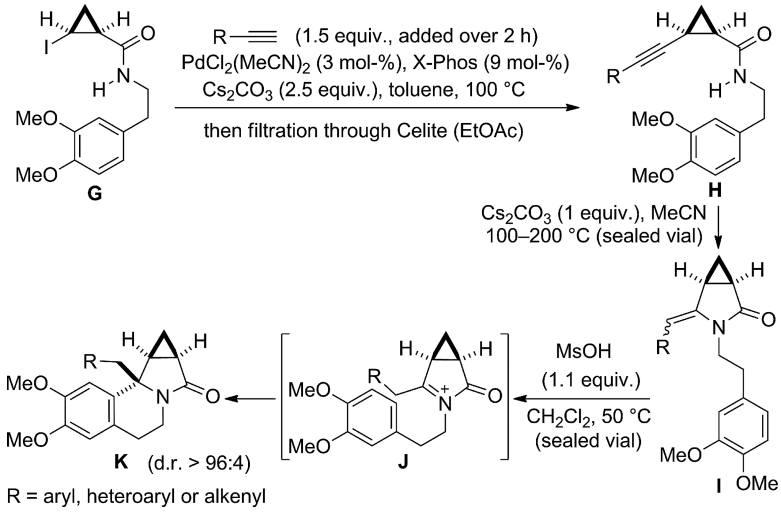


Scheme 2. Pictet–Spengler cyclization that involves π-nucleophiles and substituted *N*-acyliminium ions.

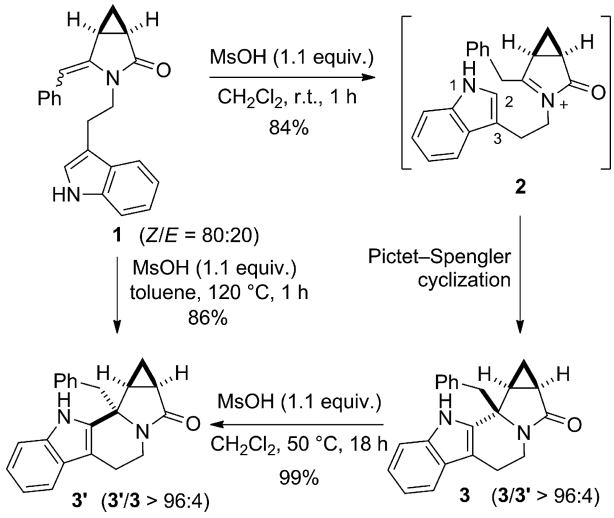
A few examples of the acid-promoted epimerization of the stereocenter of nitrogen heterocycle **F**, which resulted from a Pictet–Spengler cyclization of an indole and an *N*-acyliminium ion, have been reported.[8] Additionally, diastereodivergent Pictet–Spengler reactions that control the resulting tertiary stereocenter and involve electron-rich π-nucleophiles, such as indoles, furans, and 3,5-dimethoxyphenyl groups, have also been observed to depend on the reaction conditions (kinetic vs. thermodynamic control).[7] Recently, we reported a new access to bicyclic enamides **I**, which contain a 4-methylene-3-azabicyclo[3.1.0]-hexan-2-one core, by employing a two-step procedure that started from *cis*-2-iodocyclopropanecarboxamides **G**, derived from homoveratrylamine.[9] The sequence relied on a copper-free Sonogashira cross-coupling[10] reaction between iodocyclopropane **G** and terminal aryl alkynes, heteroaryl alkynes, or conjugated enynes [$PdCl_2(MeCN)_2$ (3 mol-%), X-Phos (2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl, 9 mol-%), Cs_2CO_3 (2.5 equiv.), toluene, 100 °C][11] to lead to *cis*-2-alkynylcyclopropanecarboxamide **H**, which was not purified but directly subjected to a 5-*exo*-*dig* cyclization (Cs_2CO_3, MeCN, 100–200 °C, sealed vial). The *N*-acyliminium ion **J**, which was generated by protonation of enamide **I** (MsOH, CH_2Cl_2, 50 °C, sealed vial), underwent a highly diastereoselective Pictet–Spengler cyclization to afford tetracyclic nitrogen heterocycle **K**. As anticipated, the diastereoselectivity that was observed in the Pictet–Spengler cyclization corresponded to the kinetically controlled addition of the 3,4-dimethoxyphenyl group to the less-hindered face (opposite to the cyclopropane) of the bicyclic *N*-acyliminium ion **J**.[9] It is worth noting that tetracyclic compound **K** is configurationally stable even upon prolonged heating in the presence of MsOH (Ms = methylsulfonyl) in toluene at reflux (Scheme 3).[12]

In contrast, we observed that enamide **1**, derived from tryptamine, exhibited a different behavior. Indeed, under the previously developed conditions (MsOH, CH_2Cl_2, 50 °C, 4 h), the Pictet–Spengler cyclization of **1** proceeded through *N*-acyliminum ion intermediate **2** to generate a mixture of epimeric nitrogen heterocycles **3** and **3′** in a 40:60 ratio (84% yield).[9] Because of the higher nucleophilic character of indole compared to the 3,4-dimethoxyphenyl group, the Pictet–Spengler cyclization of **1** could be carried out at room temperature. Under these milder conditions, the reaction produced tetracyclic compound **3** (84% yield) as a single diastereomer (**3**/**3′** > 96:4) as a result of the kinetically controlled nucleophilic attack of the C-2 indole atom on the less-hindered face of *N*-acyliminium ion **2**. In contrast, harsher conditions (MsOH, toluene, 120 °C, 1 h) resulted in the highly diastereoselective formation of tetracyclic compound **3′** (86% yield), which is an epimer of **3** at the newly formed quaternary stereocenter at the ring junction (**3′**/**3**, >96:4).[13] In this latter case, the observed diastereoselectivity was explained by a thermodynamically controlled epimerization of the initially formed kinetic product, diastereomer **3**. Indeed, this result was confirmed by subjecting nitrogen heterocycle **3** to prolonged heating in the presence of MsOH (CH_2Cl_2, 50 °C, 18 h). Under these conditions, the thermodynamic product, epimer **3′**, was obtained in nearly quantitative yield (Scheme 4).[9]

Herein, we report new examples of the diastereodivergent Pictet–Spengler cyclization of bicyclic *N*-acyliminum ion **L**, which leads to epimeric nitrogen heterocycles **M** or **M′** with a quaternary stereocenter at the newly formed ring junction. These processes can occur with high

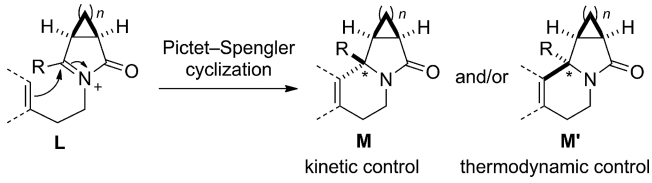


Scheme 3. Pictet–Spengler cyclization of bicyclic *N*-acyliminium ion **J** to lead to nitrogen heterocycle **K** that contains a quaternary center.



Scheme 4. Diastereodivergent Pictet–Spengler cyclization of enamide **1**, which is derived from tryptamine.

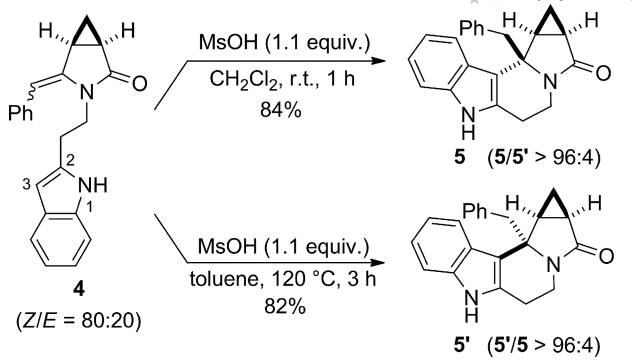
levels of diastereoselectivity for a variety of substrates, and the configuration of the quaternary stereocenter can be controlled by fine-tuning the reaction conditions, which determine whether the reaction proceeds under kinetic or thermodynamic control. Additionally, we provide evidence that a retro-Pictet–Spengler reaction is involved in the equilibration process of **M** into **M′** (Scheme 5).



Scheme 5. This work involves the diastereodivergent Pictet–Spengler cyclization of bicyclic *N*-acyliminium ion **L** and the control a the newly formed quaternary stereocenter at the ring junction.

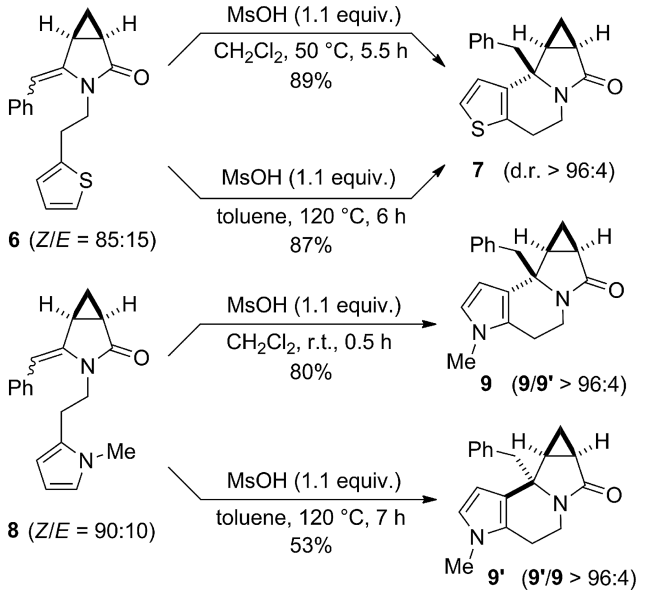
Results and Discussion

The possibility of achieving a diastereodivergent Pictet–Spengler cyclization was first explored by using other 4-benzylidene-3-azabicyclo[3.1.0]hexan-2-ones that contain different remote electron-rich π-nucleophilic heteroaromatic groups. Thus, enamide **4**, which is derived from 2-(indol-2-yl)ethylamine, underwent a highly diastereoselective kinetically controlled cyclization in the presence of MsOH (CH_2Cl_2, r.t.), which involved the C-3 nucleophilic position of the indole to produce compound **5** as a single detectable diastereomer (84% yield). Under harsher conditions (MsOH, toluene, 120 °C), a reversal of diastereoselectivity took place, and epimer **5′** was selectively obtained (82% yield) with high diastereocontrol (**5′**/**5** > 96:4; Scheme 6).[13]



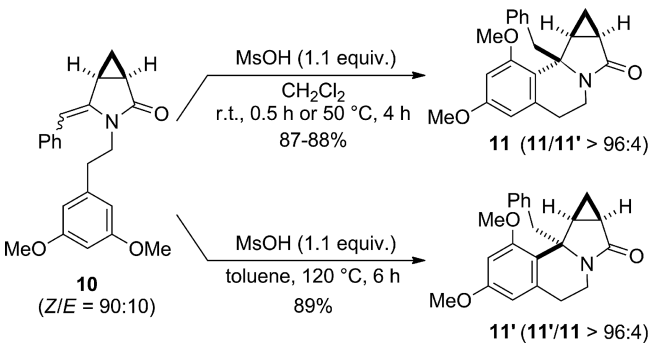
Scheme 6. Diastereodivergent Pictet–Spengler cyclization of enamide **4**.

The Pictet–Spengler cyclization of enamide **6**, which contains a remote 2-thienyl group as the π-nucleophile, delivered the same tetracyclic compound **7** as a single diastereomer irrespective of the reaction conditions (MsOH, CH_2Cl_2, 50 °C or MsOH, toluene 120 °C; Scheme 7).[9] In contrast, the structurally related enamide **8**, which contains a 1-methylpyrrol-2-yl group, displayed different behavior. Because the nucleophilic character of 1-methylpyrrole is greater than thiophene,[14] the Pictet–Spengler cyclization occurred at room temperature to afford tetracyclic compound **9** as a single diastereomer (80% yield). Although heating this reaction mixture in CH_2Cl_2 at reflux did not alter the stereochemical outcome, harsher conditions (MsOH, toluene, 120 °C, 7 h) induced a complete reversal of diastereoselectivity to give epimer **9′** selectively (**9′**/**9** > 96:4).[13] However, compound **9′** was only isolated in moderate yield (53%) because of the sensitivity of the pyrrole ring under acidic conditions, which resulted in partial decomposition (Scheme 7).



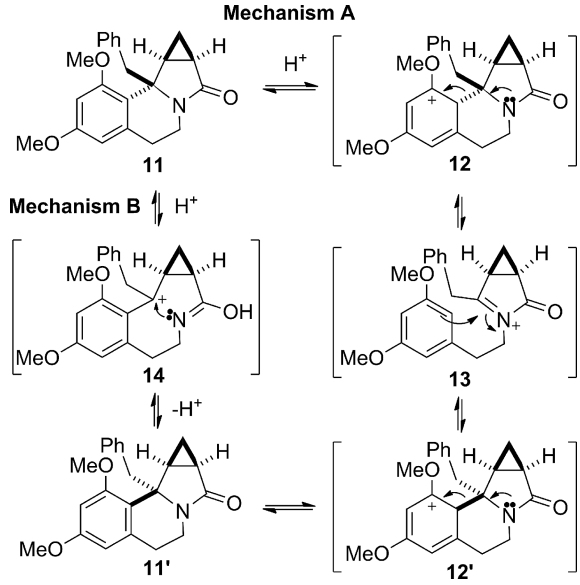
Scheme 7. Pictet–Spengler cyclization of enamides **6** and **8**.

We previously observed that in the Pictet–Spengler cyclization of *N*-acyliminium ion **J**, derived from homoveratrylamine, the 3,4-dimethoxyphenyl group acts as the π-nucleophile to provide nitrogen heterocycle **K** with a high level of diastereoselectivity. No equilibration took place under harsher conditions (Scheme 3). In contrast, a diastereodivergent cyclization was achieved for enamide **10**, which contains a 3,5-dimethoxyphenyl substituent. This latter aromatic group is much more reactive than the 3,4-dimethoxyphenyl group, and the Pictet–Spengler cyclization was achieved under standard conditions at room temperature to provide tetracyclic nitrogen heterocycle **11** (87% yield) as a single detectable diastereomer. Heating this reaction at 50 °C did not alter the stereochemical outcome, and the kinetic product, epimer **11**, was still selectively obtained (88% yield; **11**/**11′** > 96:4). However, harsher conditions (MsOH, toluene, 120 °C) led to the thermodynamic product, epimer **11′** (89% yield), with complete diastereocontrol (Scheme 8).[13]



Scheme 8. Diastereodivergent Pictet–Spengler cyclization of enamide **10**.

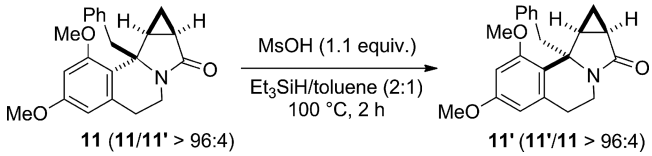
The different behaviors of the substrates, which depend on the nature of the π-nucleophile (the 2-thienyl and 3,4-dimethoxyphenyl groups vs. the indol-2-yl, indol-3-yl, 1-methylpyrrol-2-yl, and 3,5-dimethoxyphenyl groups), have already been noted by Franzén et al.[7] in their organocatalyzed asymmetric sequence toward substituted quinolizidines. Their work features a diastereoselective Pictet–Spengler cyclization, which controls the formation of a tertiary stereocenter in the final step. In contrast to the classical Pictet–Spengler cyclization of iminium ions that are generated from tryptophan esters and aldehydes (Scheme 1),[5] little information is available on the observed equilibration mechanism in the case of reactions that involve *N*-acyliminium ion intermediates and various π-nucleophiles.[15] As illustrated in the case of compound **11**, two mechanisms can be proposed to explain the observed equilibration reaction that provides the thermodynamic product, epimer **11′**. The first mechanism (Scheme 9, Mechanism A) involves a retro-Pictet–Spengler reaction, which is initiated by the protonation of the aromatic ring to generate arenium intermediate **12**. The subsequent fragmentation (by C–C bond scission) produces *N*-acyliminium ion **13**, and the nucleophilic attack on the more sterically hindered face of **13** eventually leads to the accumulation of the thermodynamic product **11′**. The second mechanism (Scheme 9, Mechanism B) involves the initial cleavage of the benzylic carbon–nitrogen bond, which is assisted by protonation of the amide moiety, to generate benzylic carbocation intermediate **14**. A subsequent transannular ring closure explains the formation of the thermodynamic product, epimer **11′**. It is worth pointing out that the location of the two methoxy groups on the aromatic ring of **11** could significantly contribute to the stabilization of either arenium intermediate **12** or benzylic cation **14**, which are the key intermediates in the two different mechanisms (Scheme 9). This could explain why the equilibration reaction does not take place in the case of tetracyclic nitrogen heterocycles **K**, which arise from the Pictet–Spengler cyclization with a 3,4-dimethoxyphenyl group as the π-nucleophile.



Scheme 9. Possible mechanisms for the equilibration reaction of **11** to give **11′**.

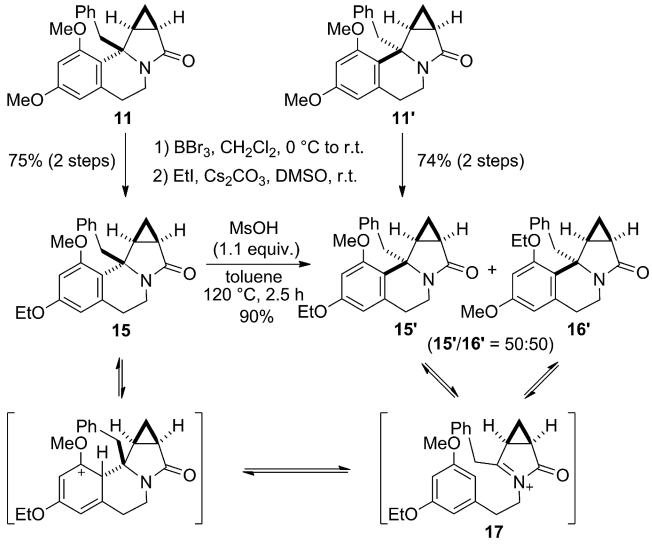
To shed light on the mechanism for the equilibration, we first envisaged trapping one of the possible cationic intermediate species, either *N*-acyliminium species **13** or benzylic cation **14**, with an external nucleophile. However, when compound **11** was heated in the presence of MsOH and a large excess amount of triethylsilane, epimer **11′**, the thermodynamic product, was isolated in nearly quantitative yield (Scheme 10). Products that would have resulted from the intermolecular reaction of either **13** or **14** with triethylsilane were not detected, presumably because of the much faster cyclization process (intramolecular reaction) taking place by either one of the two possible mechanisms.[16]

To distinguish between both mechanisms (Scheme 9, Mechanisms A and B), which involve the cleavage of a different bond, the less-hindered phenolic ether of epimer **11** was selectively demethylated (BBr_3, CH_2Cl_2, 0 °C to r.t.). The resulting phenol was then alkylated by treatment with ethyl iodide [Cs_2CO_3, dimethyl sulfoxide (DMSO), r.t.] to



Scheme 10. Equilibration of **11** into **11′** in the presence of triethylsilane.

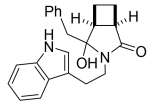
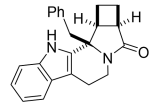
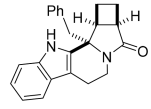
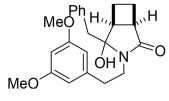
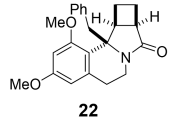
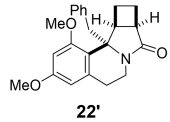
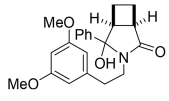
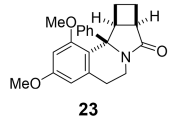
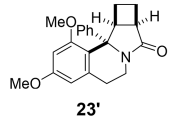
obtain ethyl ether **15** (75% yield over two steps from **11**). The same sequence was applied to epimer **11′**, which provided epimeric tetracyclic compound **15′** (74%, over two steps from **11′**). Interestingly, the treatment of **15** with MsOH in toluene (120 °C, 2.5 h) effectively gave rise to epimer **15′**, the thermodynamic product. However, this latter product was accompanied by a regioisomeric compound, the structure of which was assigned to **16′** (**15′**/**16′** = 50:50, 90% yield). The formation of compound **16′** from tetracyclic nitrogen heterocycle **15** implies the scission of a carbon-carbon bond and not the carbon-nitrogen bond.[17] Thus, compound **16′** must arise from a retro-Pictet–Spengler reaction that proceeds through *N*-acyliminium intermediate **17** (Scheme 11). This result unambiguously demonstrates that a retro-Pictet–Spengler pathway (Scheme 9, Mechanism A) is operating in the equilibration of **11** into **11′**, although the possibility of an alternative mechanistic scenario that involves the cleavage of the benzylic C–N bond (Scheme 9, Mechanism B) cannot be completely excluded.



Scheme 11. Occurrence of a retro-Pictet–Spengler pathway in the equilibration of **11** into **11′**.

The next goal was to investigate the effect of the size of the ring fused to the pyrrolidinone structure on the stereochemical outcome of the Pictet–Spengler cyclization and see if a diastereodivergent reaction could also be observed. A more conventional route, which relied on the nucleophilic addition of Grignard reagents to bicyclic imides,[18,19] was followed to prepare bicyclic hemiaminals, which were precursors to the corresponding *N*-acyliminium ions under acidic conditions.[2] The behavior of the bicyclic iminium ions that contained a bicyclo[3.2.0]heptane core and were generated from hemiaminals **18**–**20** was first investigated (Table 1).

Table 1. Diastereodivergent Pictet–Spengler cyclizations of *N*-acyliminium ions that contain a bicyclo[3.2.0]heptane core.

Entry	Substrates[a]	Conditions[b] Time	Products	Yield[c] [%]
1	 **18** (*dr* > 96:4)	**A** 1 h	 **21**	98
2		**B** 5 h	 **21'**	96
3	 **19** (*dr* > 96:4)	**A** 1.5 h	 **22**	90
4		**B** 20 h	 **22'**	92
5	 **20** (*dr* > 96:4)	**A** 1 h	 **23**	87[d]
6		**B** 44 h	 **23'**	77[d]

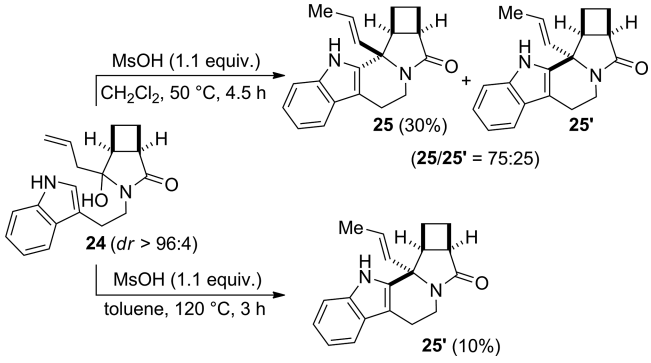
[a] Hemiaminals **18**–**20** were obtained as single diastereomers, but their relative configurations were not assigned. [b] Condition **A**: MsOH (1.1 equiv.), CH_2Cl_2, r.t.; Condition **B**: MsOH (1.1 equiv.), toluene, 120 °C. [c] Isolated yields of analytically pure products. [d] Yields for the two steps from the imide precursor.

The presence of the four-membered ring did not alter the diastereodivergent cyclization or the high diastereoselectivities. Upon treatment with MsOH, hemiaminal **18**, which is derived from tryptamine, led to either pentacyclic compound **21** (98% yield) or to epimer **21′** (96% yield) with high diastereoselectivities (*dr* >96:4), depending on the reaction conditions (Table 1, Entries 1 and 2). The same behavior was observed for hemiaminal **19**, which contains a 3,5-dimethoxyphenyl group and produced the epimeric tetracyclic compounds **22** (90% yield) or **22′** (92% yield; Table 1, Entries 3 and 4). Interestingly, hemiaminal **20**, which contains a phenyl substituent instead of a benzyl group, also participated in the diastereodivergent Pictet–Spengler cyclization to produce epimeric tetracyclic com-

pounds **23** (87% yield) and **23′** (77% yield; Table 1, Entries 5 and 6).

It is interesting to note that the isomerization of the kinetic products **22** and **23** into **22′** and **23′**, respectively, proceeded at comparable rates.[20] Thus, the presence of the phenyl group at the quaternary center of **23** did not accelerate the equilibration process, thereby suggesting that the formation of a carbocation at the position adjacent to this phenyl group may not be involved as the rate-determining step.

The behavior of hemiaminal **24** with an allyl substituent deserves specific comments. In the presence of MsOH (CH_2Cl_2, 50 °C), a 75:25 mixture of the epimers **25** and **25′** was formed, from which the kinetic product, diastereomer **25**, could be separated and isolated in 30% yield. Both stereoisomers **25** and **25′** were substituted by an (*E*)-prop-1-en-1-yl substituent at the quaternary stereocenter, as a result of isomerization of the terminal olefin of the allyl group. Under more forcing conditions, decomposition took place to a significant extent, and the thermodynamic product, diastereomer **25′**, was isolated in a very low yield (10% yield; Scheme 12).

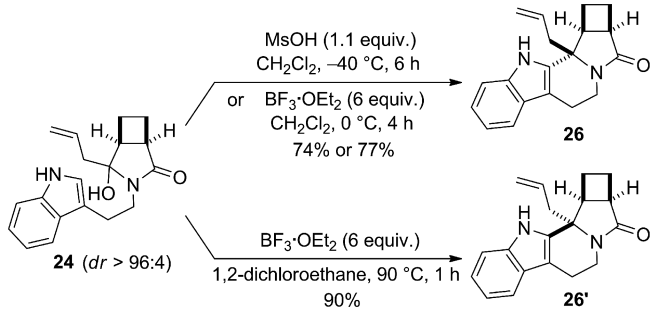


Scheme 12. Brønsted acid promoted Pictet–Spengler cyclization of hemiaminal **24**.

In the case of hemiaminal **24**, lowering the temperature (MsOH, CH_2Cl_2, –40 °C, 6 h) avoided isomerization of the terminal olefin, and compound **26** with its quaternary stereocenter substituted by an allyl group was isolated in 74% yield with no trace amounts of the regioisomeric compound **25**. An alternative option relied on the use a Lewis acid promoter. When the cyclization of **24** was carried out in the presence of $BF_3{\cdot}OEt_2$ (CH_2Cl_2, 0 °C, 4 h), compound **26** was again isolated in a similar yield of 77%. Interestingly, access to the epimer of **26** could be achieved by performing the reaction in the presence of $BF_3{\cdot}OEt_2$ in 1,2-dichloroethane at 90 °C. Compound **26′**, in which the quaternary stereocenter is substituted by an allyl group, was isolated under these conditions in an excellent 90% yield without any concurrent formation of isomerized product **25′** (Scheme 13).

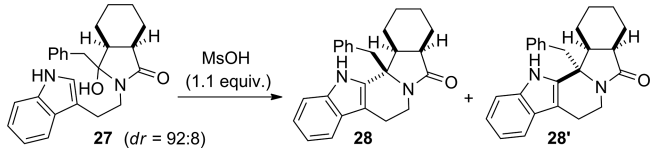
The behavior of bicyclic *N*-acyliminium ions that contain a six-membered ring fused to the pyrrolidinone unit was then investigated (Table 2).

When bicyclic hemiaminal **27** was treated with MsOH in CH_2Cl_2 at room temperature, the Pictet–Spengler cyclization provided an equimolar mixture of pentacyclic compounds **28** and **28′**, which are epimeric at the quaternary stereocenter (93% yield; Table 2, Entry 1). Decreasing the reaction temperature to –40 °C did not improve the kinetically controlled diastereoselectivity of the Pictet–Spengler reaction (**28**/**28′** = 53:47; Table 2, Entry 2). This low diastereoselectivity is probably because of the greater conformational flexibility of the six-membered ring in comparison to a three- or four-membered ring, which results in the ineffective discrimination between the two diastereofaces of the corresponding *N*-acyliminium ion. When the reaction was carried out in toluene at 120 °C for 6 h, a much improved level of diastereoselectivity was attained in favor of the thermodynamically produced epimer **28′** (94% yield; **28**/**28′** = 10:90; Table 2, Entry 3). This ratio, which was reached under thermodynamic control, did not change when the reaction time was extended (Table 2, Entry 4).



Scheme 13. Brønsted and Lewis acid promoted Pictet–Spengler cyclization of hemiaminal **24**.

Table 2. Pictet–Spengler cyclization of the *N*-acyliminium ion that is generated from hemiaminal **27**.

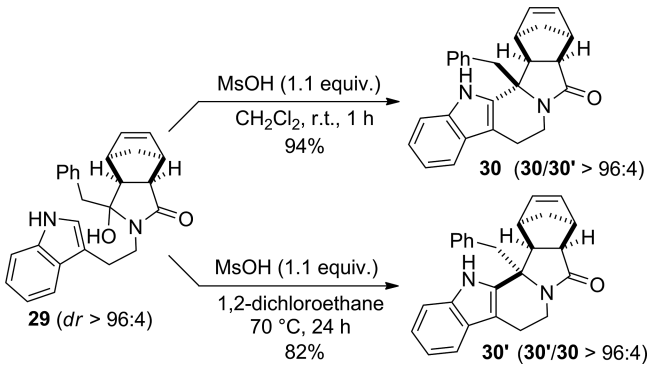


Entry	Temp. [°C]	Solvent	Time [h]	**28**/**28′**[a]	Yield [%][b]
1	20	CH_2Cl_2	1	50:50	93
2	–40	CH_2Cl_2	6	53:47	98
3	120	toluene	6	10:90	94
4	120	toluene	30	10:90	90

[a] Determined by ^{1}H NMR spectroscopic analysis of the crude product. [b] Isolated yield of the mixture of diastereomers **28** and **28′**.

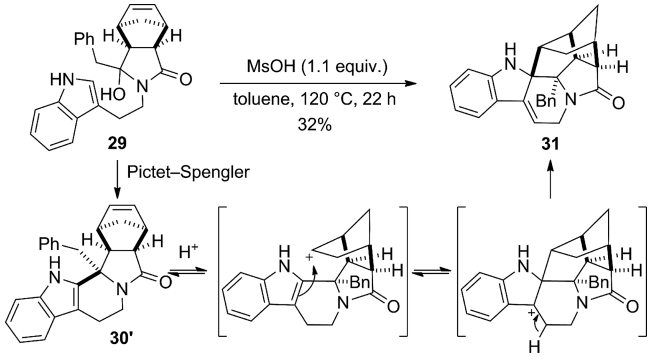
Finally, the reactivity of hemiaminal **29** with the pyrrolidinone ring fused to a norbornene unit, was studied.[18,19] This sterically hindered and conformationally locked bicyclic ring system underwent a highly diastereoselective Pictet–Spengler cyclization under kinetic control (MsOH, CH_2Cl_2, r.t.) to deliver compound **30** in an excellent 94% yield. Different conditions were then screened to achieve the diastereodivergent Pictet–Spengler cyclization of **29**. The best results were obtained by prolonged heating in 1,2-dichloroethane at 70 °C. Under these conditions, epimer **30′**

was produced with high diastereoselectivity (**30**/**30′** > 96:4) in 82% isolated yield (Scheme 14).



Scheme 14. Pictet–Spengler cyclization of the *N*-acyliminium ion that is generated from hemiaminal **29**.

Interestingly, byproduct **31** was also detected in the latter reaction (<10%). Compound **31** formally originated from an intramolecular ene reaction[21] between one allylic C–H bond (ene component) of the indole moiety and the C=C bond of the norbornene (the enophile).[22] Upon prolonged heating in toluene (120 °C, 22 h), compound **31** was formed at the expense of **30′**, but it was isolated in a low 32% yield because of partial decomposition. A control experiment revealed that compound **30′** was unaffected by heating in toluene at 120 °C, but the addition of MsOH effectively led to **31** (40% yield). Thus, formation of compound **31** can be explained by the reversible protonation of the norbornene double bond, thereby triggering the nucleophilic attack of the indole followed by the loss of a proton (Scheme 15).



Scheme 15. Formation of compound **31** by a formal intramolecular ene reaction.

Conclusions

We have demonstrated that substituted bicyclic *N*-acyliminium ions that contain a pyrrolidinone core, in which the nitrogen atom is connected to an appropriately located remote π-nucleophile such as an indol-2-yl, indol-3-yl, 1-methyl-pyrrol-2-yl, or 3,5-dimethoxyphenyl group, can undergo a diastereodivergent Pictet–Spengler cyclization to afford polycyclic nitrogen heterocycles with control of the quaternary stereocenter at the ring junction. High levels of diastereoselectivity have been obtained for bicyclic *N*-acyliminium species that have a pyrrolidinone moiety fused to a three-membered ring, a four-membered ring, or a norbornene ring system by simply fine-tuning the reaction conditions to proceed under kinetic or thermodynamic control. Mechanistic studies indicated that a retro-Pictet–Spengler reaction pathway is operating in the equilibration process to give the thermodynamic product.

Experimental Section

General Methods: Infrared (IR) spectra were recorded on a Bruker TENSOR 27 (IR-FT) with attenuated total reflectance (ATR). The NMR spectroscopic data were recorded with a Bruker AVANCE 400. The ^{1}H NMR spectra were recorded at 400 MHz, and the data are reported in the order of chemical shift in ppm from tetramethylsilane, multiplicity, and integration. The ^{13}C NMR spectra were recorded at 100 MHz, and the data are reported in the order of chemical shift in ppm from tetramethylsilane with the deuterated solvent signal used for calibration [for $CDCl_3$, δ = 77.0 ppm, for [D_6]DMSO, δ = 39.5 ppm, for [D_6]acetone, δ (C=O) = 206.2 ppm], multiplicity with respect to the number of protons (deduced from DEPT experiments, s = quaternary C, d = CH, t = CH_2, q = CH_3). Mass spectrometry was performed by electron impact (EI) ionization. The mass spectra were recorded with a Shimadzu GC–MS-QP2010S gas chromatography–mass spectrometer. High resolution mass spectra were obtained by electrospray ionization (ESI) with an orbitrap mass analyzer. Purification by flash chromatography was performed on silica gel (230–400 mesh).

(2*S,3*S**,5*R**)-2-Benzyl-7,11-diazapentacyclo[8.7.0.0^{2,7}.0^{3,5}.0^{12,17}]-heptadeca-1(10),12(17),13,15-tetraen-6-one (5):** Methanesulfonic acid (14 μL, 0.22 mmol, 1.1 equiv.) was added to a solution of enamide **4** (65.0 mg, 0.198 mmol) in CH_2Cl_2 (1.5 mL) in an oven-dried resealable vial. The vial was sealed (Teflon cap), and the reaction mixture was stirred at r.t. for 1 h. The vial was then opened, and a saturated aqueous solution of $NaHCO_3$ was added. The resulting mixture was extracted with CH_2Cl_2. The organic extract was dried with $MgSO_4$, filtered, and concentrated under reduced pressure. Analysis of the residue by ^{1}H NMR spectroscopy indicated the formation of **5** as a single detectable diastereomer (*dr* >96:4). Purification by flash chromatography on silica gel (petroleum ether/EtOAc, from 40:60 to 30:70) gave compound **5** (54.9 mg, 84% yield) as a yellow solid; m.p. 262 °C (decomposition). IR (ATR): $\tilde{\nu}$ = 3246, 1677, 1618, 1456, 1445, 1396, 1104, 979, 874, 836, 751, 697, 655, 602 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.12 (br. s, 1 H, NH), 7.27 (d, *J* = 8.1 Hz, 1 H), 7.21 (m, 1 H), 7.14 (br. t, *J* = 7.6 Hz, 2 H), 7.07 (t, *J* = 7.5 Hz, 1 H), 7.01 (d, *J* = 7.8 Hz, 2 H), 6.86 (t, *J* = 7.9 Hz, 1 H), 6.66 (d, *J* = 8.0 Hz, 1 H), 4.18 (dd, *J* = 13.4, 6.8 Hz, 1 H), 3.39 (d, *J* = 13.0 Hz, 1 H, AB syst), 3.21 (d, *J* = 13.1 Hz, 1 H, AB syst), 3.06 (ddd, *J* = 16.1, 11.4, 6.8 Hz, 1 H), 2.91 (ddd, *J* = 13.2, 11.6, 5.0 Hz, 1 H), 2.54 (td, *J* = 6.8, 5.0 Hz, 1 H), 2.46 (dd, *J* = 16.0, 5.0 Hz, 1 H), 1.83 (ddd, *J* = 8.4, 6.4, 3.2 Hz, 1 H), 1.20 (m, 1 H), 1.07 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.8 (s), 136.8 (s), 135.4 (s), 132.2 (s), 130.7 (d, 2 C), 128.1 (d, 2 C), 126.7 (d), 124.8 (s), 121.2 (d), 119.4 (d), 119.0 (d), 113.5 (s), 110.8 (d), 64.2 (s), 44.9 (t), 34.6 (t), 24.3 (d), 22.1 (t), 20.8 (d), 12.3 (t) ppm. MS (EI, 70 eV): *m*/*z* (%) = 238 (17), 237 (100), 235 (4), 207 (4), 180 (5), 168 (4), 167 (6), 144 (9), 143 (4), 115 (4), 91 (18), 65 (9). HRMS (ESI): calcd. for $C_{22}H_{20}N_2ONa$ [M + Na]$^+$ 351.14678; found 351.14706.

(2*R,3*S**,5*R**)-2-Benzyl-7,11-diazapentacyclo[8.7.0.0^{2,7}.0^{3,5}.0^{12,17}]-heptadeca-1(10),12(17),13,15-tetraen-6-one (5′):** Methanesulfonic

acid (14 μL, 0.22 mmol, 1.1 equiv.) was added to a solution of enamide **4** (65.0 mg, 0.198 mmol) in toluene (1.5 mL) in an oven-dried resealable vial. The vial was sealed (Teflon cap) and immersed in a preheated oil bath at 120 °C. After 3 h, the vial was opened, and a saturated aqueous solution of $NaHCO_3$ was added. The resulting mixture was extracted with CH_2Cl_2. The organic extract was dried with $MgSO_4$, filtered, and concentrated under reduced pressure. Analysis of the residue by ^1H NMR spectroscopy indicated the formation of **5′** as a single detectable diastereomer (*dr* >96:4). Purification by flash chromatography on silica gel (petroleum ether/EtOAc, from 40:60 to 30:70) gave compound **5′** (53.6 mg, 82% yield) as a yellow solid; m.p. 202 °C. IR (ATR): $\tilde{\nu}$ = 3253, 1659, 1453, 1419, 1327, 1265, 1216, 1017, 938, 875, 815, 734, 701, 640 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.48 (br. s, 1 H), 7.63 (br. d, J = 7.6 Hz, 1 H), 7.35 (m, 1 H), 7.22–7.14 (m, 5 H), 7.08–7.05 (m, 2 H), 4.29 (dd, J = 13.1, 5.9 Hz, 1 H), 3.43 (d, J = 13.8 Hz, 1 H, AB syst), 3.29 (d, J = 13.8 Hz, 1 H, AB syst), 2.89 (m, 1 H), 2.70 (ddd, J = 16.0, 11.4, 6.5 Hz, 1 H), 2.54 (ddd, apparent dd, J = 16.0, 4.3 Hz, 1 H), 2.27 (ddd, J = 7.4, 5.9, 4.2 Hz, 1 H), 1.68 (ddd, J = 8.4, 5.9, 3.2 Hz, 1 H), 0.76 (ddd, J = 8.4, 7.5, 5.0 Hz, 1 H), 0.10 (ddd, J = 4.9, 4.3, 3.4 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.4 (s), 136.2 (s), 136.1 (s), 132.0 (s), 130.2 (d, 2 C), 128.1 (d, 2 C), 126.7 (d), 124.4 (s), 121.6 (d), 119.7 (d), 118.5 (d), 112.9 (s), 111.2 (d), 63.6 (s), 45.9 (t), 34.3 (t), 22.8 (t), 22.3 (d), 21.3 (d), 10.5 (t) ppm. MS (EI, 70 eV): *m*/*z* (%) = 238 (17), 237 (100), 207 (4), 167 (4), 144 (8), 115 (4), 91 (16), 65 (8). HRMS (ESI): calcd. for $C_{22}H_{20}N_2ONa$ $[M + Na]^+$ 351.14678; found 351.14715.

(2*S,3*S**,5*R**)-2-Benzyl-12,14-dimethoxy-7-azatetracyclo-[8.4.0.0^{2,7}.0^{3,5}]tetradeca-1(10),11,13-trien-6-one (11):** The cyclization of enamide **10** (91.7 mg, 0.262 mmol) was carrried out in the presence of MsOH (19 μL, 0.29 mmol, 1.1 equiv.) in CH_2Cl_2 (2.0 mL) at either r.t. for 0.5 h or 50 °C for 4 h. Purification by flash chromatography on silica gel (petroleum ether/EtOAc, 50:50) afforded **11** (79.9 mg, 87% yield; *dr* >96:4) as a pale yellow solid; m.p. 49 °C. IR (ATR): $\tilde{\nu}$ = 1687, 1603, 1583, 1454, 1380, 1338, 1271, 1210, 1192, 1145, 1107, 1092, 1056, 827, 763, 700 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.18–7.14 (m, 3 H), 6.98–6.90 (m, 2 H), 6.39 (d, J = 2.4 Hz, 1 H), 6.20 (d, J = 2.4 Hz, 1 H), 3.93 (apparent dd, J = 13.4, 6.8 Hz, 1 H), 3.84 (s, 3 H), 3.79 (s, 3 H), 3.56 (d, J = 14.0 Hz, 1 H, AB syst), 3.21 (d, J = 14.0 Hz, 1 H, AB syst), 3.01 (ddd, J = 16.5, 12.4, 7.0 Hz, 1 H), 2.85 (ddd, J = 8.0, 6.2, 4.4 Hz, 1 H), 2.70 (ddd, J = 13.2, 12.7, 4.6 Hz, 1 H), 2.34 (apparent dd, J = 16.5, 4.4 Hz, 1 H), 1.71 (ddd, J = 8.9, 6.2, 3.1 Hz, 1 H), 0.87 (ddd, apparent td, J = 8.2, 4.8 Hz, 1 H), 0.55 (ddd, apparent td, J = 4.6, 3.2 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.7 (s), 159.4 (s), 157.3 (s), 137.9 (s), 137.5 (s), 130.4 (d, 2 C), 127.9 (d, 2 C), 126.3 (d), 120.5 (s), 105.2 (d), 97.4 (d), 64.4 (s), 55.2 (q), 55.1 (q), 43.0 (t), 34.7 (t), 28.1 (t), 23.4 (d), 19.5 (d), 11.7 (t) ppm. MS (EI, 70 eV): *m*/*z* (%) = 259 (17), 258 (100), 243 (6), 200 (9), 115 (4), 91 (15), 89 (2), 77 (3), 65 (9), 55 (2). HRMS (ESI): calcd. for $C_{22}H_{23}NO_3Na$ $[M + Na]^+$ 372.15701; found 372.15736.

(2*R,3*S**,5*R**)-2-Benzyl-12,14-dimethoxy-7-azatetracyclo-[8.4.0.0^{2,7}.0^{3,5}]tetradeca-1(10),11,13-trien-6-one (11′):** The cyclization of enamide **10** (90.2 mg, 0.258 mmol) was carried out in the presence of MsOH (18 μL, 0.28 mmol, 1.1 equiv.) in toluene (1.9 mL) at 120 °C for 6 h. Purification by flash chromatography on silica gel (petroleum ether/EtOAc, 50:50) afforded **11′** (80.6 mg, 89% yield; *dr* >96:4) as a white solid; m.p. 142 °C. IR (ATR): $\tilde{\nu}$ = 1678, 1603, 1591, 1455, 1413, 1273, 1208, 1152, 1106, 1054, 939, 825, 761, 752, 703, 648 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.25–7.19 (m, 3 H), 7.10 (m, 2 H), 6.44 (d, J = 2.4 Hz, 1 H), 6.23 (d, J = 2.4 Hz, 1 H), 4.17 (ddd, J = 13.3, 6.5, 1.1 Hz, 1 H), 3.94 (s, 3 H), 3.80 (s, 3 H), 3.33 (d, J = 13.7 Hz, 1 H, AB syst), 3.25 (d, J = 13.7 Hz, 1 H, AB syst), 2.99 (m, 1 H), 2.71 (ddd, J = 16.3, 12.1, 6.9 Hz, 1 H), 2.59 (ddd, apparent dd, J = 16.3, 3.9 Hz, 1 H), 2.37 (ddd, J = 7.7, 5.8, 4.3 Hz, 1 H), 1.40 (ddd, J = 8.3, 5.8, 3.3 Hz, 1 H), 0.71 (ddd, apparent td, J = 8.0, 4.7 Hz, 1 H), 0.06 (ddd, apparent td, J = 4.3, 3.7 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.9 (s), 159.2 (s), 157.2 (s), 136.7 (s), 136.1 (s), 130.3 (d, 2 C), 127.9 (d, 2 C), 126.5 (d), 121.1 (s), 104.5 (d), 97.7 (d), 63.9 (s), 55.5 (q), 55.2 (q), 43.1 (t), 33.7 (t), 29.5 (t), 22.3 (d), 20.5 (d), 9.9 (t) ppm. MS (EI, 70 eV): *m*/*z* (%) = 259 (22), 258 (100), 243 (7), 200 (10), 115 (5), 92 (6), 91 (42), 89 (5), 77 (4), 65 (24), 63 (4), 55 (4). HRMS (ESI): calcd. for $C_{22}H_{23}NO_3Na$ $[M + Na]^+$ 372.15701; found 372.15737.

(1*R,12*R**,15*S**)-3,5-Dimethoxy-1-phenyl-10-azatetracyclo-[8.5.0.0^{2,7}.0^{12,15}]pentadeca-2(7),3,5-trien-11-one (23):** A solution of phenylmagnesium chloride (1 M in Et_2O, 0.28 mL, 0.28 mmol, 2 equiv.) was added to a solution of (1*R**,5*S**)-3-[2-(3,5-dimethoxyphenyl)ethyl]-3-azabicyclo[3.2.0]heptane-2,4-dione[23] (40.0 mg, 0.138 mmol) in tetrahydrofuran (THF, 2 mL) at –78 °C. The reaction mixture was warmed to room temp., stirred for 0.5 h, and then hydrolyzed by the addition of a saturated aqueous solution of NH_4Cl. After the addition of Et_2O, the layers were separated, and the aqueous phase was extracted with Et_2O. The organic extract was dried with $MgSO_4$, filtered, and concentrated under reduced pressure. Crude hemiaminal **20** was dissolved in CH_2Cl_2 (1 mL), and MsOH (9.8 μL, 0.14 mmol, 1.1 equiv.) was added. The reaction mixture was stirred at room temp. for 5 h. Workup and purification by flash chromatography on silica gel (petroleum ether/EtOAc, 50:50) afforded **23** (42.0 mg, 87% yield; *dr* >96:4) as a white solid; m.p. 157 °C. IR (ATR): $\tilde{\nu}$ = 1671, 1604, 1583, 1454, 1423, 1337, 1212, 1195, 1145, 1106, 1055, 911, 884, 831, 728, 701, 644 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.32–7.21 (m, 5 H), 6.45 (d, J = 2.4 Hz, 1 H), 6.25 (d, J = 2.4 Hz, 1 H), 4.21–4.14 (m, 1 H), 3.95 (ddd, apparent td, J = 8.6, 5.7 Hz, 1 H), 3.86 (s, 3 H), 3.78 (s, 3 H), 3.09–3.03 (m, 1 H), 3.02–2.93 (m, 2 H), 2.54–2.46 (m, 1 H), 2.38–2.28 (m, 1 H), 2.20–2.12 (m, 1 H), 2.05–1.95 (m, 1 H), 1.89–1.81 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.8 (s), 159.5 (s), 157.3 (s), 140.8 (s), 137.3 (s), 128.0 (d, 2 C), 127.8 (d, 2 C), 127.1 (d), 122.4 (s), 105.7 (d), 97.7 (d), 70.8 (s), 55.3 (q, 2 C), 40.8 (d), 40.3 (d), 35.9 (t), 28.3 (t), 22.1 (t), 21.9 (t) ppm. HRMS (ESI): calcd. for $C_{22}H_{23}NO_3Na$ $[M + Na]^+$ 372.15701; found 372.15709.

(1*S,12*R**,15*S**)-3,5-Dimethoxy-1-phenyl-10-azatetracyclo-[8.5.0.0^{2,7}.0^{12,15}]pentadeca-2(7),3,5-trien-11-one (23′):** This compound was prepared by using (1*R**,5*S**)-3-[2-(3,5-dimethoxyphenyl)ethyl]-3-azabicyclo[3.2.0]heptane-2,4-dione[23] (40.0 mg, 0.138 mmol) and PhMgCl (1 M in Et_2O, 0.28 mL, 0.28 mmol, 2 equiv.) in THF (2.0 mL; –78 °C to room temp., 0.5 h at room temp.). Crude hemiaminal intermediate **20** underwent cyclization in the presence of MsOH (9.8 μL, 0.15 mmol, 1.1 equiv.) in toluene (1.0 mL) at 120 °C for 44 h. Purification by flash chromatography (petroleum ether/EtOAc, 50:50) gave **23′** (37.0 mg, 77% yield; *dr* >96:4) as a waxy white solid; m.p. 144 °C. IR (ATR): $\tilde{\nu}$ = 1673, 1603, 1590, 1447, 1426, 1413, 1271, 1195, 1148, 1111, 1051, 933, 840, 817, 755, 698, 633 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.24–7.19 (m, 3 H), 6.99–6.97 (m, 2 H), 6.36–6.34 (m, 2 H), 4.17–4.12 (m, 1 H), 3.82 (s, 3 H), 3.72 (dd, J = 14.5, 7.4 Hz, 1 H), 3.60 (s, 3 H), 3.42–3.37 (m, 1 H), 3.03 (m, 1 H), 2.77–2.70 (m, 2 H), 2.38 (m, 1 H), 2.02–1.93 (m, 2 H), 1.71–1.61 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.9 (s), 159.5 (s), 157.6 (s), 145.1 (s), 137.4 (s), 128.0 (d, 2 C), 127.1 (d), 126.0 (d, 2 C), 117.5 (s), 104.7 (d), 97.0 (d), 68.7 (s), 55.2 (q, 2 C), 44.2 (d), 42.8 (d), 34.0

(t), 29.0 (t), 23.5 (t), 22.5 (t) ppm. HRMS (ESI): calcd. for $C_{22}H_{23}NO_3Na$ $[M + Na]^+$ 372.15701; found 372.15712.

Supporting Information (see footnote on the first page of this article): All experimental procedures including those involved in the preparation of the substrates, detailed characterization data, and NMR spectra of all new compounds.

Acknowledgments

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[16] The intermolecular reduction of *N*-acyliminium ions **J** (Scheme 3) with a remote 3,4-dimethoxyphenyl group by treatment with Et_3SiH/TFA can compete with the Pictet–Spengler cyclization. For details, see: B. de Carné-Carnavalet, C. Meyer, J. Cossy, B. Folléas, J.-L. Brayer, J.-P. Demoute, *J. Org. Chem.* **2013**, *78*, 5794–5799. However, the cyclization is faster for structurally related compound **13** in which the π-nucleophile is the 3,5-dimethoxyphenyl group.

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[23] The preparation of this compound (imide **39**) is described in the Supporting Information.

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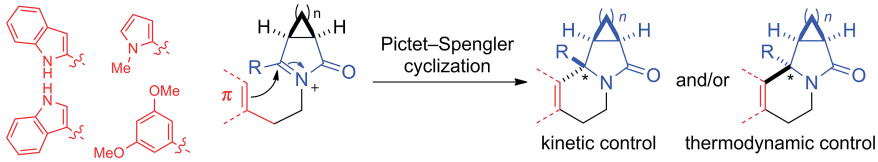

The diastereoselectivity of the Pictet–Spengler cyclization of bicyclic *N*-acyliminium ions that have a 3-azabicyclo[*n*.3.0]-alkane core and an electron-rich π-nucleophilic moiety (indol-2-yl, indol-3-yl, 1-methylpyrrol-2-yl, or 3,5-dimethoxyphenyl group) was examined. Control of the new quaternary stereocenter was achieved in a diastereodivergent manner by fine-tuning the reaction conditions.

Keywords: Synthetic methods / Polycycles / Cyclization / Diastereoselectivity / Kinetic control / Thermodynamic control

